博士論文

オメガ 3 脂肪酸由来の抗炎症性脂質メディエーターの全合成

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略語表

AA	arachidonic acid
Ac	acetyl
AIBN	2,2'-azodiisobutyronitrile
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
CAN	cerium(IV) diammonium nitrate
CBS	Corey-Bakshi-Shibata
CD	circular dichroism
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-*para*-benzoquinone
De	diastereo excess
DHA	docosahexaenoic acid
14,20-diHDHA	14,20-dihydroxydocosahexaenoic acid
DIPHOS	1,2-bis(diphenylphosphino)ethane
DIBAL-H	diisobuylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*'-dimethyl formamide
DMP	Dess-Matin periodinane
DMSO	dimethylsulfoxide
Ee	enantio excess
EPA	eicosapentaenoic acid
Et	ethyl
18-HEPE	18-hydroxy eicosapentaenoic acid
HETE	hydroxyeicosatetraennoic acid
HPLC	high performance liquid chromatography
im	imidazole
IPA	isopropylalcohol
LOX	lipoxygenase
LT	leukotriene
LX	lipoxin
MaR	maresin
Mc	monochloromethanesulfonyl
Me	methyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MS	mass spectrometry

Mts	2-mesitylenesulfonyl
MW	microwave
n	normal
NBSH	2-nitrobenzenesulfonylhydrazide
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
NPD1	neuroprotectin D1
ODS	octa decyl silyl
PD1	protectin D1
PEI	polyethyleneimine
PG	prostaglandin
Ph	phenyl
PMB	*para*-methoxy benzyl
PPTS	pyridinium *para* -toluenesulfonate
py	pyridine
Rv	resolvin
t	tertiary
TBAF	tetrabutylammmonium fluoride
TBS	*tertiary*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMS	trimethyl silyl
Trisyl	2,4,6-triisopropylbenzenesuofonyl
Ts	*para*-toluenesulfonyl
UV	ultra violet

第 1 章

序論

1-1. ω-3 脂肪酸由来の抗炎症性新規脂質メディエーター

脂質メディエーターは、生体内で脂肪酸から生合成される酸化脂質分子であり、低濃度で、特異的受容体を介して多種多様な生理活性を発現する。末端から 6 番目炭素が二重結合である ω-6 脂肪酸のうち、炭素数 20 の脂肪酸であるアラキドン酸 (AA) から生合成されるエイコサノイドの中には、炎症を起炎する脂質メディエーターであるプロスタグランジン (PG) やロイコトリエン (LT)[1]、炎症収束期に関わるメディエーターであるリポキシン (LX)[2] などが存在する。脂質メディエーターは、その他にも心疾患やアルツハイマーなどの病態に優位な効果を示す[3]ことが知られている。一方で、それらの詳細な活性発現機構は、多くが未解明である。

近年、ドコサヘキサエン酸 (DHA) やエイコサペンタエン酸 (EPA) の酸化代謝に代表される新規脂質メディエーターが多く発見され、注目されている[4]。これらはいずれも末端から 3 番目が sp^2 炭素である ω-3 脂肪酸である。DHA は炭素数 22 の脂肪酸であり、6 つの Z-アルケンを有する。また、EPA は炭素数 20 の脂肪酸であり、5 つの Z-アルケンを有する。これまでに、DHA 由来のプロテクチン D1 (PD1) やマレシン (MaR1) や、EPA 由来のレゾルビン E 類 (RvE1, RvE2, RvE3, Figure 1-1) などが見出されており[5]、それらの強力な抗炎症作用が報告されている。

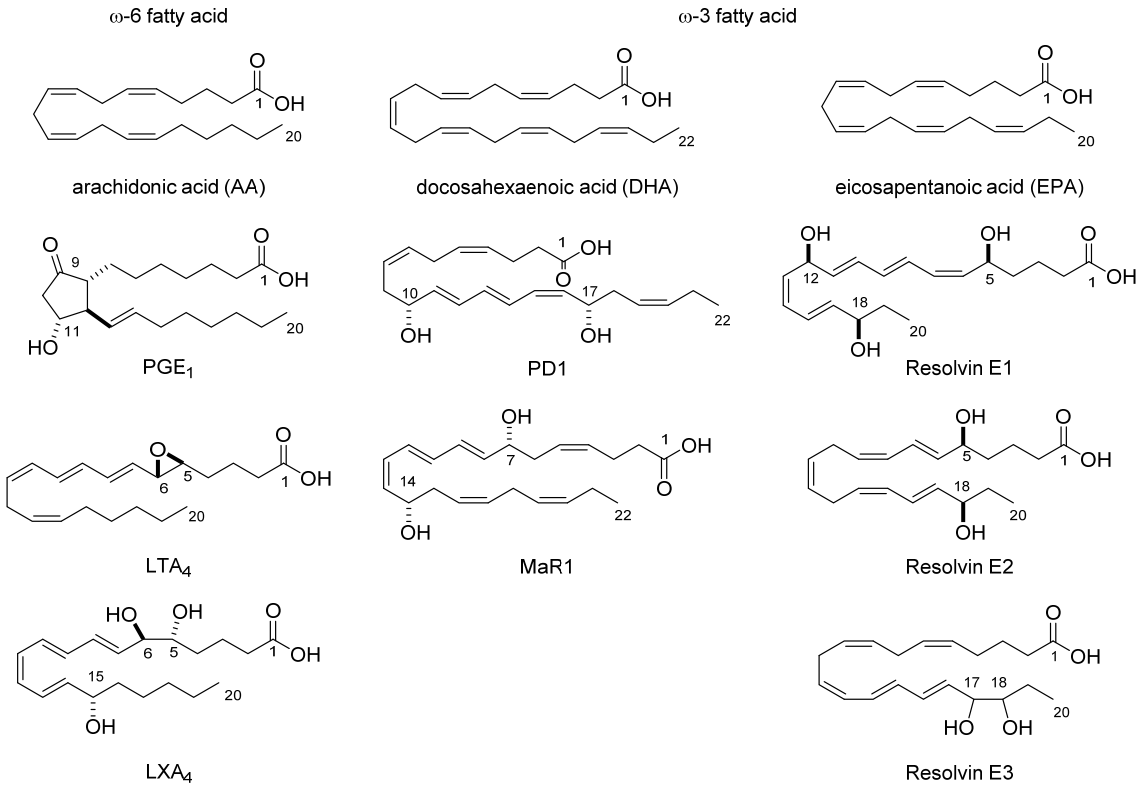


Figure 1-1. Structures of AA, DHA, EPA and their oxidized metabolites

元来 DHA や EPA は魚油に多く含まれ、炎症性疾患、免疫修飾、自己免疫疾患、リウマチ、心疾患、アルツハイマー病、神経変性疾患、2 型糖尿病、がんなど様々な病気の予防に関連しているとされてきた。しかし、その生理活性発現メカニズムは未解明な部分が多く、発現機構解明に向けて、精力的に研究が行われている。その中でも、ω-3 脂肪酸由来の脂質メディエーターが炎症性疾患に及ぼす影響について、次のようなことがわかってきている。

急性炎症においては、外傷や感染に反応して好中球が生体防御機能として組織に集積する。好中球は、AA 由来の脂質メディエーターを含む炎症物質を放出して組織障害を引き起こす。一方、炎症反応を収束へ導く機構が存在しており、この機構に ω-3 脂肪酸由来の脂質メディエーターが関わることで、生体内の炎症反応が制御されている。このような制御機構が適切に働かない場合、慢性炎症や組織傷害を伴う関節炎、動脈硬化、喘息、がんなどへと発展することとなる。

抗炎症として用いられる主な薬剤は、急性炎症反応によるアラキドン酸由来の起炎性脂質メディエーターを産生する酵素の阻害剤 (シクロオキシゲナーゼ阻害剤、リポキシゲナーゼ阻害剤) や受容体アンタゴニストといった、非ステロイド系抗炎症薬 (non steroidal anti-inflammatory drugs ; NSAIDs) である。しかし、シクロオキシゲナーゼ-2 阻害剤が、心臓発作のリスクを高めることに加え[6]、炎症の収束を遅らせること[7]などが報告された。このため、炎症の収束期に積極的に関与することが示唆されている、ω-3 脂肪酸由来の抗炎症性脂質メディエーターが、既存の抗炎症剤に代わる新たな創薬ターゲットとして注目されている。

ω-3 脂肪酸の抗炎症性は、AA 代謝経路に拮抗することにより発現されていると考えられてきた。しかし、近年ハーバード大学の Serhan らのグループの研究により、ω-3 脂肪酸由来の酸化代謝物そのものが抗炎症性を有することが明らかにされた[4]。Serhan らはマウス急性腹膜炎モデルにおける炎症収束期の腹腔内滲出液を、リピドミクスにより包括的に解析し、炎症収束に関わる新規脂質メディエーター群として EPA, DHA の酸化代謝物を見出した[8]。すなわち、DHA 由来のレゾルビン D 類 (RvD1, RvD2, RvD3, RvD4, RvD5, RvD6)、ニューロプロテクチン／プロテクチン (NPD1/ PD1[9])、マレシン[10] (MaR1) や、EPA 由来のレゾルビン E 類 (RvE1, RvE2)である。また 2012 年、有田らによりレゾルビン E3 と名付けられた新規 EPA 酸化代謝物が発見された[11]。これらの新規脂質メディエーターは、マウス急性腹膜炎モデルにおいて、極微量 (ng/マウス) で強力な好中球浸潤抑制活性、つまり抗炎症活性を示すことが報告された。

脂肪酸由来の脂質メディエーターは、いずれの化合物も、生体内でわずかの量が生成されるのみである。そのため、概してその希少性に由来する以下の問題が生じる。

①脂質メディエーターの詳細な生物学的研究を行うことが困難である。

②分子の平面構造は、MS/MS 解析や UV スペクトルにより推定できるが[12]、ヒドロキシ基などの極性官能基の立体構造が決定できない。

このため、新規脂質メディエーターの完全立体構造の決定や、生理活性発現機構の解明に向けた研究を行うには、有機合成化学による試料供給が不可欠かつ重要な役割を果たす。

1-2. 当研究室における DHA および EPA 由来の新規脂質メディエーターの合成研究

脂質の化学全合成は、構造決定や、詳細な生物学的研究の試料供給を目的として行われており、これまでに脂質科学の研究に大きな役割を果たしてきた。特に、化学全合成は、天然からは得られない立体構造を有する脂質類縁体の供給を可能とし、創薬科学においても大きく貢献した。特に、Corey らがロイコトリエン類縁体の全合成を通して、ロイコトリエン拮抗薬が発見されたことからも、有機合成化学分野の寄与は大きい[13]。

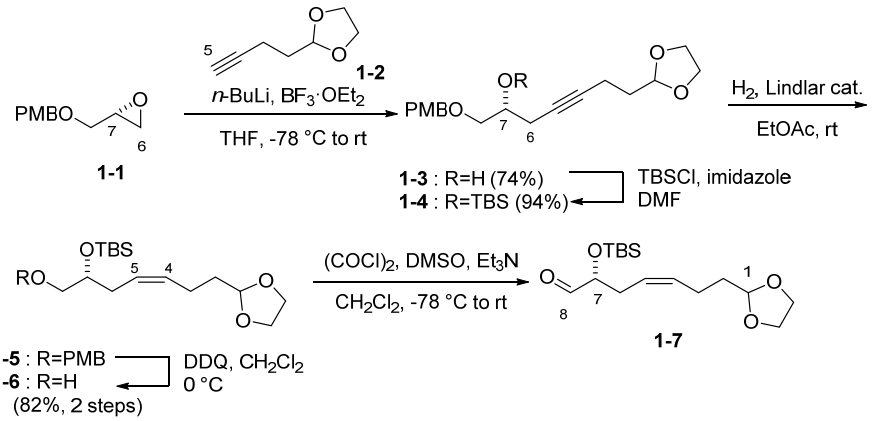
今日までに様々なグループにより脂質メディエーターの全合成が報告されているが[14]、それらの全合成に共通して鍵となるのが、①ヒドロキシ基の立体化学の制御、②*Z*-アルケンの構築、③効率的なフラグメントの連結、④純度の高い最終物の単離である。

当研究室では、これまで ω-3 脂肪酸由来の新規脂質メディエーターの全合成研究を行っており、MaR1[15], RvE2[16], RvE3[17]の数種の立体異性体の全合成を達成している。以下にその概要を示す。

1-2-1. マレシンの全合成

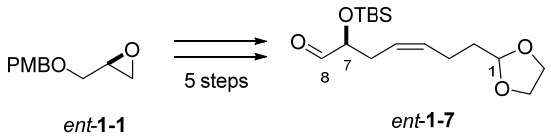
DHA 由来の抗炎症性新規脂質メディエーターとして、マクロファージから単離された MaR1 は、平面構造は決定されていたが、C7 位のヒドロキシ基の立体化学については不明であった。これまでに、Serhan ら[18]、 Spur ら[19]、 小林ら[20]、 Hansen ら[21]によって、MaR1 の全合成が報告されている。当研究室では、MaR1 の構造決定を目的とした、(7*R*,14*S*)-, (7*S*,14*S*)-MaR1 の二種のジアステレオマーの合成が行われた。C1-8 フラグメントは以下の方法で合成された (Scheme 1-1)。三フッ化ホウ素存在下、光学活性なグリシドール保護体 (7*R*)-**1-1** に対するリチウムアルキニドの求核付加反応により C7 位のヒドロキシ基を立体選択的に導入した。第二級ヒドロキシ基を TBS エーテルとして保護し、Lindlar 還元により C4-5 アルキンを *Z*-アルケンへと還元した。PMB 基を除去した後、得られた第一級ヒドロキシ基を酸化し、C1-8 フラグメント **1-7** を合成した。

Scheme 1-1. Synthesis of (7*R*)-C1-8 fragment



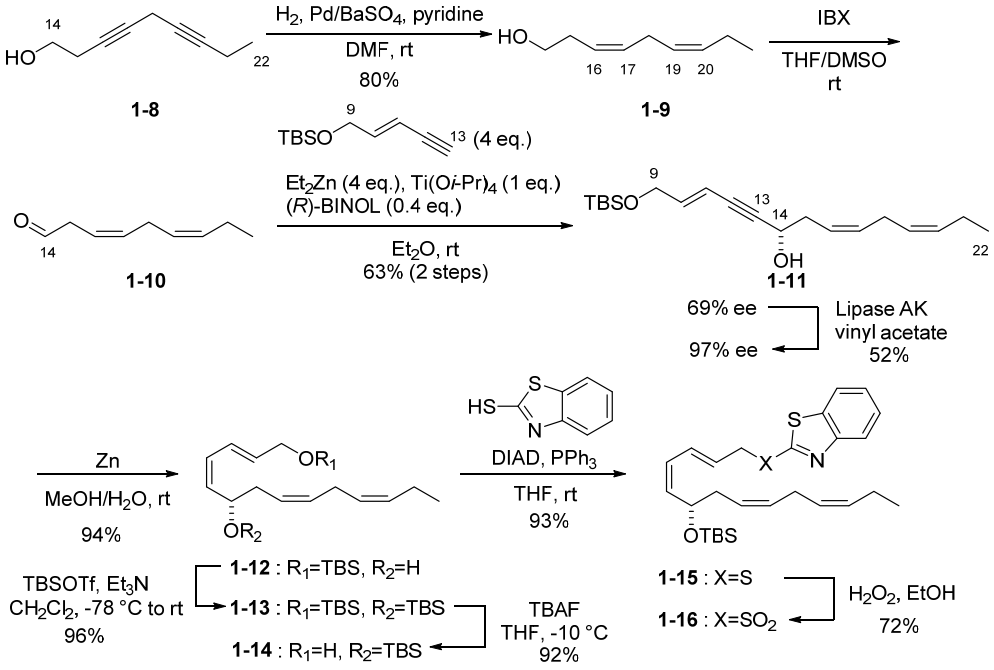
C7 ヒドロキシ基のエナンチオマーである (7*S*)-**1-7** は、原料に **1-1** のエナンチオマーを用いて、同様の経路を経ることで、合成された (Scheme 1-2)。

Scheme 1-2. Synthesis of (7*S*)-C1-8 fragment



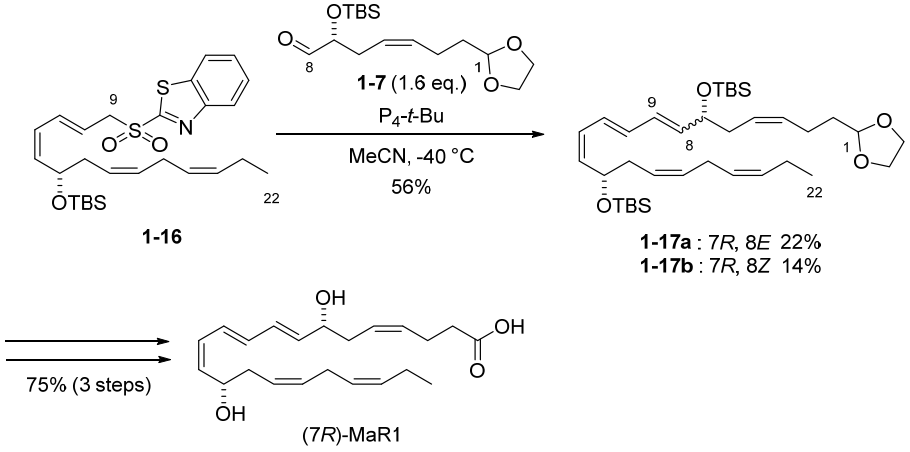
MaR1 の C9-22 フラグメントは、C14-22、および C9-13 フラグメントを連結して合成された (Scheme 1-3)。すなわち、ジイン **1-8** を *Z*-アルケンへと部分還元した後、第一級ヒドロキシ基を酸化し、アルデヒド **1-10** とした。このアルデヒドに対し、(*R*)-BINOL を不斉配位子とした亜鉛アルキニドのエナンチオ選択的付加反応により C9-22 位部分を構築した。この時点で C14 位の不斉収率は 69%であったため、リパーゼ AK を用いた光学分割を行い 97% ee の **1-11** を得た。続いて、共役エンインのアルキン部分を亜鉛還元し *Z*-アルケンと還元した後、保護基の変換、光延反応を利用した 2-メルカプトベンゾチアゾールの導入、酸化を経て、C9-22 フラグメント **1-16** を合成した。

Scheme1-3. Synthesis of C9-22 fragment



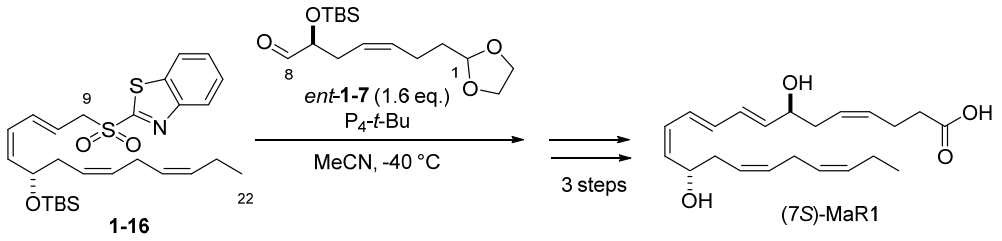
得られた **1-16** に対し、先に合成した C1-8 フラグメント **1-7** を 1.6 等量、塩基として P_4*t*-Bu を用いた Julia-Kosienski オレフィン化反応を行い、両フラグメントを連結した (Scheme 1-4)。C8-9 位のオレフィンの幾何異性体がそれぞれ生成したため、それらを HPLC により分離し、*E* 体 **1-17a** から三段階の変換を経て、(7*R*)-MaR1 へと導いた。

Scheme 1-4. Synthesis of (7*R*)-MaR1



(7*S*)-MaR1 についても、C1-8 フラグメントのエナンチオマー***ent*-1-7** と C9-22 フラグメント **1-16** を用い、同様の合成法で合成した (Scheme 1-5)。

Scheme 1-5. Synthesis of (7*S*)-MaR1

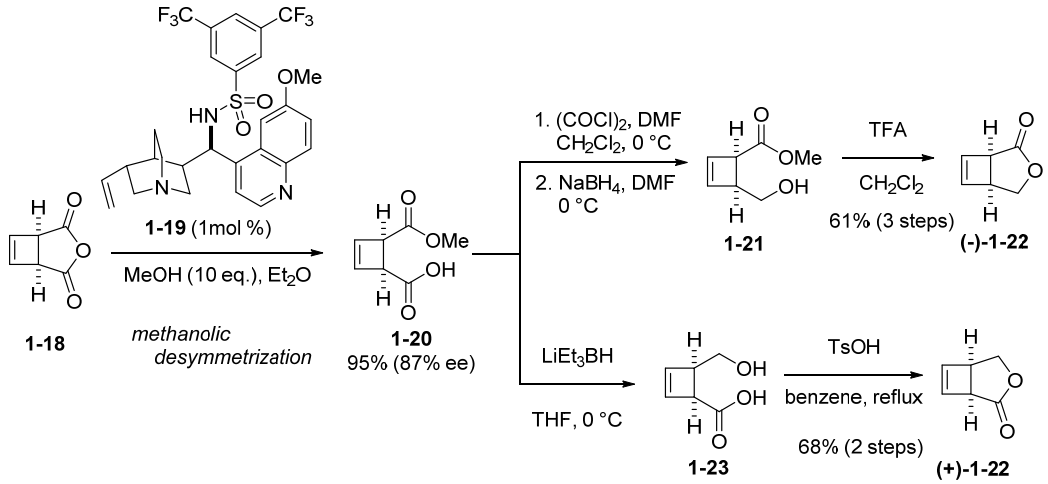


これら二種のジアステレオマーは ^{1}H NMR, ^{13}C NMR ともに一致していたため、分光学的に区別することは困難であったが、HPLC の保持時間の違いで各々の区別が可能であった。市販の MaR1 と、合成した (7*S*)- および (7*R*)-MaR1 の HPLC 分析により、C7 位立体化学が *S* 配置であることを初めて実験的に明らかにした。一方で、Serhan らによって生体内で合成される MaR1 は、7*R* の立体配置を有する事が報告されており、現在 MaR1 は 7*R* 配置であると認識されている。その後のザイモザン腹膜炎誘導モデルを用いた好中球浸潤抑制試験において、(7*S*)-, (7*R*)-MaR1 のいずれも低濃度 (1 ng/マウス) で活性を示すことが明らかとなった。

1-2-2. レゾルビン E2 の全合成

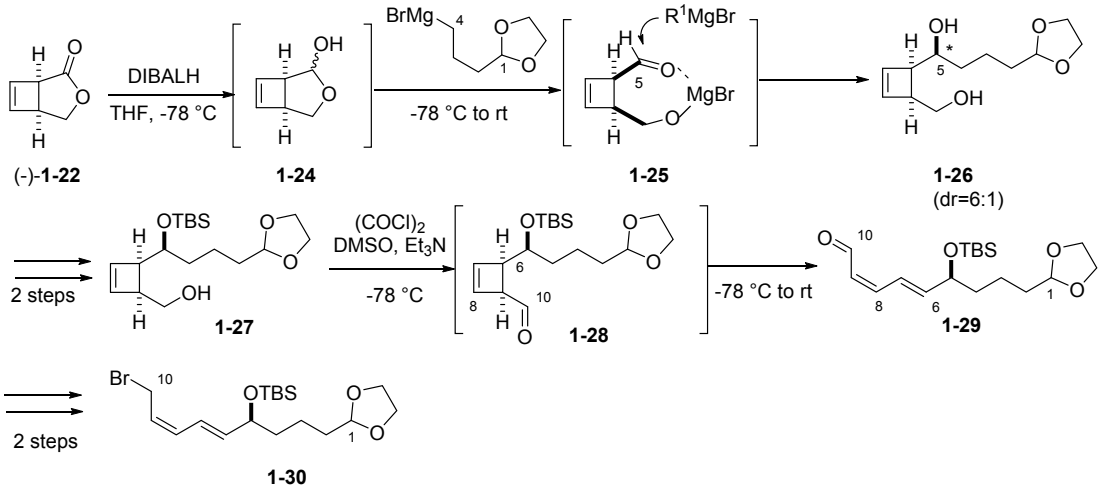
RvE2 の全合成はこれまでに、小林ら[22]、Spur ら[23]によって報告されている。当研究室では、RvE2 の分子の対称性部分構造に着目し、効率的な全合成が行われた。メソ体酸無水物の **1-18** に対し、エナンチオ選択的に加メタノール分解を行い、**1-20** を 87% ee で得た (Scheme 1-6)。**1-20** のカルボン酸を選択的に還元し、TFA によりラクトン環を形成し、(-)-**1-22** を得た。一方、**1-20** のエステルを化学選択的に還元し、TsOH によりラクトン環を形成し、エナンチオマーである (+)-**1-22** を合成した。

Scheme 1-6. Synthesis of lactone **1-22** by enantioselective methanolysis



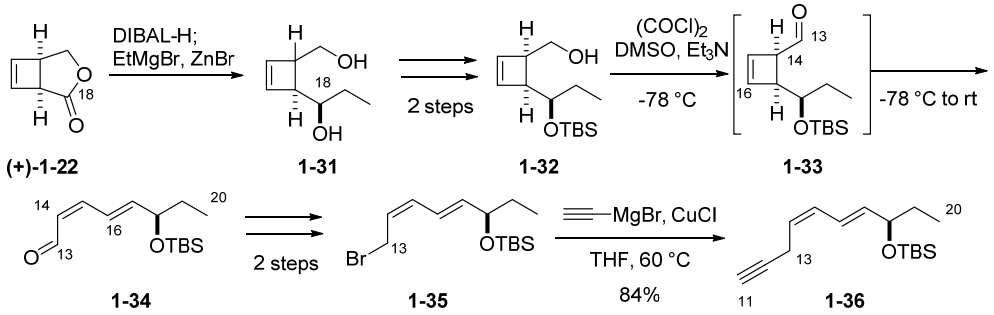
その後、酸素原子とマグネシウム原子のキレーションを利用した立体選択的 C1-4 フラグメント導入により C5 ヒドロキシ基の立体化学を構築している (Scheme 1-7)。続く **1-27** のシクロブテンの回転選択的な電子環状反応により RvE2 に特徴的な (6*E*, 8*Z*)-ジエンの構築に成功し、C1-10 フラグメント **1-30** の合成を完了している。

Scheme 1-7. Synthesis of C1-10 fragment **1-30**



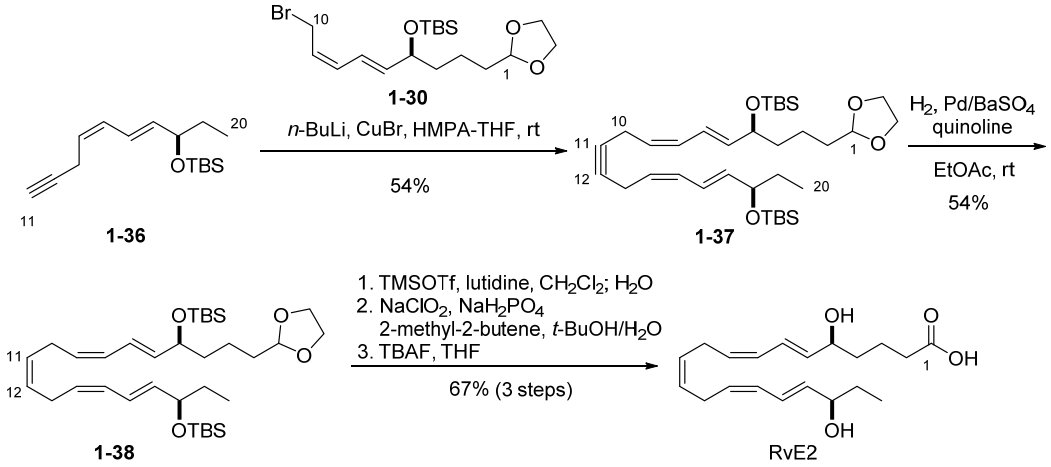
また、同様の合成経路を経て (14*Z*,16*E*)-ジエンを構築し、C11-20 フラグメント **1-36** を合成した (Scheme 1-8)。

Scheme 1-8. Synthesis of C11-20 fragment **1-36**



先に合成した **1-30** と **1-36** を、銅を用いたカップリング反応により連結し、RvE2 の炭素骨格を構築した後、**1-37** の C11-12 アルキンを $Pd/BaSO_4$ を用いた水素添加反応により *Z*-アルケンへと還元した (Scheme 1-9)。最後に三段階の変換を経て RvE2 の合成を達成した。

Scheme 1-9. Total synthesis of RvE2



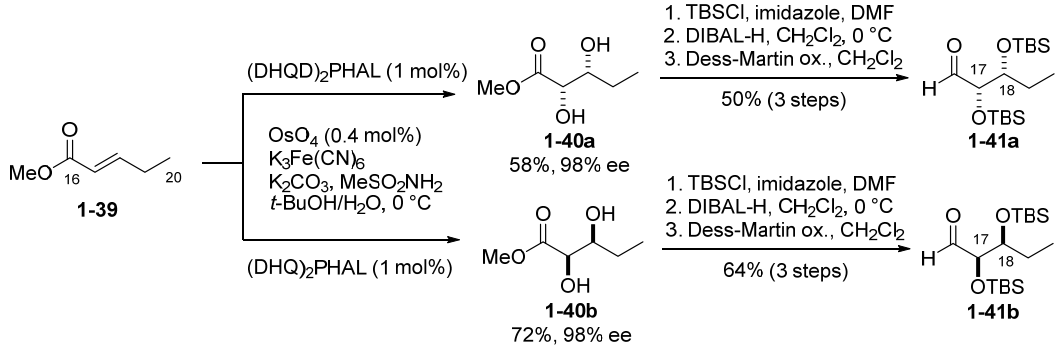
本合成法はメソ化合物である **1-18** の非対称化が利用されており、脂質の合成において非常に独創的な合成法であるといえる。一方、メソ体の合成に光反応を利用するためスケールアップ時の再現がとりにくいこと、**1-20** の不斉収率が 87%であること、求核付加反応の選択性に課題を残している。

1-2-3. レゾルビン E3 の全合成

RvE3 は、EPA から得られる 18-ヒドロキシエイコサペンタエン酸 (18-HEPE) が 12/15-リポキシゲナーゼ (12/15-LOX) により酸化された、17,18-ジヒドロキシエイコサペンタエン酸である。本化合物は、当研究室により唯一の合成例が報告されている。本合成では、不明であった C17,18 位の立体化学の決定のため、C17,18 位の 2 つのヒドロキシ基の立体配置の違いによる 4 種のジアステレオマーを立体選択的に合成してい

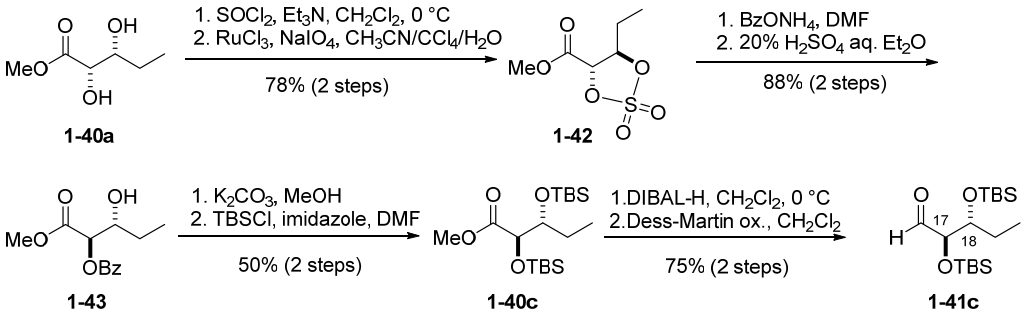
る。**1-39** から、$(DHQD)_2PHAL$ と $(DHQ)_2PHAL$ を不斉配位子とした Sharpless の不斉ジヒドロキシ化によりヒドロキシ基を二つ導入し、ジオール **1-40a** と **1-40b** をそれぞれ 98% ee で得た。その後、二つのヒドロキシ基の保護、エステルの還元、第一級ヒドロキシ基の酸化を経てアルデヒド **1-41a**、**1-41b** をそれぞれ合成した (Scheme 1-10)。

Scheme 1-10. Synthesis of (17*R*,18*R*)-, (17*S*,18*S*)-C16-20 fragments



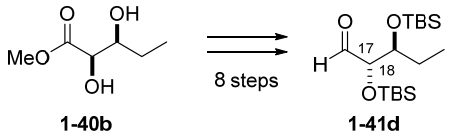
一方、ジオール **1-40a** を環状スルフェート **1-42** へと誘導した後、アンモニウムベンゾエートを用いた位置選択的な開環反応により C17 位の立体化学を反転させたベンゾエート **1-43** を得た。その後 **1-43** から 4 段階の変換でアルデヒド **1-41c** を得た (Scheme 1-11)。

Scheme 1-11. Synthesis of (17*S*,18*R*)-C16-20 fragment **1-41c**



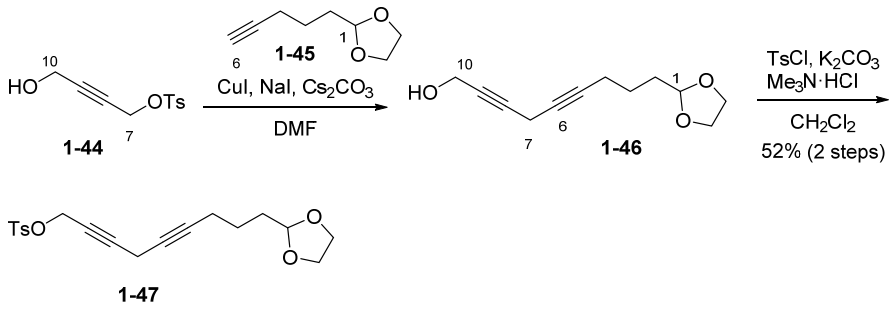
アルデヒド **1-41d** についてもジオール **1-40b** から同様の変換を経て合成された (Scheme 1-12)。

Scheme 1-12. Synthesis of (17*R*,18*S*)-C16-20 fragment **1-41d**



RvE3 の C1-10 フラグメント **1-47** はプロパルギルトシレートと末端アルキンを、銅を用いた S_N2 カップリングにより連結した後、プロパルギルアルコールを田辺らの方法[24]によりトシル化し、合成された (Scheme 1-13)。

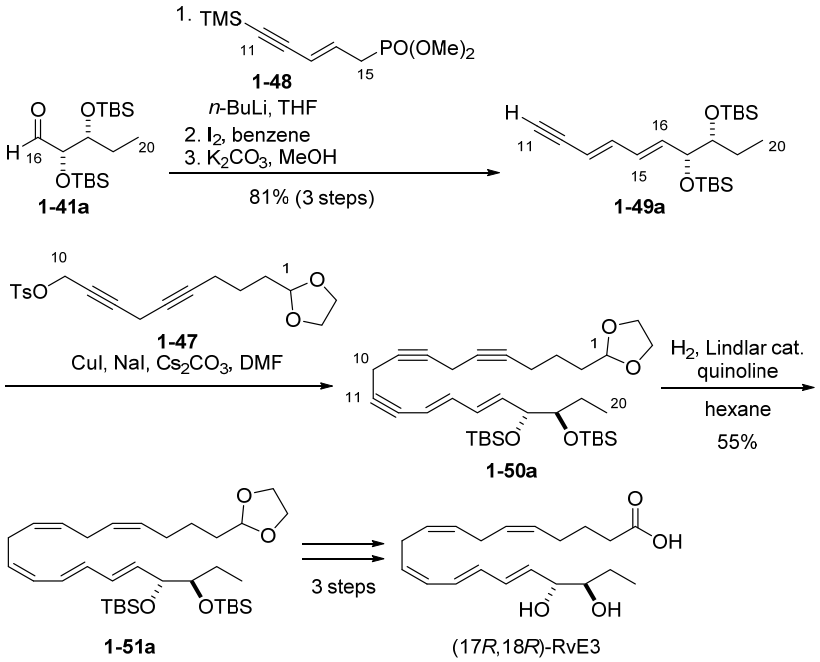
Scheme 1-13. Synthesis of C1-10 fragment **1-47**



Scheme 1-14 に (17*R*,18*R*)-RvE3 の合成を示した。**1-41a** と **1-48** の Hornor-Wadsworth-Emmons 反応により C11-20 フラグメントを合成した後、ヨウ素により C15-16 オレフィンを異性化させ、*E* の立体化学を有する **1-49a** を合成した。TMS 基を除去した後、末端アルキンとした C11-20 フラグメント **1-49a** と先に合成した C1-10 フラグメント **1-47** とを銅を用いた S_N2 カップリング反応に供し、トリイン **1-50a** を得た。トリイン **1-50a** に対し Lindlar 還元を行い、3 つのアルキンを化学選択的に同時に還元し、55%でヘキサエン **1-51a** を得た。その後 3 段階の変換を経て、(17*R*,18*R*)-RvE3 の合成を達成した。

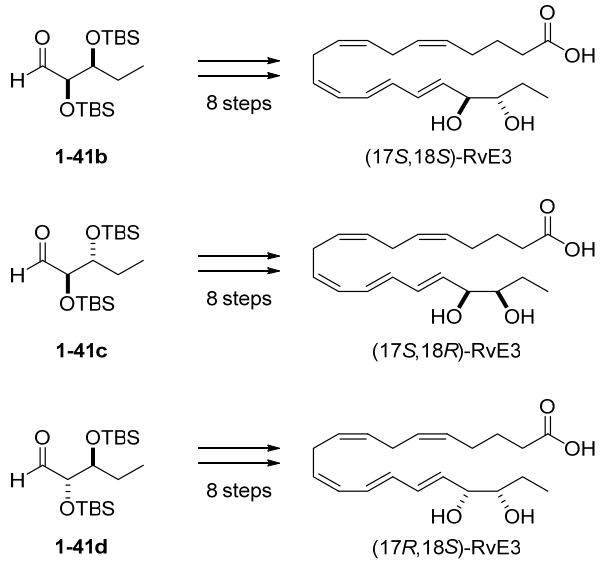
本合成の最も注目すべき特徴は、RvE3 に存在する 3 つの *Z*-アルケンを、Lindlar 還元により一段階で構築した点である。これにより、*Z*-アルケンを段階的に導入する直線方法に比べて、工程数が削減できる収束的な合成経路を確立した。また合成終盤に化学的に不安定な (*Z, E, E*)-トリエンを導入できた点も、この合成経路の利点として挙げられる。

Scheme 1-14. Total synthesis of (17*R*,18*R*)-RvE3



その他の三つの異性体 (17*S*,18*S*)-, (17*S*,18*R*)-, (17*R*,18*S*)-RvE3 についても、先に述べた合成経路に従い、合成された (Scheme 1-15)。

Scheme 1-15. (17*S*,18*S*)-, (17*S*,18*R*)-, (17*R*,18*S*)-RvE3 の合成



キラル HPLC を用いた 4 つの合成品と、天然由来の RvE3 との保持時間の比較により、天然物の立体化学は (17*R*,18*R*)-, (17*R*,18*S*)-RvE3 であることが明らかとなった[25]。収束的な合成法で 4 種のジアステレオマーを合成したことで、今後これらについての構造活性相関研究が可能となり、抗炎症活性以外の新たな知見が得られることが期待される。

1-3. 14,20-ジヒドロキシドコサヘキサエン酸と 12-ヒドロキシ-17,18-エポキシテトラエン酸

2010 年、東京大学の有田らは、マウス急性腹膜炎モデルにおける包括的リピドミクス解析により、ω-3 脂肪酸である DHA や EPA の新規代謝物が生成することを見出した[26]。

DHA の C14 位と C20 位が酸化された 14,20-ジヒドロキシドコサヘキサエン酸 (14,20-diHDHA) は、ザイモザン腹膜炎誘導モデルにおいて、10 ng/マウスという極微量の投与量で好中球浸潤を 29%抑制する強力な抗炎症活性を有することが明らかにされた。また、14,20-diHDHA は、白血球の中で唯一 12/15-リポキシゲナーゼ (12/15-LOX) を発現している好酸球で主に生成したこと、12/15-LOX ノックアウトマウス由来の好酸球では、14,20-diHDHA の産生量が大きく減弱することから、炎症時に 12/15-LOX を介して産生することが示された。

EPA の酸化代謝物として単離された、12-ヒドロキシ-17,18-エポキシエイコサテトラエン酸 (12-hydroxy-17,18-EpETE)[27]は、酸化過程の中間体であるエポキシドを含むユニークな構造を有する。本化合物は、2 つの化合物の混合物であるが、そのうち一つがザイモザン腹膜炎誘導モデルにおいて、10 ng/マウスでの好中球浸潤抑制率が 39%と、強力な抗炎症活性をもつことが示された[28]。このため、14,20-diHDHA および 12-hydroxy-17,18-EpETE の生体分子としての活性発現メカニズムの解明や、その機能の新規性が注目されている。

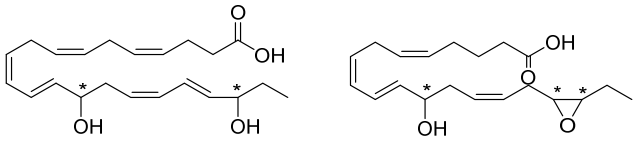
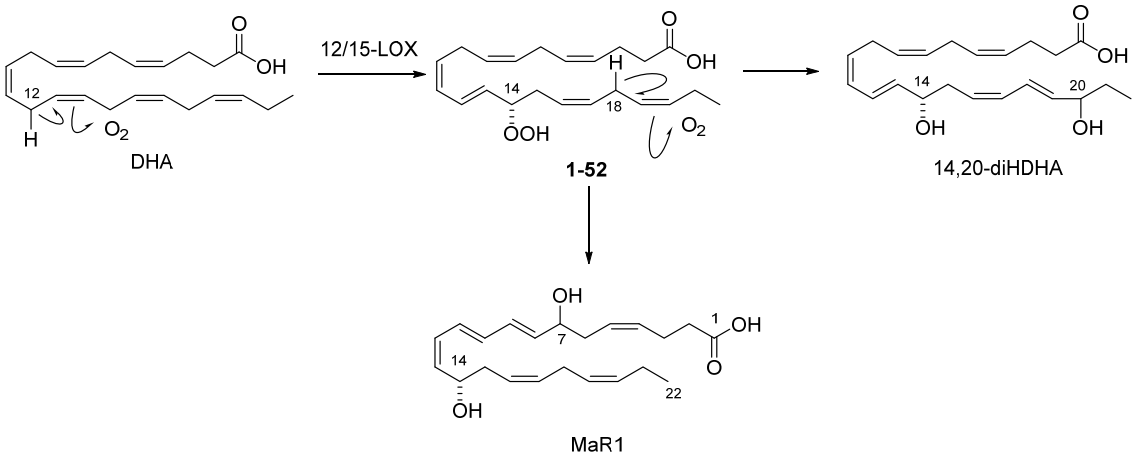


Figure1-2. Structures of 14,20-diHDHA and 12-hydroxy-17,18-EpETE

14,20-diHDHA および 12-hydroxy-17,18-EpETE の生合成経路は Scheme 1-16 に示すとおりに予想されている。14,20-diHDHA は、12/15-LOX により DHA の C14 位に *S* 配置のヒドロパーオキシ基が導入され **1-52** となり [10a]、その後 C14 位のヒドロパーオキシ基がヒドロキシ基に還元された後、C20 位にヒドロキシ基が導入されて生成すると考えられている。この際生成する C12-13 と C18-19 アルケンは *E* 体となる。

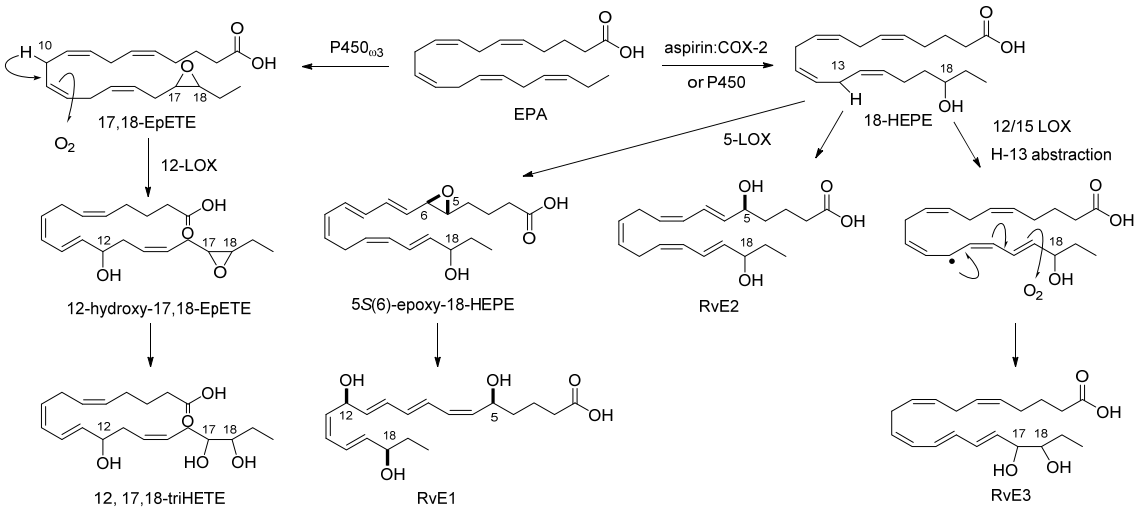
14*S* 配置を有する MaR1 も同様に DHA から 12/15-LOX によって生成する **1-52** から生合成されていると考えられているため、14,20-diHDHA の C14 位立体配置は MaR1 の C14 ヒドロキシ基の立体化学と同一の *S* 配置であると推察されている。

Scheme 1-16. Biosynthesis of 14,20-diHDHA



RvE1, E2, E3 が EPA の C18 位が酸化された 18-HEPE 由来であるの対し、12-hydroxy-17,18-EpETE は全く異なる経路、すなわち末端の *Z*-アルケンが酸化された 17,18-EpETE から生合成されていると考えられている。17,18-EpETE が 12-LOX により酸化代謝を受けて C12 位にヒドロキシ基が導入されることで、12-hydroxy-17,18-EpETE が生合成されると考えられている。12-hydroxy-17,18-EpETE は強力な抗炎症活性を有する一方で、12-ヒドロキシエイコサペンタエン酸 (12-HEPE) や、12-hydroxy-17,18-EpETE の生合成の前駆体である 17,18-EpETE、および 12-hydroxy-17,18-EpETE のエポキシドが開裂した 12,17,18-トリヒドロキシエイコサテトラエン酸 (12,17,18-triHETE) は活性がほとんど見られない。そのため、構造選択的に活性が発現している点で非常に興味深い。

Scheme 1-17. Proposed biosynthetic route of EPA metabolites



1-4. 本研究の目的

1-3 で述べたように、14,20-diHDHA および 12-hydroxy-17,18-EpETE は非常に強力な抗炎症活性を有している。しかし、マウス腹腔液から得られた 14,20-diHDHA および 12-hydroxy-17,18-EpETE の量は極微量であった[29]。14,20-diHDHA と 12-hydroxy-17,18-EpETE の平面構造と、二重結合の立体化学は、MS/MS 解析と、UV スペクトルからそれぞれ 14,20-ジヒドロキシ-4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*-ドコサヘキサエン酸, 12-ヒドロキシ-5*Z*,8*Z*,10*E*,14*Z*-17,18 エポキシエイコサペンタエン酸と推定された。しかし、構造決定に有用な NMR 実験に供することが不可能であったため、これらの構造は完全には決定されず、ヒドロキシ基やエポキシドの立体化学は未決定であった。

本研究では、有田らによって単離された新規脂質メディエーターである 14,20-diHDHA および 12-hydroxy-17,18-EpETE の全合成を目的とした。具体的には、完全構造決定と、構造活性相関研究を視野に入れ、Figure 1-3 に示すヒドロキシ基とエポキシ基に関する可能な立体異性体 4 種 (14*R*,20*S*)-, (14*S*,20*R*)-, (14*R*,20*R*)-, (14*S*,20*S*)-diHDHA および (12*R*)-hydroxy-(17*S*,18*R*)-, (12*S*)-hydroxy-(17*S*,18*R*), (12*S*)-hydroxy-(17*R*,18*S*)-, (12*R*)-hydroxy-(17*R*,18*S*)-EpETE の合成を行うことを計画した。

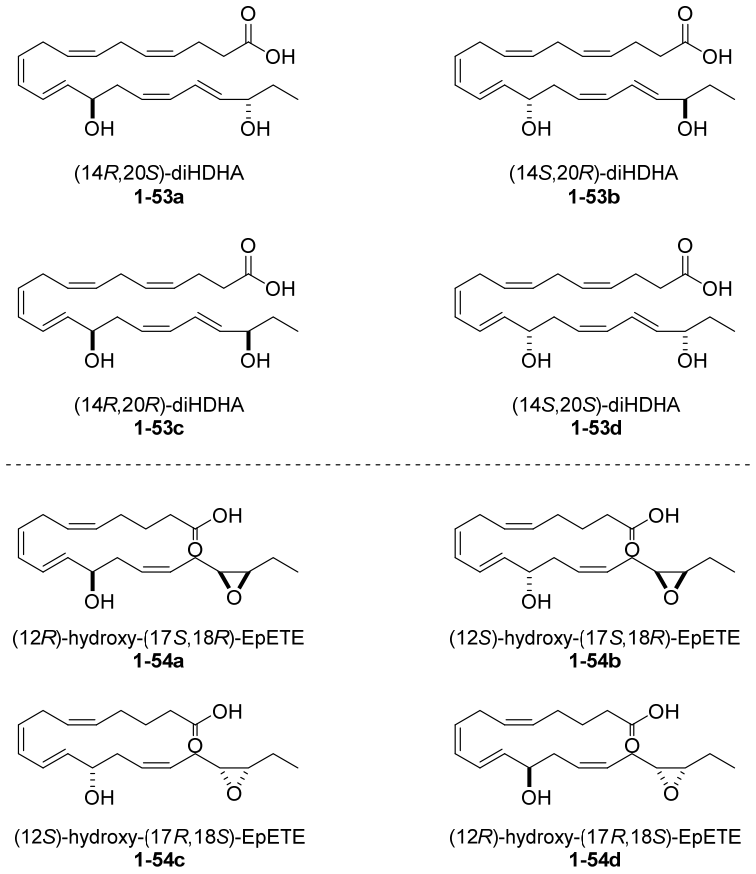


Figure 1-3. Four stereoisomers of 14,20-diHDHA and 12-hydroxy-17,18-EpETE

前節で述べたように、12/15-LOX は DHA との反応で C14 位に *S* 配置で酸素を導入されることが知られていることから、14,20-diHDHA の C14 ヒドロキシ基も *S* 配置であると推察される。しかし本研究では、C14,20 位に関する可能な立体異性体 4 種を合成した。

また 12-hydroxy-17,18EpETE については、EPA の末端の *Z*-アルケンが酸化された 17,18-EpETE の C12 位にヒドロキシ基が導入されたと考えられる。そのため C12 位の立体化学と、シス C17-18 エポキシドの立体化学について可能な立体異性体 4 種を合成した。

本博士論文では、第 2 章にて 14,20-diHDHA の全合成、第 3 章にて 12-hydroxy-17,18-EpETE の全合成について述べる。また、本研究の過程で見出されたアルキン-コバルト錯体を介した *Z*-アルケン形成反応について第 4 章に述べる。

なお、本研究で合成した立体異性体と天然物との HPLC 分析は有田らによって行われ、DHA 由来の天然物は (4*Z*,7*Z*,10*Z*,12*E*,14*S*,16*Z*,18*E*,20*R*)-14,20-ジヒドロキシ-4,7,10,12,16,18-ドコサヘキサエン酸 (**1-53b**) [30]、EPA 由来の天然物は (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*S*,18*R*)-, (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*R*,18*S*)-12-ヒドロキシ-17,18-エポキシ-5,8,10,14-エイコサテトラエン酸 (**1-54b**, **1-54c**)[31]であることが後に明らかにされた。

1-5. 参考文献

(1) Samuelsson, B.; Dahlén, S. E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. *Science*, **1987**, *237*, 1171-1176.

(2) Chiang, N.; Serhan, C. N.; Dahlén, S. E.; Drazen, J. M.; Hay, D. W. P.; Rovati, G. E.; Shimizu, T.; Yokomizo, T.; Brink, C. *Pharmacol. Rev.* **2006**, *58*, 463-487.

(3) (a) Mukherjee, P. K.; Marcheselli, V. L.; Serhan, C. N.; Bazan, N, G. *Proc. Natl. Acad. Sci. USA.* **2004**, *101*, 8491-8496. (b) Lukiw, W. J.; Cui, J-G.; Marcheselli, V. L.; Bodker, M.; Botkjaer, A.; Gotlinger, K.; Serhan, C. N.; Bazan, N, G. *J. Clin. Invest.* **2005**, *115*, 2774-2783.

(4) For reviews, see: (a) Serhan, C. N.; Chiang, N.; Van Dyke, T. E. *Nat. Rev. Immunol.* **2008**, *8*, 349-361. (b) Serhan, C. N.; Chiang, N. *Br. J. Pharmacol.* **2008**, *153*, S200-S215. (c) Serhan, C. N.; Petasis, N. A. *Chem. Rev.* **2011**, *111*, 5922-5943.

(5) Gilroy, D. W.; Lawrence. T.; Perretti, M.; Rossi, A. G. *Nature Rev. Drug Discov.* **2004**, *3*, 401-416.

(6) Fitzgerald, G. A. *Nature Rev. Drug Discov.* **2003**, *2*, 879.-890.

(7) (a) Gilroy, D. W.; Colville-Nash, P. R.; Willis, D.; Chivers, J.; Paul-Clark, M. J.; Willoughby, D. A. *Nature Med.* **1999**, *5*, 698-701. (b) Fukunaga, K. *J. Immunol.* **2005**, *174*, 5033-5039.

(8) (a) Arita, M.; Bianchini, F.;Aliberti, J.; Sher, A.; Chiang, N.; Hong, S.; Yang, R.; Petasis, N. A.;Serhan, C, N. *J.Exp. Med.* **2005**, *201*, 713-722. (b) Marcheselli, V. L.; Hong, S.; Lukiw, W. J.; Tian, X. H.; Gronert, K.; Musto, A.; Hardy, M.; Gomenez, J. M.; Chiang, N.; Serhan, C. N.; Bazan, N. G. *J. Biol. Chem.* **2003**, *278*, 43807-43817.

(9) Serhan, C. N.; Gotlinger, K.; Hong, S.; Lu, Y.; Siegelman, J.; Baer, T.; Yang, R.; Colgan, S. P.; Petasis, N. A. *J. Immunol*. **2006**, *176*, 1848-1859.

(10) (a) Serhan, C. N.; Yang, R.; Martinod, K.; Kasuga, K.; Pillai, P. S.; Porter, T. F.; Oh, S. F.; Spite, M. *J. Exp. Med*. **2009**, *206*, 15-23. (b) Serhan, C. N.; Dalli, J.; Karamnov, S.; Choi, A.; Park, C.-K.; Xu, Z.-Z.; Ji, R.-R.; Zhu, M.; Petasis, N. A. *FASEB J.* **2012**, *26*, 1755-1765.

(11) Isobe, Y., Arita, M., Matsueda, S.; Iwamoto, R., Fujihara, T., Nakanishi, H., Taguchi, R., Masuda, K., Sasaki, K., Urabe, D., Inoue, M., Arai, H. *J. Biol. Chem. 2012*, **287**, 10525-10534.

(12) LC-MS/MS の解析から、組成式とフラグメントパターンによる解離しやすい結合が特定できる。これらの結果と経験則に基づく仮想フラグメントパターンにより部分構造は推定される。また、共役ジエンや共役トリエンは特徴的な UV 吸収波長が見られるため、LC-MS/MS 解析とあわせて平面構造が推定されている。

(13) 長　秀連　創薬化学　南山堂

(14) DHA由来の脂質メディエーターの全合成 Protectin D1: (a) Petasis, N. A.; Yang, R.; Winkler, J. W.; Zhu, M.; Uddin, J.; Bazan, N. G.; Serhan, C. N. *Tetrahedron Lett.* **2012**, *53*, 1695-1698. (b) Ogawa, N. Kobayashi, Y. *Tetrahedron Lett.* **2011**, *52*, 3001-3004. (c) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2014**, *55*, 6011-6015. (d) Aursnes, M.; Tungen, J. E.; Vik, A.; Dalli, J.; Hansen, T. V. *Org. Biomol. Chem.*, **2014**, *12*, 432–437. Maresin 1: (e) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 4169-4172. (f) Ogawa, N.; Tojo, T.; Kobayashi, Y. *Tetrahedron Lett.* **2014**, *55*, 2738-2741. (g) Tungen, J. E.; Aursnes, M.; Hansen, T. V. *Tetrahedron Lett.* **2015**, *56*, 1843-1846. Maresin 2 : (h) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2015**, *56*, 256-259. Resolvin D2: (i) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2004**, *45*, 8717-8720. (j) Li, J.; Leong, M. M.; Stewart, A.; Rizzacasa, M. A. *Beilstein J. Org. Chem.* **2013,** *9*, 2762–2766. Resolvin D3: (k) Winkler, J. W.; Uddin, J.; Serhan, C. N.; Petasis, N. A. *Org. Lett.* **2013**, *15*, 1424-1427. Resolvin D5: (l) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2005**, *46*, 3623-3627. Resolvin D6: (m) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 86-89. EPA由来の脂質メディエーターの全合成 Resolvin E1: (n) Ogawa, N.; Kobayashi, Y. Tetrahedron Lett. 2009, 50, 6079-6082. (o) Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* 2009, *50*, 6079–6082. (p) Allard, M.; Barnes, K.; Chen, X.; Cheung, Y-Y.; Duffy, B.; Heap, C.; Inthavongsay, J.; Johnson, M.; Krishnamoorthy, R.; Manley, C.; Steffke, S.; Varughese, D.; Wang, R.; Wang, Y.; Schwartz, C. E. *Tetrahedron Lett.* **2011**, *52*, 2623-2626. For a review on syntheses on eicosanoids, see: (q) Nicolaou, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed.* **1991**, *30*, 1100-1116. (r) Scheinmann, F. Ackroyd, J. *Leukotriene Syntheses: A New Class of Biologically Active Compounds Including SRS-A.*; Raven Press: New York, 1984.

(15) Sasaki, K.; Urabe, D.; Arai, H.; Arita, M.; Inoue, M. *Chem. Asian J.* **2011**, *6*, 534-543.

(16) Ogawa, S.; Urabe, D.; Yokokura, Y.; Arai, H.; Arita, M.; Inoue, M. *Org. Lett.* **2009**, *11*, 3602-2605.

(17) Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Tetrahedron* **2012**, *68*, 3210-3219.

(18) Serhan, C. N.; Dalli, J.; Karamnov, S.; Choi, A.; Park, C.-K.; Xu, Z.-Z.; Ji, R.-R.; Zhu, M.; Petasis, N. A. *FASEB J.* **2012**, *26*, 1755-1765.

(19) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, 53, 4169-4172.

(20) Ogawa, N.; Tojo, T.; Kobayashi, Y. *Tetrahedron Lett.* **2014**, *55*, 2738-2741.

(21) Tungen, J. E.; Aursnes, M.; Hansen, T. V. *Tetrahedron Lett.* **2015**, *56*, 1843-1846.

(22) Kosaki, Y.; Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2010**, *51*, 1856-1859.

(23) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 1912-1915.

(24) (a) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183-2192. (b) Kessabi, J.; Beaudegnies, R.; Jung, P. M. J.; Martin, B.; Montel, F.; Wendenborn, S. *Synthesis* **2008**, 655-659.

(25) Isobe, Y.; Arita, M.; Iwamoto, R.; Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M.; Arai,

H. *J. Biochem.* **2013**, *153*, 355-360.

(26) Arita, M.; Arai, H.; Isobe, Y.; Taguchi, R. PCT Int. Pat. Appl. WO 2010/095706.

(27) Arita, M.; Arai, H.; Isobe, Y.; Kubota, T. PCT Int. Pat. Appl. WO 2012/023254.

(28) 比較としてステロイド系抗炎症薬として代表的なデキサメタゾンの好中球浸潤抑制活性を示す。デキサメタゾンは投与量 10μg/mouse において、好中球浸潤抑制活性が 35%程度であった。

(29) 生体内から得られた量は共に pg レベルであった。

(30) Yokokura, Y.; Isobe, Y.; Matsueda, S.; Iwamoto, R.; Goto, T.; Yoshioka, T.; Urabe, D.; Inoue, M.; Arai, H.; Arita, M. *J. Biochem.*, **2014**, *156*, 315-321.

(31) Kubota, T.; Arita, M.; Isobe, Y.; Iwamoto, R.; Goto, T.; Yoshioka, T.; Urabe, D.; Inoue, M.; Arai, H. *FASEB J.*, **2014**, *28*, 586-593.

第 2 章

(4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14, 20-ジヒドロキシ-4,7,10,12,16,18-ドコサヘキサエン酸の 4 種立体異性体の合成

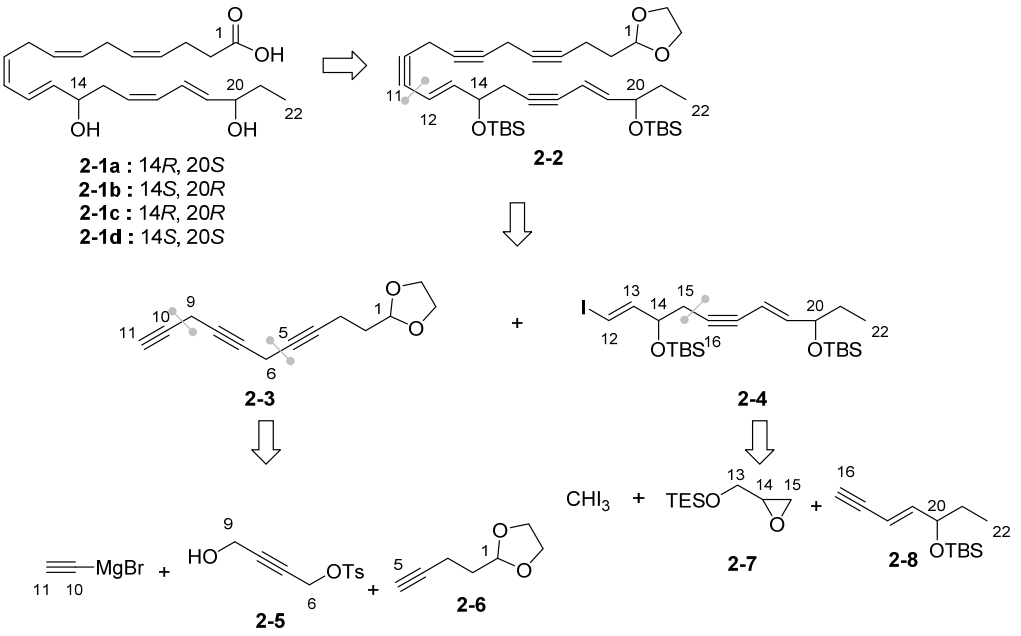
本章では、(4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-ジヒドロキシ-4,7,10,12,16,18-ドコサヘキサエン酸 (14,20-diHDHA) の C14 および C20 位のヒドロキシ基立体化学に関する 4 つの立体異性体の収束的合成法について述べる。

2-1. 合成計画

脂質メディエーターの合成は第一章で示した合成例のほか、数多くのグループによって報告されている。これらの合成を通して、ポリエン化合物の合成計画を立てる際に考慮するべきことを以下に示す。生物学的研究への試料供与を目的とする場合が多いため、標的化合物の純度の高さが要求される。すなわち、①ヒドロキシ基の十分な光学純度、②アルケンの立体化学の制御が確保される必要がある。また、③スケールアップが可能な経路を設定するのが実用的である。そのためには収束的な合成ルートの設定が不可欠となる。①および②を実現するためには構築したヒドロキシ基および共役ジエン、トリエンは合成経路中で異性化しないことを確認する。特に共役ジエン、トリエンは合成の終盤に構築するのが望ましい。また、アルケン構築には立体選択的な反応 (Wittig, Horner-Wadsworth-Emmons, Julia-Kocienski 反応など) を用いると必ず分離の問題が生じるため、立体特異的な反応 (Lindlar 還元など) を選択したほうがよいと考えた。③を実現するためには、収束的な合成ルートの確立、また、最終物以外での HPLC 精製を必要としない合成ルートの設定が理想的である。以上の事項を踏まえ合成計画を立案した。

14,20-diHDHA (**2-1**) の逆合成解析を Scheme 2-1 に示す。本合成では、アルキンの多様な反応性を最大限利用することとした。すなわち、14,20-diHDHA の有する *Z*-アルケンは、全て対応する **2-2** の内部アルキンの部分還元により構築することとした。**2-2** は C1-11 位に相当するトリイン (**2-3**) と、C12-22 に相当するヨウ化ビニル (**2-4**) とを銅アルキニドを用いた薗頭カップリングにより連結することを計画した。トリイン **2-3** は、銅アルキニドを用いた 2 回の S_N2 反応により **2-6**、**2-5**、C10-11 位に相当する 2 炭素ユニットを順次連結することとした。一方、**2-4** は **2-8** から誘導したアルキニドの、グリシドール保護体 **2-7** に対する開環反応の後、ヨードビニル化により合成できると考えた。なお、それぞれ光学活性な **2-7** および **2-8** の組み合わせを変えることで、14,20-diHDHA の C14,20 位に関する 4 種立体異性体を合成することとした。本合成計画に基づく (14*R*,20*R*)-diHDHA の合成は一度増田によって行われた[1]。しかし、**2-7** と **2-8** のフラグメント連結における低収率と再現性の乏しさ、また合成品の (14*R*,20*R*)-diHDHA の純度の低さに大きな問題があり、構造決定や生物学的研究に供することはできなかった。そこで、合成経路や条件を精査し直し、再現性、純度ともに良好な 14,20-diHDHA の合成経路を確立することとした。

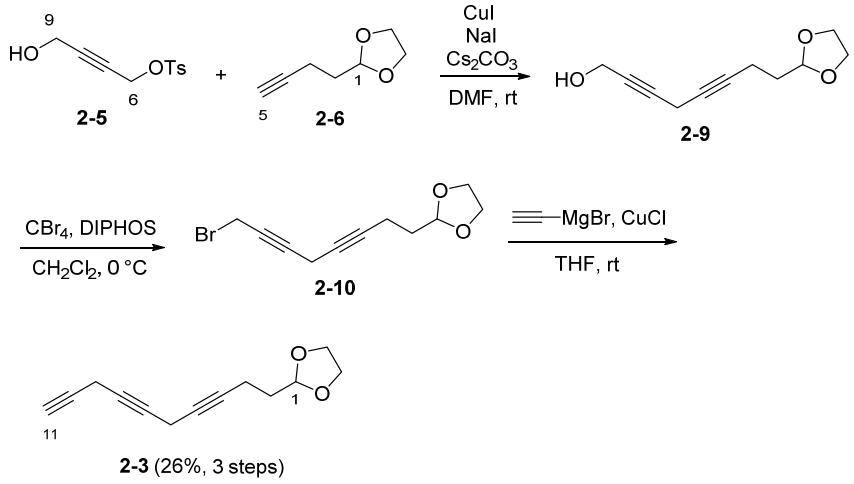
Scheme 2-1. Synthetic plan of 4 stereoisomers of 14,20-diHDHA



2-2. C1-11 フラグメントの合成

トリイン **2-3** は、銅アルキニドを用いた S_N2 反応により合成した。既知化合物である末端アルキン **2-6**[2]を塩化銅および炭酸セシウム[3]で処理して、反応系中で銅アルキニドとした後、トシレート **2-5**[4]に対する求核置換反応を進行させ、ジイン **2-9** を得た (Scheme 2-2)。**2-5** は無保護のアルコールを有するが、銅アルキニドのプロトン化による反応の阻害はされなかった。末端アルキン (pK_a 25) に銅が配位すると pK_a は 10 程度低下する[5]。このため、炭酸セシウムのような弱い塩基でプロトンの引き抜きが可能となり、温和な条件で銅アルキニドが生成したと考えられる。また、本反応においては S_N2'反応が競合することが懸念されたが、**2-5** が内部アルキンであるため、プロパルギル位のメチレンが立体障害となり、目的の S_N2 アルキニル化のみが進行した。C9 位の第一級ヒドロキシ基を 1,2-ビス（ジフェニルホスフィノ）エタン (DIPHOS) と四臭化炭素を用いてブロモ基へと変換[6]した後、エチニル銅試薬による二回目の S_N2 反応を行い、目的のトリイン **2-3** を合成した。得られたトリイン **2-3** はダブルプロパルギル位を 2 か所有する化学的に不安定な構造のため、精製後直ちに次の反応へ供した。

Scheme 2-2. Synthesis of C1-11 fragment **2-3**

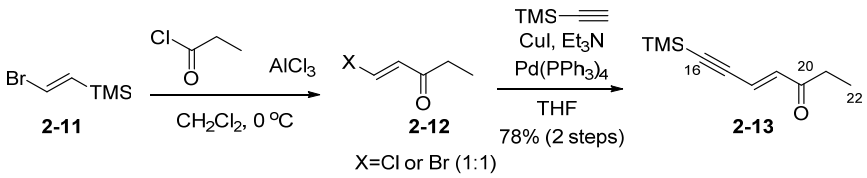


2-3. C12-22 フラグメントの合成

2-3-1. ケトン **2-13** の合成

C16-22 フラグメント **2-13** は、市販の *E*-ブロモビニルトリメチルシラン **2-11** に対するアシル化[7]により **2-12** をブロマイドとクロライドの 1:1 混合物として得た後、TMS アセチレンとの薗頭カップリングにより導いた (Scheme 2-3)。**2-12**、**2-13** は共に低沸点化合物であるため、カラムクロマトグラフィーによる精製はエーテル/ペンタンの混合溶媒を溶出液として用いた。

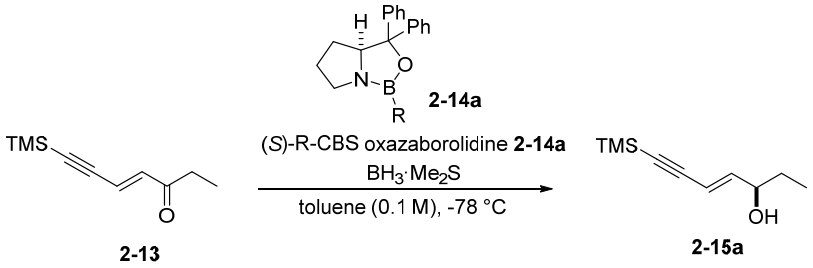
Scheme 2-3. Synthesis of ketone **2-13**



2-3-2. C20 位ケトンの不斉還元

C20 ヒドロキシ基は、ケトン **2-13** の不斉還元によりエナンチオ選択的に構築することとし、**2-13** に対する CBS 還元[8]を種々検討した (Table 2-1)。ここでは、**2-15a** を与える(*S*)-オキサザボロリジン **2-14a** を用いた。トルエン中、2 当量の(*S*)-Me-CBS オキサザボロリジンと 2.2 当量の $BH_3{\cdot}Me_2S$ を用いたところ、**2-15a** は収率良く得られるものの、不斉収率は 79% ee であった (entry 1)。本条件では、CBS 試薬に対して、過剰の $BH_3{\cdot}Me_2S$ を用いたため、これらが複合体を形成せずボランのみで還元が進行したと考えた。そこで、$BH_3{\cdot}Me_2S$ の当量を減らした条件を試みたが、この反応では収率、不斉収率共に大きく低下する結果となった (entry 2)。一方、反応溶媒をトルエンから CH_2Cl_2 に変更したところ、不斉収率は 87%に向上することを見出したが、満足のいく不斉収率ではなかった (entry 3)。トルエン中、CBS 試薬のホウ素原子上の置換基を *n*-ブチルに変更すると、飛躍的に不斉収率が向上し、目的物を高選択的に得ることが出来た (entry 4)。しかし、entry 5 ではこの試薬の組み合わせで当量を 1 当量へと減らすと、不斉収率が大きく低下することから、entry 4 を不斉還元の最適条件に設定した。

Table 2-1. The asymmetric reduction of ketone **2-13** with the CBS reagents



entry	R=	**2-14a** (eq.)	$BH_3 \cdot Me_2S$	yield	ee [a]
1	Me	2.0	2.2	quant.	79%
2	Me	2.2	1.8	71%	33%
3 [b]	Me	2.0	2.2	<99% (including impurity)	87%
4	*n*-Bu	2.0	2.2	64%	96%
5	*n*-Bu	1.0	1.1	80%	78%

[a] The ee value was determined by ^{1}H NMR analysis of the corresponding MTPA ester.
[b] CH_2Cl_2 was used as a solvent.

本反応で構築したヒドロキシ基の立体化学は、改良 Mosher 法[9]により決定した。**2-15a** の第二級ヒドロキシ基に対し、MTPACl をそれぞれ Et_3N, DMAP を用いて縮合させ、MTPA エステルを合成した。続いて、改良 Mosher 法の定義に従い、^{1}H NMR スペクトルから化学シフト値の差を求め、C20 ヒドロキシ基の絶対立体配置は *R* 配置と決定した (Figure 2-1)。

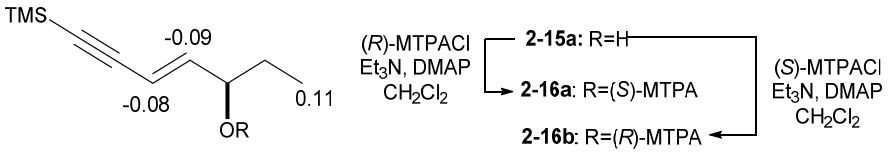
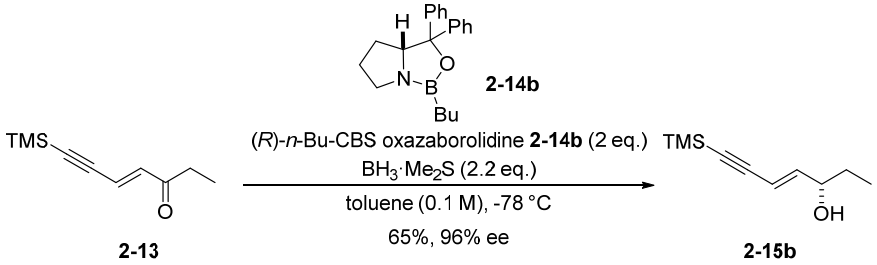


Figure 2-1. Determination of the absolute stereochemistry at C20. The numbers are difference ($\Delta\delta$) in the ^{1}H chemical shifts between **2-16a** and **2-16b** ($\Delta\delta = \delta$(**2-16a**) − δ(**2-16b**)) in $CDCl_3$

(*R*)-*n*-Bu-CBS-オキサザボロリジン **2-14b** を用いた **2-13** の還元も同様に行い、高い不斉収率で C20 位に *S* 配置のヒドロキシ基を有する **2-15b** を得た (Scheme 2-4)。

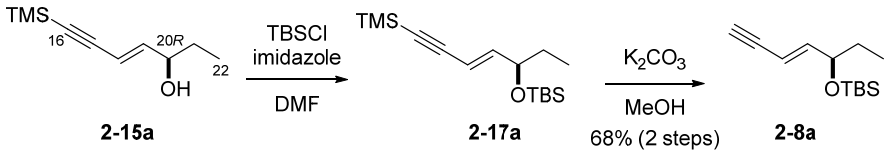
Scheme 2-4. Asymmetric reduction of ketone **2-13**



2-3-3. 金属アルキニドのグリシドールへの付加反応による C12-22 フラグメントの合成

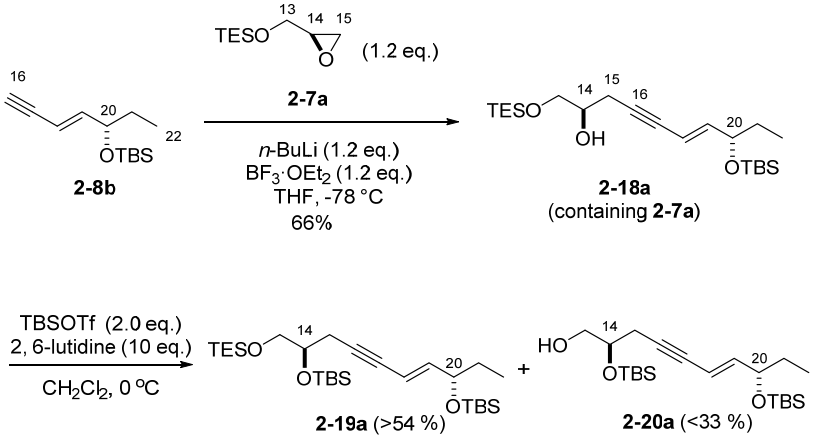
これ以降は、*R* 配置の C20 ヒドロキシ基を有する **2-15a** を用いた変換について述べる。不斉還元で得られた **2-15a** のヒドロキシ基を TBS エーテルとし、C16 位の TMS 基の除去を行い、末端アルキン **2-8a** へと誘導した (Scheme 2-5)。

Scheme 2-5. Synthesis of terminal alkyne **2-8a**



続いて、アルキン **2-8a** を用いたグリシドール誘導体への開環付加反応[10]による C12-22 フラグメントの合成を検討した。Scheme 2-6 には 20*S* 配置の **2-8b** を用いた前任者の結果を示した。この反応では、グリシドール誘導体を 1 当量以上用いたにも関わらず、原料である **2-8b** が消失せず、目的物の収率は中程度に留まった。また、目的物と未反応のグリシドール誘導体との分離精製が困難であるという問題があった。さらに、**2-18a** の C14 ヒドロキシ基の TBS エーテル化において、カラムクロマトグラフィー精製の際に、第一級の TES 基が一部除去されることが報告されていた。

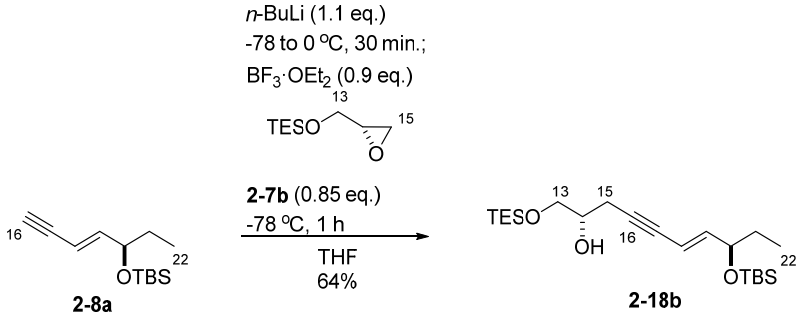
Scheme 2-6. Masuda's result



そこでこの 2 点についてより詳しく原因を追究した。その結果、**2-8** から誘導したリチウムアルキニドと **2-7** との S_N2 反応では、末端アルキンの脱プロトン化が十分進行していない、あるいはグリシドール誘導体や、その他の試薬に含まれる水によりアルキニドがプロトン化されていることが考えられた。そこで、以下の点に留意し反応を行った。

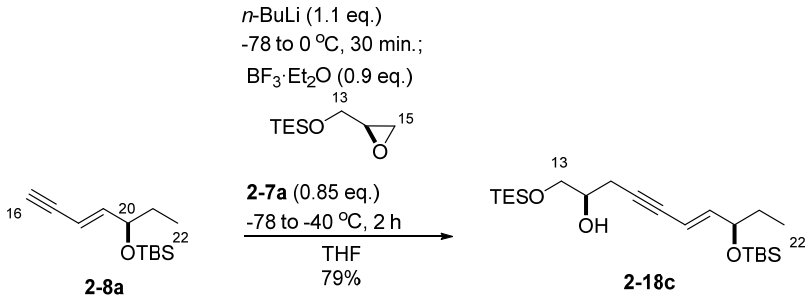
(1) 原料はトルエン共沸を行い、原料に含まれる水分は極力除去した。
(2) 反応溶媒の THF をベンゾフェノンケチルから蒸留した。
(3) 三フッ化ホウ素は P_2O_5 より蒸留したものをすぐ反応に供した。
(4) リチウムアルキニド生成を促進させる目的で、*n*-BuLi を-78 度で加えた後、系を 0 度まで昇温した。
(5) 精製をより簡便に行えるよう、グリシドール **2-7** を **2-8** に対し、0.85 当量用いた。その結果、再現性良く目的の **2-18b** を 64%で単離した (Scheme 2-7)。

Scheme 2-7. Investigation of nucleophilic addition with protected glycidol **2-7b**



この条件下で、グリシドール誘導体のエナンチオマー **2-7a** を用いて同様の反応を行った。この場合も再現よく **2-18b** のジアステレオマー体である **2-18c** を得た (Scheme 2-8)。

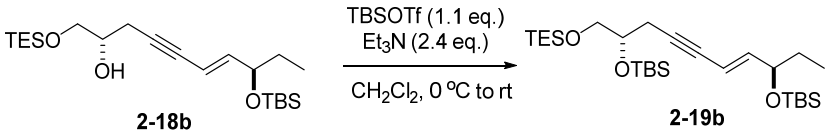
Scheme 2-8. Nucleophilic addition with protected glycidol **2-7a**



2-3-4. C12-22 フラグメントの合成

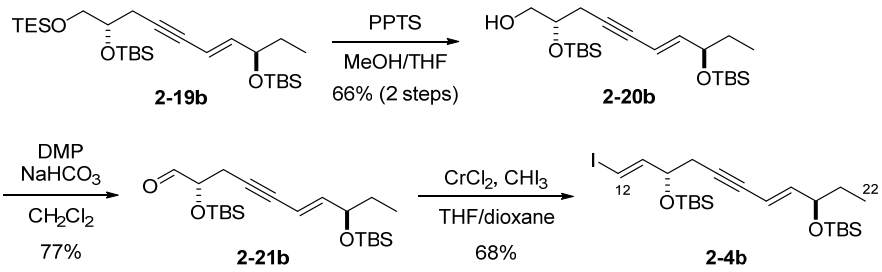
2-18 の C14 ヒドロキシ基の TBS エーテル化では、2-3-3 で述べたように、精製時に TES 基の一部が除去されてしまうという問題点があった。そこで種々検討した結果、本反応で得られる **2-19** は、粗精製物の状態で不安定であり、カラム精製においてシリカゲル上への担持時間が長いと、C13 位の TES 基が除去される上、TBS 基の除去も起こり、化合物の総収量が著しく低下することがわかった。このため反応を停止し、後処理した後、シリカゲルのショートカラムに通して夾雑物を除去し、シリル基が脱保護されないことを確認した後、再度溶媒を留去し、精製を行った。この手順を用いることで、原料のアルコールに対し、1.1 当量の TBSOTf、2.4 当量の Et_3N を作用させることで、目的の TBS エーテル **2-19b** を再現性よく得た (Scheme 2-9)。

Scheme 2-9. TBS protection of C14 hydroxygroup of **2-18b**



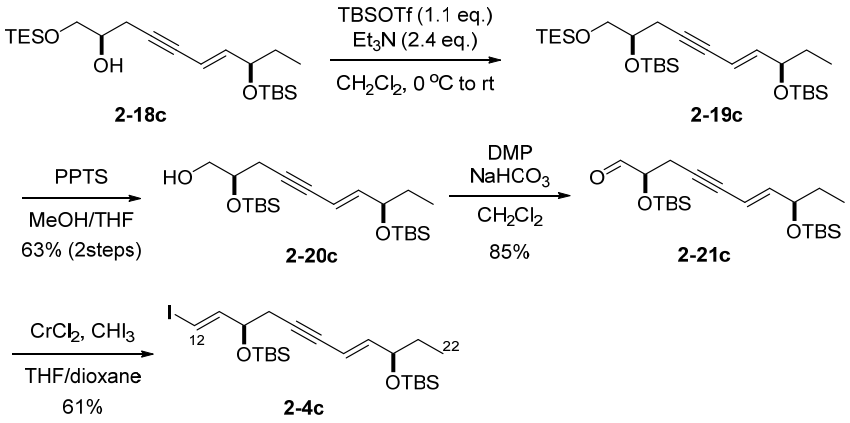
続いて **2-19b** の TES 基を、PPTS を用いた酸性条件下で選択的に除去し、目的物 **2-20b** を 2 段階収率 66%で得た (Scheme 2-10)。**2-20b** のヒドロキシ基を Dess-Martin 酸化[11]してアルデヒド **2-21b** とした。最後に THF/ジオキサン混合溶媒中で高井オレフィン化[12]を行い、*E* 体のヨウ化ビニル(14*S*,20*R*)-**2-4b** を得た。この反応では *Z* 体のヨウ化ビニルは全く得られなかった。

Scheme 2-10. Synthesis of C12-22 fragment **2-4b**



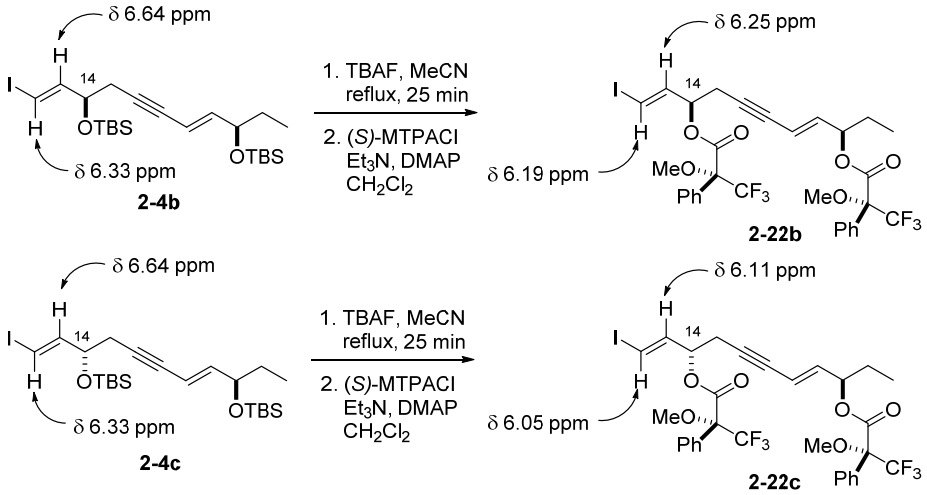
2-18b から **2-4b** の合成経路に従い、**2-4b** のジアステレオマーである C12-22 フラグメント (14*R*,20*R*)-**2-4c** についても同様に合成した (Scheme 2-11)。

Scheme 2-11. Synthesis of C12-22 fragment **2-4c**



一般的に α-シロキシアルデヒドはエピメリ化しにくいとされているが、アルデヒド **2-21b** および **2-21c** においても、C14 位のエピメリ化が進行していないか、確認することとした。しかし、ジアステレオマーの関係である **2-4b** と **2-4c** の ^{1}H NMR は同一であり (**2-4b** : δ_{H12} 6.33 ppm, δ_{H13} 6.64 ppm, **2-4c** : δ_{H12} 6.33 ppm, δ_{H13} 6.64 ppm)、化学シフトの違いからエピメリ化の有無を確認することはできなかった。そこで **2-4b**, **2-4c** のシリル基をそれぞれ除去した後、(*S*)-MTPACl で処理し、ビス(*R*)-MTPA エステル **2-22b** および **2-22c** へと誘導した (Scheme 2-12)。C12,13 位の ^{1}H NMR 化学シフト値を比較したところ、**2-22b** と **2-22c** 間でそれらの化学シフト値が異なることを確認した (**2-22b** : δ_{H12} 6.19 ppm, δ_{H13} 6.25 ppm, **2-22c** : δ_{H12} 6.05 ppm, δ_{H13} 6.11 ppm)。それぞれ **2-4b** および **2-4c** から誘導した化合物の中には、^{1}H NMR で **2-22c** および **2-22b** のピークが観測されなかったことから C14 位のエピメリ化は全く起きていないと結論した。

Scheme 2-12. Confirmation of no epimerization at C14

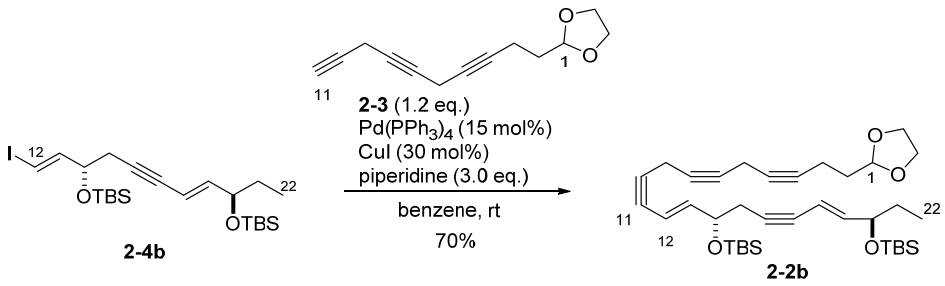


2-4. (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-ジヒドロキシ-4,7,10,12,16,18-ドコサヘキサエン酸の合成

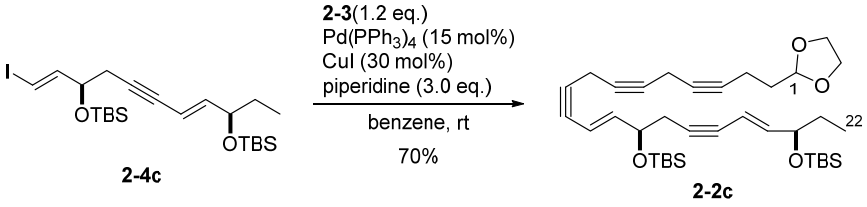
2-4-1. 薗頭カップリングによる C1-11 および C12-22 フラグメントの連結

2-2 および 2-3 節でそれぞれ合成した C1-11 フラグメント **2-3** と、C12-22 フラグメント **2-4** とを薗頭カップリング[13]により連結した (Scheme 2-13)。ヨウ化ビニル **2-4b** に対し、トリイン **2-3** を 1.2 当量用い、$Pd(PPh_3)_4$ を 15 mol%、塩化銅 30 mol%、塩基としてピペリジンを 3.0 当量用いて、ベンゼン中室温で反応を行ったところ、目的物のテトライン **2-2b** を 70%の収率で得た。本反応は **2-4b** のジアステレオマーである **2-4c** を用いた場合も同様に進行した (Scheme 2-14)。これにより、14,20-diHDHA のすべての炭素骨格を有する **2-2** の合成に成功した。**2-2** は複数のダブルプロパルギル位、多重結合を有するため化学的に極めて不安定であったため、すぐに次の反応に供した。

Scheme 2-13. Synthesis of full carbon structure by Sonogashira coupling of **2-4b** and **2-3**



Scheme 2-14. Synthesis of full carbon structure by Sonogashira coupling of **2-4c** and **2-3**

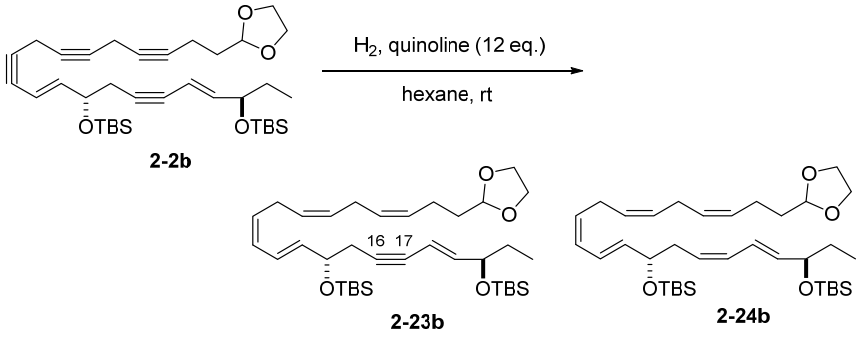


2-4-2. 鍵中間体の単離の検討

2-4-1 で得られたテトライン **2-2** の内部アルキンの *Z*-アルケンへの変換を試みた。本変換は 2 つのアルケン存在下、4 つのアルキンをシス還元し、ヘキサエンを得ようとする非常に挑戦的な変換である。まず、**2-2** に対する Lindlar 還元を検討した (Table 2-2)。試薬のロットの違いによる再現性の低下を防ぐため、反応には市販物ではなく、調製した Lindlar 触媒を用いた[14]。**2-2b** に対する Lindlar 還元が途中で停止したため、その都度触媒を追加し、反応を追跡した (entry 1)。しかし、**2-2b** は消失するものの、C16-17 アルキンを有する化合物 **2-23b** と目的物 **2-24b** は TLC 上で分離しにくく、反応追跡が困難であった。反応溶液の質量分析において過還元体の存在が確認されたことから、望み

の化合物 **2-24b** を優先的に得ることは困難であることがわかった。C16-17 アルキンの還元速度が他のアルキンに比べ遅いのは、近傍に存在する C14,20 位の TBS エーテルの嵩高さのためであると考えられる。生物活性試験に供与するためには、純度の高い化合物を合成しなければならないので、還元条件を検討精査し、**2-23b** を選択的に得ることとした。$Pd/BaSO_4$ を用いて還元を行ったところ、3.8 : 1 の比で、**2-23b** が **2-24b** に対して選択的に生成した (entry 2)。さらに、Lindlar 還元において TLC と質量分析により注意深く反応を追跡することで、**2-23b** 選択的に合成することに成功した (entry 3)。順相カラムを用いた HPLC にて **2-23b** と **2-24b** の分離条件を検討したが、これらを分離する条件は見つからなかった。しかし、カルボン酸担持シリカゲルを用いた場合に、**2-24b** との分離が可能となり、**2-23b** を純品として 55%の収率で単離した。この方法は実用性が高く、**2-23b** の大量合成が可能となった。

Table 2-2. Partial reduction of **2-2b**



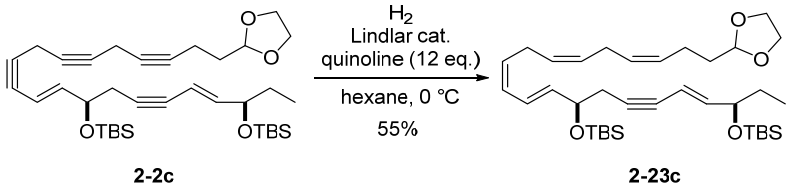
2-2b **2-23b** **2-24b**

entry	conditions	result	
		2-23b : **2-24b**	yield
1	Lindlar cat. (up to 500 wt%)	1 : 5.3	**2-23b** and **2-24b** 30% [a]
2	$Pd/BaSO_4$ (up to 830 wt%)	3.8 : 1	N.D.
3	Lindlar cat. (up to 400 wt%)	5 : 1	**2-23b** 55%[b]

[a] NMR yield
[b] **2-23b** was purified by COOH-supported silica gel (Fuji silysia).

(14*R*,20*R*)-**2-2c** についても同様に Lindlar 還元を行い、**2-23c** を単離した (Scheme 2-15)。

Scheme 2-15. Partial reduction of tetrayne **2-2c**



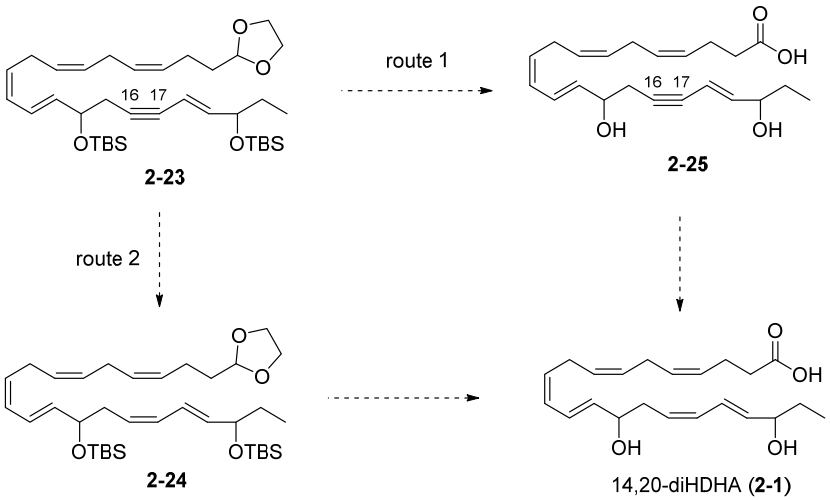
2-2c **2-23c**

2-4-3. C16-17 アルキンの化学選択的還元

2-23 から C16-17 アルキンの部分還元を経て、14,20-diHDHA へと誘導するべく、二つの合成経路を考案した (Scheme 2-16)。2-4-2 で C16-17 アルキンの Lindlar 還元が他のアルキンに対して遅いのは、C14,20 位の嵩高い TBS オキシ基により立体的に遮蔽されているためだと考えた。そこで、経路 1 として、C16-17 アルキンを残したまま、**2-25** へと導いた後、最終段階で C16-17 アルキンの部分還元を行うことにより、14,20-diHDHA を合成する計画を立てた。**2-25** はすでに C14,20 位が無保護のヒドロキシ基であるため、立体障害が少なく、アルキン特異的に還元が進行すれば目的物が得られると考えた。また、14,20-diHDHA が作用する細胞を特定する、バインディングアッセイには 14,20-diHDHA トリチウム標識体を用いる。この標識体を合成する際、合成の最終段階でトリチウムを導入することが望ましいため、この経路で最終物が合成できれば、同時にトリチウム標識体の合成も可能となると考えた。

一方、経路 2 として、**2-23** に対して Lindlar 還元以外のアルキンの部分還元法を適用することで、立体的に混み合った C16-17 アルキンをシス還元し **2-24** とした後、最終物へと誘導することを計画した。

Scheme 2-16. Two synthetic strategies toward 14,20-diHDHA



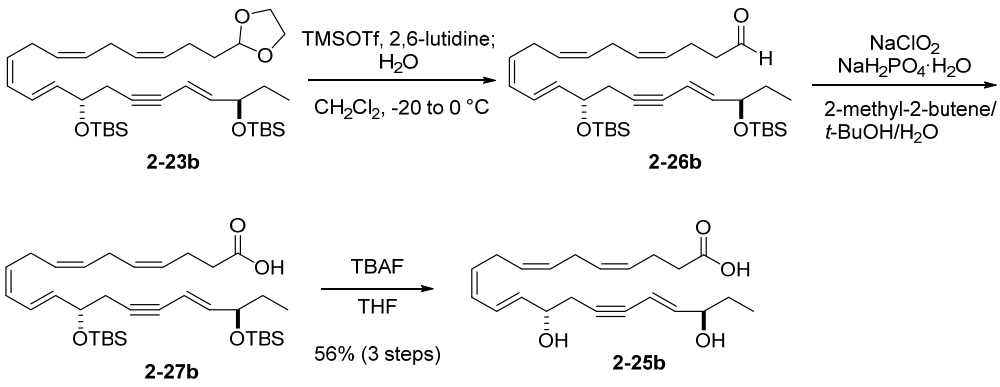
2-23 **2-25**

2-24 14,20-diHDHA (**2-1**)

2-4-4.　経路 1 による 14,20-diHDHA の全合成

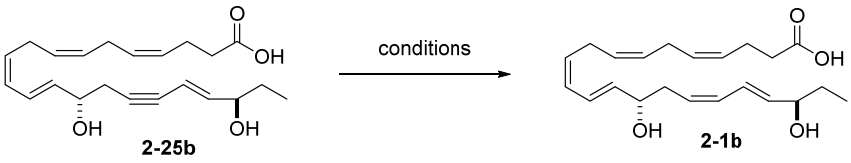
まず、経路 1 を検討した (Scheme 2-17)。**2-23b** のアセタールを TBS エーテル存在下、藤岡らの手法[15]により選択的に加水分解し、アルデヒド **2-26b** とした。次いで、アルデヒドを Pinnick 酸化[16]によりカルボン酸とし、TBAF によるシリル基の除去を行い **2-25b** を得た。

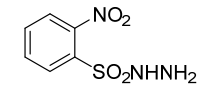
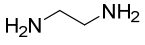
Scheme 2-17.　Transformation of **2-23b** to **2-25b**



続いて、**2-25b** から C16-17 アルキンの化学選択的な還元を検討した (Table 2-3)。entry 1 では佐治木らが開発した Pd/PEI[17]を用いた水素添加反応を試みた。この触媒は Lindlar 触媒に比べ活性が低く、複数のアルケンが存在していても、反応性の高いアルキンを選択的に還元出来るという特長を有している。しかし、**2-25b** に対してこの反応を適用したところ、アルキンとアルケンの還元速度に差がなく、過還元体が得られるのみであった。そこで、NBSH[18]を前駆体としたジイミド還元を試みた。この反応では、目的物 **2-1b** は生成するものの、複数の構造未決定の副生成物を確認した (entry 2)。次いで、共役エンインのアルキンを選択的に *Z*-アルケンへと還元することができる Zn(Cu/Ag)[19]を用いて反応を行った (entry 3)。しかし、目的物は質量分析では観測できるものの、高純度にて単離精製することはできなかった。P2-Ni[20]を用いた場合には、全く反応が進行しなかった (entry 4)。

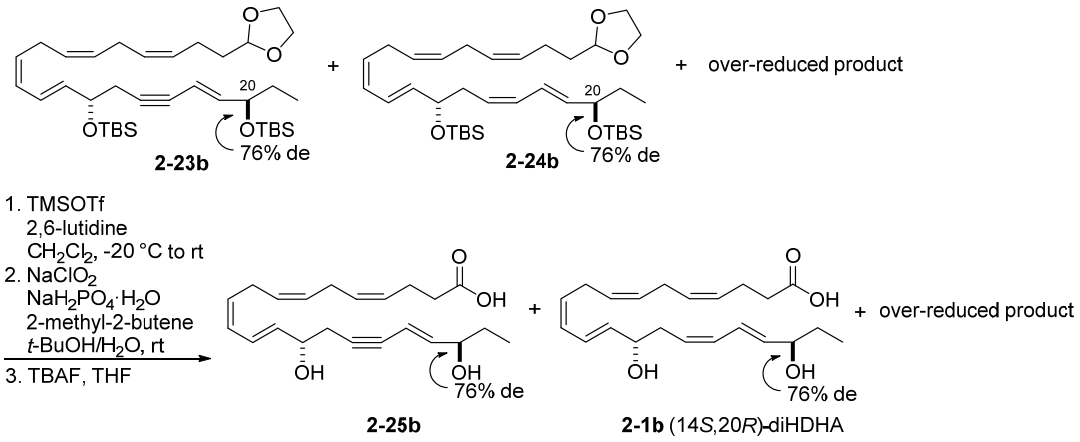
Table 2-3. Chemoselective reduction of **2-25b**



entry	conditions	results and comments
1	H_2, Pd/PEI (large excess) dioxane/MeOH(1/2, v/v), rt	Only over-reduced products were detected.
2	 NBSH, Et_3N *i*-PrOH/THF (1/1, v/v), rt	**2-1b** and some products (unknown structure) were detected.
3	Zn(Cu/Ag) MeOH, rt	TM was detected by ESI-MS, but it was decomposed under concentration.
4	P2-Ni  EtOH, rt to 50 °C	No reaction was occured.

上記の検討では **2-1b** を選択的に得ることが困難であったため、これらの条件で得られる **2-1b** と副生成物である過還元体との分離精製を検討した。Table 2-3 で得られた **2-23b**、**2-24b** および過還元体の混合物を 3 工程の変換を経て、(14*S*,20*R*)-diHDHA を含む混合物へと導いた (Scheme 2-18)。この際、C20 位に関して 76% de の化合物を用いた。

Scheme 2-18. Total synthesis of impure (14*S*,20*R*)-diHDHA



得られた混合物の HPLC 分取条件を種々検討した結果、順相のカラムを用い、EtOAc と CH_2Cl_2 を溶出液とした場合にピークが分離した。Figure 2-2 に示す 2 つのピークを単

離し、^{1}H NMR, ESI-MS によりそれぞれ構造を確認した。**2-25b** (peak①) と **2-1b** (peak②) は、分離可能であるものの、peak②は **2-1b** と過還元体の混合物であったため、これらの分離は困難であった。この結果から、**2-1b** と過還元体が HPLC を用いても分離不可能であると判断した。そこで経路 1 を断念し、経路 2 にて (14*S*,20*R*)-diHDHA の全合成を試みた。その際、C16-17 アルキンの還元は極めて高い化学選択性で進行し、高純度の **2-24** を得ることが必須となる。

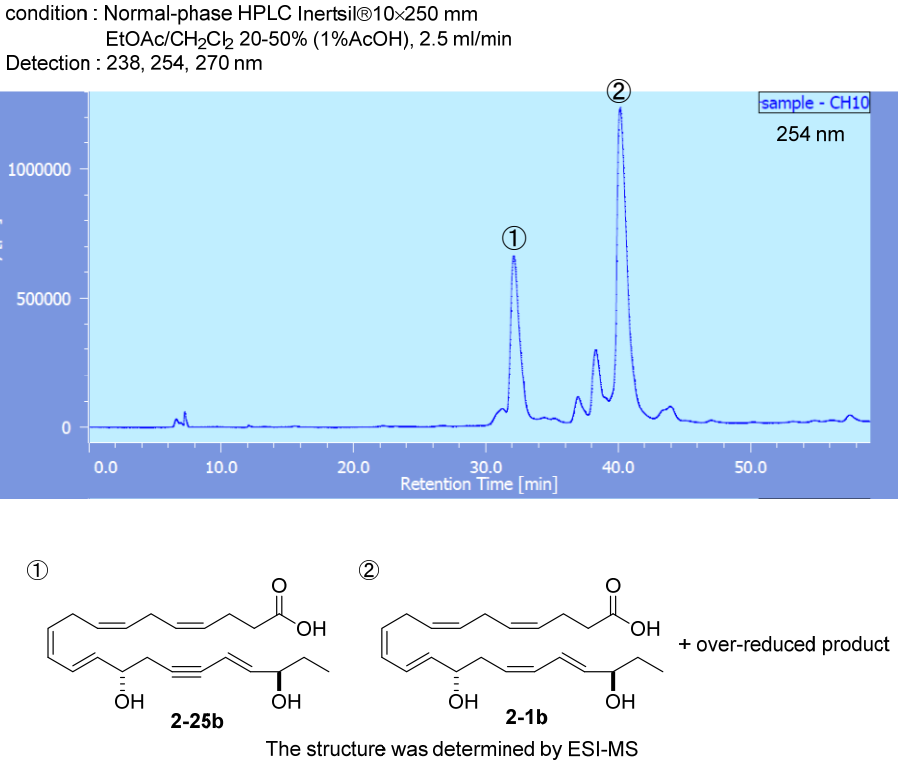


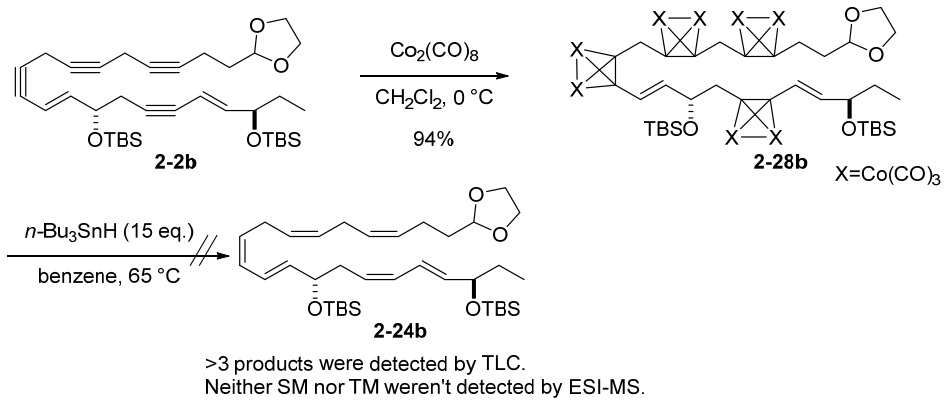
Figure 2-2. HPLC chart of the mixture of **2-25b**, **2-1b** and over-reduced product

2-4-5. 経路 2 による 14,20-diHDHA の合成

2-4-2 で用いた水素添加による還元法では、**2-23** の C16-17 アルキンを選択的に還元できる可能性が低いと考え、反応様式の全く異なる還元法を試みることとした。すなわち磯部らによって Lindlar 還元の別法として報告された、アルキン-コバルト錯体の還元的脱コバルト化反応[21]を試みた。本方法による条件最適化に関する詳細な検討は第 4 章に述べる。ここでは最適化した条件のみ示す。

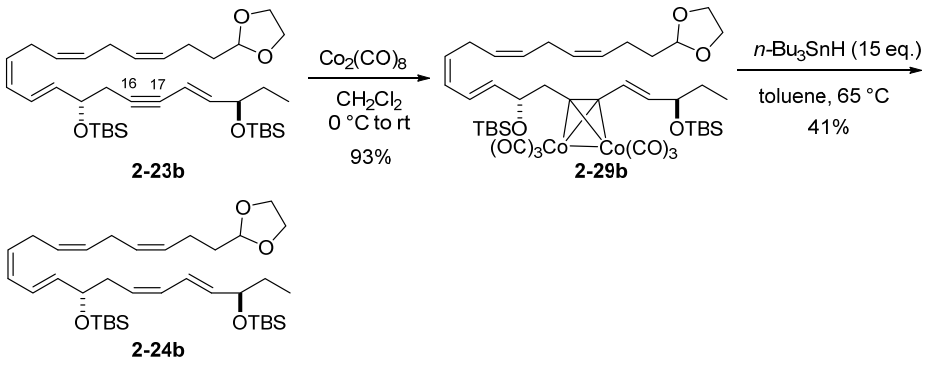
まず、テトライン **2-2b** に対し、$Co_2(CO)_8$ を作用させ、テトラキスアルキン-コバルト錯体 **2-28** へと誘導し、4 つのアルキン-コバルト錯体を、磯部らの条件、すなわち、65 度において水素化トリブチルスズを作用させ、一度に *Z*-アルケンへと還元することを試みた (Scheme 2-19)。しかし本反応条件では、基質の分解を伴う複雑な混合物を与えるのみで、望む **2-24b** は全く生成しなかった。

Scheme 2-19. Reductive decomplexation of tetrakis alkyne-dicobalt complex **2-28b**



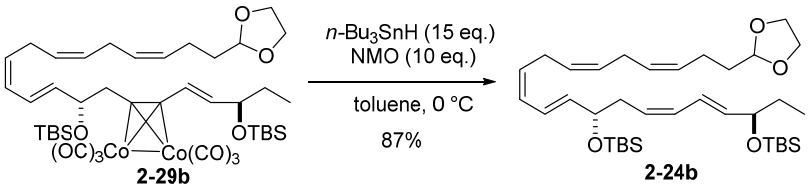
そこで、モノアルキン **2-23b** をアルキン-コバルト錯体 **2-29b** へと誘導し、これに対し磯部らの条件を適用したところ、収率 41%で目的のヘキサエン **2-24b** を単離した (Scheme 2-20)。本反応条件下では原料は消失し、一部基質の損壊が見られた。**2-29b** は、反応性の高いダブルアリル位や共役ジエン、アリルアルコールを有しているため、加熱条件下でこれらが起点となり分解が起こったと考えた。

Scheme 2-20. Chemoselective reduction of C16-17 alkyne of **2-23b** by reductive decomplexation



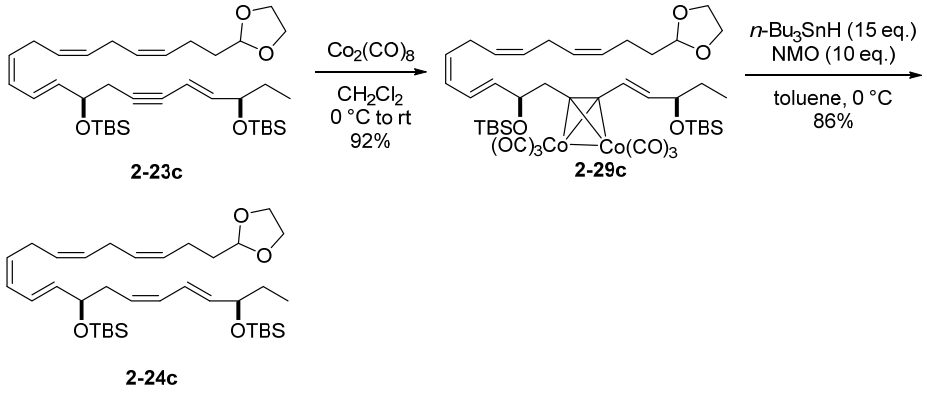
このため、より低温で反応を進行させるべく、過剰量の水素化トリブチルスズとともに添加剤として NMO を加えて反応を行った。その結果、0 度で望みの還元的脱コバルト化が進行し、ヘキサエン **2-24b** が生成した (Scheme 2-21)。この際、全く過還元体は生成しなかった。また、過剰の水素化トリブチルスズはシリカゲルカラムクロマトグラフィーでの精製において、フッ化カリウムを 10wt%含むシリカゲルを、カラムの上部 1/5-1/10 量使用することにより完全に除くことができた[22]。

Scheme 2-21. The modified Isobe reduction of mono alkyne-dicobalt complex **2-29b**



なお、**2-23b** のジアステレオマー**2-23c** についても同様の変換でヘキサエン **2-24c** を単離した (Scheme 2-22)。

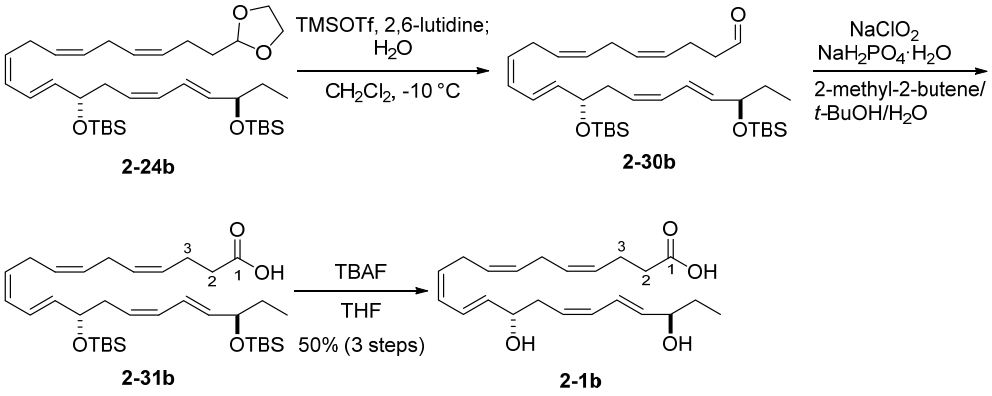
Scheme 2-22. Chemoselective reduction of C16-17 alkyne of **2-23c** by the modified Isobe reduction



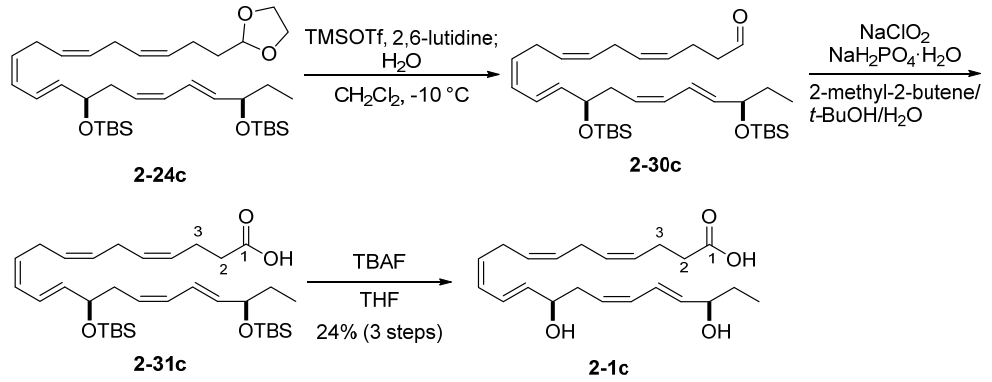
得られたヘキサエン **2-24** から 3 段階の変換を経て、(14*S*,20*R*)-diHDHA (**2-1b**)、(14*R*,20*R*)-diHDHA (**2-1c**)を全合成した (Scheme 2-23, 2-24)。両化合物とも、藤岡らの条件下でアセタールの加水分解を行い、アルデヒド **2-30** へ変換した。アルデヒドを酸化し、カルボン酸 **2-31** とした。得られた **2-31** に対し、TBAF を作用させることで 2 つの TBS 基を除去し、14,20-diHDHA へと導いた。最終物はシリカゲルカラムクロマトグラフィーで粗精製を行い、その後 HPLC で精製した (Inertsil® ODS-4 10×250 mm MeOH/H_2O/AcOH=7:3:0.1, 3.0 ml/min, **2-1b** : 33 min, **2-1c** : 40 min)。(14*S*,20*R*)-diHDHA と (14*R*,20*R*)-diHDHA の ^{13}C NMR スペクトルを測定したところ、C1-3 位に相当するピークが観測されないことがわかった。このため、HMBC の測定を行ったが、3 つの ^{13}C の化学シフトを特定することはできなかった。一方で、アルデヒド **2-30b** の炭素原子はすべて NMR 上で確認され、カルボン酸 **2-31b** の炭素原子は、C1 位以外確認された。このことから、14,20-diHDHA はカルボン酸と、C14 あるいは C20 ヒドロキシ基が分子内で相互作用し、比較的緩やかな配座変換をしていると予測した。なお、14,20-diHDHA はそれぞれ UV スペクトルを測定し、その極大吸収波長からジエンの構造を有することを確認した。また、^1H NMR のカップリング定数から、*E*/*Z* ジエンは異性化していないこと

を確認した。HPLC 精製において複数回に分けて分取を行ったところ、サンプル濃度が異なると、ピークの形状や保持時間が異なることが明らかとなった。これは、分子内で水素結合をとっており、その会合状態が濃度によって異なるためであると考えた。このため今回の精製では、インジェクション試料の濃度、体積を一定にし、精製時も保持時間の再現性がとれるよう工夫した。さらに、1 つのピークを分割して分取し、それぞれの純度を確認した。得られた最終物は空気酸化を最小限にするため、1mg 程度を濃縮し、減圧解除時はアルゴン置換した。また、異性化、分解を最小限にするため、サンプル保存には、遮光バイアルを用い、1 バイアル 3mg 以下とし、濃度は 1mg/mL 以下とした。メタノール中-20 度で保存した場合、最終物は分解しないことを確認している。

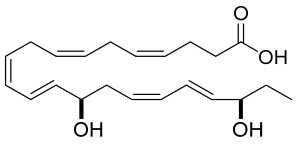
Scheme 2-23. Transformation from **2-24b** to (14*S*,20*R*)-diHDHA (**2-1b**)



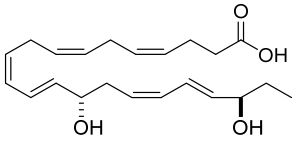
Scheme 2-24. Transformation from **2-24c** to (14*R*,20*R*)-diHDHA (**2-1c**)



合成した **2-1b** および **2-1c** は、中間体を含め、それぞれの化合物の ^{1}H, ^{13}C NMR データがジアステレオマー間で、ほぼ一致した。このため、分光学的手法を用いずに、それぞれの化合物を区別する条件を探索した。(14*S*,20*R*)-diHDHA (**2-1b**), (14*R*,20*R*)-diHDHA (**2-1c**) の HPLC での分離条件を種々検討した結果、Figure 2-3 に示すように、逆相の ODS-4 カラムを用いて MeOH/H_2O の混合溶液で溶出させた場合に、二つの化合物を分離できることを見出した[23]。

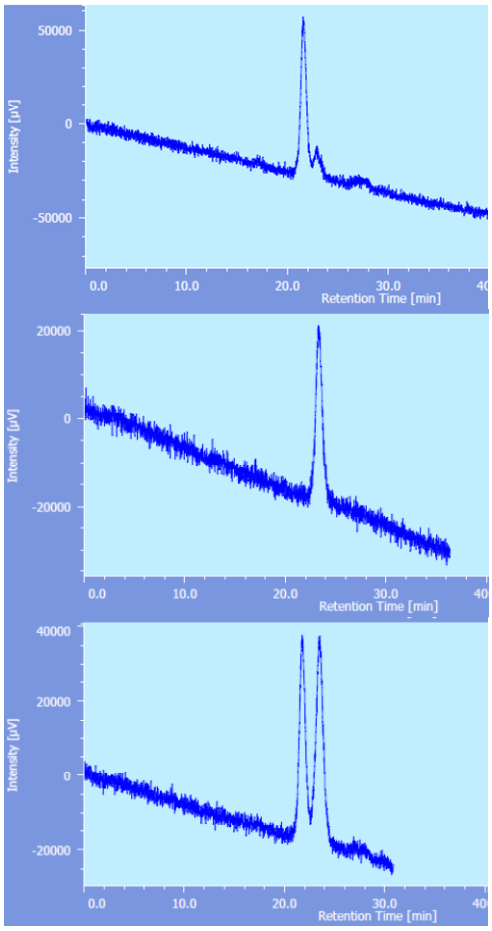


(14*R*,20*R*)-diHDHA (**2-1c**)
purified by silica gel



(14*S*,20*R*)-diHDHA (**2-1b**)
purified by HPLC

2-1c + 2-1b



HPLC condition:ODS-4 (4.6×250 mm), MeOH/H_2O 70% (AcOH 0.05%), 1.0 ml/min

Figure 2-3. HPLC analysis of diastereomers of 14,20-diHDHA

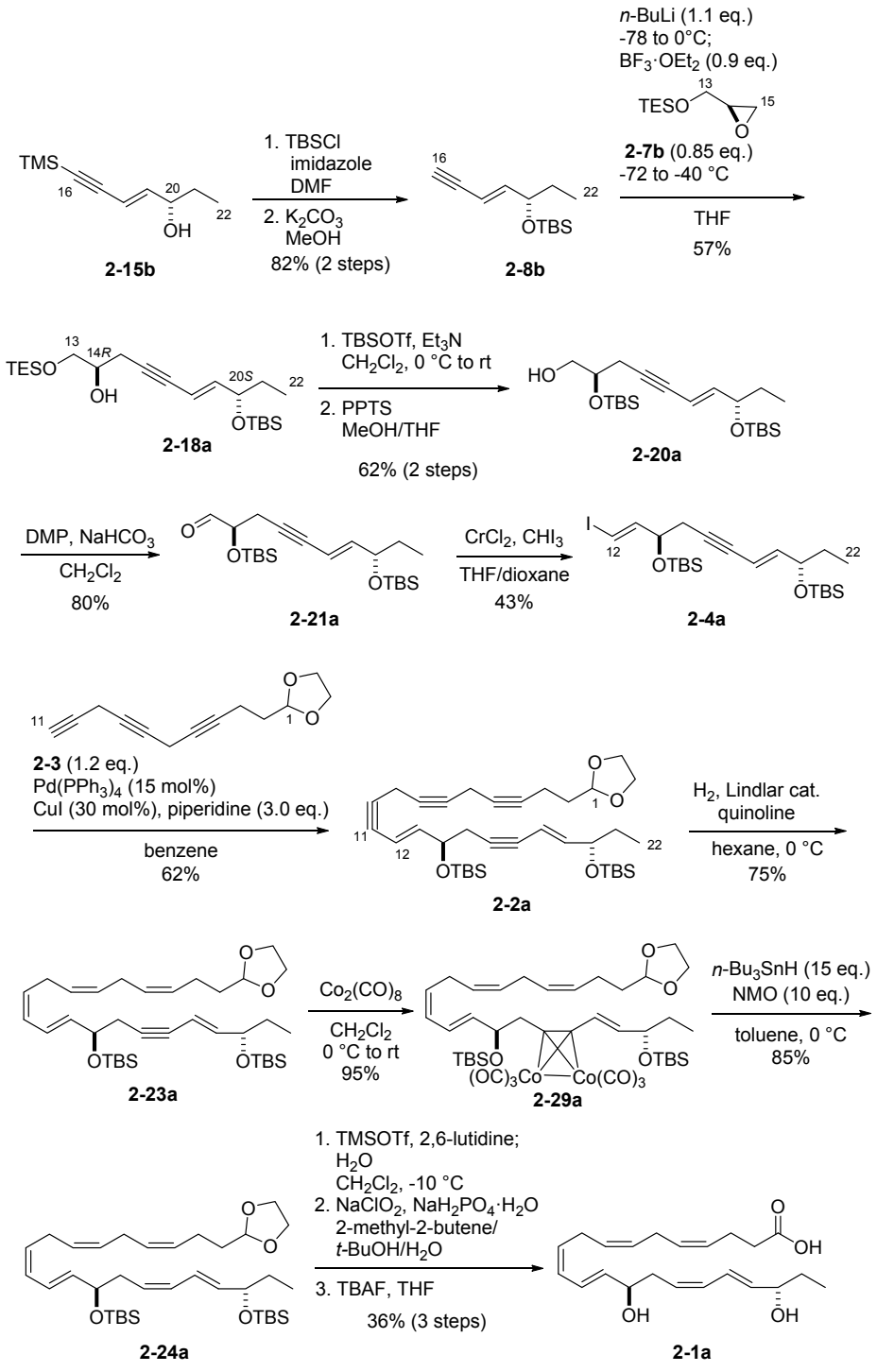
2-5. (14*R*,20*S*)-diHDHA および (14*S*,20*S*)-diHDHA の合成

2-4 までの検討結果を基に、(14*S*,20*R*)- および (14*R*,20*R*)-diHDHA のエナンチオマーである (14*R*,20*S*)-diHDHA (**2-1a**) および (14*S*,20*S*)-diHDHA (**2-1d**) を末端アルキン **2-8b** から合成した。

2-5-1. (14*R*,20*S*)-diHDHA の合成

(14*R*,20*S*)-diHDHA の合成を Scheme 2-25 に示す。**2-15b** の C20 ヒドロキシ基を TBS 基で保護し、TMS 基の除去を行い、**2-8b** とした。**2-8b** をリチウムアルキニドへと変換し、三フッ化ホウ素存在下グリシドール保護体 **2-7a** に対する求核付加反応を行い、**2-18a** を得た。C14 ヒドロキシ基を TBS エーテル化し、C13 位の TES 基を選択的に除去し、**2-20a** へと変換した。Dess-Martin 酸化と続く高井オレフィン化を経てヨウ化ビニル **2-4a** を合成した[24]。次いで、**2-4a** と C1-11 フラグメント **2-3** とを薗頭カップリングにより連結し、良好な収率でテトライン **2-2a** を得た。テトライン **2-2a** の Lindlar 還元では、反応温度を 0 度にすることで、より穏和に反応が進行することを見出し、ペンタエン **2-23a** を定量的に得た。ペンタエン **2-23a** をアルキン-コバルト錯体へと誘導し、続く還元的脱コバルト化反応を行い、ヘキサエン **2-24a** を得た。その後、アセタールの除去、Pinnick 酸化を行い、カルボン酸を合成した段階で、系中の塩を除くためシリカゲルカラムクロマトグラフィーを行った。最後に、2 つの TBS 基の除去を行い、(14*R*,20*S*)-diHDHA (**2-1a**) の合成を完了した。

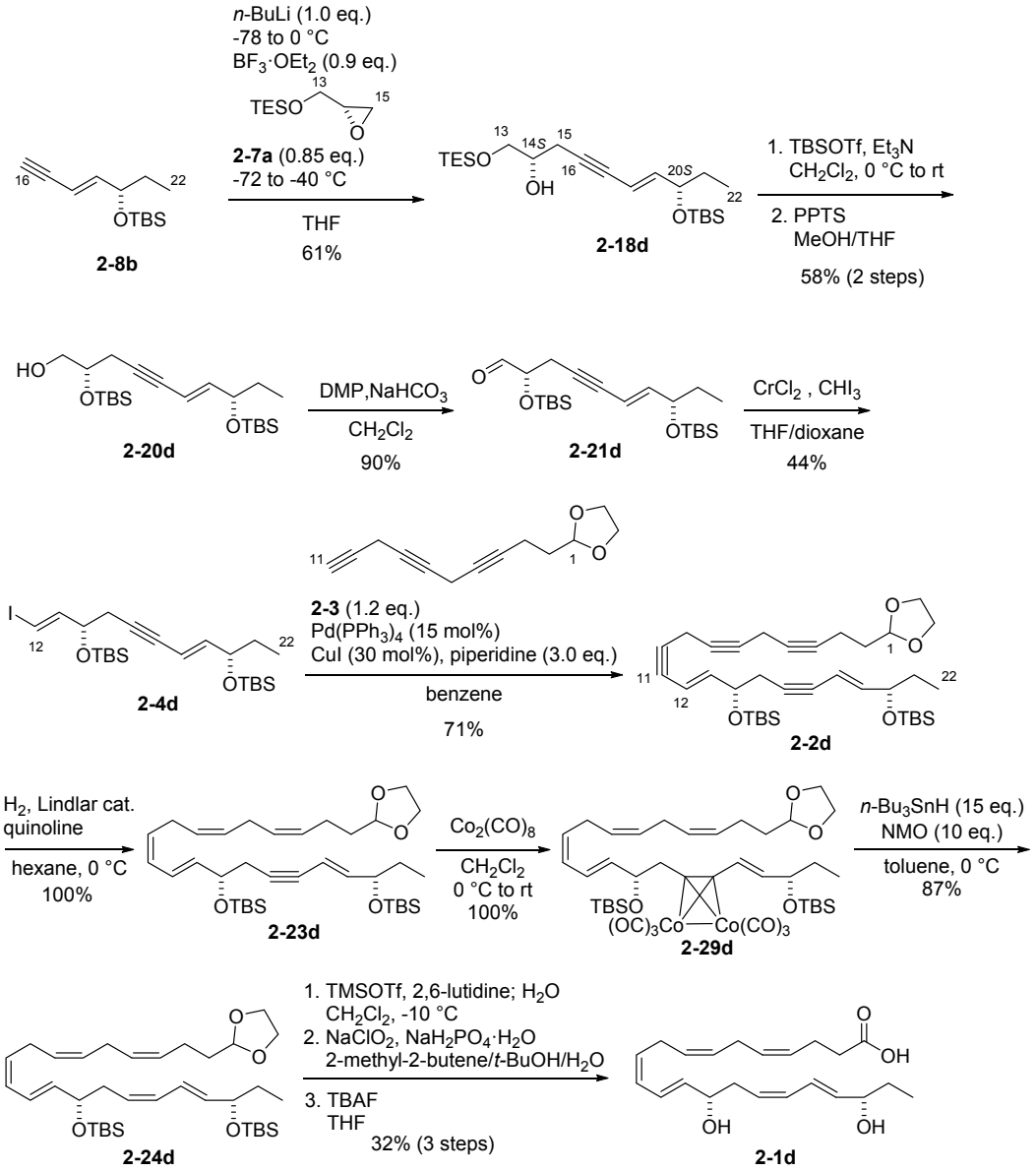
Scheme 2-25. Total synthesis of (14*R*,20*S*)- diHDHA (**2-1a**)



2-5-2. (14*S*,20*S*)-diHDHA の合成

(14*S*,20*S*)-diHDHA についても同様に合成した (Scheme 2-26)。本化合物においても UV スペクトルを測定し、ジエン構造を有することを確認している。

Scheme 2-26. Total synthesis of (14*S*,20*S*)-diHDHA



2-6. 注釈および参考文献

(1) 増田功嗣、占部大介、井上将行　未発表データ

(2) Ma, D.; Lu, X. *Tetrahedron* **1990**, *46*, 6319-6330.

(3) Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59*, 7787-7790.

(4) Falck, J. R.; Barma, D. K.; Mohapatra, S.; Bandyopadhyay, A.; Reddy, K. M.; Qi, J.; Campbell, W. B. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 4987-4990.

(5) Wu, Peng.; Folkin, V. V. *Aldrichimica ACTA* **2007**, *40*, 7-17.

(6) (a) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789-793. (b) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767-768.
本変換反応を、別の基質、トリフェニルホスフィンを用いて行ったところ、アセタールが除去されたアルデヒドを含む複数の生成物を確認した。これは系中で生じるトリフェニルホスフィンブロミドのリン原子が、DIPHOSと臭素の複合体のリン原子と比較して電子不足であるため、アセタールが反応したことが原因であると考えられる。

(7) Pillot, J. P.; Dunogués, J.; Calas, R. *Synth. Commun.* **1979**, *9*, 395-406.

(8) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.

(9) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

(10) Yamaguchi, M.; Hirano, I. *Tetrahedron Lett.* **1983**, *24*, 391-394.

(11) Dess, D. B.; Martin, J. C.; *J. Org. Chem.* **1983**, *48*, 4155-4156.

(12) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410. (b) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, 109, 951-953.

(13) Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.* **1975**, *50*, 4467-4469.

(14) Organic Syntheses, **1966**, *46*, 89.

(15) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930-5938.

(16) Lindgren, B. O., Nilsson, T. *Acta Chemica Scandinavica* **1973**, *27*, 888-890.

(17) (a) Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Bora, U.; Kurita, T.; Kozaki, A.; Maegawa, T.; Sajiki, H. 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006 (2006).; (b) Sajiki, H.; Mori, S.; Kitamura, Y.; Ikawa, T.; Hattori, K.; Monguchi, Y.; Maegawa, T. 234th ACS National Meeting, Boston, MA, United States, August 19-23, 2007 (2007).

(18) Myers, A.G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

(19) Boland, W.; Schroer, N.; Sieler, C. *HELVETICA CHEMICA ACTA* **1987**, *70*, 1025-1040.

本反応は共役エンインや、共役アルキン特異的に還元反応が進行する。Na などのアルカリ金属でも還元は可能だが、反応性が高く、また塩基性も高いため複雑な基質には適用できない。生成するアルケンの立体選択性については、アルケニル銅が立体障害を避けるように生成するため、生成物はシスのアルケンになると考えられる。

(20) (a) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc. Chem. Commun*. **1973**, 553-554. (b) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226-2230. (c) Orger, C.; Bultel-Poncé V.; Guy, A.; Balas, L.; Rossi, J-C.; Durand, T.; Galano, J-M. *Chem. Eur. J.* **2010**, *16*, 13976-13980.

(21) (a) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609-2612. (b) Takai, S.; Ploypradith, P.; Hamajima, A.; Kira, K.; Isobe, M. *Synlett* **2002**, 588-592.

(22) Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010**, *46*, 6335-6337.
本文献ではK_2CO_3をシリカゲルに混ぜた条件で、ハロゲン化トリアルキルスズや酸化トリブチルスズが除けると報告されているが、K_2CO_3を用いた精製で除くことができない水素化トリブチルスズはフッ化カリウムを用いた精製で効率よく除けた。

(23) 合成した 4 種立体異性体は、有田らによって以下の逆相 HPLC の条件で分離した。(column: CHIRALPAK AD-3R, 4.6 mm x 150 mm, eluent: 50% CH_3CN/MeOH (4/1) in 0.1 % aqueous AcOH for 5 min, 50-95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH over 22.5 min, and then 95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH for 8 min at 0.5 mL/min, retention times of the synthetic 1: t_R = 17.3 min for **2-1b**, 14.6 min for **2-1a** and **2-1c**, 14.0 min for **2-1d**, retention time of the natural **2-1b**: t_R = 17.2 min).

これら 4 種異性体を in vivo 抗炎症モデルである、ザイモザン A における好中球浸潤抑制活性試験が有田らによって行われた。Goto, T.; Urabe, D.; Masuda, K.; Isobe, Y.; Arita, M.; Inoue, M. *J. Org. Chem.* **2015**, *80*, 7713-7726.に報告された試験結果を Figure 2-4 に示した。ここでは (14*R*, 20*S*)-diHDHA (**2-1a**)が **1bb**、(14*S*, 20*R*)-diHDHA (**2-1b**)が **1aa**、(14*R*, 20*R*)-diHDHA (**2-1c**)が **1ba**、(14*S*, 20*S*)-diHDHA (**2-1d**) が **1ab** に相当する。非天然体である **2-1a**, **2-1c**, **2-1d** は、天然物である **2-1b** と同等の抗炎症活性を示した。この結果から、14,20-diHDHA の有する 2 つのヒドロキシ基の立体化学は抗炎症活性に影響を及ぼさないことが明らかとなった。

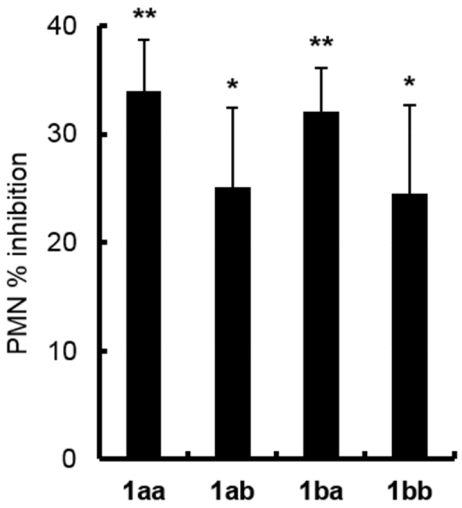
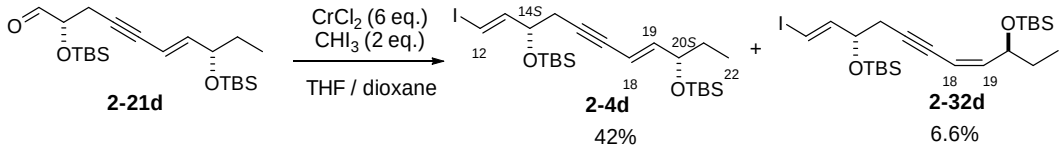


Figure 2-4. Bioassay of synthetic **2-1b**, **2-1a, 2-1c** and **2-1d**. The compounds (1 ng) were injected intravenously through the tail vein, followed by peritoneal injection of zymosan A (1 mg/ mL). After 2 h, peritoneal lavages were collected and the number of PMN leucocytes was counted. Values represent mean ± SE, n ≥3, **P*＜0.05, ***P*＜0.01 versus vehicle control.

(24) アルデヒド **2-21d** からヨードオレフィン化を行った際に、副生成物として C18-19 位の *E*-アルケンが *Z*-アルケンンへと異性化した **2-32d** を確認した。



第 3 章

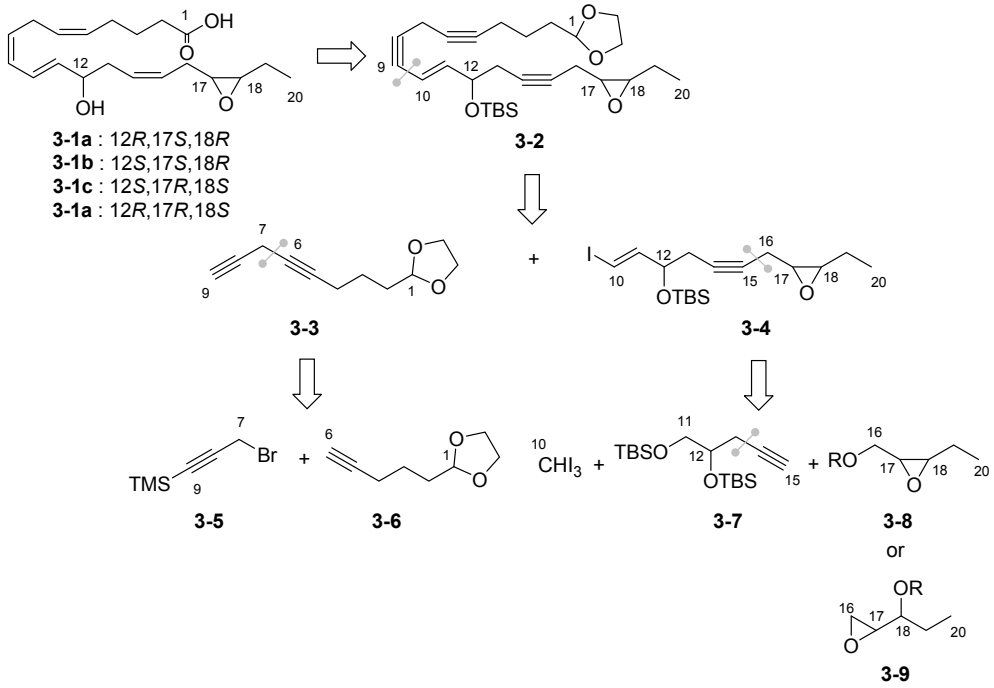
(5*Z*,8*Z*,10*E*,14*Z*)-12-ヒドロキシ-17,18-エポキシ-5,8,10,14-エイコサテトラエン酸の 4 種異性体の合成

本章では、(5*Z*,8*Z*,10*E*,14*Z*)-12-ヒドロキシ-17,18-エポキシ-5,8,10,14 エイコサテトラエン酸 (12-hydroxy-17,18-EpETE) の C12 ヒドロキシ基、および C17,18 位のシス-エポキシドに関する 4 つの立体異性体の収束的合成について述べる。

3-1. 合成計画-1

14,20-diHDHA の全合成を基にして、12-hydroxy-17,18-EpETE (**3-1**) の合成計画を立案した (Scheme 3-1)。**3-1** の 3 つの *Z*-アルケンは、対応する内部アルキンの化学選択的な部分還元により得ることとした。トリイン **3-2** は C1-9 位に相当するフラグメント **3-3** と、C10-20 位に相当するフラグメント **3-4** との薗頭カップリングにより合成する計画を立てた。C1-9 フラグメント **3-3** は、C7-9 の 3 炭素ユニット **3-5** と、末端アルキンを有する C1-6 フラグメント **3-6** とのカップリングにより得ることとした。一方、C10-20 フラグメント **3-4** は、C11-15 フラグメント **3-7** をアルキニドへと誘導し、C16-20 フラグメント **3-8** もしくは **3-9** に対する求核置換反応によって合成できると考えた。(12*R*) および (12*S*) の C11-15 フラグメント **3-7** と、(17*R*,18*S*) および (17*S*,18*R*) の C16-20 フラグメント **3-8**、もしくは **3-9** を用いることで、**3-1** の 4 つの立体異性体を合成することとした。

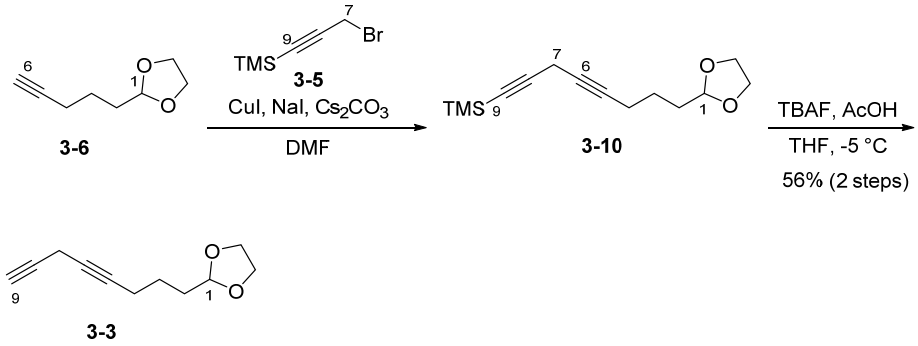
Scheme 3-1. Synthetic plan of 4 stereoisomers of 12-hydroxy-17,18-EpETE



3-2.　C1-9 フラグメントの合成

C1-9 フラグメント **3-3** はヨウ化銅、炭酸セシウム存在下、**3-6** を銅アルキニドへと導き、**3-5** との S_N2 アルキニル化反応により **3-10** とした後、酢酸添加の条件下、TBAF による TMS 基の除去を経て合成した (Scheme 3-2)[1]。酢酸を添加することで、ダブルプロパルギル位である C7 位の脱プロトン化による分解を抑制し、**3-3** を収率よく合成することができた。

Scheme 3-2.　Synthesis of C1-9 fragment

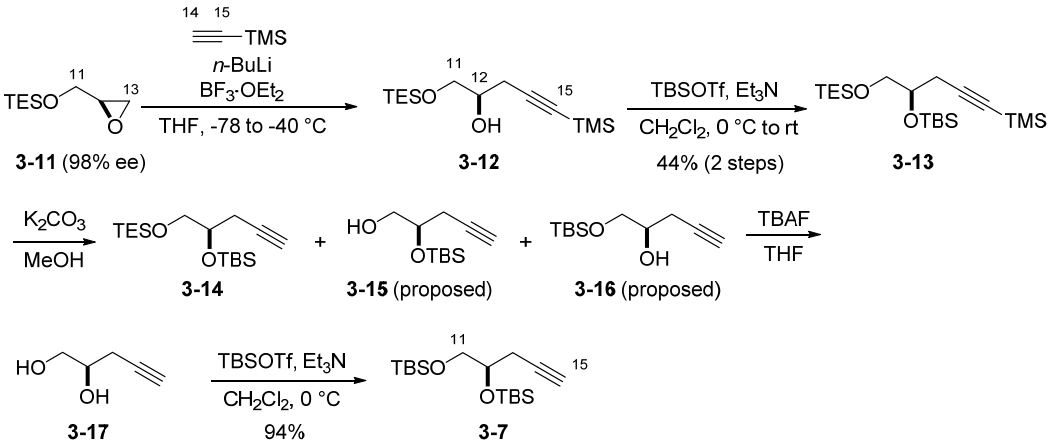


3-3. C10-20 フラグメントの合成

3-3-1. C11-15 フラグメント **3-7** の合成

光学的にほぼ純粋なグリシドール **3-11** (98% ee) に対して、三フッ化ホウ素存在下、過剰量のリチウムアセチリドを付加させ、アルコール **3-12** を得た後、C12 ヒドロキシ基を TBS 基で保護し、**3-13** とした (Scheme 3-3)。**3-13** の C15 位 TMS 基の除去を行ったところ、原料が消失する前に、目的物 **3-14** の C11 位の TES 基が除去された **3-15**、さらに **3-14** の C12 位の TBS 基が C11 位に転位した **3-16** の生成が確認できた。このためこれらを混合物のまま TBAF を作用させ、ジオール **3-17** へと変換した後、C11,12 ヒドロキシ基を TBS 基で保護し、**3-7** を合成した。

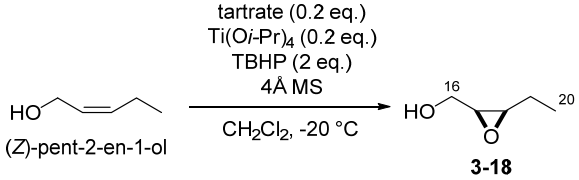
Scheme 3-3. Synthesis of C11-15 fragment **3-7**

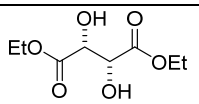
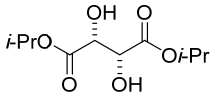


3-3-2. C16-20 フラグメント **3-8** の合成

C16-20 フラグメントとなる光学活性エポキシアルコールの合成に着手した。まず市販の(*Z*)-pent-2-en-1-ol に対して、Sharpless 不斉エポキシ化[2]を試みた (Table 3-1)。 (+)-酒石酸ジエチルを用いて反応を行ったところ、反応は円滑に進行し、目的のエポキシアルコール **3-18** を中程度の収率で得た (entry 1)。しかし、不斉収率は 82%と満足のいくものではなかった。このため、不斉収率の向上を目的とし、より嵩高い (+)-酒石酸ジイソプロピルを用いて反応を行ったが、期待した改善は見られなかった (entry 2)。

Table 3-1. Sharpless asymmetric epoxydaion for (*Z*)-pent-2-en-1-ol

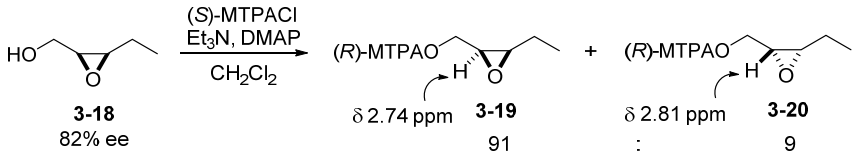


entry	tartrate	yield	ee [a]
1		41%[b]	82%
2		48%[b]	84%

[a] Enantiopurity was determined by the analysis of ^{1}H NMR of the correspondingMosher ester.
[b] Yield was determined by ^{1}H NMR analysis due to the inseparable impurity derived from tartrate.

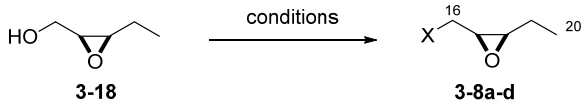
3-18 の光学純度は、 (*S*)-MTPACl を用いて、**3-19** に変換した後、^{1}H NMR により決定した (Scheme 3-4)。

Scheme 3-4. Conversion of epoxy alcohol **3-18** to MTPA ester **3-19**.



続いて、得られたエポキシアルコール **3-18** の C16 ヒドロキシ基を種々の脱離基へと変換した (Table3-2)。トシレート **3-8a** への変換反応は円滑に進行し、目的物を定量的に得た (entry 1)。トリフラート **3-8b** は、不安定であったものの、生成物をカラム精製により単離することができた (entry 2)。また、モノクレート[3]**3-8c**、ホスフェート **3-8d** も **3-18** より導く事ができた (entry 3, 4)。

Table 3-2. Conversion of **3-18** to **3-8**

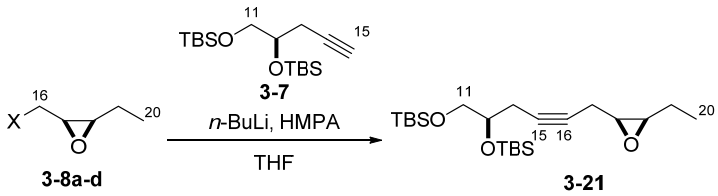


3-18 **3-8a-d**

entry	conditions	yield
1	TsCl, Et_3N, DMAP CH_2Cl_2, rt, o.n.	**3-8a** : X=OTs quant.
2	Tf_2O, Et_3N CH_2Cl_2, -78 °C, 40 min	**3-8b** : X=OTf 42%
3	McCl pyridine, 0 °C, 40 min	**3-8c** : X=OSO_2CH_2Cl 19%
4	$(PhO)_2P(O)Cl$, DMAP CH_2Cl_2, rt, 1 h	**3-8d** : X=$OP(O)(OPh)_2$ quant.

Table 3-2 で合成したエポキシドに対し、3-3-1 で合成した C11-15 アルキン **3-7** から誘導したアルキニドによる求核置換反応を試みた (Table 3-3)。**3-8a** を用いた場合、目的物の生成は確認できるものの、昇温しても反応は進行せず、目的物は 17%でしか得られなかった (entry 1)。entry 2 では、14%で **3-21** が得られたものの、基質の分解により生じた少量の TfOH が、THF の重合化を促進させた。そのため、**3-8b** を基質として使用することは困難であると判断した。一方、モノクレート **3-8c** やホスフェート **3-8d** を用いた場合、反応は全く進行しなかった (entry 3, 4)。

Table 3-3. Nucleophilic substitution



3-8a-d **3-21**

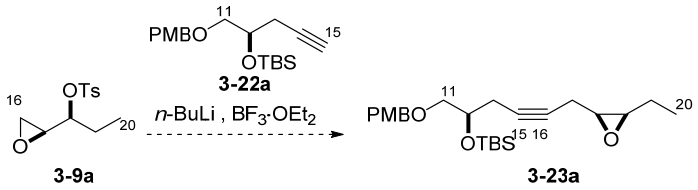
entry	substrate	conditions	yield(%)
1	**3-8a** : X = OTs	-78 °C to rt, 12 h	17
2	**3-8b** : X = OTf	-78 °C, 30 min	14
3	**3-8c** : X = OMc	-78 °C to rt, 2 h	0
4	**3-8d** : X = $OP(O)(OPh)_2$	-78 °C to rt, 12 h	0

3-3-3. C11-15 フラグメント **3-22** の合成

3-3-1, 3-3-2 における検討から、求核置換に用いるエポキシドの光学純度が不十分かつ、収率が低いこと、また C11-15 フラグメントと C16-20 フラグメントの連結がほとん

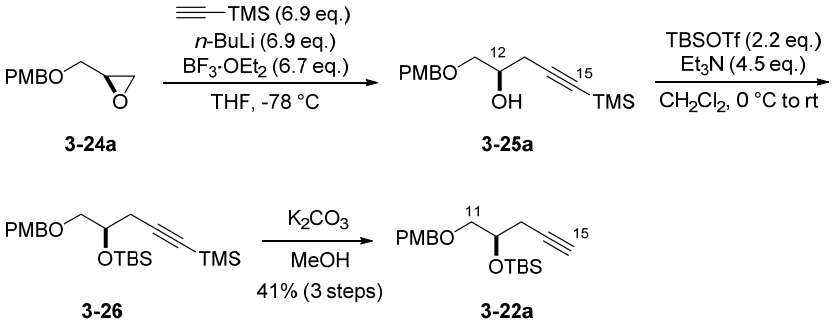
ど進行しなかったことから、合成計画を変更した。C16-20 の 5 炭素ユニットとして新たに **3-9a** を設定した。**3-9a** に対し、**3-22a** から生じさせたリチウムアルキニドを作用させ、C11-20 フラグメント **3-23a** を得る計画を考案した (Scheme 3-5)。エポキシドに対する S_N2 反応は、Table 3-3 で示したような通常の S_N2 反応よりも進行しやすいと予想した。なお、C11-15 フラグメントは後の変換を考慮して、C11 位の第一級ヒドロキシ基の保護基を PMB 基へと変更した **3-22a** を用いることとした。

Scheme 3-5. Synthetic plan for **3-23a**



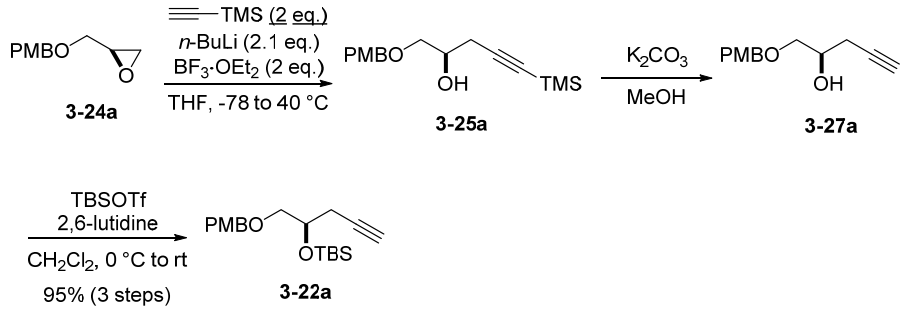
C11-15 フラグメントの合成を Scheme 3-6 に示す。PMB 基で保護されたグリシドール誘導体 **3-24a** (98% ee) に対して、三フッ化ホウ素存在下、過剰量のリチウムアセチリドを付加させ、アルコール **3-25a** とした。次いで C12 ヒドロキシ基の保護、C15 位 TMS 基の除去を経て **3-22a** を得た。しかし、C12 ヒドロキシ基の保護では、試薬を追加しても原料が消失せず、収率は三段階で 41%と中程度にとどまった。

Scheme 3-6. Synthesis of C11-15 fragment **3-22a**



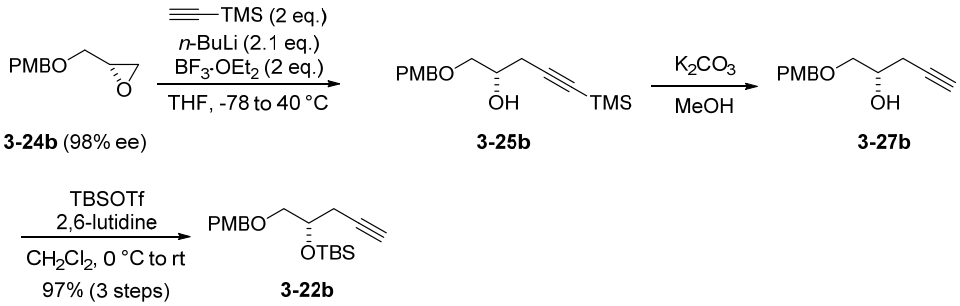
C12 ヒドロキシ基の反応性の低さは、C15 位 TMS 基の立体障害であると考えた。そこで、C15 位 TMS 基を除去した後に C12 ヒドロキシ基を TBS 基で保護したところ、反応は円滑に進行し、ほぼ定量的に目的物を与えた (Scheme 3-7)。また、一段階目のリチウムアルキニドは、基質に対して 2 当量でも十分に反応が進行することがわかった。これにより **3-22a** の大量合成が可能となった。

Scheme 3-7. Synthesis of **3-22a**



グリシドール誘導体のエナンチオマーである **3-24b** (98% ee) を用いた場合も、同様の変換で C11-15 フラグメントが得られた (Scheme 3-8)。

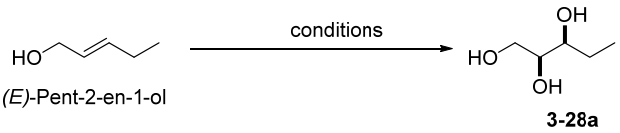
Scheme 3-8. Synthesis of C11-15 fragment **3-22b**



3-3-4. C16-20 フラグメント **3-9** の合成

光学活性 C16-20 フラグメント **3-9** を合成した。まず、(*E*)-pent-2-en-1-ol に対する Sharpless 不斉ジヒドロキシ化を行った (Table 3-4)。entry 1 では目的物のトリオール **3-28a** は 85%と高収率で得られるものの、不斉収率は 84%と満足のいくものではなかった。また、AD-mix α を用いて不斉ジヒドロキシ化を行うと、不斉収率は 88%であったものの、収率が 40%と大幅に低下した (entry 2)。

Table 3-4. Asymmetric dihydroxylation of (*E*)-pent-2-en-1-ol



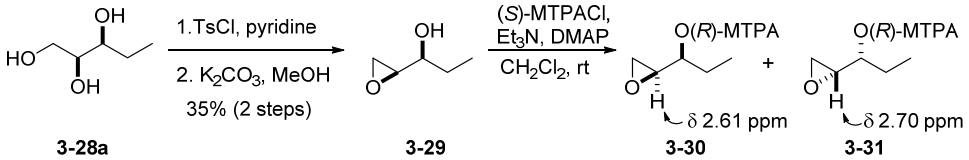
(E)-Pent-2-en-1-ol　　**3-28a**

entry	conditions	result
1	OsO_4 (0.4 mol%) $K_3Fe(CN)_6$ (3 mol%) $(DHQ)_2PHAL$ (10 mol%) $MeSO_2NH_2$ (1 eq.) K_2CO_3 (3 eq.) *t*-BuOH/H_2O = 1/1 (0.19 M) 0 °C, 13 h	85% (84% ee)[a]
2	AD-mix α $MeSO_2NH_2$ (1 eq.) *t*-BuOH/H_2O = 1/1 (0.33 M) 0 °C, 17 h	40% (88% ee)[a]

[a] The ee value was determined by ^{1}H NMR analysis of the corresponding MTPA ester.

3-28a の光学純度の向上について行った詳細な検討については下に示す。ここでは、**3-28a** の光学純度の決定について示した。**3-28a** の第一級ヒドロキシ基選択的なトシル化と塩基処理によりエポキシ化した後、(*S*)-MTPACl により MTPA エステル化した。**3-30** と **3-31** の比を、^{1}H NMR で確認することで **3-28a** を 84% ee であると決定した (Scheme 3-9)。

Scheme 3-9. Conversion of triol **3-28a** to MTPA ester **3-30**

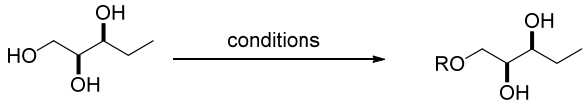


3-28a
84% ee　　**3-29**　　**3-30**　　**3-31**

トリオール **3-28a** の第一級ヒドロキシ基の選択的なトシル化は、以下に示す方法で行った (Table 3-5)。TsCl を 2 当量用いてトシル化を行ったところ、第二級ヒドロキシ基もトシル化された化合物が副生し、かつ原料も残存したため、目的物の **3-32a** は 42%と中程度の収率でしか得られなかった (entry 1)。このため TsCl の当量を減らし、濃度を濃くすることで、選択的トシル化を試みたが、収率は低下した (entry 2)。文献例に従い、1,2-ジオールの一級選択的な反応として、スズアセタールを経由したトシル化を試みた (entry 3)[4]。しかし、原料の **3-28a** がトリオール構造を有するため、スズアセタールの形成が一種類に限定されず、目的とする **3-32a** は低収率で得られるのみであった。そこで、

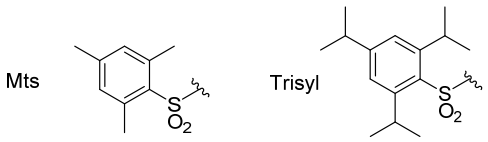
トシル基よりも嵩高いメシチル基を用いれば、より第一級ヒドロキシ基選択的な反応が進行するのではないかと考え、メシチルクロリドを用いて反応を行った (entry 4)。しかし、目的物は 18%しか得られなかった。トシル化試薬を TsCl からトシルイミダゾールに変更したが、全く目的物が得られなかった (entry 5)。entry 6, 7 ではメチルイミダゾール中、メチルトリフラートにより、トシルイミダゾール (あるいはトリシルイミダゾール)を *N*-メチル化し、より反応性の高い試薬に調製したものを使用したが、トシラート **3-32a** の収率は向上しなかった[5]。

Table 3-5. Transformation of **3-28a** to **3-32**



3-28a **3-32a-c**

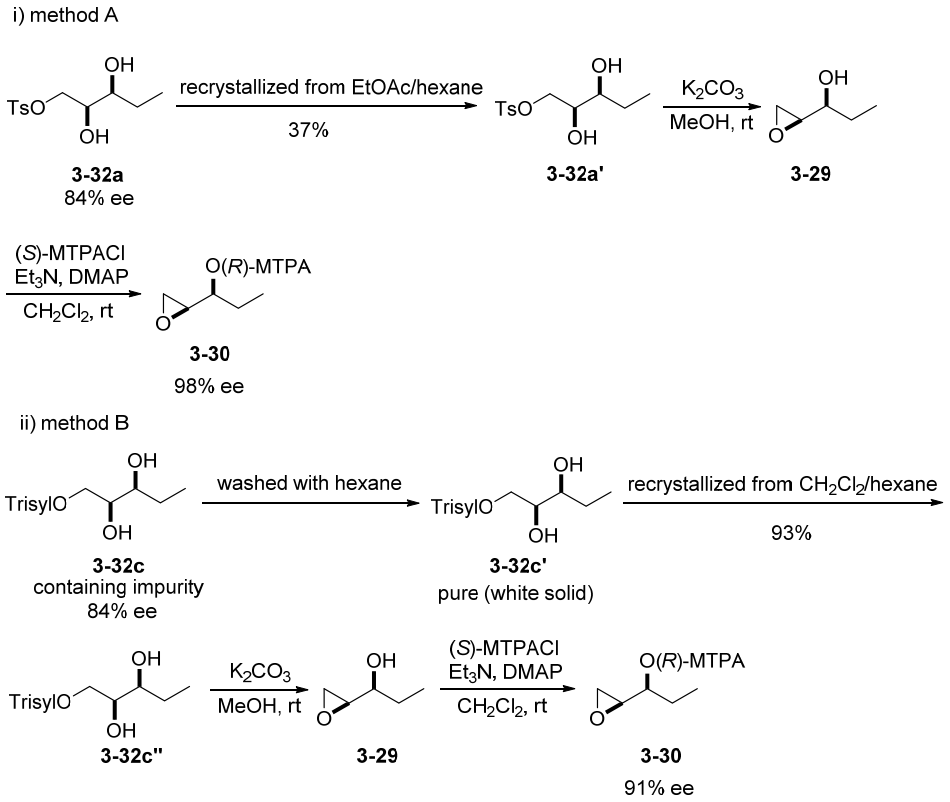
entry	conditions	result
1	TsCl (2 eq.), py. (0.1 M), rt, 22 h	**3-32a** : R=Ts, 42%
2	TsCl (1.2 eq.), py. (0.5 M), rt, 11.5 h	**3-32a** : R=Ts, 28%
3	Bu_2SnO (1.05 eq.), toluene, reflux, 2 h; TsCl (1.05 eq.), $CHCl_3$, rt, 18.5 h	**3-32a** : R=Ts, 28%
4	MtsCl (1.0 eq.) py. (0.1 M), MW (80 °C, 40 min)	**3-32b** : R=Mts, 18%
5	Ts-imidazole (1.0 eq.), Et_3N (1.0 eq.) THF (0.1 M), rt, 1.5 d	no reaction
6	Ts-imidazole (1.0 eq.), MeOTf (1 eq.) Me-imidazole (2.0 eq.) THF (0.1 M), 0 °C to rt, 13.5 h	**3-32a**: R=Ts, 35%
7	Trisyl-imidazole (1.0 eq.), MeOTf (1.0 eq.) Me-imidazole (1.0 eq.) THF (0.1 M), rt, 1.5 d	**3-32c** : R=Trisyl, < 56%



上記の検討で得られた脱離基を有するジオール **3-32a**、**3-32c** は固体であったため、再結晶による不斉収率向上の検討を行った (Scheme 3-10)。**3-32a** を再結晶し、得られた固体をエポキシアルコール **3-29** へと誘導した後、MTPA エステル化し光学純度を確認した (method A)。原料が 84% ee であったのに対し、再結晶後は 98% ee まで向上した。しかしながら、再結晶の回収率は 37%と低収率であった。一方 **3-32c** は、まず固体をヘキサンで洗浄し、不純物を取り除いた後に、ジクロロメタン/ヘキサン混合溶媒中で固体化させ、**3-32c''**を得た (method B)。エポキシアルコールへと誘導後、エナンチオ過剰率を確認したところ、91%と原料よりも向上したものの、光学的に純粋な結晶は得られなか

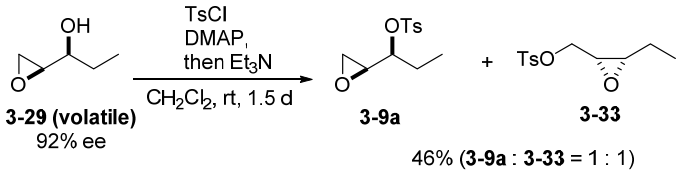
った。また、エポキシアルコール **3-29** は非常に揮発性が高く、再現よく合成することが困難であった。

Scheme 3-10. Recrystallization of **3-32a** and **3-32c**



Scheme 3-9 で得られたエポキシアルコール **3-29** のトシル化により、C16-20 フラグメント **3-9a** の合成を行った (Scheme 3-11)。その結果、トリエチルアミンを用いたことが原因であると考えられるが、Payne 転位によりエポキシドが転位した後、ヒドロキシ基がトシル化された **3-33** と目的物の **3-9a** が、収率 46%, 1:1 の比で生成した。

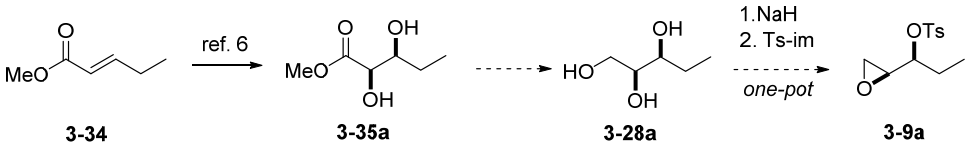
Scheme 3-11. Tosylation of epoxy alcohol **3-29**



以上の結果から、①不斉ジヒドロキシ化の不斉誘起が不十分である、②再結晶により光学純度の向上は見られるものの結晶化効率が低い、③エポキシアルコール **3-29** が低沸点のため単離が困難であるという問題があったため、**3-9a** の合成法を変更することとした。

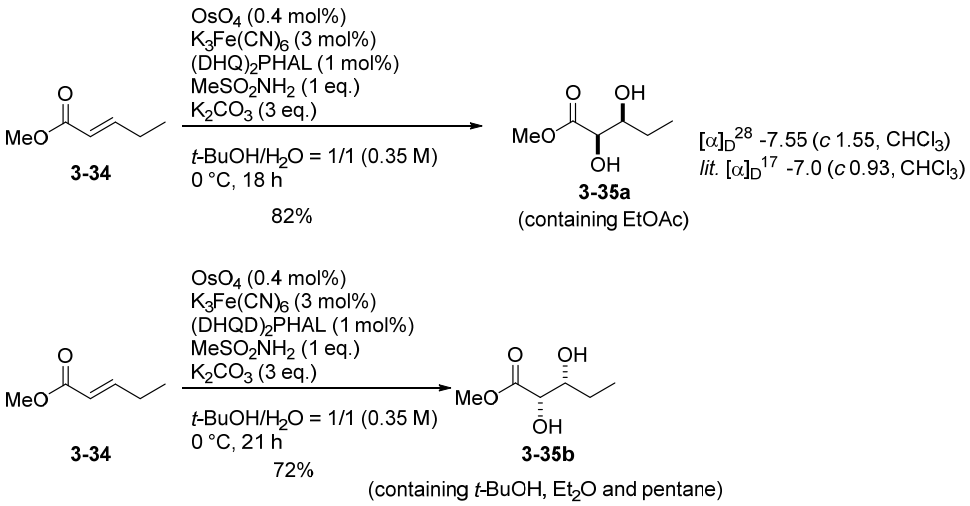
Scheme 3-12 に示した方法により、**3-9a** を合成する計画を立てた。この方法では、すでに当研究室にて、光学的に純粋に合成可能であることが実証されている **3-35a**[6]を用いることで、上記問題点①、②を改善できると考えた。また、トリオール **3-28a** から **3-9a** への変換では、ワンポット合成を適用すれば[7]、低沸点の中間体の単離を回避できる (問題点③) と考えた。

Scheme 3-12. Synthetic plan for epoxy alcohol **3-9a**



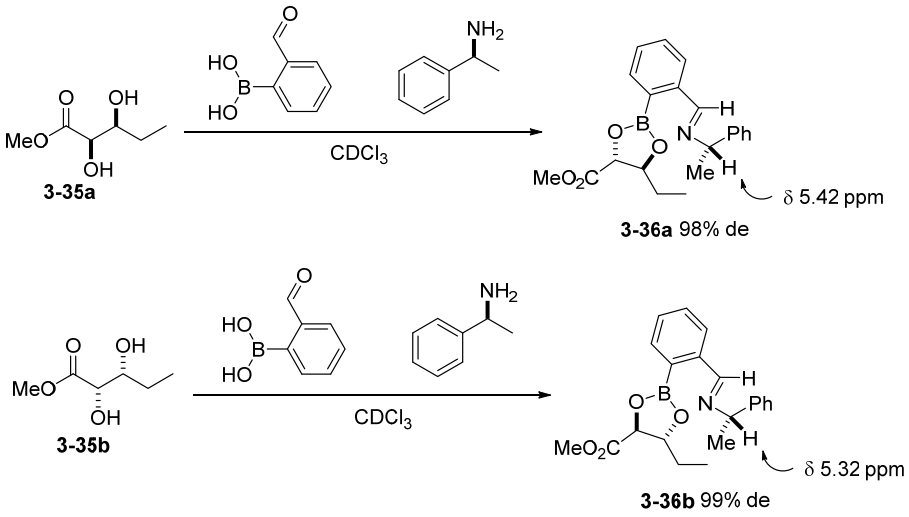
α, β-不飽和エステル **3-34** に対し、不斉エポキシ化を行い、目的のジオール **3-35a** を得た (Scheme 3-13)[6]。エナンチオマー**3-35b** についても同様に合成した。**3-35a** および **3-35b** は揮発性であったため、それぞれ酢酸エチル、エーテル、ペンタンを含む状態で、次の反応に使用した。

Scheme 3-13. Asymmetric dihydroxylation of α, β-unsaturated ester **3-34**



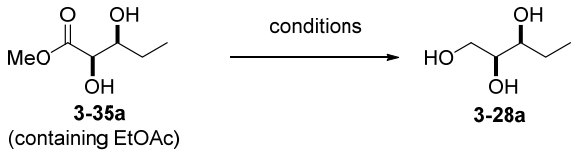
3-35a は比旋光度を文献値と比較し、絶対立体配置を確認した[8]。さらに 1,2-ジオールの不斉収率の算出法として報告されている手法[9]、すなわちホルミルフェニルボロン酸と光学活性なフェネチルアミンとを縮合させる方法を用い、^{1}H NMR により **3-35a** の不斉収率を 98%以上と決定した (Scheme 3-14)。エナンチオマーである **3-35b** も同様の手法を用いて不斉収率 99%であることを確認した。

Scheme 3-14. Determination of enantiomeric purity of 1,2-diol



続いて、**3-35a** のエステル部分の還元を行った (Table 3-6)。還元剤として水素化リチウムアルミニウムを用いた (entry 1)。目的物が高極性のトリオールであるため、還元後、水と水酸化ナトリウム水溶液を加え、水酸化アルミニウムを析出させた後、セライトろ過した残渣をカラムクロマトグラフィーで精製した。その結果、目的のトリオール **3-28a** を 46%で得た。低収率の原因として、トリオールとアルミニウムの配位が強く、上記の後処理では目的物とアルミニウムとの解離が不十分であることが考えられた。そこで、後処理に Rocchelle 塩の飽和水溶液を加え、一晩撹拌し、その後クロロホルムと 1-ブタノールで複数回抽出し、精製を行った (entry 2)。この場合の収率は 96%と後処理が効果的であったことを示唆している。entry 3 では、福山らによるゲルセモキソニンの全合成[10]にて報告された水素化ホウ素ナトリウムによる還元反応の後処理を適用することとした。ゲルセモキソニンの合成においても、中間体として高極性なトリオールを経由した際、後処理で分液操作を行うと抽出が困難であるという問題点があった。福山らは、反応後処理に酢酸を加え、メタノール処理と減圧留去を繰り返し、ホウ酸トリメチルを除去し、高収率でトリオールを得ることに成功している。そこで同様の手法を適用し、まず基質であるエステル **3-35a** の THF 溶液に水素化ホウ素ナトリウムを加え加熱し、反応を完結させた。その後福山らの方法に従い、メタノール処理と減圧濃縮を繰り返した。得られた残渣をシリカゲルカラムにより精製したところ、目的物は得られるものの、ホウ酸由来の不純物を取り除くことができず、これが原因となり、次の反応の再現性が乏しいことがわかった。このため、純粋なトリオールを良好な収率で得ることができる、entry 2 の条件を最適条件とした。

Table 3-6. Reduction of ester **3-35a** to triol **3-28a**



3-35a
(containing EtOAc)

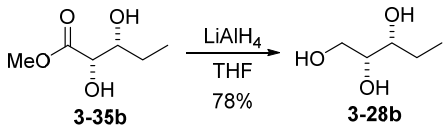
3-28a

entry	conditions / workup precedue	result
1	$LiAlH_4$, THF, 0 °C to rt , 4.5 h workup : addition of H_2O, 15 wt% NaOH aq., then filteration through celite	46%
2	$LiAlH_4$, THF, 0 °C to rt , 6 h workup : addition of sat. K^+/Na^+ tartrate aq., then extraction with $CHCl_3$, 1-butanol (×5)	96%
3	$NaBH_4$, THF, rt to 60 °C, 1 h workup : dilution with MeOH, quenching with AcOH, evapolation, addition of MeOH (×3)	N.D.[a]

[a] The product contains impurity generated from boronic acid.

エナンチオマーである **3-35b** に対して最適化した条件で還元を行い、トリオール **3-28b** を良好な収率で得た (Scheme 3-15)。

Scheme 3-15. Reduction of ester **3-35b** to triol **3-28b**

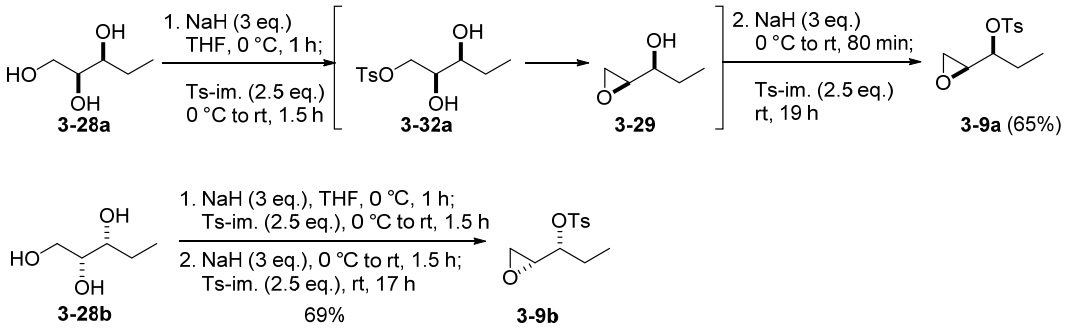


3-35b
(containing *t*-BuOH, Et_2O and pentane)

3-28b

トリオール **3-28a** を収率良く得たため、**3-28a** からワンポットで化合物 **3-9a** への変換を試みた (Scheme 3-16)[7]。反応の進行を注意深く TLC で追跡することで、収率良く **3-9a**[11]を得ることができた。すなわち、トリオール **3-28a** に対し、水素化ナトリウムとトシルイミダゾールを室温下、1.5 時間反応させ、中間体のエポキシアルコール **3-29** の生成を確認した。その後、水素化ナトリウムとトシルイミダゾールを加え、室温下で長時間撹拌した。反応停止にはリン酸バッファーを用いた。本行程は、**3-9a** のエナンチオマー**3-9b** の合成においても、再現性のある手順であることを確認した。

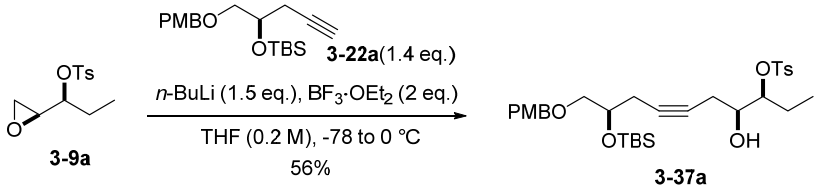
Scheme 3-16. One-pot conversion of **3-28** to **3-9**



3-3-5. 求核置換反応による C10-20 フラグメントの合成

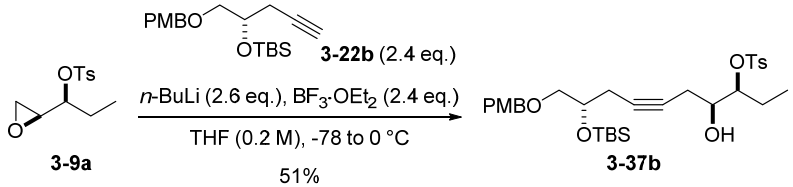
本節より以下は C16-20 フラグメント **3-9a** を用いた検討について述べる。(12*R*)-C11-15 アルキン **3-22a** と C16-20 エポキシド **3-9a** を用い、三フッ化ホウ素存在下、求核置換反応による C10-20 フラグメントを合成した。エポキシド **3-9a** に対し、アルキン **3-22a** を 1.4 当量用い、基質の濃度 0.2 M で反応を行うと、付加体 **3-37a** が 56%の収率で得られた (Scheme 3-17)。なお本反応では、生成する C17 位アルコキシドが、C18 位のトシレートへと求核攻撃することでエポキシド **3-23a** が生成する可能性があったが、得られる化合物は **3-37a** のみであった。

Scheme 3-17. Nucleophilic addition of **3-22a** to **3-9a**



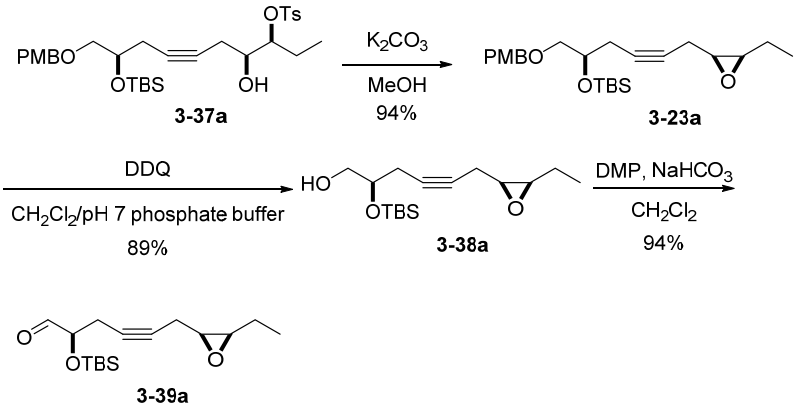
(12*S*)-C11-15 フラグメント **3-22b** を用いた場合[12]も、同程度の収率で目的物を得た (Scheme 3-18)。

Scheme 3-18. Nucleophilic addition of **3-22b** to **3-9a**



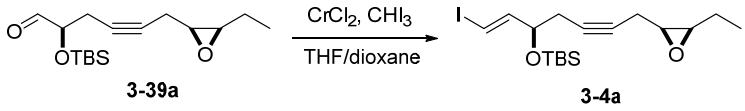
付加体 **3-37** が得られたため、C10-20 フラグメント **3-40** への変換を行った (Scheme 3-19)。**3-37a** を塩基で処理し、エポキシド **3-23a** を得た。続いて PMB の脱保護とアルコールの Dess-Martin 酸化を経て、アルデヒド **3-39a** を良好な収率で得た。

Scheme 3-19. Synthesis of aldehyde **3-39a**

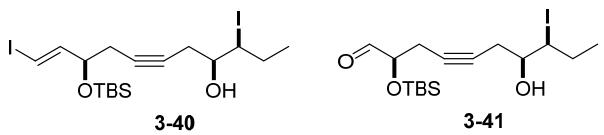


アルデヒド **3-39a** に対し高井オレフィン化を行い、ヨウ化ビニル **3-4a** への変換を試みた (Table 3-7)。塩化クロム 6 当量、ヨードホルム 2 当量用いた条件では、ヨードオレフィンは構築できたものの、系中で発生したヨウ化水素によるエポキシドの開環反応が起こった化合物 **3-40** が単一の生成物として得られた (entry 1)。そこで、エポキシドの開環反応を抑制するべく、塩化クロムとヨードホルムの当量を減らして反応を行った (entry 2)。しかし、**3-39a** に対するエポキシドの開環が起こった化合物 **3-41** のみが得られた。そこで、反応系中で生じるヨウ化水素を緩衝する目的で 2,6-ルチジンを系中に加えたが、この場合もヨウ化ビニルは全く得られなかった (entry 3)。

Table 3-7. Takai olefination for aldehyde **3-39a**

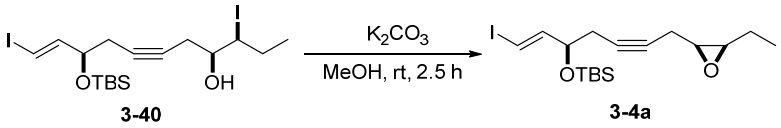


entry	$CrCl_2$ (eq.)	CHI_3 (eq.)	additive	result
1	6	2	-	**3-40** : 26%
2	3	1	-	**3-41** : 52%
3	6	2	2,6-lutidine (10 eq.)	**3-41**: 14%



上記の検討の結果から、エポキシドを有する **3-39a** を原料として用いると、高井オレフィン化での開環反応が不可避であることがわかった。そこで、得られた化合物 **3-40** を再度塩基処理し、エポキシドへと変換し、C10-20 フラグメント **3-4a** を得た (Scheme 3-20)。

Scheme 3-20. Conversion for epoxide **3-4a**



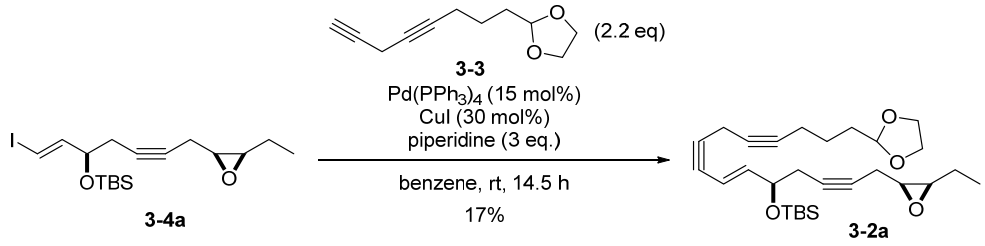
3-40 **3-4a**

Yield was not determined.

3-4.　薗頭カップリングによる C1-9 と C10-20 フラグメントの連結

3-2 で得られたジイン **3-3** と 3-3-6 で得られたヨウ化ビニル **3-4a** を、薗頭カップリングにより連結した (Scheme 3-21)。条件は第 2 章で述べた 14,20-diHDHA の合成の際に用いた条件、すなわち基質に対しジイン **3-3** を 2.2 当量、テトラキスとリフェニルホスフィンパラジウムを 15 mol%、ヨウ化銅 30 mol%、ピペリジン 3 当量をベンゼン中室温で反応させた。しかし、これらの基質を用いた場合は、目的物のトリイン **3-2** は 17%と非常に低収率であった。これは、エポキシドの不安定性に起因すると考えた。

Scheme 3-21.　Sonogashira coupling of vinyl iodide **3-4a** and diyne **3-3**

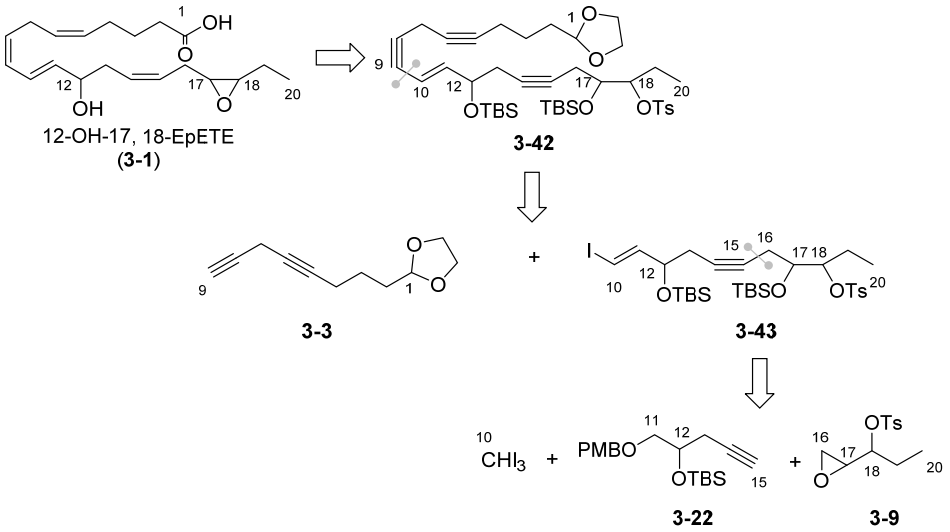


以上の検討より、合成の初期段階にエポキシドを導入した戦略では、その不安定さから、その後の種々の変換に問題が生じると結論した。

3-5.　合成計画-2

3-4 までの検討で、特にエポキシドを合成の初期段階に形成することにより、高井反応によるヨードビニル化において問題が生じることが明らかとなった。このため、薗頭カップリングに用いるフラグメントとして新たに C10-20 フラグメント **3-43** を設定し、エポキシドは合成の最終段階で構築する新たな計画を立案した (Scheme 3-22)。

Scheme 3-22.　Revised synthetic plan of 12-hydroxy-17,18-EpETE

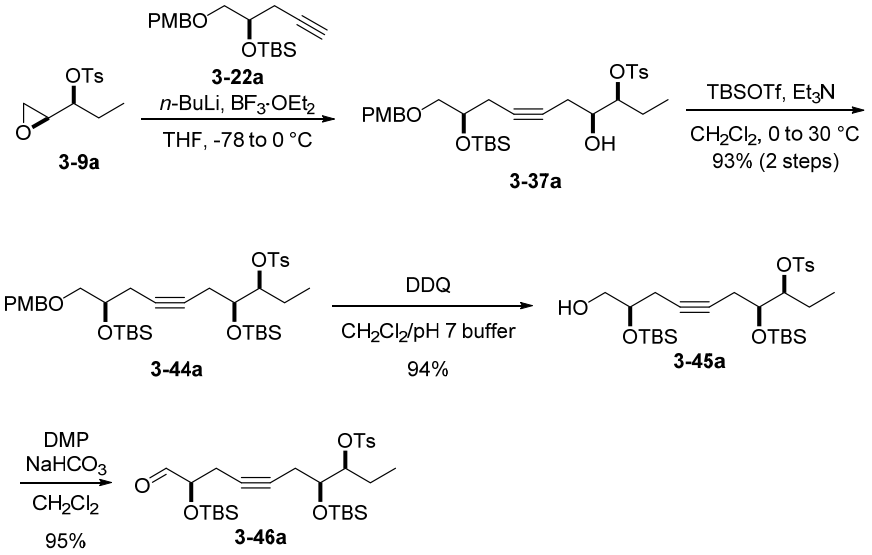


なお、3-6 から 3-9 においては、(12*R*)-および(12*S*)-C11-15 フラグメント **3-22** と、(17*S*,18*S*)-C16-20 フラグメント **3-9a** を用いた、(12*R*,17*S*,18*S*)-および(12*S*,17*S*,18*S*)-12-hydroxy-17,18-EpETE の合成について述べる。

3-6. C10-20 フラグメントの合成

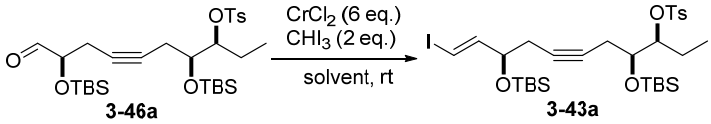
新たに設定した C10-20 フラグメント **3-43** は、先の合成中間体 **3-9a** より誘導した (Scheme 3-23)。**3-22a** から誘導したリチウムアルキニドの **3-9a** への求核付加反応により、アルコール **3-37a** を得た。**3-37a** の第二級ヒドロキシ基を TBS 基で保護し、化合物 **3-44a** とした後、PMB 基の除去、得られたヒドロキシ基の酸化を行い、アルデヒド **3-46a** を合成した。

Scheme 3-23. Synthesis of aldehyde **3-46a**



続いて **3-46a** に対し、高井反応によりヨードビニル化を行った (Table 3-8)。14,20-diHDHA の合成に際に用いていた条件、すなわち塩化クロムおよびヨードホルムを THF/ジオキサン (1/14) で作用させる条件を適用すると、長い反応時間を要するうえ、目的物は 22%と低収率であった (entry 1)。Evans らは、高井反応において、溶媒の THF は反応速度の促進、ジオキサンはアルケンの幾何異性選択性に効果的であることを報告している[13]。このためアルケンの幾何異性選択性の低下の懸念があるものの、反応速度を加速させるため、THF の割合を増加した条件で反応を行った。その結果、収率 50%で C10-20 フラグメント **3-43a** を得ることができた (entry 2)。また、*Z*-アルケンの生成は確認されなかった。さらに最適化に向け、選択性、収率ともに良好な文献を参考に[14]、THF とジオキサンの 1:3 の混合溶媒で反応を行ったところ、収率は 63%まで向上した (entry 3)。溶媒を THF のみで行った場合は、目的物は中程度の収率で得られるものの、反応系が複雑化し、目的とする **3-43a** は不純物との混合物でしか得られなかった (entry 4)。以上の結果から、THF/ジオキサン 1:3 を最適溶媒混合比とし、さらに塩化クロムとヨードホルムの当量をそれぞれ 6.9 当量、2.3 当量へと増やして反応を行ったところ、収率を 87%まで向上させることに成功した (entry 5)。このため、entry 5 の条件を最適条件とした。

Table 3-8. Takai olefination of aldehyde **3-46a**



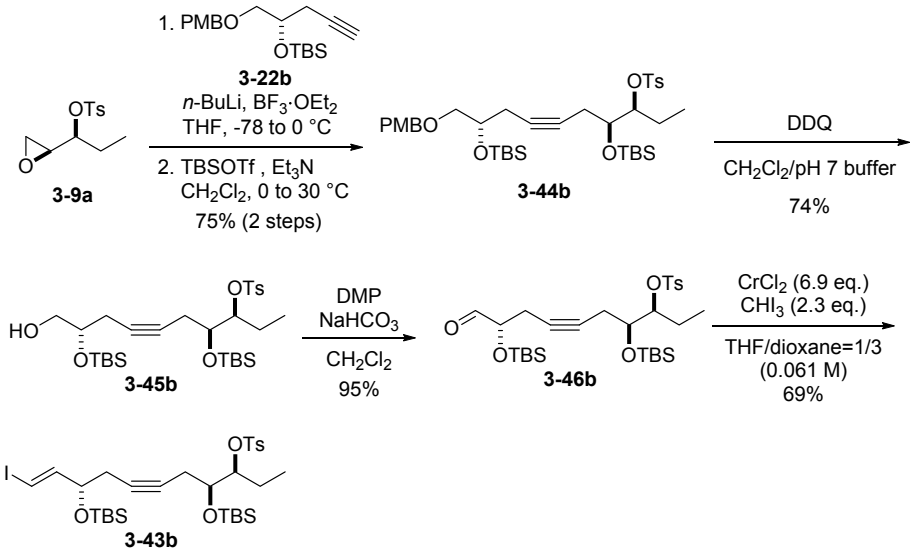
3-46a **3-43a**

entry	solvent	time	result
1	THF/dioxane=1/14	26.5 h	22%
2	THF/dioxane=1.2/1	18 h	50%
3	THF/dioxane=1/3	12.5 h	63%
4	THF (0.061 M)	18 h	<47%
5 [a]	THF/dioxane=1/3	13 h	88%

[a] $CrCl_2$ (6.9 eq.) and CHI_3 (2.3 eq.) were used.

3-43a のジアステレオマーである C10-20 フラグメント **3-43b** についても同様の合成法を用いて、再現性良くヨウ化ビニル **3-43b** を得た (Scheme 3-24)。

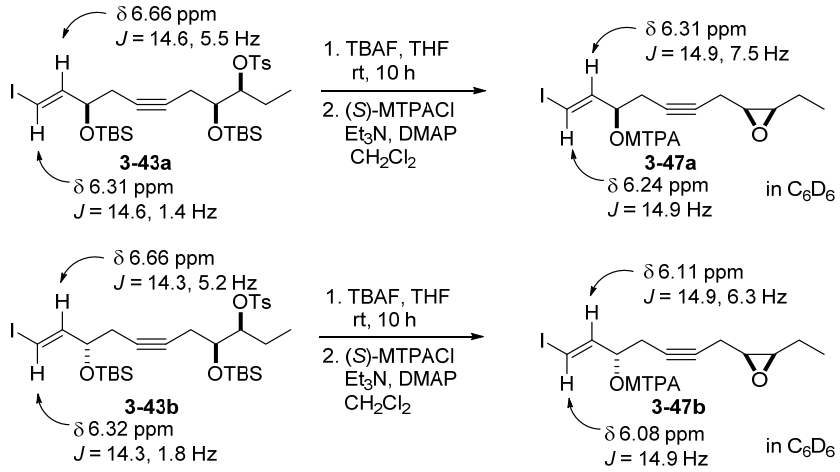
Scheme 3-24. Synthesis of (12*S*,17*S*,18*R*)-C10-20 fragment **3-43b**



本合成経路においては、合成中間体としてアルデヒド **3-46a** および **3-46b** を経由するため、C12 位のエピメリ化の懸念があった。**3-46a** と **3-46b** の ^{1}H NMR は区別できなかったため、以下の方法により C12 位にエピメリ化の有無を確認した (Scheme 3-25)。**3-46a** および **3-46b** より誘導したヨウ化ビニル **3-43a**、**3-43b** それぞれについて、TBAF によりシリル基の除去とエポキシド形成を行い、生じた C12 位のアルコールを(*S*)-MTPACl を用い、(*R*)-MTPA エステル **3-47a**、および **3-47b** へと変換した。この MTPA エステルの C_6D_6 中での ^{1}H NMR を測定し、C10 位、C11 位の化学シフトが **3-47a** および **3-47b** で一致しないこと、また、それぞれの反応粗精製物中には、一致する化合物を全く含まないこと

から、C12 位でのエピメリ化は起こっていないと結論した。

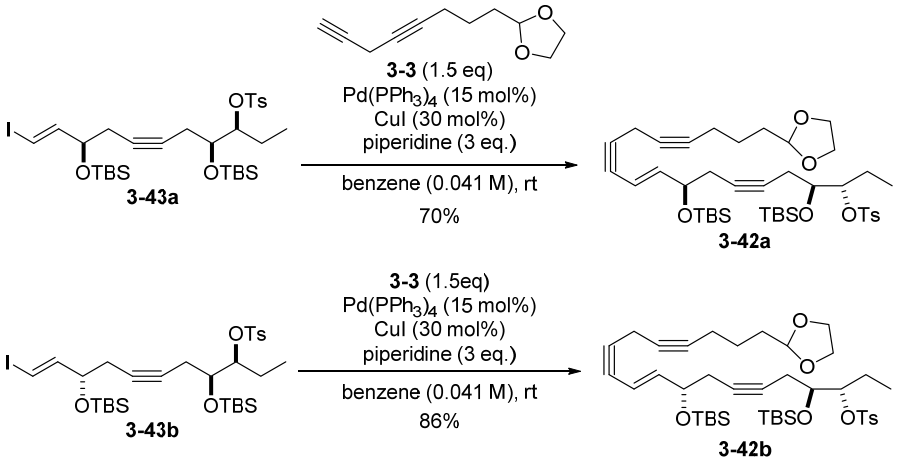
Scheme 3-25. Confirmation of no epimerization at C12 hydroxy group.



3-7.　C1-9 フラグメントと C10-20 フラグメントの薗頭カップリング

3-6 で合成した C10-20 フラグメント **3-43a** および **3-43b** と C1-9 フラグメント **3-3** との薗頭カップリングを行ったところ、反応は円滑に進行し、目的のトリイン **3-42a**, **3-42b** をそれぞれ、70%および 86%と高収率で得ることに成功した (Scheme 3-26)。

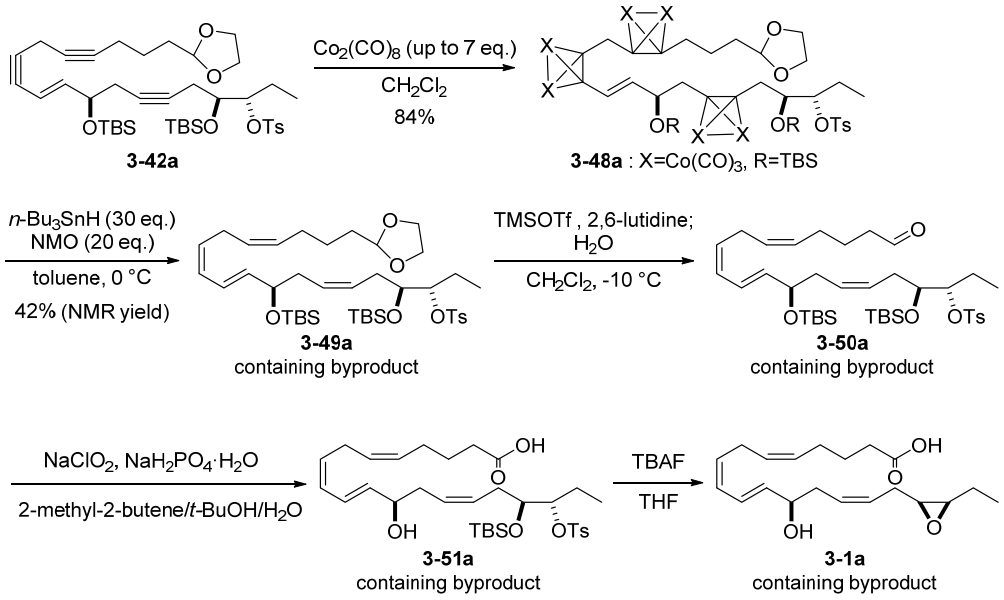
Scheme 3-26.　Sonogashira coupling of vinyl iodide **3-43a**, **3-43b** and diyne **3-3**



3-8. トリスアルキン-コバルト錯体の還元を経由した 12-hydroxy-17,18-EpETE の全合成

カップリング成績体 **3-42** が得られたため、3 つアルキンの *Z*-アルケンへの部分還元を行った。まず、第 2 章で述べた NMO を添加した改良磯部還元を適用した。**3-42a** をトリスアルキン-コバルト **3-48a** へと誘導した (Scheme 3-27)。これに対して、30 当量の水素化トリブチルスズと 20 当量の NMO を 0 度で作用させ、還元的脱コバルト化を行うと、目的物 **3-49a** と、分離困難な副生成物が生成した (収率 42%)。得られた混合物から、第 2 章で述べた条件に従い、TBS 存在下、アセタールを藤岡らの条件によって選択的に除去し、アルデヒドとした後、酸化を経てカルボン酸 **3-51a** へと誘導した。得られた化合物に対し、TBAF を作用させたところ、2 つの TBS 基の除去と生じた C17 アルコキシドの C18 トシルオキシ基への S_N2 反応が進行した。その結果エポキシドが形成され、(12*R*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1a**) を合成することができた。

Scheme 3-27. Total synthesis of 12-hydroxy-17,18-EpETE **3-1a**



HPLC にて分取精製を行い、比較的純粋な (12*R*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1a**) を単離し、^{13}C NMR を測定した。δ_{C17} 58.0 ppm, δ_{C18} 59.8 ppm のピークよりエポキシドの生成を確認した (Figure 3-1)。また、副生成物を含むピークの NMR 解析を行い、副生成物のうちの 1 つは C14,15 位の *Z*-アルケンが *E*-アルケンへと異性化した **3-52** と推定した。

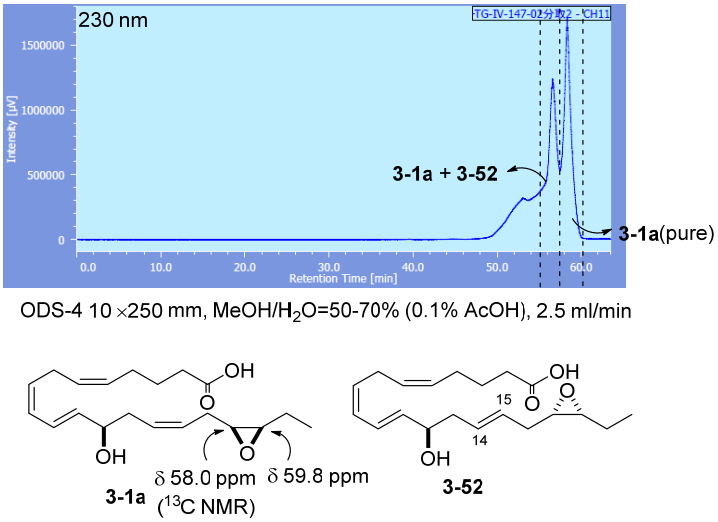
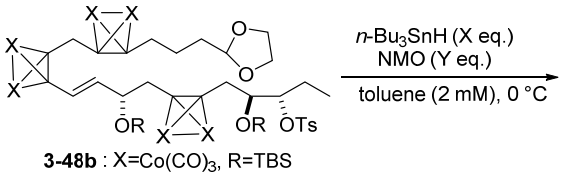


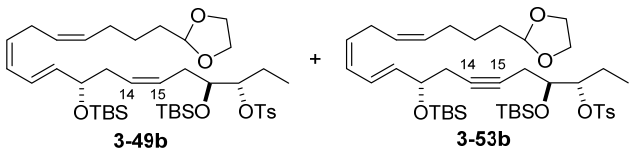
Figure 3-1. HPLC chart of impure 12-hydroxy-17,18-EpETE

副生成物は還元的脱コバルト化反応の際に生成したことから、この反応の反応条件や後処理法を見直すこととした (Table 3-9)。この検討は、トリスアルキン-コバルト錯体 **3-49b** を用いて検討を行った。Scheme 3-27 中の反応では、反応終了後、反応溶液を直接シリカゲルカラムにチャージして精製を行ったため、カラム上で反応液が濃縮された状態であった。そのため、反応系中で発生すると考えられるコバルトヒドリド種が副反応を促進した可能性がある。このため、フッ化カリウム水溶液で反応を停止させた後、分液操作を行うことで、コバルト種由来の夾雑物を除く後処理へと変更したところ、アルケンの異性化は確認されなかった (entry 1)。この結果を受け、試薬の当量を減らし、円滑に反応が進行するか検討した。entry1 では、3 つのアルキン-コバルト錯体を還元するのに 45 当量の水素化トリブチルスズを用いた。これに対し、entry 2 では 15 当量の水素化トリブチルスズを用いて反応を行ったところ、1 時間半で原料が消失した。しかし、生成物は目的物の **3-49b** と C14-15 位アルキンが残った **3-53b** との混合物であった。以上の結果から、①目的物の **3-49b** を選択的に得るためには大過剰の試薬が必要であること、②3 つのアルキン-コバルト錯体部位を一度に還元すると目的物が低収率で得られた、という問題点を解決できないため、この方法での還元を断念した。

Table 3-9. Reductive decomplexation of tris alkyne-cobalt complex



3-48b : X=$Co(CO)_3$, R=TBS



3-49b **3-53b**

entry	X	Y	time (h)	yield
1 [a]	up to 45	up to 30	3.5	**3-49b** : <40%[b]
2 [a]	15	10	1.5	**3-49b** and **3-53b** : <68%[b]

[a] Reduction was quenched with sat. KF aq., then extracted Et_2O/hexane

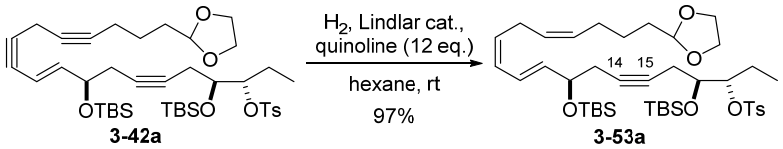
[b] The ratio of **3-49b** and **3-53b** could not be determined due to the impure mixture.

3-9. Lindlar 還元と磯部還元を用いた 12-hydroxy-17,18-EpETE の全合成

3-9-1. Lindlar 還元と磯部還元を用いたトリインの部分還元

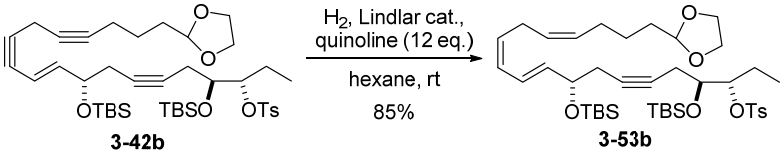
トリスアルキン-コバルト錯体の還元が困難であったため、トリイン **3-42** に対し、Lindlar 還元による部分還元を試みた。トリイン **3-42a** を用いて、注意深く反応追跡を行った結果、モノイン **3-53a** を高収率で単離した (Scheme 3-28)。これは、C14-15 アルキンは、C12,17 位の 2 つの TBS エーテルによって立体的に遮蔽されており、反応性が低いことが原因であると考えた。**3-53a** をさらに Lindlar 還元の条件に付した場合は、C14-15 アルキンに優先して分子内に複数存在するアルケンの還元が起こった。

Scheme 3-28. Lindlar reduction of triyne **3-42a**



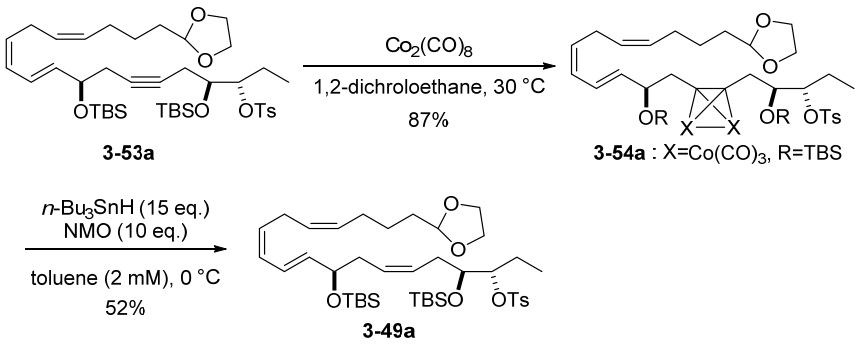
3-42a のジアステレオマーである **3-42b** に対しても Lindlar 還元を試みたところ、再現性良く目的物のモノイン **3-53b** を高収率で単離することに成功した (Scheme 3-29)。

Scheme 3-29. Lindlar reduction of triyne **3-42b**



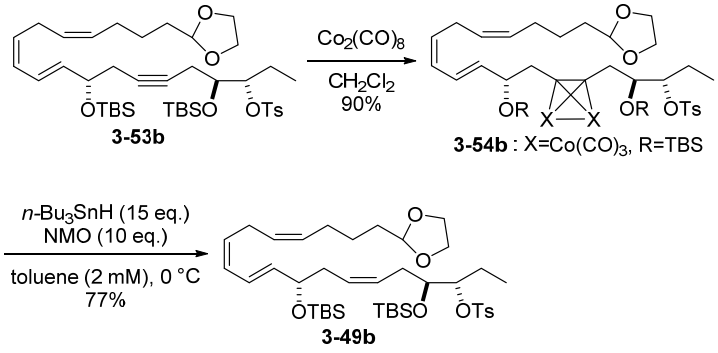
得られたモノイン **3-53a** をアルキン-コバルト錯体へと誘導し、改良磯部還元に付した (Scheme 3-30)。15 当量の水素化トリブチルスズと 10 当量の NMO を 0 度で作用させた後、反応をフッ化カリウム水溶液で停止させたところ、目的のテトラエン **3-49a** を、単一の生成物として 52%で得た。

Scheme 3-30. Chemoselective reduction of C14-15 alkyne to *Z*-alkene by modified Isobe reduction



3-50a のジアステレオマーである **3-49b** についても同様に合成した (Scheme3-31)。

Scheme 3-31. Synthesis of tetraene **3-49b**

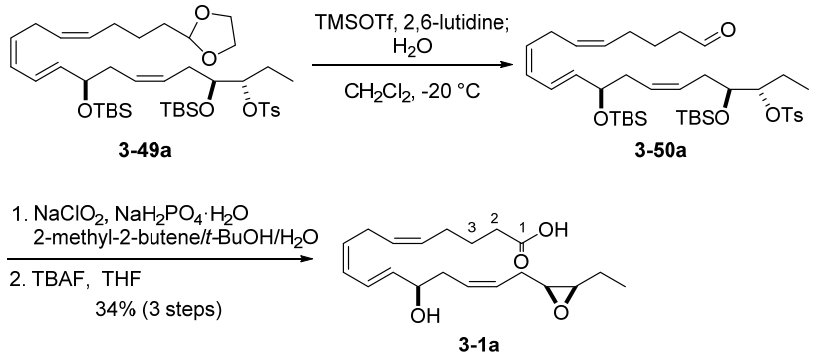


以上の検討結果より、トリインの部分還元において、アルキン-コバルト錯体の還元的脱コバルト化反応、Lindlar 還元をそれぞれ単独で用いた場合は、選択的にテトラエン **3-49** を得られないものの、これらを組み合わせて用いることで、目的物を単一の生成物として得ることに成功した。

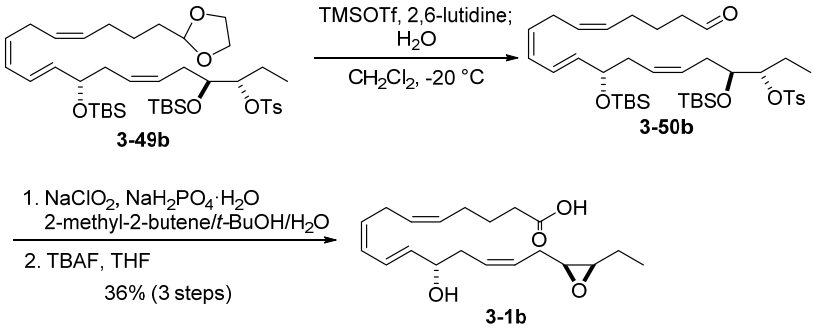
3-9-2. (12*R*)-hydroxy-(17*S*,18*R*)- および (12*S*)-hydroxy-(17*S*,18*R*)-EpETE の合成

3-9-1 でテトラエン **3-49** が得られたので、三段階の変換を経て(12*R*)-hydroxy-(17*S*,18*R*)- および (12*S*)-hydroxy-(17*S*,18*R*)-EpETE を合成した (Scheme 3-32, 3-33)。**3-49** に対して、藤岡らの手法により TBS 基を残したままアセタールを除去し、アルデヒド **3-50** を得た。続いて Pinnick 酸化と、TBAF によるシリル基の除去と C17 アルコキシドの C18 トシルオキシ基に対する S_N2 反応によりエポキシドを構築し、**3-1a** および **3-1b** の合成をそれぞれ達成した。**3-1a** に対して、種々NMR 測定を行ったが、14,20-diHDHA と同様に、C1-3 位の ^{13}C NMR ピークは観測されなかった。このため、アルデヒド **3-50a** に誘導した段階で ^{13}C NMR の測定を行い、全ての炭素が存在することを確認した。

Scheme 3-32. Total synthesis of (12*R*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1a**)



Scheme 3-33. Total synthesis of (12*S*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1b**)



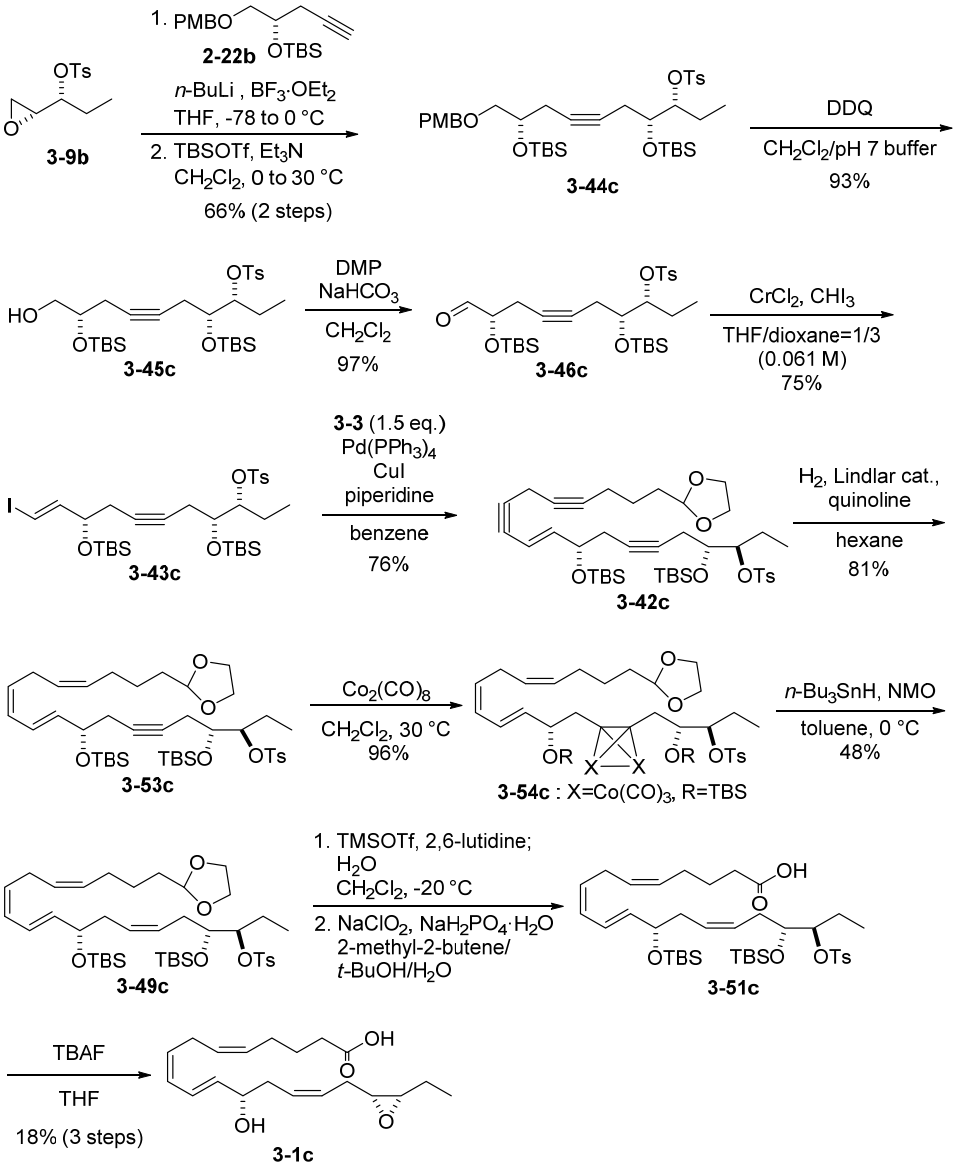
3-10. (12*S*)-hydroxy-(17*R*,18*S*)- および (12*R*)-hydroxy-(17*R*,18*S*)-EpETE の合成

3-9 までの検討結果を基に、(12*R*)-hydroxy-(17*S*,18*R*)- および (12*S*)-hydroxy-(17*S*,18*R*)-EpETE のエナンチオマーである (12*S*)-hydroxy-(17*R*,18*S*)- および (12*R*)-hydroxy-(17*R*,18*S*)-EpETE を C16-20 フラグメント **3-9b** から合成した。

3-10-1. (12*S*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**)の合成

求核付加反応に C16-20 フラグメント **3-9b** および C11-15 フラグメント **3-22b** を用い、3-9 と同様に合成した (Scheme 3-34)。還元的脱コバルト化反応のカラムクロマトグラフィーの生成の際にヘキサンを用いると、濃縮後、減圧乾燥してもヘキサンが除けなかった。そこで、化合物データを収集する際、再度酢酸エチル/ペンタンで精製を行ったところ、テトラエン **3-49c** が化学的に不安定であるため、一部カラム中で分解することが判明した。そのため、**3-49c** の収率は若干低下した。3-9 での合成において (12*R*)-hydroxy-(17*S*,18*R*)- および (12*S*)-hydroxy-(17*S*,18*R*)-EpETE の C1-3 位に相当する ^{13}C NMR のピークが観測されなかったため、今回はカルボン酸 **3-51c** に誘導したところで、^{13}C NMR を測定した。その結果、カルボン酸 **3-51c** については、全ての炭素に相当するピークを確認した。

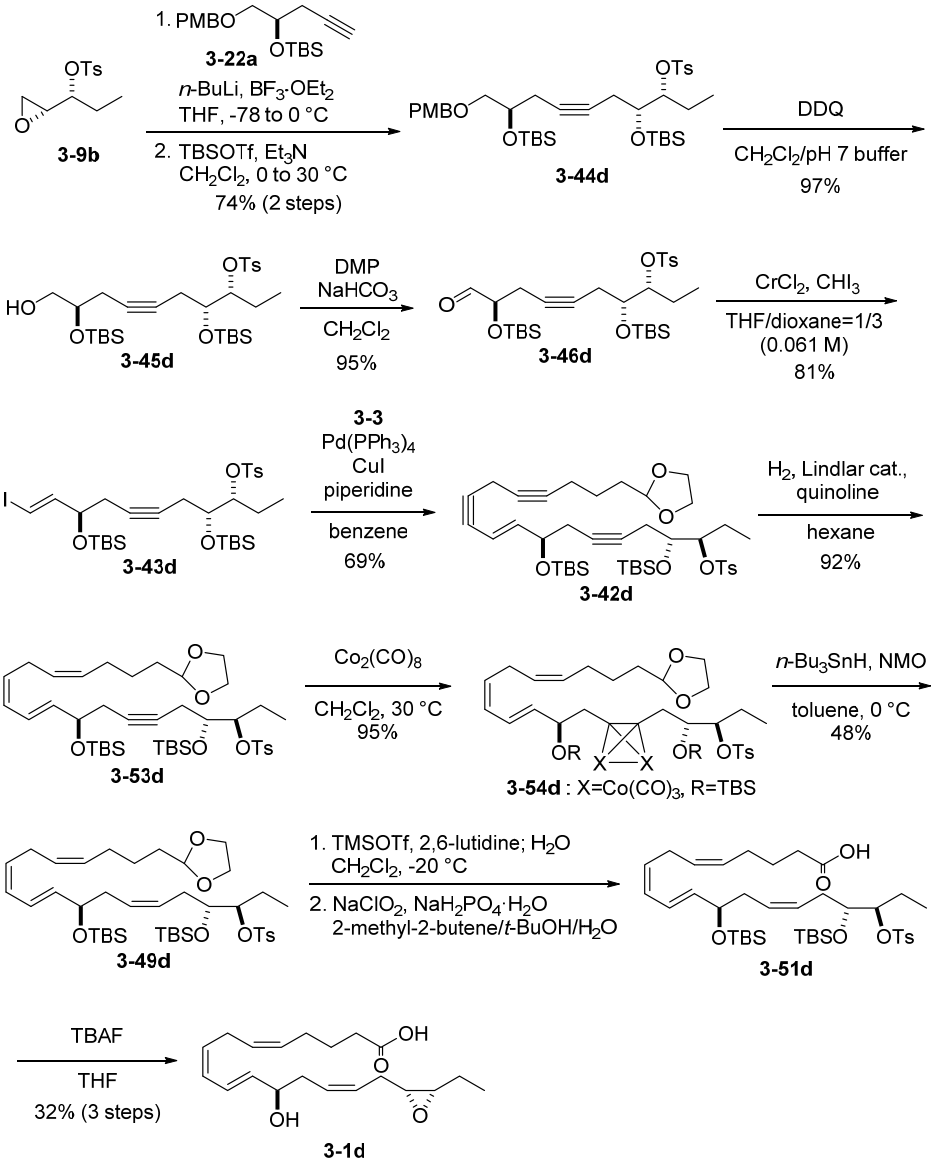
Scheme 3-34. Total synthesis of (12*S*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**)



3-10-2.　(12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1d**)の合成

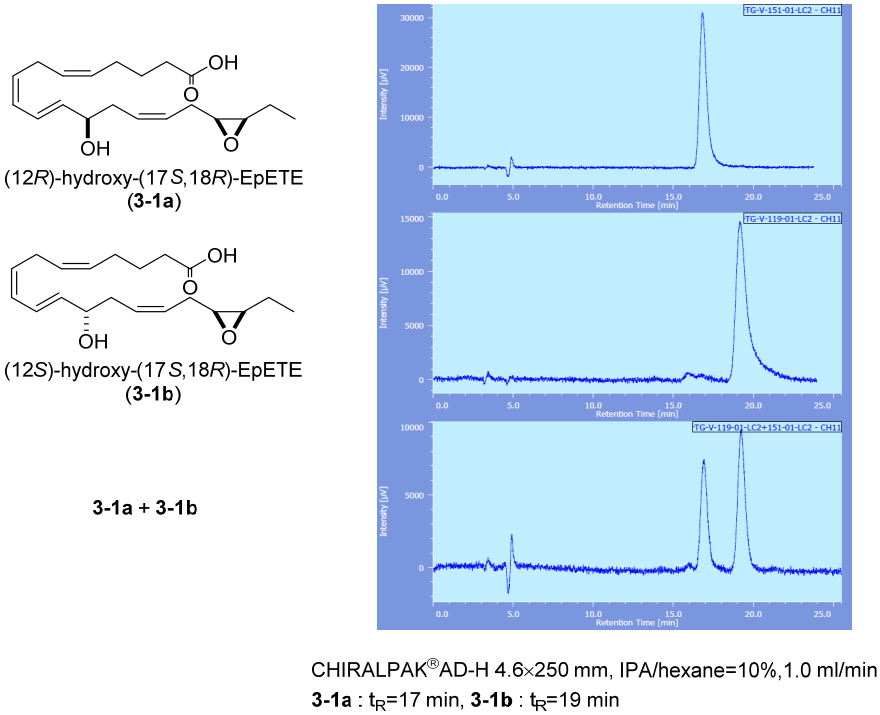
3-10-1 と同様に、(12*R*)-hydroxy-(17*R*,18*S*)-EpETE の合成を行った (Scheme 3-35)。本化合物の合成においても、カルボン酸 **3-51d** の ^{13}C NMR を測定し、全ての炭素に相当するピークを確認した。

Scheme 3-35.　Total synthesis of (12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1d**)



3-11. 12-hydroxy-17,18EpETE のジアステレオマーの HPLC 分析

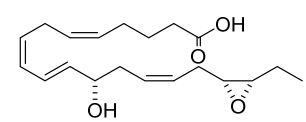
14,20-diHDHA の場合と同様、合成した 4 種立体異性体において、^{1}H および ^{13}C NMR がジアステレオマー間で一致した。そこで、天然物との比較を可能にするため、HPLC 分析による区別化を試みた。逆相、順相の種々のカラムを用いてジアステレオマーを分析したが、ピークが分離することはなかった。そこで、順相のキラルカラムを用いて分析を行ったところ、CHIRALPAK® AD-H で移動相が IPA/hexane=10%の場合にジアステレオマーが分離することを見出した (Figure 3-2)。



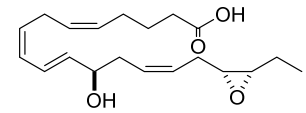
CHIRALPAK®AD-H 4.6×250 mm, IPA/hexane=10%,1.0 ml/min
3-1a : t_R=17 min, **3-1b** : t_R=19 min

Figure 3-2. HPLC analysis of **3-1a** and **3-1b**

合成した (12*S*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**), (12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1d**) についても同様にキラルカラムにより分析を行った (Figure 3-3)。その結果、Figure 3-2 と同様の条件で二種のジアステレオマーは分離した。

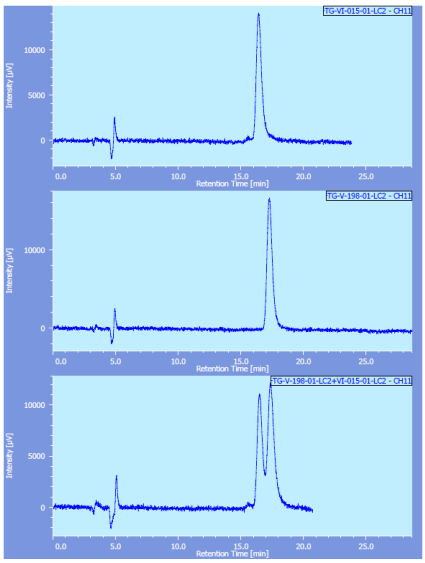


(12*S*)-hydroxy-(17*R*,18*S*)-EpETE
(**3-1c**)



(12*R*)-hydroxy-(17*R*,18*S*)-EpETE
(**3-1d**)

3-1c + **3-1d**



CHIRALPAK®AD-H 4.6×250 mm, IPA/Hex=10%;
3-1c : t_R=16 min, **3-1d** : t_R=18 min

Figure 3-3. HPLC analysis of **3-1c** and **3-1d**

二種のジアステレオマー間で保持時間が異なることを確認したので、4 種のジアステレオマーを混合して分析した (Figure 3-4)。その結果 3 つのピークが確認できた。(12*R*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1a**) とエナンチオマーの (12*S*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**) でピークが重複したが、これらは CD スペクトルを測定することで、区別が可能なため、以上の分析と併せて、4 種のジアステレオマーの絶対立体配置を区別することができた[15]。

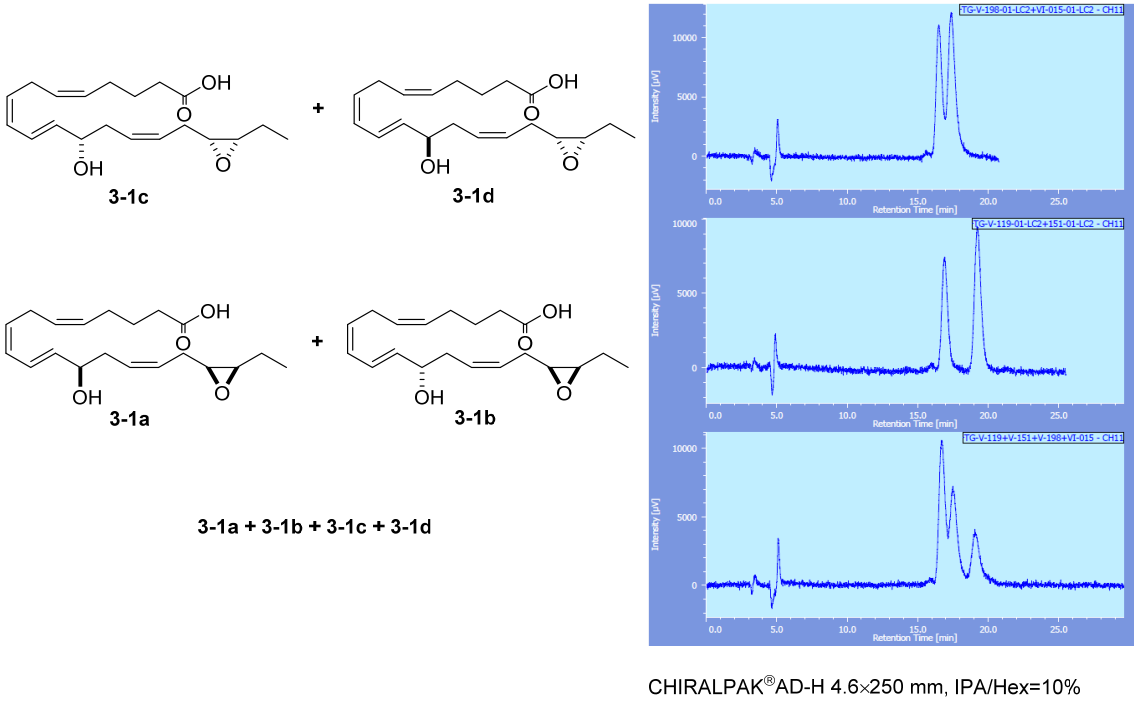


Figure 3-4. HPLC analysis of 4 isomers of 12-hydroxy-17,18-EpETE

3-12. 注釈および参考文献

(1) Balas, L.; Durand, T.; Saha, S.; Johnson, I.; Mukhopadhyay, S. *J. Med. Chem.* **2009**, *52*, 1005-1017.

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

(3) (a) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.*, **1996**, *37*, 6145-6148. (b) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373-1385.

(4) (a) Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.*, **1983**, *31*, 1612-1624. (b) Sun, C.; Bittman, R. *J. Org. Chem.*, **2004**, *69*, 7694-7699.

(5) Gerspacher, M.; Rapoport, H. *J. Org. Chem.*, **1991**, *56*, 3700-3706.

(6) (a) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.;Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.*, **2002**, *124*, 12078-12079. (b) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268-3274.(c) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677-683.

(7) Zhang, Z.-B.; Wang, Z.-M.; Wang, Y.-X.; Liu, H.-Q.; Lei, G.-X.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 837-840.

(8) Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Tetrahedron* **2012**, *68*, 3210-3219.

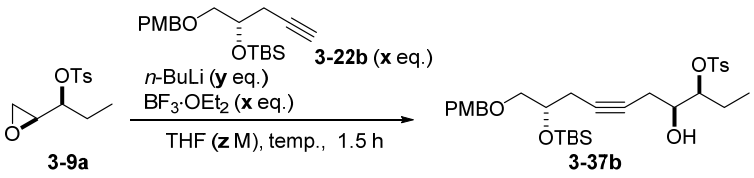
(9) Kelly, A. M.; Pérez-Fuertes, Y.; Fossy, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nature protocols* **2008**, *3*, 215-219.

(10) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.*, **2011**, *133*, 17634-17637.

(11) De Silva, E. C. A.; Silk, P. J.; Mayo, P.; Hillier, N. K.; Magee, D.; Cutler, G. C. *J. Chem. Ecol.* **2013**, *39*, 1169-1181.

(12) 本反応の反応条件は (12*S*)-C11-15 アルキン **3-22b** を用いて検討を行った (Table 3-10)。求核置換反応を、30 mM で行ったところ、**3-37b** の収率はわずか 5.5%であった (entry 1)。これは基質の濃度が薄いことが原因であると考え、濃度を 0.2 M とした (entry 2)。その結果、収率は 53%と飛躍的に向上した。entry1, 2 では、アルキニドの調製時に温度を 0 度まで昇温していたが、entry 3 では-78 度でアルキニドを調製し、**3-22b** の当量も減らした。その結果、**3-37b** の収率は低下してしまった。entry 4 では、entry3 と同様の条件で、反応系中の濃度を 0.5 M にしたが、収率に大きな改善はみられなかった。entry3, 4 の結果より、アセチリドの調製は-78 度で行っても反応系中の TLC は entry1, 2 と同様帯状になること、アセチリドの当量を減らすと系の濃度を濃くしても収率が低下することがわかったため、entry 5 ではアセチリドは 0 度まで昇温して調製し、アセチリドをエポキシドに対し 2.4 当量用いたところ、**3-37b** は 51%で得られた。entry5 の条件を用いると再現性が得られるため、この条件を最適条件として設定した。

Table 3-10. Nucleophilic addition of **3-22b** to **3-9a**



entry	x	y	z	temp.	**3-37b**
1 [a]	2	2.2	0.03	-78 °C to rt	5.5% (containing rac-**3-9a**)
2 [a]	2	2	0.2	-78 °C	<53% (containing rac-**3-9a**)
3 [b]	1.4	1.5	0.2	-78 to 0 °C	38%
4 [b]	1.4	1.5	0.5	-78 to 0 °C	<43% (containing **3-9a**)
5	2.4	2.6	0.2	-78 to 0 °C	<51% (containing **3-9a**)

[a] *Rac*-**3-9a** and **3-22b** were used.
[b] Alkynide was prepared at -78 °C. In other entries, alkynide was prepared at -78 to 0 °C.

(13) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513.

(14) Phoenix, S.; Reddy, M. S.; Deslongchamps, P. *J. Am. Chem. Soc.*, **2008**, *130*, 13989-13995.

(15) 合成した 4 種立体異性体は、有田らによって以下の逆相 HPLC の条件で分離した。(column: CHIRALPAK AD-3R, 4.6 mm x 150 mm, eluent: 50% CH_3CN/MeOH (4/1) in 0.1 % aqueous AcOH for 5 min, 50-95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH over 22.5 min, and then 95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH for 8 min at 0.5 mL/min, retention times of the synthetic **3-1**: t_R = 19.0 min for **3-1a**, 22.3 min for **3-1b**, 25.9 min for **3-1c**, 19.4 min for **3-1d**, retention times of the natural **1**: t_R = 28.4 min for **3-1c**, 24.0 min for **3-1b**).

これら 4 種異性体を in vivo 抗炎症モデルである、ザイモザン A における好中球浸潤抑制活性試験が有田らによって行われた。Goto, T.; Urabe, D.; Isobe, Y.; Arita, M.; Inoue, M. *Tetrahedron* **2015**, *71*, 8320-8332. に報告された試験結果を Figure 3-5 に示した。ここでは、(12*R*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1a**) が **1bb**、および (12*S*)-hydroxy-(17*S*,18*R*)-EpETE (**3-1b**) が **1ab**、(12*S*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**) が **1aa**、(12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1c**) が **1ba** に相当する。天然物の **3-1c** は、他方の天然物 **3-1b** と比較して非常に強力な抗炎症活性を示し、さらに、非天然である **3-1d** は天然物の **3-1b** や非天然の **3-1a** よりも強い活性を示した。この結果から、強力な抗炎症活性の発現には、(17*R*,18*S*)-エポキシドの構造が重要である一方、C12 位ヒドロキシ基の立体化学は活性に影響しないことが明らかとなった。

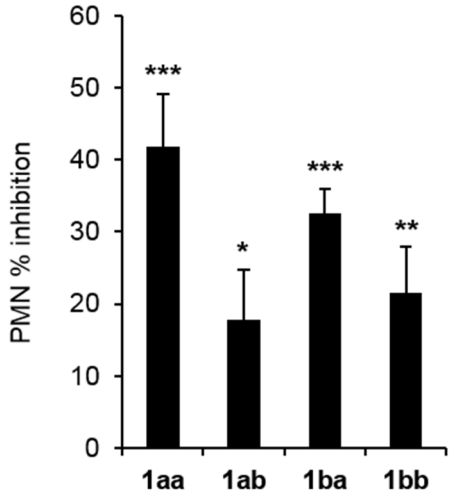


Figure 3-5. Bioassay of synthetic **3-1c**, **3-1b, 3-1d** and **3-1a**. The compounds (1 ng) were injected intravenously through the tail vein followed by peritoneal injection of zymosan A (1 mg/ mL). After 2 h, peritoneal lavages were collected, and the number of PMN leucocytes was counted. Values represent mean ± SE, n ≥3, **P* <0.05, ***P* <0.01, ****P* <0.001 versus vehicle control.

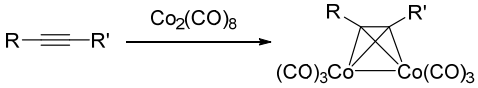
第 4 章

還元的脱コバルト化反応の条件最適化

4-1.　アルキン-コバルト錯体を用いた反応

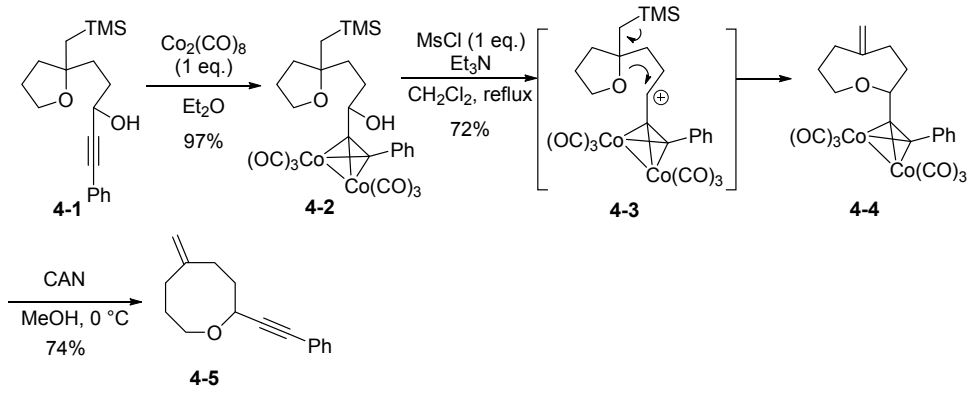
アルキンに対して $Co_2(CO)_8$ を作用させると速やかに 2 分子の一酸化炭素を失い、アルキンとジコバルトヘキサカルボニルの錯体を形成する (Scheme 4-1)。以下この錯体をアルキン-コバルト錯体と呼ぶ。

Scheme 4-1.　Formation of alkyne-dicobalt complex



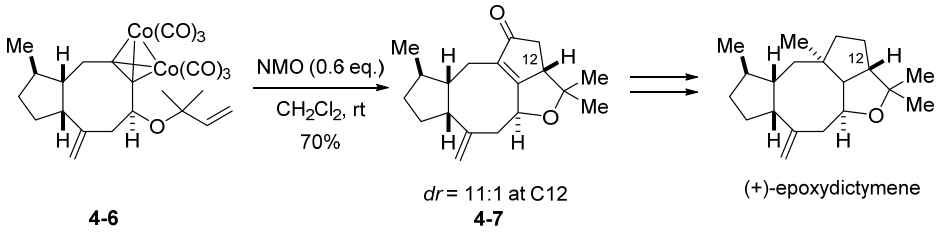
このアルキン-コバルト錯体は、穏和な条件下での酸化処理でアルキンへと再生するため、アルキンの保護基として使用されてきた[1]。また、アルキン-コバルト錯体の α 位のカルボカチオンが安定化されることを利用し、様々な求核剤との反応が報告されている。この反応は Nicholas 反応と呼ばれ、向井らによる oxocane の合成に適用されている[2] (Scheme 4-2)。アルキン-コバルト錯体の α 位のアルコールをメシル化すると、メシラートの脱離によりカチオンが生じた。その後、THF 環の酸素原子が求核反応し、oxocane を単一の生成物として与えた。

Scheme 4-2.　Synthesis of oxocane by Mukai *et al.*



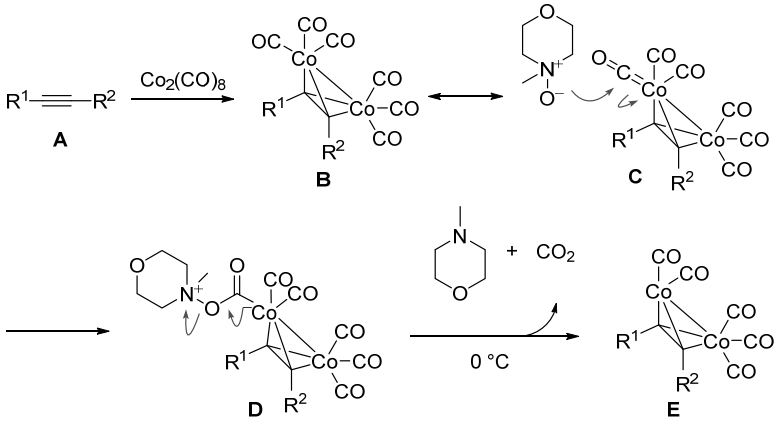
このほかアルキン-コバルト錯体を利用した反応に Pauson-Khand 反応がある[3]。本反応は、アルキン-コバルト錯体とアルケン、および一酸化炭素から[2+2+1]環化付加により置換シクロペンテノンに変換する反応である。アルキン-コバルト錯体にアルケンが配位した後、一酸化炭素の挿入と $Co_2(CO)_X$ の脱離を伴ってシクロペンテノンが生成する。本反応を利用し、シクロペンテノンモチーフを有する多様な天然物の全合成が行われているが、代表例として、S. L. Schreiber らによる (+)-epoxydictymene の合成が挙げられる[4] (Scheme 4-3)。

Scheme 4-3. Synthesis of (+)-epoxydictymene by S. L. Schreiber *et al.*



上記の反応で *N*-メチルモルホリン *N*-オキシド (NMO) が添加されているように、本反応は第三級アミンオキシドにより促進されることが報告されている[5]。Yoo らも同時期にアミンオキシドが Pauson-Khand 反応を促進することを報告した[6]。第三級アミンオキシドはアルキンが配位するコバルト原子上の一酸化炭素を酸化的に脱離させ、コバルト上に空の配位場を提供する役割を果たしていると考えられている (Scheme 4-4)。

Scheme 4-4. Suggested effect of NMO

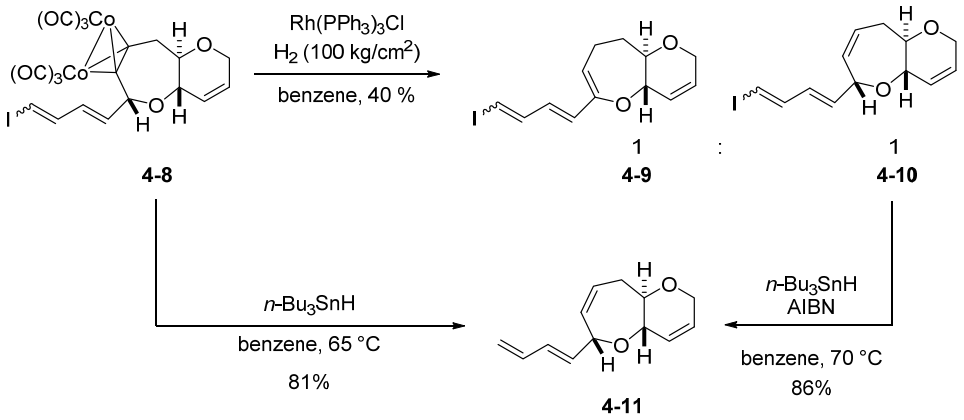


4-2. 還元的脱コバルト化反応
(アルキン-コバルト錯体の *Z*-アルケンへの還元反応)

アルキン-コバルト反応を用いた、還元的脱コバルト化反応により、*Z*-アルケンの合成が可能である。

磯部らは、1993 年にアルキン-コバルト錯体に対して、Wilkinson 触媒を用いた高圧水素添加反応を行うと、アルケンが導入された環状エーテルが得られることを報告した[7]。すなわち **4-8** に対して、Wilkinson 触媒を用いた高圧水素添加反応を試みたところ、アルケンを含む環状エーテル **4-9** と **4-10** をおよそ 1:1 の生成比で得た[8]。望みの化合物 **4-10** はその後、水素化トリブチルスズ、AIBN を用いたラジカル還元により、オレフィン **4-11** へと変換された。本合成経路では、アルキン-コバルト錯体の還元的脱コバルト化反応を選択的に進行させるものの、オレフィンの異性化が問題となっていた。しかし、種々検討の結果、アルキン-コバルト錯体 **4-8** に対し、加熱条件下水素化トリブチルスズを作用させると化合物 **4-11** が高収率で得られることを見出した (Scheme 4-5)。

Scheme 4-5. Reductive decomplexation of alkyne-dicobalt complex by Isobe *et al.*



磯部らによる様々な検討から水素化トリブチルスズを用いた還元的脱コバルト化の一般性は以下のようにまとめられる。

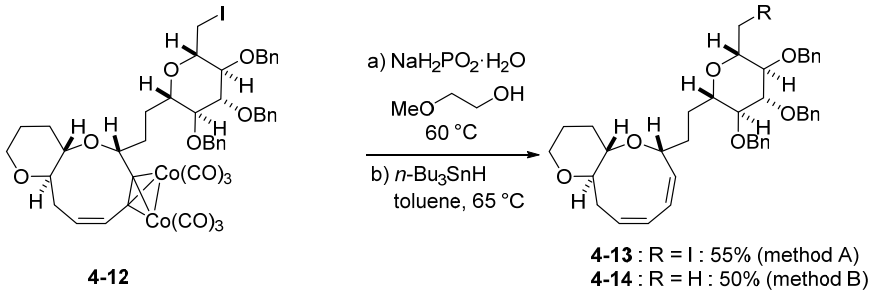
1. 無保護のヒドロキシ基は還元的脱コバルト化反応を阻害しない。
2. 末端アルキン、二置換アルキンいずれも反応は進行する。
3. 二置換アルキンは、*Z*-アルケンに変換される。

本反応は、ラジカル捕捉剤 galvinoxyl によって阻害されることから、ラジカル機構であると推定されている。しかし、AIBN のようなラジカル開始剤を必要としないため、アルキン-コバルト錯体自身、あるいは系中に存在する酸素がその役割を果たしていると考えられている。

また、還元剤は水素化トリブチルスズの他、無機塩の次亜リン酸ナトリウムも適用できることが明らかにされている[9] (Scheme 4-6)。次亜リン酸ナトリウムを用いた場合

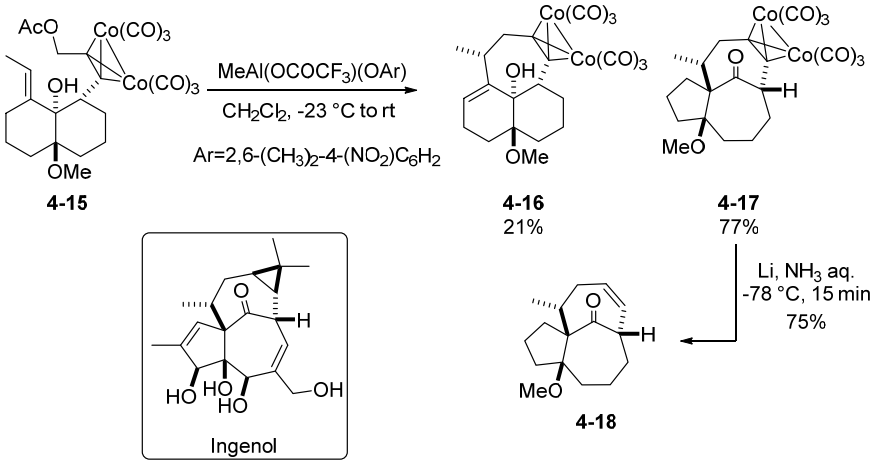
も水素化トリブチルスズとほぼ同様の反応性で、アルキン-コバルト錯体を Z-アルケンに変換できることが示された。一方で、水素化トリブチルスズを用いた場合は基質のアルキルヨウ素は還元されるものの、次亜リン酸ナトリウムを用いた場合は、それらは還元されない。また、本反応には還元剤が過剰 (10-12 当量) に必要となるため、毒性の高い水素化トリブチルスズに対し、次亜リン酸ナトリウムを使用できるメリットは大きいといえる。

Scheme 4-6. Comparison of NaH_2PO_2 and *n*-Bu_3SnH in reductive decomoplexation



一方で、谷野らは全く異なる方法によりアルキン-コバルト錯体からアルケンを得ている。1997 年に Ingenol の全合成においてアルキン-コバルト錯体を用いた分子内 Nicholas 反応により 5-7-7 員環の特異なインサイド-アウトサイド骨格を形成した後、環化後のアルキン-コバルト錯体に対し Birch 還元の条件を適用し、環内にオレフィンを導入している[10] (Scheme 4-7)。

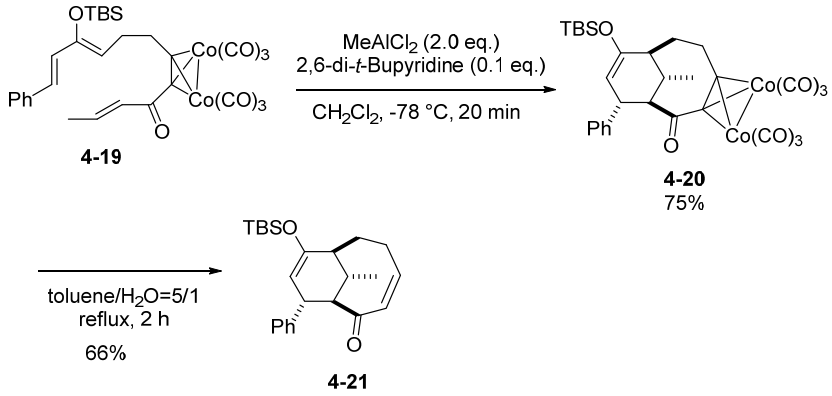
Scheme 4-7. Reductive decomplexation under Birch conditions



岩澤らは、アルキン-コバルト錯体を加熱のみで還元できることを報告した (Scheme 4-8)[11]。基質の **4-19** に対し、ルイス酸の $MeAlCl_2$ を用いてジクロロメタン中室温で反応させて得られた、ビシクロ[5.3.1]化合物 **4-20** を、水/トルエン中加熱還流を行ったところ、還元反応が進行したエノン **4-21** が得られた。本反応は中員環アルキン-コバルト錯体に対して

一般的な反応であることが知られており、アルキン-コバルト錯体の分解時に生成するコバルトヒドリド HCo(CO)x が還元剤として機能していると考えられている[12]。

Scheme 4-8. Decomplexation under the heating conditions

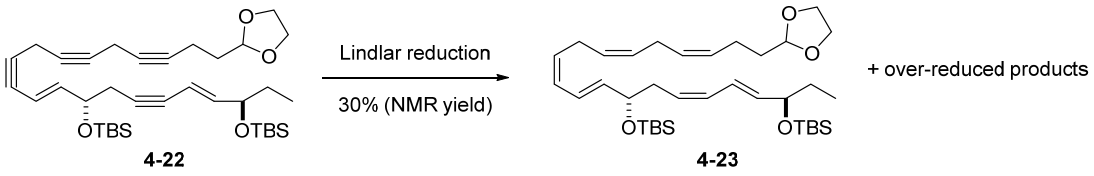


アルキンからアルキン-コバルト錯体を経て、Z-アルケンを得ることができる一方で、アルキンの Z-アルケンへの還元反応は Lindlar 還元[13]やジイミド還元[14]、P2-Ni[15]による還元などが知られている[16]。最近では佐治木らにより新たな不均一系触媒として Pd/PEI[17]が報告されている。また、共役エンインに対する部分還元には Zn(Cu/Ag)[18]が適用できることが報告されている。これらの中でも Lindlar 還元は良好な化学選択性と基質適用範囲の大きさから、アルキンの Z-アルケンへの部分還元の第一選択として広く用いられる手法である。そのため、アルキン-コバルト錯体を経由した段階的なアルキンから Z-アルケンへの変換はほとんど報告されていない。

4-3.　14,20-ジヒドロキシドコサヘキサエン酸の中間体への適用

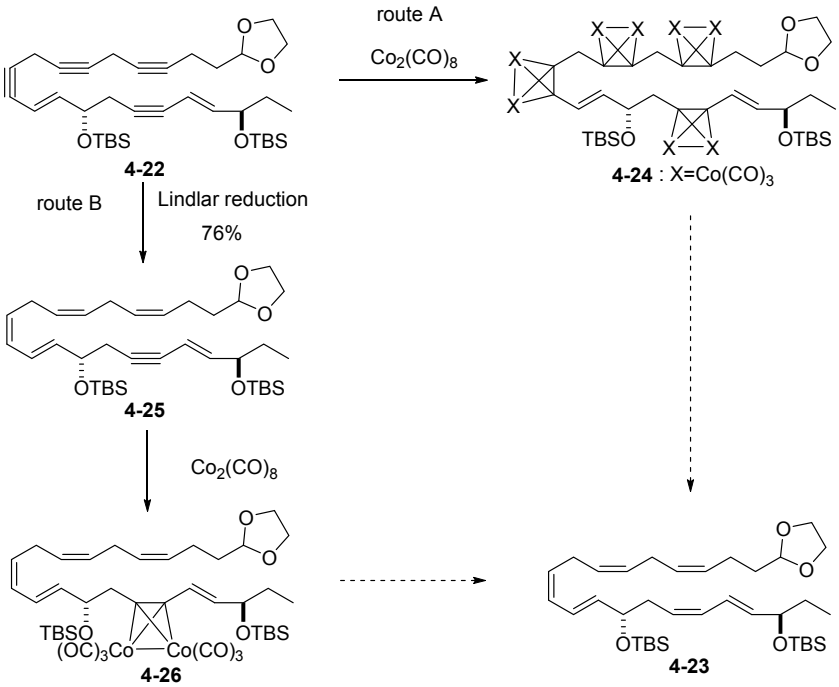
第 2 章で述べた通り、14,20-diHDHA の中間体であるテトライン **4-22** から、Lindlar 還元によりヘキサエン **4-23** へ収率良く変換することは困難であった (Scheme 4-9)。そこで、磯部らによって報告された還元的脱コバルト化反応の適用を試みた。

Scheme 4-9.　Transformation of tetrayne **4-22** to hexaene **4-23**



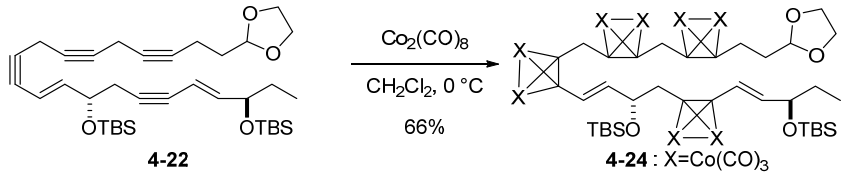
4-22 から **4-23** を得る合成経路として 2 つ立案した (Scheme 4-10)。テトライン **4-22** を出発原料として、テトラキスアルキン-コバルト錯体 **4-24** の還元的脱コバルト化反応を適用する経路 A、あるいは **4-22** を Lindlar 還元によりペンタエン **4-25** とし、アルキン-コバルト錯体 **4-26** に対し、還元的脱コバルト化反応を用いヘキサエン **4-23** を得る経路 B の二通りである。まずは経路 A のテトラキスアルキン-コバルト錯体の還元を試みた。

Scheme 4-10.　Two possible routes to synthesis hexaene **4-23**



テトライン **4-22** に対して、$Co_2(CO)_8$ を過剰量作用させると、速やかにテトラキスアルキン-コバルト錯体 **4-24** が生成した (Scheme 4-11)。

Scheme 4-11. Synthesis of tetrakis alkyne-dicobalt complex



4-22 **4-24** : X=Co(CO)$_3$

磯部らの文献例[17]を参考にテトラキスアルキン-コバルト錯体 **4-24** の還元的脱コバルト化反応を試みた (Table 4-1)。水素化トリブチルスズを還元剤に用いた場合は、原料は消失するものの、目的物は得られず、構造不明の 3 つの化合物が得られるのみだった (entry 1)。また、次亜リン酸ナトリウムを還元剤として反応を行うと、基質の損壊がみられた (entry 2)。そこで、基質が損壊しない、より低温下で反応が行えないかと考えた。磯部らによって提案されている還元的脱コバルト化反応の反応機構を Scheme 4-12 に示した。アルキン-コバルト錯体を加熱することで、**B** の Co-Co 結合が均等開裂し、還元剤と反応する。その後水素原子が Co-C 結合に転位し、**H**, **I** が生じた後、還元的脱離により $Co_2(CO)_6$ の脱離を伴い、*Z*-アルケンが生成する。ここでは Co-Co 結合が均等開裂されるために熱が必要とされている。一方で、アルキン-コバルト錯体を加熱すると、一酸化炭素が脱離し、空の配位場が一つ生じると報告されている[19]。このことは、還元的脱コバルト化においても、熱は Co-Co 結合均等開裂よりも、一酸化炭素の脱離に必要であることを示唆する。このため、より低温で反応を行うには、熱に変わり反応を促進させる添加剤を利用すればよいと考えられる。4-1 で述べたように、アルキン-コバルト錯体を用いた反応には Pauson-Khand 反応が知られているが、この反応を促進させる添加剤が様々報告されている。そこで、還元的脱コバルト化反応においても、それらの添加剤を加えることでより低温での反応の進行を期待した。NMO を過剰量加え、水素化トリブチルスズを 60 当量加えた条件で反応を行ったところ、反応は室温で進行することがわかり、目的物のヘキサエンを過還元体との混合物として得た (entry 3)。添加剤を加えることで、より低温で反応が可能になったため、さらに低温の-15 度から 0 度の条件で反応を行ったところ、**4-23** の収率は 38%と 10%ほど上昇した (entry 4)。

続いて、還元剤を水素化トリフェニルスズに変えたが、**4-23** の収率は低下した (entry 5)。また、entry 6 では、トリストリメチルシリルシランを用いて反応を行ったが、**4-23** は全く得られなかった。これは、トリストリメチルシリルシランは水素化トリブチルスズと比較して、Si-H 結合の結合解離エネルギーが Sn-H 結合のそれより高いことが原因であると考える[20]。以上から、還元剤は水素化トリブチルスズが最適と判断した。

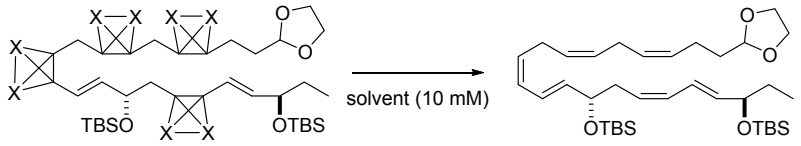
反応溶媒をトルエンからアセトニトリル、ジクロロメタン、メタノール/トルエンの混合溶媒、THF に変えて反応を行ったが、これらの場合は同等の収率か、顕著な低下がみ

られたため (entry 7~10)、トルエンを最適な反応溶媒とした。

上記の検討から還元剤は水素化トリブチルスズ、反応溶媒はトルエンとし、Pauson-Khand 反応において報告例のある添加剤を種々検討した (entry 11~17)。*n*-ブチルメチルチオエーテル[21]を用いた場合は、0 度で反応が進行しなかったため、80 度まで加熱したが、過還元体のみが得られた (entry 11)。続いて亜リン酸トリフェニル[22]を用いて反応を行ったが、加熱すると脱コバルト化反応が競合し、目的のヘキサエン **4-23** とテトライン **4-22** の混合物を与えた (entry 12)。トリフェニルホスフィン[23]を添加剤として用いると、ヘキサエンは得られるものの、7%と非常に低収率であった (entry 13)。NMO と同じアミンオキシドであるトリメチルアミン *N*-オキシド (TMANO) を用いた場合 (entry 14) と、DMSO[24]を用いた場合 (entry 15) は、entry 3 とほぼ同様の結果を与え、NMO と優位な差はないことがわかった。シクロヘキシルアミンを用いた場合は、目的物を 45%で与えるものの、ペンタエン以上に還元された化合物が得られた。

以上の結果から目的物 **4-23a** が生成する条件はいくつかあるものの、**4-23** と過剰に用いた還元剤との分離が困難であり、また分離不可能な過還元体を副生成物として与える結果となった。そのため、純粋なヘキサエン **4-23** を単離するには至らなかった。過還元体は、反応系中で生成すると考えられる $HCo(CO)_X$ によりヘキサエン **4-23** がさらに還元されて生成していると考察した。本反応系中での $HCo(CO)_X$ の存在は確認できていないが、磯部らはトリエチルシランと、還元的脱コバルト化により生じた $Co_2(CO)_6$ から、$HCo(CO)_3$ と $Et_3SiCo(CO)_3$ が生じる可能性を示唆している (Scheme 4-13)。$HCo(CO)_3$ は末端オレフィンの内部異性化や還元を引き起こす活性種であると推察されている。そのため、水素化トリブチルスズと $Co_2(CO)_6$ からも同様に $HCo(CO)_X$ が生じていると考えた。そこで、この $HCo(CO)_X$ を捕捉すると報告されているビス TMS アセチレン[25]を系に加えて反応を行ったが、過還元体の生成抑制には至らなかった (entry 17)。

Table 4-1. Investigation of reductive decomplexation of tetrakis alkyne-dicobalt complex



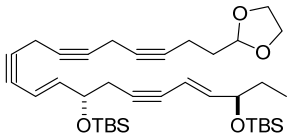
4-24 : X=$Co(CO)_3$ **4-23**

entry	reductant (eq.)	additive (eq.)	solvent	temp.	result [a]
1	*n*-Bu_3SnH (15)		benzene	65 °C	Over 3 products was detected by TLC. Neither **4-24**nor **4-23** weren't detected by ESI-MS.
2	$NaH_2PO_2 \cdot H_2O$ (32)		MeO⁄⁄OH	65 °C	decomp.
3	*n*-Bu_3SnH (up to 60)	NMO (large excess)	benzene	rt	<28%
4	*n*-Bu_3SnH (30)	NMO (large excess)	toluene	-15 to 0 °C	38%
5	Ph_3SnH (60)	NMO (large excess)	toluene	0 °C	27%
6	$(TMS)_3SiH$ (60)	NMO (large excess)	toluene	0 °C	0%
7	*n*-Bu_3SnH (60)	NMO (large excess)	MeCN	0 °C	11%
8	*n*-Bu_3SnH (60)	NMO (large excess)	CH_2Cl_2	0 °C	<30%
9	*n*-Bu_3SnH (60)	NMO (large excess)	toluene	0 °C	34%
10	*n*-Bu_3SnH (60)	NMO (large excess)	THF	0 °C	<3%
11	*n*-Bu_3SnH (60)	*n*-BuSMe (20 eq.)	toluene	0 to 80 °C	Only over-reduced products were obtained.
12	*n*-Bu_3SnH (60)	$P(OPh)_3$ (10 eq.)	toluene	0 to 80 °C	The mixture of **4-23** and decomplexation product **4-22** were obtained.
13	*n*-Bu_3SnH (60)	PPh_3 (20 eq.)	toluene	0 to 65 °C	7%
14	*n*-Bu_3SnH (up to 60)	TMANO (20 eq.)	toluene	0 °C	22%
15	*n*-Bu_3SnH (60)	DMSO (20 eq.)	toluene	0 to 80 °C	31%

[a] The yield was determined by ^1H NMR analysis after column chromatography

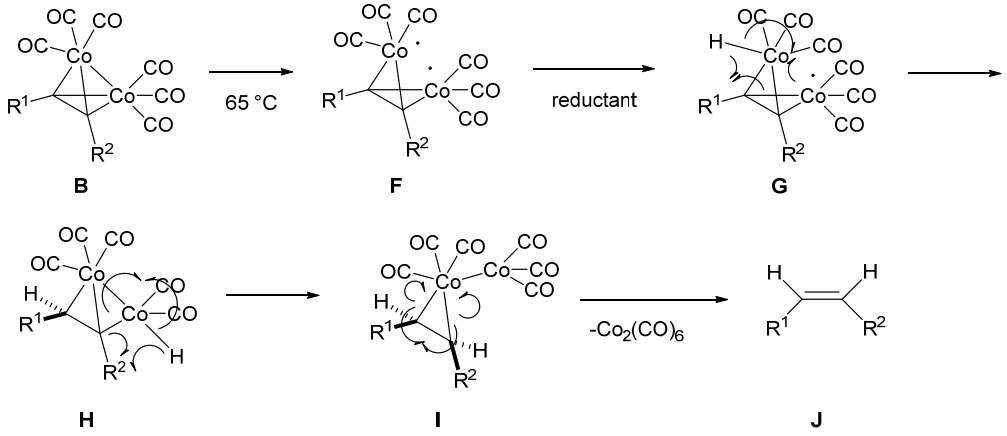
entry	reductant (eq.)	additive (eq.)	solvent	temp.	result [a]	
16	*n*-Bu_3SnH (60)	$CyNH_2$ (20 eq.)	toluene	0 to 80 °C	<45% over-reduced product(s)	39%
17 [b]	*n*-Bu_3SnH (60)	NMO (up to 45 eq.)	toluene	0 °C	48%	

[a] The yield was determined by ^1H NMR analysis after column chromatography.
[b] TMS—≡—TMS (up to 50 eq.) was added.

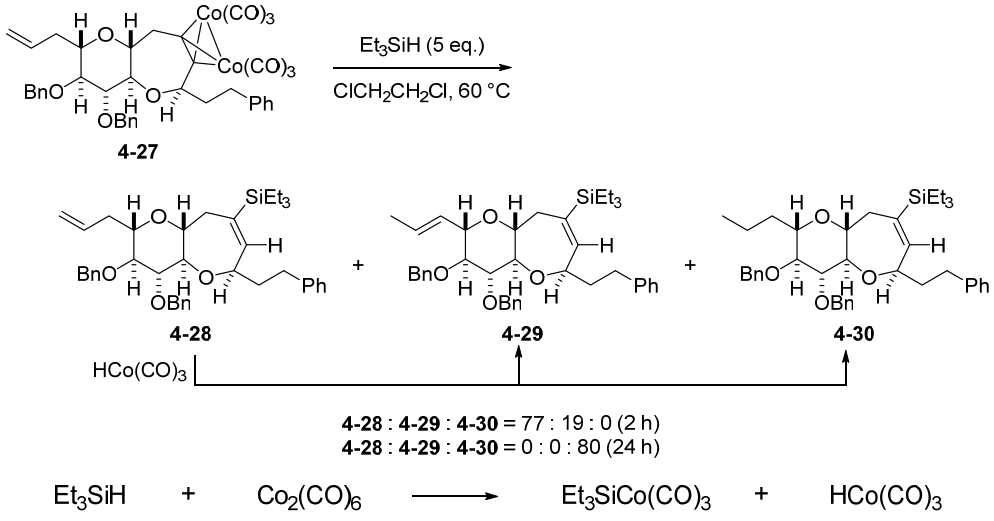


4-22

Scheme 4-12. Peoposed reaction mechanism by Isobe *et al*.

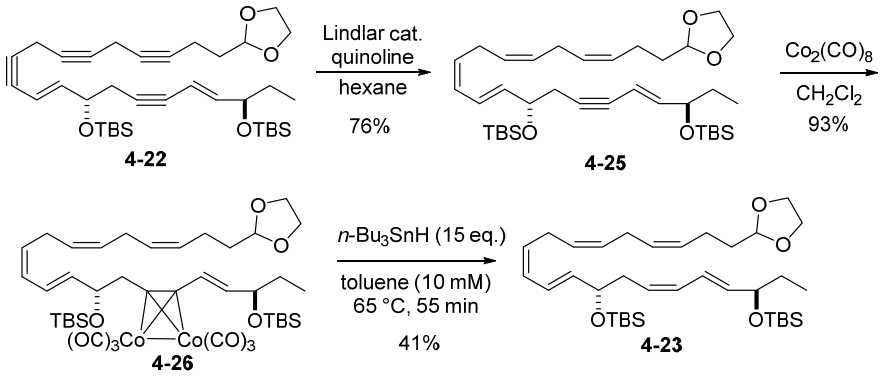


Scheme 4-13. Reported undesired reactions probably caused by $HCo(CO)_3$ species.



テトラキスアルキン-コバルト錯体 **4-24** は反応点が 4 つ存在し、TLC や MS での反応の追跡が困難であるため、反応の終点を見極めるのが困難であった。また系中に大量に生成するであろう HCo(CO)x による副反応が問題であった。そこで、**4-22** から Lindlar 還元によってペンタエンとした後、残るアルキンをアルキン-コバルト錯体 **4-26** へと変換した (経路 B, Scheme 4-10)。この二段階の変換は再現性、収率ともに良好であることがわかった。次いで、アルキン-コバルト錯体 **4-26** に対する還元の検討を行った。添加剤を使用しない熱的な条件で反応を行ったところ、目的物のヘキサエン **4-23** が 41%ながら得られることがわかった (Scheme 4-14)。一方で、その他は基質の分解が競合した。これは前述の検討の結果からも、反応温度が高いことが原因と考えられる。

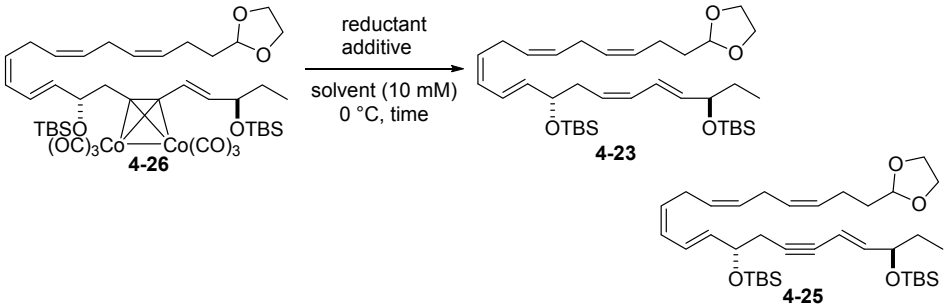
Scheme 4-14. Application of the original condition of reductive decomplexation to **4-26**



そこで Table 4-1 と同様に、添加剤を用いた、より低温での還元的脱コバルト化反応の検討を行った (Table 4-2)。entry 1, 2 では、ホスフィンオキシド、ホスフィンスルフィド[26]をそれぞれ添加剤として用いたが、反応の進行は遅く、ほぼ定量的に原料を回収した。entry 3 で NMO を添加剤として用いると、0 度で反応は円滑に進行し、目的物を 84%と高収率で得た。同じくアミン-オキシドである TMANO を添加した場合も、同様の結果を与えた (entry 4)。*N*-オキシドの種類によって反応に与える影響はさほどないため、より安価な NMO を用いて、還元剤の検討を行った。次亜リン酸ナトリウムを還元剤に用いて、NMO 存在下、反応を行ったところ、0 度で反応が進行し、目的物 **4-23** を与えた (entry 5)。しかし、脱コバルト化反応が進行した **4-25** も同時に生成した。これは、水素化トリブチルスズに比べて、次亜リン酸ナトリウムの還元力が弱いためであると考えた[27]。トリストリメチルシリルシランは前述したとおり、Si-H 結合の結合解離エネルギーが Sn-H 結合よりも高い。このため、還元的脱コバルト化反応に用いると、目的物の収率は著しく低下した (entry 6)。また、反応性の低さからか **4-25** も副生し、その他ヒドロシリル化が進行した副生成物も確認した[28]。水素化トリフェニルスズは水素化トリブチルスズと同様の反応促進効果を示し、目的物が 94%で得られた (entry 7)。しかし、還元剤を過剰量使用する本反応には、より安価な水素化トリブチルスズを用いるのが妥当と考え、さらに試薬の当量を検討した。水素化トリブチルスズ (3 当量), NMO

(2 当量)という entry 8 の条件では反応速度が低下してしまい、反応時間が 6.5 時間で、目的物の収率は 58%であった。しかし、水素化トリブチルスズ (7.5 当量), NMO (5 当量)を用いた場合は、ヘキサエン **4-23** が 81%と良好な収率で得られた (entry 9)。以上の検討より 0 度で本反応を行う際は、水素化トリブチルスズが 7.5 当量以上、NMO が 5 当量以上が必要であると判断した[29]。

Table 4-2. Optimization of reductive decomplexation to alkyne-dicobalt complex **4-26**



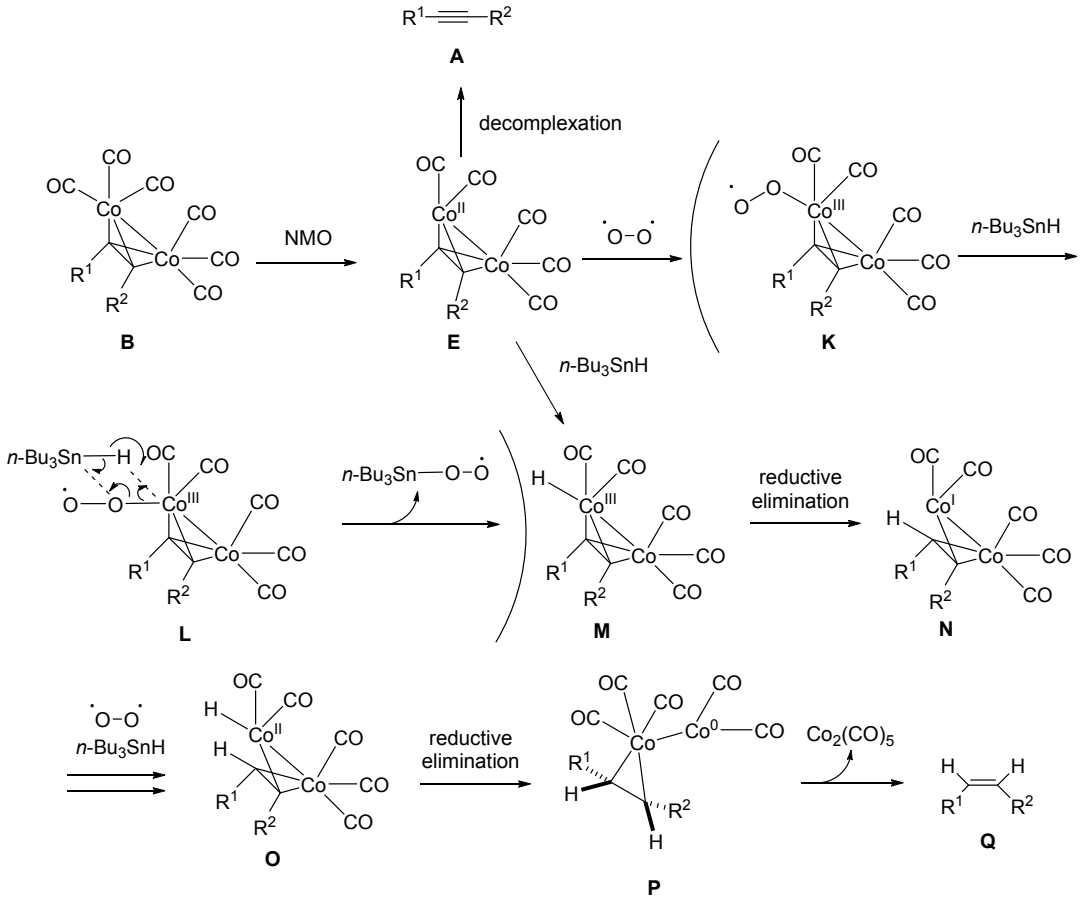
entry	reductant (eq.)	additive (eq.)	solvent	time	result		
					4-23	**4-26**	**4-25**
1	*n*-Bu_3SnH (15)	O=PPh_3 (10)	toluene	5 h	14%[b]	81%[b]	
2	*n*-Bu_3SnH (15)	S=PPh_3 (10)	toluene	5 h	9%[b]	89%[b]	
3	*n*-Bu_3SnH (15)	NMO (10)	toluene	50 min	84%[a]		
4	*n*-Bu_3SnH (15)	TMANO (10)	toluene	35 min	84%[a]		
5	$NaH_2PO_2·H_2O$ (15)	NMO (10)	MeO⟋⟍OH	6 h	48%[b]		17%[b]
6	$(TMS)_3SiH$ (15)	NMO (10)	toluene	2 h	18%[c]		3.5%[c]
7	Ph_3SnH (15)	NMO (10)	toluene	2 h	94%[a]		
8	*n*-Bu_3SnH (3)	NMO (2)	toluene	6.5 h	58%[b]	19%[b]	
9	*n*-Bu_3SnH (7.5)	NMO (5)	toluene	2.5 h	81%[a]		

[a] Isolated yield
[b] The yield was calculated from ^1H NMR of a mixture of **4-26**, **4-23** and **4-25** due to their inseparable nature.
[c] The yield was calculated from ^1H NMR of a mixture of **4-23**, **4-25** and hydrosilylated product due to their inseparable nature.

アミンオキシドの効果は、これまで報告されているように、コバルト原子上に空の配位場を生成するために機能していると考えられる (Scheme 4-4)。そこに還元剤が作用し、還元的脱コバルト化反応が進行すると考えられる。しかし、還元速度が遅い、または立体的な要因で還元剤が基質に近づきにくい場合、脱コバルト化反応が進行し、entry 5, 6 で見られるように **4-25** が副生したと考えた。このため、反応系中で進行し得る二つの反応のうち、還元的脱コバルト化を優先的に進行させるため、反応に用いる添加剤は還元剤よりも当量を減らした。

還元的脱コバルト化の反応機構は、磯部らによって Scheme 4-12 に示すように推定されたが、これまでの実験結果を踏まえ、筆者は本反応の機構を Scheme 4-15 のように推定した。系中で生じるであろう **E** が、酸素によって酸化されることで **K** となる[30]。その後、水素化トリブチルスズとのトランスメタル化が起こり、コバルト-水素結合ができることで **M** が生じると考えた。還元的脱離により **N** が生じた後、同様の過程を経て **P** が生じる。最後にコバルトの還元的脱離が進行し、目的の *Z*-アルケン **Q** が生成するものと考えた[31]。一方で、本反応機構に酸素が関与しているかは不明である。**E** と水素化トリブチルスズから、酸素を介さず M が生成する可能性も考えられる。

Scheme 4-15. The role of NMO and the proposed reaction mechanism

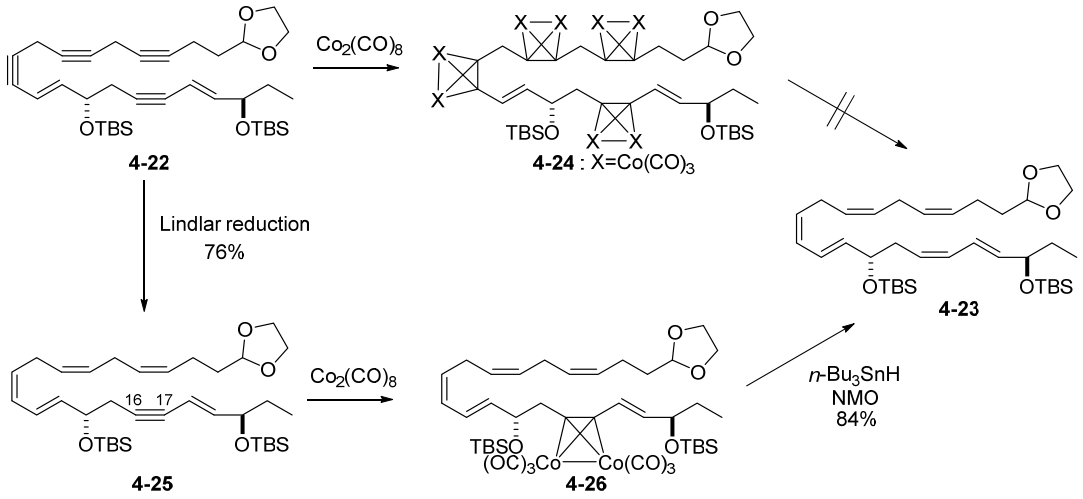


上記の検討の結果、モノイン **4-22** に対応するアルキン-コバルト錯体 **4-26** の還元的脱コバルト化反応によりヘキサエン **4-23** を、過還元体が生成することなく得られた。

以上の結果を Scheme 4-16 にまとめる。テトライン **4-22** をテトラキスアルキン-コバルト錯体 **4-24** へと誘導し、これに対する一連の還元的脱コバルト化では、目的物が低収率かつ分離困難な副生成物が問題となっていた。しかし、テトライン **4-22** を Lindlar 還元によりペンタエン **4-25** へと還元し、C16-17 位のアルキン-コバルト錯体 **4-26** に対する還元的脱コバルト化反応を行うことで、過還元体が生成することなく、高収率で目

的のヘキサエンを得ることに成功した。

Scheme 4-16. Successful constraction of hexaene **4-23**



本章で、還元的脱コバルト化反応において添加剤を加えることにより、0 度で望みの反応のみが進行し、副生成物の生成を抑制することを見出した[32]。その結果、化学的に不安定な合成中間体を再現性よく合成することが可能となった。

また、第 3 章においても、本方法が有効に機能した。Lindlar 還元、還元的脱コバルト化それぞれ単独で用いた場合には選択的に目的物が得られない、トリインの *Z*-アルケンへの部分還元において、2 つのアルキンに対して Lindlar 還元を適用した。次いで、Lindlar 還元では選択的に還元できない、嵩高い置換基に囲まれた残りのアルキンに対し、還元的脱コバルト化反応を適用することで、12-hydroxy-17,18-EpETE の合成に成功した。

4-4. 注釈および参考文献

(1) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207-214.

(2) Mukai, C.; Yamashita, H.; Ichiryu, T.; Hanaoka, M. *Tetrahedron*, **2000**, *56*, 2203-2209.

(3) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *Chem. Commun.* **1971**, 36. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977-981.

(4) Jamison, T. F.; Shambayani, S.; Crowe, W. E.; Stuart L. Schreiber, S. L. *J. Am. Chem. Soc.*, **1994**, *116*, 5505-5506.

(5) Shambayani, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289-5292.

(6) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204-206.

(7) (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1993**, *34*, 5757-5760. (b) Isobe, M.; Nishizawa, R.; Hoshikawa, S.; Nishikawa, T. *Chem. Commun*. **1998**, 2665.

(8) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609-2612.

(9) Takai, S.; Ploypradith, P.; Hamajima, A.; Kira, K.; Isobe, M. *Synlett* **2002**, 588-592.

(10) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.*, **1997**, *62*, 3032-3033.

(11) Iwasawa, N.; Inaba, K.; Nakayama, S.; Aoki, M. *Angew. Chem. Int. Ed.*, **2005**, *44*, 7447-7450.

(12) Goetz, R. W.; Orchin, M. *J. Org. Chem.* **1962**, *27*, 3698.

(13) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446-450.

(14) (a) Annunziata, R.; Fornasier, R.; Montanari, F. *J. Org. Chem.* **1974**, *39*, 3195-3197. (b) Cusack, J.; Reese, B.; Risius, C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157-2162.

(15) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.*, **1973**, *38*, 2226-2229.

(16) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313-1350.

(17) (a) Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Bora, U.; Kurita, T.; Kozaki, A.; Maegawa, T.; Sajiki, H. 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006 (2006). (b) Sajiki, H.; Mori, S.; Kitamura, Y.; Ikawa, T.; Hattori, K.; Monguchi, Y.; Maegawa, T. 234th ACS National Meeting, Boston, MA, United States, August 19-23, 2007 (2007). (c) Sajiki, H.; Mori, S.; Ohkubo, T.; Ikawa, T.; Kume, A.; Maegawa, T.; Monguchi, Y. *Chem. Eur. J.* **2008**, *14*, 5109-5111.

(18) Boland, W.; Schroer, N.; Sieler, C. *Helv. Chim. Acta.* **1987**, *70*, 1025-1040.

(19) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.*, **2001**, *123*, 1703-1708.

(20) 結合解離エネルギー : Si-H : 79-84 kcal/mol, Sn-H : 65 kcal/mol

(21) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *SYNLETT* **1999**, 771-773.

(22) Jeong, N.; Hwang, S. H.; Lee, Y. *J. Am. Chem. Soc.* **1994**, *116*, 3159-3160.

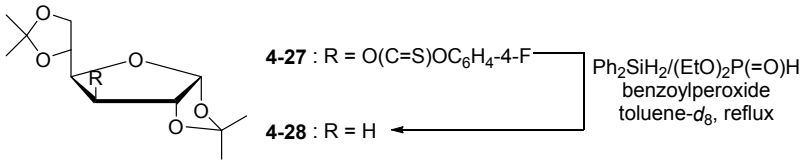
(23) Hamajima, A.; Nakata, H.; Goto, M.; Isobe, M. *Chem. Lett.* **2006**, *35*, 464-465.

(24) Rajesh, T.; Periasamy, M. *Tetrahedron Lett.* **1998**, *39*, 117-118.

(25) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485-6492.

(26) Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem.* **2000**, *112*, 645-647.

(27) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838-6842. において、**4-27** に対し、当モルのジフェニルシランと亜リン酸ジエチルを用いて還元反応が行われた。ジフェニルシランは 69%消費したのに対し、亜リン酸ジエチルは 29%の消費であった。本実験結果より、亜リン酸ジエチルに比べ、ジフェニルシランは還元力が強いといえる。参考文献(20)の結合解離エネルギーの比較により、スズのほうがシランより強い還元剤であるため、亜リン酸はスズよりも弱い還元剤であるといえる。



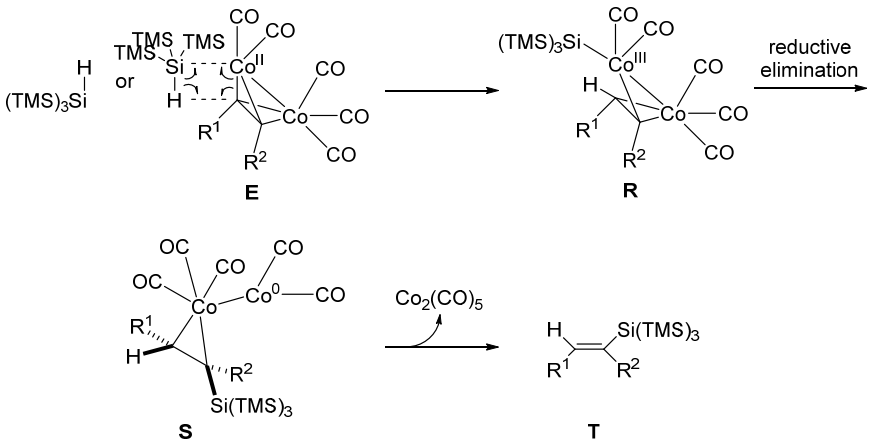
69% of diphenylsilane and 29% of diethyl phosphite were consumed.

(28) $(TMS)_3SiH$ を用いた系の場合、アルキンのヒドロシリル化も進行する。これに対して水素化トリブチルスズを用いた場合にもヒドロスタニル化が起こる可能性がある。還元的脱コバルト化反応において生成した *Z*-アルケンがヒドロスタニル化の後、プロトデスタニル化によって生成したと考えると、スズはケイ素と同様にβ位のカチオンを安定化できるため、カルボカチオンを経由するはずである。そのため、生成するアルケンは *E*/*Z* 混合物である可能性がある。しかしながら、今回水素化トリブチルスズを用いた系では *Z*-アルケンのみ生成したため、この経路は経由していないと考えている。

(29) 本還元的脱コバルト化反応は、ラジカル機構で進行すると考えると、系中で発生するスズラジカル、スズラジカルは生成物のダブルアリル位の水素を引き抜き、分解を促進する可能性がある。しかし、ダブルアリル位プロトンの結合解離エネルギーは 76 kcal/mol のため、引き抜きは起こらなかったと考えた。

(30) (a) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595-3598. (b) Wu, J.-M.; Kunikawa, S.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Wataya, Y. *Tetrahedron* **2005**, *61*, 9961-9968.

(31) 一方で、推測した本反応機構を基に、$(TMS)_3SiH$ を用いたヒドロシリル化について考察した。注釈 20 に示したように、Si-H の結合解離エネルギーは Sn-H のそれと比べて高いため、同様の反応性は示さず、**E** から Co-C 結合とのトランスメタル化を起こした場合に、ヒドロシリル化は進行すると考えられる。



(32) より低温で磯部還元を行った例 ：Shibuya, S.; Isobe, M. *Tetrahedron* **1998**, *54*, 6677-6698.

第 5 章

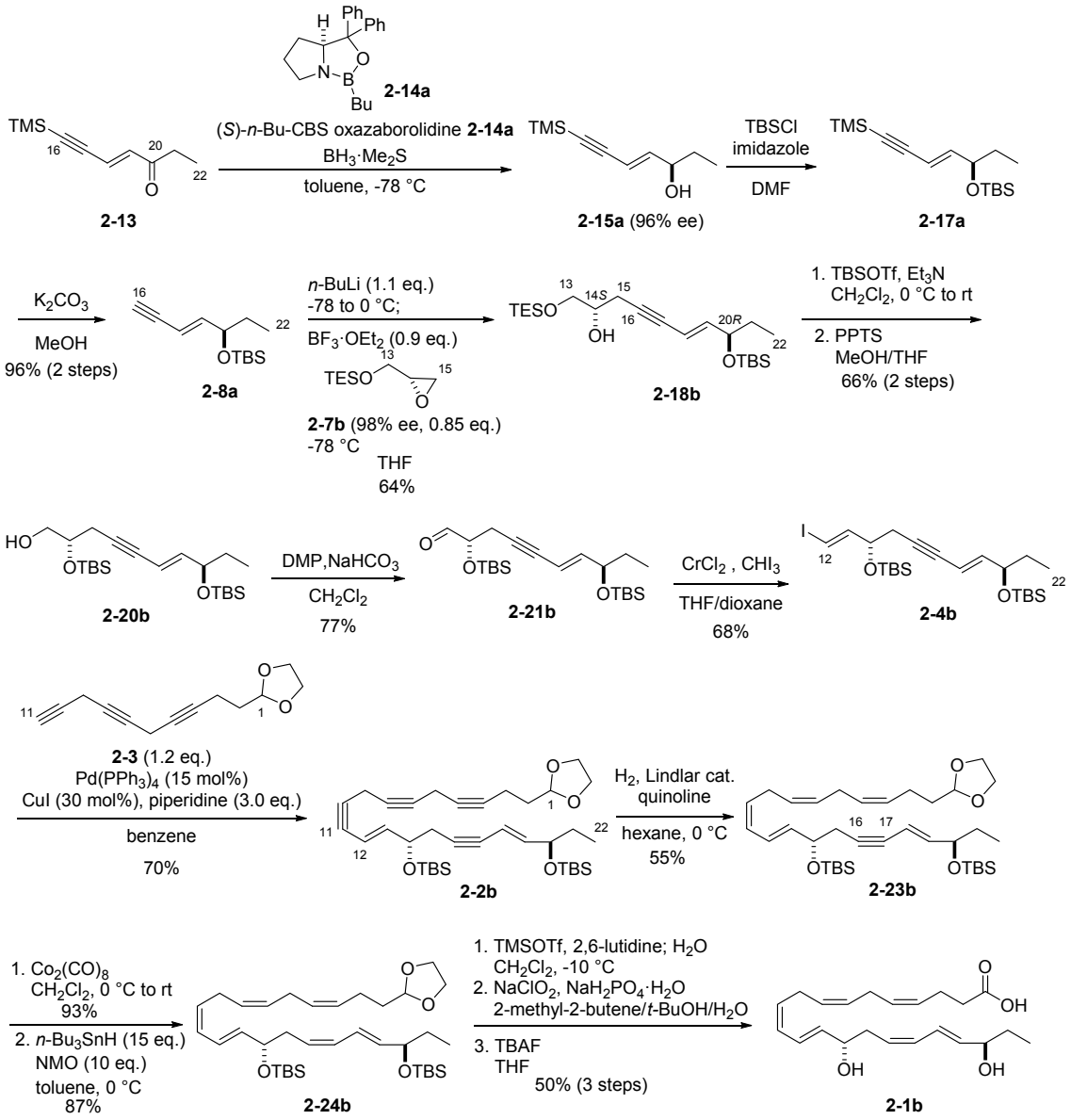
結論

筆者は DHA と EPA 由来の新規脂質メディエーターである 14,20-diHDHA と 12-hydroxy-17,18-EpETE のヒドロキシ基とエポキシドに関する 4 種立体異性体をそれぞれ全合成した。いずれの合成も、アルキンの反応性を最大限活用した合成経路にて合成した。すなわち、炭素骨格は単純なフラグメントを S_N2 アルキニル化と薗頭カップリングにより、収束的に連結し構築した。また、*Z*-アルケンは全て対応する内部アルキンの部分還元により構築した。

第 2 章では、14,20-diHDHA の 4 種立体異性体を合成した。4 種を代表して (14*S*,20*R*)-diHDHA (**2-1b**) の合成を Scheme 5-1 に示す。ケトン **2-13** に対し、(*S*)-CBS オキサザボロリジン **2-14a** を用いた不斉還元を適用し、*R* 配置の C20 ヒドロキシ基をエナンチオ選択的に構築した (96% ee)。その後、C20 ヒドロキシ基の TBS エーテル化と TMS 基の除去を経て、C16-22 フラグメント **2-8a** を合成した。**2-8a** から調製したリチウムアルキニドを三フッ化ホウ素存在下、光学活性グリシドール **2-7b** (98% ee) との S_N2 アルキニル化に付し、**2-18b** を得た。新たに生じた **2-18b** の C14 ヒドロキシ基を TBS 基で保護した後、TES 基の除去を行いアルコール **2-20b** へと変換した。**2-20b** の Dess-Martin 酸化と、続くジオキサン/THF 混合溶媒中での高井オレフィン化により、*E* 体のヨウ化ビニルを有する C12-22 フラグメント **2-4b** を単一の生成物として得た。別途合成した C1-11 フラグメント **2-3** と C12-22 フラグメントを薗頭カップリングにより連結し、14,20-diHDHA の全ての炭素骨格を有するテトライン **2-2b** を合成した。**2-2b** に対し 0 度にて Lindlar 還元を行い、4 つのうち 3 つのアルキンを部分還元した **2-23b** を得た。続いて、残る C16-17 アルキンをアルキン-コバルト錯体へと誘導し、水素化トリブチルスズ、NMO を用いた還元的脱コバルト化反応を行うと、0 度で望みの反応が進行し、目的のヘキサエン **2-24b** を単離した。なお、この際過剰還元体の生成は確認されなかった。最後に **2-24b** のアセタールを TBS 基存在下、藤岡らの条件によって選択的に除去した。次いで生じたアルデヒドの酸化と、2 つの TBS 基の除去を経て (14*S*,20*R*)-diHDHA (**2-1b**) を全合成した。

確立した本合成経路に則り、他の 3 種立体異性体についても光学活性なフラグメント **2-7** と **2-8** の組み合わせを変えることにより合成した。

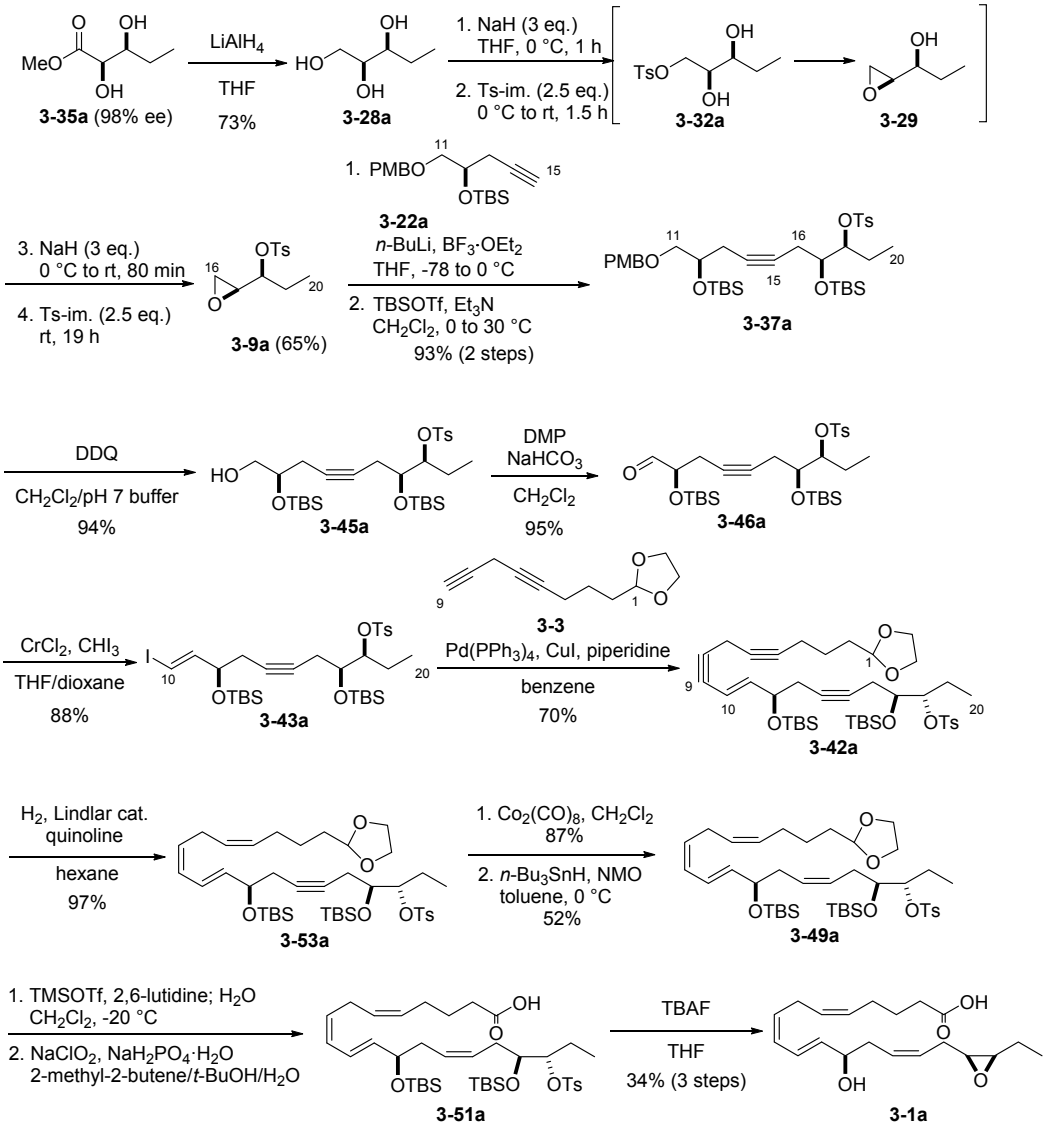
Scheme 5-1. The overview of total synthesis of (14*S*,20*R*)-diHDHA (**2-1b**)



第 3 章では、12-hydroxy-17,18-EpETE の 4 種立体異性体を合成した。4 種を代表して (12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1a**) の合成を Scheme 5-2 に示す。光学活性ジオール **3-35a** (98% ee) を $LiAlH_4$ により還元し、トリオール **3-28a** を得た。**3-28a** に対して、水素化ナトリウム存在下、トシルイミダゾールを作用させ、第一級ヒドロキシ基を選択的にトシル化した。生成した **3-32a** からエポキシ化を進行させた後、**3-29** の第二級ヒドロキシ基を室温下にてトシル化し、高収率にてキラルな C16-20 フラグメント **3-9a** を合成した。別途合成した C11-15 フラグメント **3-22a** (98% ee)と **3-9a** から C10-20 フラグメント **3-43a** を合成した。まず **3-22a** をリチウムアルキニドに変換した後、**3-9a** との S_N2 アルキニル化を進行させた後、C17 ヒドロキシ基の保護を行い、**3-37a** を得た。PMB 基の除去、および C11 ヒドロキシ基の酸化によりアルデヒド **3-46a** を合成した。**3-46a** に高井オレフィン化を適用し、単一の生成物として C10-20 フラグメント **3-43a** を得た。別途合成した C1-9 フラグメント **3-3** と、C10-20 フラグメント **3-43a** とを薗頭カップリングにより連結し、標的化合物の炭素骨格を有するトリイン **3-42a** を得た。続いて、**3-42a** が有する 3 つのアルキンの部分還元を試みた。**3-42a** を Lindlar 還元に付すと、3 つのアルキンのうち 2 つが還元されたトリエン **3-53a** が得られた。そこで、**3-53a** を先の合成と同様にアルキン-コバルト錯体へと誘導した後、水素化トリブチルスズと NMO を用いた還元的脱コバルト化に付した結果、テトラエン **3-49a** を選択的に得ることに成功した (収率 48%)。最後に、アセタールの除去と生じたアルデヒドのカルボン酸への酸化、TBAF による TBS 基の除去と続く C17-18 エポキシドの構築により、 (12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1a**) の全合成を達成した。

確立した本合成経路を用い、他の 3 つの立体異性体についても光学活性なフラグメントである **3-9** と **3-22** の組み合わせを変えることにより、再現性良く合成した。

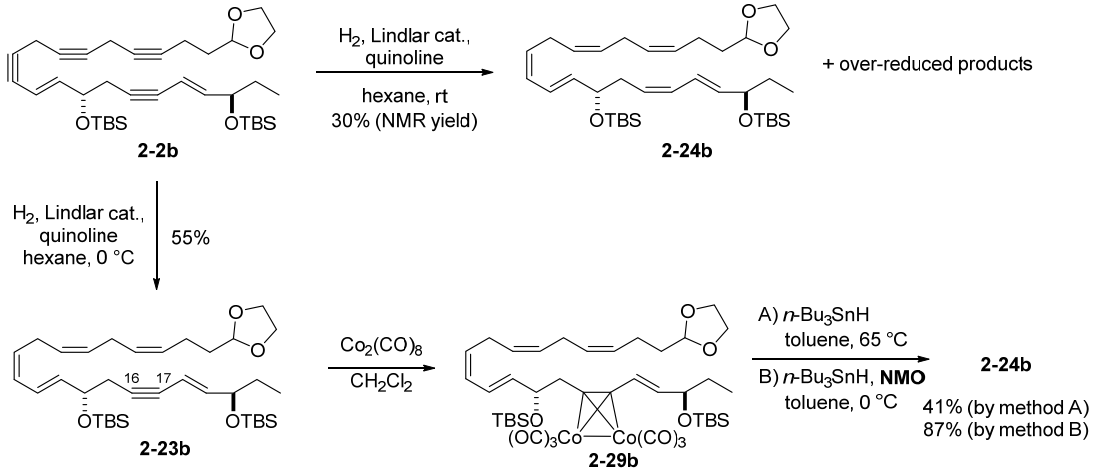
Scheme 5-2. The overview of total synthesis of (12*R*)-hydroxy-(17*R*,18*S*)-EpETE (**3-1a**)



上記 2 つの新規脂質メディエーターの合成において最も困難であったのは、複数のアルキンの *Z*-アルケンへの部分還元であった。結果として、以下に示す検討を経て、Lindlar 還元と還元的脱コバルト化反応を組み合わせる新規手法を確立した (第 2 章および第 4 章)。14,20-diHDHA の合成では、テトライン **2-2b** からヘキサエン **2-24b** への変換に、Lindlar 還元を適用した (Scheme 5-3)。しかし、室温下では、目的としていたヘキサエン **2-24b** は生成するものの、アルケンの過剰還元が競合した。一方、0 度で Lindlar 還元を行うと、4 つのアルキンのうち 3 つが還元された **2-23b** が収率よく得られた。これは、嵩高い TBS エーテルによって立体的に遮蔽されているため、C16-17 アルキンの部分還元が遅いことが原因であると考えた。そこで、アルキン特異的な部分還元法として磯部らによって報告された還元的脱コバルト化反応を試みることとし、

2-23b の C16-17 アルキンを $Co_2(CO)_8$ を用いてアルキン-コバルト錯体 **2-29b** へと変換した。得られたアルキン-コバルト錯体 **2-29b** に対し、磯部らのオリジナルの加熱条件に付したところ、**2-24b** は生成するものの、基質の分解も起こった (method A)。基質には反応性の高いダブルアリル位や共役ジエン、アリルアルコールを含むため、より低温下での反応の進行が必須であった。そこで、アルキン-コバルト錯体を用いる Pauson-Khand 反応において、反応促進効果のある添加剤として知られている NMO を添加したところ、0 度で望みの還元反応が進行し、**2-24b** を得ることができた (method B)。

Scheme 5-3. Transformation of tetrayne **2-2b** to hexaene **2-24b**



12-hydroxy-17,18-EpETE の合成においても、C12,17 位の 2 つの TBS エーテルによって立体的に遮蔽されているため、Lindlar 還元で還元できなかった C14-15 アルキンに対し、NMO を添加した還元的脱コバルト化反応を適用し、目的物を単一の生成物として得ることに成功した。

このように複数のアルキンの *Z*-アルケンへの還元において、Lindlar 還元と改良磯部還元を組み合わせることで、目的物への高化学選択的な還元を実現した。特に還元的脱コバルト化において、NMO を添加することにより低温下での還元反応を可能にした点は、脂質合成における *Z*-アルケンの新たな構築法として意義深いと言える。

確立した上記の合成経路において、*E*/*Z* 共役ジエンの異性化は起こらず、アルキンの部分還元の際も、過還元体の生成を抑制することに成功した。HPLC 精製は最終物に対してのみ行い、目的の新規脂質メディエーター2 つについて、各々4 種立体異性体を再現性よく、また純度よく得ることができた (Figure 5-1)。本合成により、これまで不明であった天然物の構造を完全に決定することができた。また、構造活性相関研究から、ヒドロキシ基やエポキシドの立体化学の重要性を明らかにした。現在までに (14*S*,20*S*)-diHDHA (**2-1d**) を 130 mg 合成することに成功している。これは、本合成経路が生物学的研究に必要となる試料の供給を実現し得ることを示している。本研究により 14,20-diHDHA および 12-hydroxy-17,18-EpETE の機能解明研究が大きく推進されると考えている。

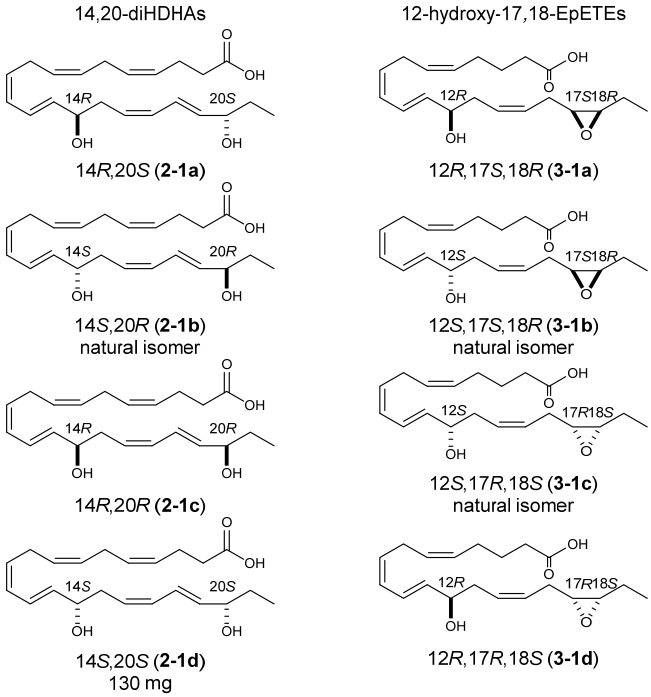


Figure 5-1. Four stereoisomers of 14,20-diHDHA and 12-hydroxy-17,18-EpETE

EXPERIMENTAL SECTION

General methods: All reactions sensitive to air or moisture were carried out under argon atmosphere in dry solvents, unless otherwise noted. THF, CH_2Cl_2 and toluene were purified by Glass Contour solvent dispensing system. Et_3N and piperidine were purified by distillation over CaH_2. $BF_3{\cdot}OEt_2$ was purified by distillation over P_2O_5. All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel [spherical, neutral, 40-50 μm; granular, neutral, 32-53 μm; spherical, carboxylic acid supported (Chromatorex-ACD COOH), 45-75 μm]. Medium pressure liquid chromatography was carried out by using a system equipped with a pre-packed silica gel 40 μm [14 g (20 x 75 mm), 45 g (26 x 150 mm) or 120 g (46 x 130 mm)]. Melting points are reported uncorrected. Optical rotations were measured using the sodium D line. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using a FT/IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 or 500 MHz, and 100 or 150 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ for ^1H NMR (δ = 7.26), $CDCl_3$ for ^{13}C NMR (δ = 77.0), C_6HD_5 for ^1H NMR (δ = 7.16), C_6D_6 for ^{13}C NMR (δ = 128.06), CD_2HOD for ^1H NMR (δ = 3.31), and CD_3OD for ^{13}C NMR (δ = 49.0) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. High resolution mass spectra were measured on ESI-TOF or DART-TOF mass spectrometers. Elemental analysis was performed by the Analytical Laboratory at the Graduate School of Pharmaceutical Sciences, The University of Tokyo.

Triyne 2-3. [TG-III-116, 117, 118] A mixture of CuI (833 mg, 4.37 mmol), NaI (650 mg, 4.34 mmol) and Cs_2CO_3 (1.41 g, 4.32 mmol) was dried at 95 °C in vacuo. After the mixture was cooled to 0 °C, a solution of alcohol **2-5** (548 mg, 4.35 mmol) in DMF (4.0 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **2-6** (1.18 g, 4.91 mmol) in DMF (4.8 mL) was added. The reaction mixture was warmed to room temperature and stirred for 16 h, and then saturated aqueous NH_4Cl (20 mL) was added. The resultant solution was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (30 mL and 20 mL x2). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and

concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/2) to afford the crude diyne **2-9**, which was used in the next reaction without further purification.

DIPHOS (1.48 g, 3.72 mmol) and CBr_4 (827 mg, 2.49 mmol) were successively added to a solution of the above crude **2-9** in CH_2Cl_2 (12 mL) to 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then was directly subjected to medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 8/1) to afford bromide **2-10**, which was immediately used in the next reaction.

CuCl (181 mg, 1.83 mmol) was dried at 90 °C in vacuo, and then THF (25 mL) was added. Ethynyl magnesium bromide (0.5 M in THF, 27 mL, 14 mmol) was added to the suspension at room temperature. The mixture was stirred for 10 min at room temperature, and then a solution of the above bromide **2-10** in THF (30 mL) was added. The reaction mixture was stirred at room temperature for 14 h, and then saturated aqueous NH_4Cl (50 mL) was added. The resultant solution was filtered through a pad of Celite, and the filtrate was extracted with EtOAc (50 mL and 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1 to 9/1) to afford triyne **2-3** (228 mg, 1.13 mmol) in 26% yield over 3 steps. Triyne **2-3**was immediately used in the next reaction due to its instability under air: yellow oil; IR (neat) ν 3287, 2887, 1413, 1317, 1138, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (2H, td, *J* = 7.3, 4.6 Hz, H2), 2.06 (1H, t, *J* = 2.7 Hz, H11), 2.30 (2H, tt, *J* = 7.2, 2.3 Hz, H3), 3.13 (2H, tt, *J* = 2.3, 2.3 Hz, H6), 3.17 (2H, dt, *J* = 2.7, 2.3 Hz, H9), 3.82-3.91 (2H, m, acetal), 3.91-4.00 (2H, m, acetal), 4.96 (1H, t, *J* = 4.6 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 9.7, 13.6, 32.9, 64.9 (x2), 68.7, 73.4, 73.9, 75.5, 78.1, 79.7, 103.2.

Ketone 2-13. [TG-I-191, TG-II-002] A solution of propionylchloride (0.2 mL, 117 mmol) in CH_2Cl_2 (50 mL) and a solution of **2-11** (15.0 mL, 97.6 mmol) in CH_2Cl_2 (50 mL) were successively added to a solution of $AlCl_3$ (15.8 g, 118 mmol) in CH_2Cl_2 (300 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then saturated aqueous NH_4Cl (200 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (150mL, 50mL x2), and the combined organic layers were washed with water (150 mL) and brine (150 mL),dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (120 g, pentane

to pentane/Et_2O 9:1) to afford **2-12** (a 1 : 1 mixture of bromide chloride and chloride bromide) along with pentane and Et_2O, which was used in the next reaction without further purification due to volatility of **2-12** (X = Br).

$Pd(PPh_3)_4$ (1.14 g, 0.987 mmol), CuI (375 mg, 1.97 mmol), Et_3N (34 mL, 240 mmol) and trimethylsilyl acetylene (15 g, 110 mol) were successively added to a solution of the above **2-12** at room temperature. The reaction mixture was stirred at room temperature for 20 h. After the reaction mixture was cooled to 0 °C, saturated aqueous NH_4Cl (200 mL) was added. The resultant mixture was extracted with pentane (400 mL, 100 mL x2), and the combined organic layers were washed with water (150 mL) and brine (150 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (150 g, hexane to hexane/EtOAc 47/3) to afford ketone **2-13** (24.8 g, 76.5 mmol, a 1 : 0.0375 : 1.97 mixture of ketone **2-13**, Et_2O and pentane). The yield of **2-13** was determined to be 78% over 2 steps by the ^1H NMR analysis of the mixture. For characterization of **2-13**, the residual solvents of the above mixture were completely removed: colorless oil; IR (neat) ν 2962, 2940, 2902, 1692, 1677, 1596, 1252, 1081, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.22 (9H, s, C*H*$_3$ of TMS), 1.10 (3H, t, *J* = 7.3 Hz, H22), 2.56 (2H, q, *J* = 7.3 Hz, H21), 6.53 (1H, d, *J* = 16.0 Hz, H19), 6.64 (1H, d, *J* = 16.0 Hz, H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.5 (x3), 7.8, 34.3, 101.9, 105.5, 122.4, 137.7, 199.4; HRMS (DART) calcd for $C_{10}H_{17}OSi$ 181.1043 $[M+H]^+$, found 181.1076.

Alcohol 2-15a. [TG-II-158] $BH_3 \cdot Me_2S$ (1.5 mL, 16 mmol) was added to a solution of (*S*)-2-butyl-CBS-oxazaborolidine **2-14a** (1.0 M solution in toluene, 14 mL, 14 mmol) in toluene (46 mL) at room temperature. The mixture was stirred at room temperature for 30 min. After the mixture was cooled to -78 °C, a solution of ketone **2-13** (2.42 g, 7.41 mmol, a 27 : 53 : 1 mixture of **2-13**, pentane and Et_2O,) in toluene (23 mL) was added over 35 min. The reaction mixture was stirred at -78 °C for 1 h, and then 0.4 M aqueous HCl (60 mL) was added. The mixture was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (100 mL and 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 5/1) to afford alcohol **2-15a** (868 mg, 4.77 mmol) in 64% yield. The enantiopurity of **2-15a** was determined to be 96% ee by the ^1H NMR analysis of the

corresponding MTPA-ester: colorless oil; $[\alpha]_D^{28}$ -4.2 (*c* 1.1, $CHCl_3$); IR (neat) ν 3357, 2962, 2935, 2877, 2155, 2130, 1457, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.19 (9H, s, C*H*$_3$ of TMS), 0.94 (3H, t, *J* = 7.3 Hz, H22), 1.46 (1H, d, *J* = 4.6 Hz, O*H*), 1.57 (2H, qd, *J* = 7.3, 6.0 Hz, H21), 4.09 (1H, m, H20), 5.73 (1H, dd, *J* = 16.0, 1.4 Hz, H19), 6.20 (1H, dd, *J* = 16.0, 6.0 Hz, H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.12 (x3), 9.5, 29.8, 73.5, 95.1, 103.1, 110.0, 146.5; HRMS (DART) calcd for $C_{10}H_{19}OSi$ 183.1200 $[M+H]^+$, found 181.1208.

(*S*)-MTPA ester 2-16a. [TG-IV-153] (*R*)-MTPACl (12 μL, 64 μmol) was added to a solution of **2-15a** (3.0 mg, 16 μmol), Et_3N (16 μL, 0.12 mmol) and DMAP (10 mg, 82 μmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min, and then H_2O (5 mL) was added. The resultant mixture was extracted with EtOAc (5 mL x3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 20/1) to afford (*S*)-MTPA ester **2-16a** (4.9 mg, 13 μmol) in 81% yield: colorless oil; ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, C*H*$_3$ of TMS), 0.94 (3H, t, *J* = 7.3 Hz, H22), 1.67-1.80 (2H, m, H21), 3.55 (3H, s, OMe), 5.40 (1H, dt, *J* =7.3, 6.4 Hz, H20), 5.70 (1H, d, *J* = 16.0 Hz, H18), 6.02 (1H, dd, *J* = 16.0, 7.3 Hz, H19), 7.36-7.42 (3H, m, aromatic), 7.48-7.51 (2H, m, aromatic).

(*R*)-MTPA ester 2-16b. [TG-IV-159] According to the synthetic procedure of **2-16a**, (*R*)-MTPA ester **2-16b** (4.1 mg, 11 μmol) was synthesized from **2-15a** (2.6 mg, 14 μmol) in 79% yield by using (*S*)-MTPACl (5.5 μL, 29 μmol), Et_3N (10 μL, 0.12 mmol) and DMAP (4.4 mg, 36 μmol) in CH_2Cl_2 (0.7 mL). The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 20/1): colorless oil; ^1H NMR ($CDCl_3$) δ 0.19 (9H, s, C*H*$_3$ of TMS), 0.83 (3H, t, *J* = 7.3 Hz, H22), 1.55-1.75 (2H, m, H21), 3.54 (3H, s, OMe), 5.42 (1H, td, *J* =6.8, 6.8 Hz, H20), 5.79 (1H, d, *J* = 16.0 Hz, H18), 6.10 (1H, dd, *J* = 16.0, 6.8 Hz, H19), 7.38-7.42 (3H, m, aromatic), 7.48-7.51 (2H, m, aromatic).

Alcohol 2-15b. [TG-III-085] According to the synthetic procedure of alcohol **2-15a**, alcohol **2-15b** (965 mg, 5.30 mmol) was synthesized from ketone **2-13** (2.82 g, 8.65 mmol, a 27 : 53 : 1 mixture of **2-13**, pentane and Et_2O) in 65% yield by using (*R*)-2-butyl-CBS-oxazaborolidine **2-14b** (1.0 M solution in toluene, 16.3 mL, 16.3 mmol) and $BH_3 \cdot Me_2S$ (1.8 mL, 18 mmol) in toluene (83 mL). Purification was performed twice by medium pressure liquid

chromatography on silica gel (120 g, hexane to hexane/EtOAc 6/1; 45 g, hexane to hexane/EtOAc 6/1). The enantiopurity of **2-15b** was determined to be 96% ee by the ^{1}H NMR analysis of the corresponding MTPA-ester: colorless oil; $[\alpha]_D^{30}$ +4.3 (*c* 0.84, $CHCl_3$); Anal. Calcd for $C_{10}H_{18}OSi$: C, 65.87; H, 9.95; found: C, 66.04; H, 9.71. The other analytical data of **2-15b** were identical to those of **2-15a**.

C16-22 fragment 2-8a. [TG-II-163, 164] TBSCl (1.43 g, 9.49 mmol) was added to a solution of alcohol **2-15a** (864 mg, 4.75 mmol) and imidazole (1.29 g, 20.0 mmol) in DMF (47 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h, and then H_2O (100 mL) was added. The resultant solution was extracted with Et_2O (60 mL and 40 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude TBS ether **2-17a**, which was used in the next reaction without further purification.

K_2CO_3 (980 mg, 7.10 mmol) was added to a solution of the above crude TBS ether **2-17a** in MeOH (45 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. After the reaction mixture was cooled to 0 °C, Et_2O (50 mL) and saturated aqueous NH_4Cl (60 mL) were successively added. The resultant mixture was extracted with Et_2O (100 mL and 50 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified three times by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 25/1; 30 g, hexane/EtOAc 100/1 to 50/1; 30 g, hexane to hexane/EtOAc 100/1) to afford C16-22 fragment **2-8a** (718 mg, 3.21 mmol) in 68% over 2 steps: colorless oil; $[\alpha]_D^{24}$ +19 (*c* 0.16, $CHCl_3$); IR (neat) ν 3427, 2956, 2930, 2858, 2221, 1471, 1463, 1362, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.88 (3H, t, *J* = 7.3 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 1.52 (2H, m, H21), 2.86 (1H, d, *J* = 2.3 Hz, H16), 4.12 (1H, dtd, *J* = 6.0, 6.0, 1.8 Hz, H20), 5.65 (1H, ddd, *J* = 16.0, 2.3, 1.8 Hz, H18), 6.23 (1H, dd, *J* = 16.0, 6.0 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.6, 9.2, 18.2, 25.8 (x3), 30.5, 73.3, 77.2, 82.2, 107.6, 148.3; Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78; found: C, 69.42; H, 10.48.

Alcohol 2-18b. [TG-II-157] *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) was added to a solution of C16-22 fragment **2-8a** (714 mg, 3.19 mmol) in THF (25 mL) at -78 °C over 10 min. The mixture was stirred at -78 °C for

10 min, warmed to 0 ºC and stirred for 30 min. After the mixture was cooled to -78 °C, $BF_3{\cdot}OEt_2$ (0.36 mL, 2.9 mmol) and a solution of glycidol derivative **2-7b** (503 mg, 2.68 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at -78 °C for 1 h and warmed to -40 °C over 3 h, and then saturated aqueous NH_4Cl (30 mL) was added. The resultant mixture was extracted with Et_2O (30 mL x3), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1) and flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford alcohol **2-18b** (707 mg, 1.71 mmol) in 64% yield: colorless oil; $[\alpha]_D^{28}$ +31 (*c* 1.3, $CHCl_3$); IR (neat) ν 3566, 2956, 2926, 2852, 1956, 1478, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.63 (6H, q, *J* = 8.2 H, CH_3CH_2 of TES x3), 0.86 (3H, t, *J* = 7.8 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.97 (9H, t, *J* = 8.2 Hz, C*H*$_3$CH$_2$ of TES x3), 1.50 (2H, qd, *J* = 7.8, 6.0 Hz, H21), 2.50-2.60 (2H, m, H15), 3.62 (1H, dd, *J* = 10.0, 5.9 Hz, H13a), 3.72 (1H, dd, *J* = 10.0, 4.1 Hz, H13b), 3.81 (1H, m, H14), 4.08 (1H, dtd, *J* = 6.0, 6.0, 1.8 Hz, H20), 5.61 (1H, dtd, *J* = 16.0, 1.8, 1.8 Hz, H18), 6.04 (1H, dd, *J* = 16.0, 6.0 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.6, 4.3 (x3), 6.7 (x3), 9.3, 18.2, 24.1, 25.8 (x3), 30.7, 65.4, 70.4, 73.6, 80.8, 85.8, 108.7, 145.6; HRMS (ESI) calcd for $C_{22}H_{44}O_3SiNa$ 435.2721 $[M+Na]^+$, found 435.2726.

Alcohol 2-18c. [TG-IV-160] According to the synthetic procedure of **2-18b**, **2-18c** (760 mg, 1.84 mmol) was synthesized from C16-22 fragment **2-8a** (610 mg, 2.72 mmol) and glycidol derivative **2-7a** (436 mg, 2.32 mmol) in 79% yield by using *n*-BuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.4 mmol) in THF (26 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{30}$ +6.2 (*c* 1.2, $CHCl_3$); IR (neat) ν 3429, 2956, 2931, 2877, 1463, 1362, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.63 (6H, q, *J* = 7.8 H, CH_3CH_2 of TES x3), 0.86 (3H, t, *J* = 7.3 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.97 (9H, t, *J* = 7.8 Hz, C*H*$_3$CH$_2$ of TES x3), 1.50 (2H, qd, *J* = 7.3, 5.5 Hz, H21), 2.50-2.60 (2H, m, H15), 3.62 (1H, dd, *J* = 10.0, 6.0 Hz, H13a), 3.72 (1H, dd, *J* = 10.0, 4.1 Hz, H13b), 3.81 (1H, m, H14), 4.08 (1H, dtd, *J* = 6.0, 5.5, 1.4 Hz, H20), 5.61 (1H, dtd, *J* = 16.0, 2.3, 1.4 Hz, H18), 6.03 (1H, dd, *J* = 16.0, 6.0 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.5, 4.3 (x3), 6.7 (x3), 9.3, 18.2, 24.1,

25.8 (x3), 30.7, 65.3, 70.4, 73.6, 80.8, 85.8, 108.7, 145.6; HRMS (ESI) calcd for $C_{22}H_{44}O_3SiNa$ 435.2721 $[M+Na]^+$, found 435.2744.

Alcohol 2-20b. [TG-II-160, 161] TBSOTf (0.43 mL, 1.9 mmol) was added to a solution of alcohol **2-18b** (704 mg, 1.70 mmol) and Et_3N (0.60 mL, 4.3 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 20 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford the crude TBS ether, which was used in the next reaction without further purification.

PPTS (37 mg, 0.15 mmol) was added to a solution of the above crude TBS ether in a mixture of MeOH (15 mL) and THF (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min. After the reaction mixture was cooled at 0 °C, saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 20 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified three times by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 20/1) to afford TBS ether **2-20b** (463 mg, 1.12 mmol) in 66% over 2 steps: colorless oil; $[\alpha]_D^{21}$ +21 (*c* 1.2, $CHCl_3$); IR (neat) ν 3449, 2955, 2929, 2857, 1471, 1461, 1362, 1255, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.12 (3H, s, C*H*$_3$ of TBS), 0.86 (3H, t, *J* = 7.3 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.3, 6.4 Hz, H21), 2.42 (1H, ddd, *J* = 17.0, 6.4, 1.8 Hz, H15a), 2.53 (1H, ddd, *J* = 17.0, 6.9, 1.8 Hz, H15b), 3.58 (1H, dd, *J* = 11.4, 5.0 Hz, H13a), 3.68 (1H, dd, *J* = 11.4, 3.7 Hz, H13b), 3.91 (1H, m, H14), 4.07 (1H, tdd, *J* = 6.4, 6.0, 1.4 Hz, H20), 5.60 (1H, dtd, *J* = 16.0, 1.8, 1.4 Hz, H18), 6.02 (1H, dd, *J* = 16.0, 6.0 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, -4.5, -4.24, -4.21, 9.6, 18.4, 18.5, 25.1, 26.1 (x3), 26.2 (x3), 31.0, 66.2, 72.0, 74.0, 81.0, 86.7, 109.1, 145.8; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M+Na]^+$, found 435.2709.

Aldehyde 2-21b. [TG-II-165] Dess-Martin periodinane (693 mg, 1.63 mmol) was added to a suspension mixture of alcohol **2-20b** (449 mg, 1.09 mmol) and $NaHCO_3$ (887 mg, 10.6 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The mixture

was warmed to room temperature and stirred for 5 h, and then H_2O (50 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL x2), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1) to afford aldehyde **2-21b** (343 mg, 0.835 mmol) in 77% yield: colorless oil; $[\alpha]_D^{29}$ -3.4 (*c* 1.2, $CHCl_3$); IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.13 (6H, s, C*H*$_3$ of TBS x2), 0.86 (3H, t, *J* = 7.3 Hz, H22), 0.89 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.3, 6.0 Hz, H21), 2.57 (1H, ddd, *J* = 16.9, 7.8, 1.8 Hz, H15a), 2.71 (1H, ddd, *J* = 16.9, 5.0, 1.8 Hz, H15b), 4.07 (1H, td, *J* = 6.0, 5.5 Hz, H20), 4.13 (1H, ddd, *J* = 7.8, 5.0, 1.4 Hz, H14), 5.60 (1H, br d, *J* = 16.0 Hz, H18), 6.04 (1H, dd, *J* = 16.0, 5.5 Hz, H19), 9.65 (1H, d, *J* = 1.4 Hz, H13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.82, -4.78, -4.6, 9.3, 18.22, 18.23, 24.1, 25.7 (x3), 25.8 (x3), 30.7, 73.6, 76.2, 81.2, 85.0, 108.6, 145.9, 202.2; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 $[M+MeOH+Na]^+$, found 465.2819.

C12-22 fragment 2-4b. [TG-II-167] Iodoform (644 mg, 1.63 mmol) and a solution of aldehyde **2-21b** (334 mg, 0.813 mmol) in 1,4-dioxane (13.5 mL) were successively added to a suspension of $CrCl_2$ (600 mg, 4.88 mmol) in THF (0.98 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (40 mL) and H_2O (20 mL) were successively added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1; 40 g, hexane/EtOAc 20/1) to afford **2-4b** (297 mg, 0.555 mmol) in 68% yield: colorless oil; $[\alpha]_D^{31}$ +47 (*c* 1.0, $CHCl_3$); IR (neat) ν 2956, 2929, 2857, 1607, 1471, 1463, 1362, 1255, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.87 (3H, t, *J* = 7.8 Hz, H22), 0.896 (9H, s, *t*-Bu of TBS), 0.899 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.3, 6.0 Hz, H21), 2.42 (1H, ddd, *J* = 16.9, 6.9, 2.3 Hz, H15a), 2.49 (1H, ddd, *J* = 16.9, 6.9, 2.3 Hz, H15b), 4.08 (1H, td, *J* = 6.0, 6.0 Hz, H20), 4.24 (1H, td, *J* = 6.9, 5.5, 1.4 Hz, H14), 5.61 (1H, ddt, *J* = 16.0, 2.3, 1.8 Hz, H18), 6.03 (1H, dd, *J* = 16.0, 6.0 Hz, H19), 6.33 (1H, dd, *J* = 14.8, 1.4 Hz, H12), 6.64 (1H, dd, *J* = 14.8, 5.5 Hz, H13); ^{13}C

NMR (100 MHz, $CDCl_3$) δ -4.89, -4.86, -4.7, -4.5, 9.3, 18.19, 18.22, 25.7 (x3), 25.9 (x3), 28.8, 30.7, 73.6, 74.0, 76.7, 81.1, 86.1, 108.8, 145.7, 147.6; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 $[M+Na]^+$, found 557.1733.

Alcohol 2-20c. [TG-II-170, 171] According to the synthetic procedure of **2-20b**, **2-20c** (427 mg, 1.04 mmol) was synthesized from alcohol **2-18c** (676 mg, 1.64 mmol) in 63% yield over 2 steps by using Et_3N (0.58 mL, 4.2 mmol), TBSOTf (0.42 mL, 1.8 mmol) in CH_2Cl_2 (16 mL) for the first step, and PPTS (37 mg, 0.15 mmol) in a mixture of MeOH (15 mL) and THF (2.5 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step, and twice on silica gel (30 g, hexane to hexane/EtOAc 9/1; 30 g, hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{31}$ +17 (*c* 1.2, $CHCl_3$); IR (neat) ν 3434, 2956, 2929, 2857, 2221, 1634, 1472, 1464, 1362, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.12 (3H, s, C*H*$_3$ of TBS), 0.86 (3H, t, *J* = 7.8 Hz, H22), 0.895 (9H, s, *t*-Bu of TBS), 0.904 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.8, 6.0 Hz, H21), 1.87 (1H, t, *J* = 6.0 Hz, O*H*), 2.47 (1H, ddd, *J* = 16.9, 6.0, 2.3 Hz, H15a), 2.53 (1H, ddd, *J* = 16.9, 7.3, 2.3 Hz, H15b), 3.58 (1H, ddd, *J* = 11.4, 6.0, 5.0 Hz, H13a), 3.68 (1H, ddd, *J* = 11.4, 6.0, 3.7 Hz, H13b), 3.91 (1H, m, H14), 4.07 (1H, tdd, *J* = 6.0, 6.0, 1.4 Hz, H20), 5.60 (1H, ddt, *J* = 16.0, 2.3, 1.4 Hz, H18), 6.01 (1H, dd, *J* = 16.0, 6.0 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.6, -4.5, 9.3, 18.1, 18.2, 24.8, 25.77 (x3), 25.84 (x3), 30.7, 65.9, 71.7, 73.6, 80.7, 86.4, 108.8, 145.5; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M+Na]^+$, found 435.2744.

Aldehyde 2-21c. [TG-II-173] According to the synthetic procedure of **2-21b**, **2-21c** (352 mg, 0.856 mmol) was synthesized from alcohol **2-20c** (418 mg, 1.01 mmol) in 85% yield by using $NaHCO_3$ (818 mg, 10.8 mmol) and Dess-Martin periodinane (645 mg, 1.52 mmol) in CH_2Cl_2 (21 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ +47 (*c* 1.1, $CHCl_3$); IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.132 (3H, s, C*H*$_3$ of TBS), 0.136 (3H, s, C*H*$_3$ of TBS), 0.86 (3H, t, *J* = 7.3 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.3, 6.0 Hz. H21), 2.57 (1H, ddd, *J* = 17.0, 7.8, 1.8 Hz, H15a), 2.71 (1H, ddd, *J* = 17.0, 5.0, 1.8 Hz, H15b), 4.08 (1H, td, *J* = 6.0, 6.0 Hz, H20), 4.13 (1H, ddd, *J* = 7.8, 5.0, 1.0 Hz, H14), 5.60 (1H, dd, *J* = 16.0, 1.8 Hz, H18), 6.04 (1H, dd, *J* = 16.0, 6.0 Hz, H19), 9.65 (1H,

d, *J* = 1.0 Hz, H13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.82, -4.78, -4.6, 9.3, 18.2 (x2), 24.1, 25.7 (x3), 25.8 (x3), 30.7, 73.6, 76.2, 81.2, 85.0, 108.6, 146.0, 202.2; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 $[M+MeOH+Na]^+$, found 465.2851.

C12-22 fragment 2-4c. [TG-II-174] According to the synthetic procedure of **2-4b**, **2-4c** (270 mg, 0.505 mmol) was synthesized from aldehyde **2-21c** (342 mg, 0.832 mmol) in 61% yield by using iodoform (657 mg, 1.67 mmol) and $CrCl_2$ (615 mg, 5.00 mmol) in a mixture of THF (1.0 mL) and 1,4-dioxane (14 mL). Purification was performed three times by flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ -16 (*c* 1.0, $CHCl_3$); IR (neat) ν 2956, 2929, 2857, 1607, 1463, 1362, 1255, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.87 (3H, t, *J* = 7.8 Hz, H22), 0.896 (9H, s, *t*-Bu of TBS), 0.899 (9H, s, *t*-Bu of TBS), 1.50 (2H, qd, *J* = 7.8, 6.0 Hz, H21), 2.42 (1H, ddd, *J* = 16.9, 6.9, 1.8 Hz, H15a), 2.49 (1H, ddd, *J* = 16.9, 6.9, 1.8 Hz, H15b), 4.08 (1H, dt, *J* = 6.0, 6.0 Hz, H20), 4.24 (1H, td, *J* = 6.9, 5.5 Hz, H14), 5.61 (1H, dd, *J* = 16.0, 1.4 Hz, H18), 6.03 (1H, dd, *J* = 16.0, 6.0 Hz, H19), 6.33 (1H, dd, *J* = 14.6, 1.4 Hz, H12), 6.64 (1H, ddd, *J* = 14.6, 5.5 Hz, H13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.89, -4.86, -4.7, -4.5, 9.3, 18.19, 18.23, 25.7 (x3), 25.9 (x3), 28.8, 30.7, 73.7, 74.0, 76.7, 81.0, 86.1, 108.8, 145.7, 147.6; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 $[M+Na]^+$, found 557.1754.

Tetrayne 2-2b. [TG-III-018] $Pd(PPh_3)_4$ (91.6 mg, 79.2 μmol), CuI (31.9 mg, 0.167 mmol), a solution of C12-C22 fragment **2-4b** (278 mg, 0.520 mmol) in benzene (4.5 mL), and piperidine (0.16 mL, 1.6 mmol) were successively added to a solution of **2-3** (157 mg, 0.777 mmol) in benzene (14 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (10 mL) and saturated aqueous NH_4Cl (40 mL) were successively added. The resultant mixture was extracted with Et_2O (30 mL and 10 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 15/1) to afford tetrayne **2-2b** (223 mg, 0.366 mmol) in 70% yield. Tetrayne **2-2b** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 0.00 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of

TBS), 0.05 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.83 (3H, t, *J* = 7.3 Hz, H22), 0.95 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.42 (2H, qd, *J* = 7.3, 6.0 Hz, H21), 1.86 (2H, td, *J* = 7.8, 5.0 Hz, H2), 2.28 (2H, br t, *J* = 7.8 Hz, H3), 2.30 (1H, dd, *J* = 16.0, 6.4 H15a), 2.41 (1H, dd, *J* = 16.0, 6.9 Hz, H15b), 2.85 (2H, br s, H6), 2.94 (2H, s, H9), 3.25-3.33 (2H, m, acetal), 3.38-3.47 (2H, m, acetal), 3.91 (1H, td, *J* = 6.0, 5.5 Hz, H20), 4.16 (1H, td, *J* = 6.0, 5.5 Hz, H14), 4.87 (1H, t, *J* = 5.0 Hz, H1), 5.78-5.87 (2H, m, H12 and H18), 6.16 (1H, dd, *J* = 15.6, 5.5 Hz, H13 or H19), 6.20 (1H, dd, *J* = 15.6, 5.5 Hz, H13 or H19); ^{13}C NMR (100 MHz, C_6D_6) δ -4.73, -4.71, -4.5, -4.3, 9.5, 9.9, 10.5, 14.0, 18.41, 18.43, 26.0 (x3), 26.1 (x3), 29.5, 31.1, 33.6, 64.8 (x2), 71.9, 74.1, 74.4, 74.5, 75.8, 79.1, 80.1, 81.2, 85.2, 87.5, 103.4, 109.9, 110.1, 144.8, 145.6; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 $[M+Na]^+$, found 631.3587.

Tetrayne 2-2c. [TG-III-055] According to the synthetic procedure of **2-2b**, **2-2c** (174 mg, 0.286 mmol) was synthesized from **2-4c** (218 mg, 0.407 mmol) and **2-3** (127 mg, 0.629 mmol) in 70% yield by using $Pd(PPh_3)_4$ (74 mg, 64 μmol), CuI (23 mg, 0.12 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14.5 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 15/1): pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 0.00 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.83 (3H, t, *J* = 7.3 Hz, H22), 0.95 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.41 (2H, qd, *J* = 7.3, 6.0 Hz, H21), 1.86 (2H, td, *J* = 7.3, 5.0 Hz, H2), 2.28 (2H, tt, *J* = 7.3, 2.3 Hz, H3), 2.30 (1H, ddd, *J* = 16.5, 6.0, 1.8 Hz, H15a), 2.42 (1H, ddd, *J* = 16.5, 6.9, 1.8 Hz, H15b), 2.85 (2H, tt, *J* = 2.3, 2.3 Hz, H6), 2.94 (2H, d, *J* = 2.3 Hz, H9), 3.27-3.33 (2H, m, acetal), 3.38-3.47 (2H, m, acetal), 3.92 (1H, dt, *J* = 6.0, 6.0 Hz, H20), 4.16 (1H, dt, *J* = 6.0, 6.0 Hz, H14), 4.87 (1H, t, *J* = 5.0 Hz, H1), 5.78-5.88 (2H, m, H12 and H18), 6.16 (1H, dd, *J* = 15.6, 5.5 Hz, H13 or H19), 6.20 (1H, dd, *J* = 15.1, 5.0 Hz, H13 or H19); ^{13}C NMR (100 MHz, C_6D_6) δ -4.74, -4.72, -4.5, -4.3, 9.5, 9.9, 10.5, 14.0, 18.42, 18.43, 26.0 (x3), 26.1 (x3), 29.5, 31.1, 33.6, 64.8 (x2), 71.9, 74.1, 74.4, 74.5, 75.8, 79.1, 80.1, 81.2, 85.2, 87.5, 103.4, 109.9, 110.1, 144.8, 145.6; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 $[M+Na]^+$, found 631.3613.

Alkyne 2-23b. [TG-III-032] A suspension of tetrayne **2-2b** (32.4 mg, 53.2 μmol), quinoline (75 μL, 0.64 mmol) and Lindlar catalyst (65 mg) in hexane (3.0 mL) was stirred 0 ºC for 1 h under H_2 atmosphere (1 atm). Then

Lindlar catalyst (39 mg) was added. The reaction mixture was stirred 0 ºC for further 40 min under H_2 atmosphere, and was filtered through a pad of Celite with hexane. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1), and twice on Chromatorex-ACD (10 g, hexane/EtOAc 500/1 to 300/1; 8 g, hexane/EtOAc 500/1 to 200/1) to afford alkyne **2-23b** (18.1 mg, 29.4 μmol) in 55% yield: colorless oil; $[\alpha]_D^{27}$ +41 (*c* 0.81, $CHCl_3$); IR (neat) ν 2961, 2926, 2855, 1733, 1457, 1260, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.12 (3H, s, C*H*$_3$ of TBS), 0.16 (3H, s, C*H*$_3$ of TBS), 0.83 (3H, t, *J* = 7.3 Hz, H22), 0.97 (9H, s, *t*-Bu of TBS), 1.04 (9H, s, *t*-Bu of TBS), 1.43 (2H, m, H21), 1.81 (2H, m, H2), 2.31 (2H, m, H3), 2.45 (1H, ddd, *J* = 16.9, 5.9, 2.3 Hz, H15a), 2.59 (1H, ddd, *J* = 16.9, 7.3, 2.3 Hz, H15b), 2.87 (2H, m, H6), 2.99 (2H, t, *J* = 6.4 Hz, H9), 3.35-3.42 (2H, m, acetal), 3.52-3.60 (2H, m, acetal), 3.93 (1H, dt, *J* = 6.0, 6.0 Hz, H20), 4.38 (1H, dt, *J* = 6.4, 6.0 Hz, H14), 4.84 (1H, t, *J* = 4.6 Hz, H1), 5.47-5.50 (5H, m, H4, H5, H7, H8 and H10), 5.77 (1H, dd, *J* = 15.6, 6.0 Hz, H13), 5.86 (1H, ddt, *J* = 15.6, 1.4, 1.4 Hz, H18), 6.02 (1H, dd, *J* = 11.4, 11.4 Hz, H11), 6.19 (1H, dd, *J* = 15.6, 6.0 Hz, H19), 6.74 (1H, dd, *J* = 15.6, 11.4 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.6, -4.5, 9.3, 18.2, 18.3, 21.9, 25.5, 25.80 (x3), 25.83 (x3), 26.0, 29.6, 30.7, 33.7, 64.9 (x2), 72.0, 73.7, 80.4, 87.3, 104.1, 109.0, 124.7, 127.6, 128.0, 128.3, 128.6, 129.2, 129.9, 135.6, 145.2; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 $[M+Na]^+$, found 637.4094.

Alkyne 2-23c. [TG-IV-176] According to the synthetic procedure of **2-23b**, **2-23c** (34.0 mg, 55.3 μmol) was synthesized from **2-2c** (61.7 mg, 0.101 mmol) in 55% yield by using Lindlar catalyst (500 mg) and quinoline (0.14 mL, 1.2 mmol) in hexane (6.2 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 30/1 to 20/1), and three times on Chromatorex-ACD (20 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{24}$ -20 (*c* 1.7, $CHCl_3$); IR (neat) ν 2956, 2928, 2856, 1472, 1255,1136 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.12 (3H, s, C*H*$_3$ of TBS), 0.17 (3H, s, C*H*$_3$ of TBS), 0.84 (3H, t, *J* = 7.3 Hz, H22), 0.97 (9H, s, *t*-Bu of TBS), 1.04 (9H, s, *t*-Bu of TBS), 1.43 (2H, m, H21), 1.81 (2H, m, H2), 2.31 (2H, m, H3), 2.45 (1H, ddd, *J* = 16.9, 5.9, 2.3 Hz, H15a), 2.59 (1H, ddd, *J* = 16.9, 7.3, 2.3 Hz, H15b), 2.87 (2H, m, H6), 3.00 (2H, t, *J* = 6.4 Hz, H9), 3.35-3.42 (2H, m, acetal), 3.52-3.60 (2H, m, acetal), 3.93 (1H, dt, *J* = 6.0, 6.0 Hz, H20), 4.38 (1H, dt, *J* =

6.4, 6.0 Hz, H14), 4.84 (1H, t, *J* = 4.6 Hz, H1), 5.47-5.50 (5H, m, H4, H5, H7, H8 and H10), 5.77 (1H, dd, *J* = 15.6, 6.0 Hz, H13), 5.86 (1H, ddt, *J* = 15.6, 1.4, 1.4 Hz, H18), 6.02 (1H, dd, *J* = 11.4, 11.4 Hz, H11), 6.19 (1H, dd, *J* = 15.6, 6.0 Hz, H19), 6.75 (1H, dd, *J* = 15.6, 11.4 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.6, -4.5, 9.3, 18.2, 18.3, 21.9, 25.6, 25.81 (x3), 25.84 (x3), 26.0, 29.6, 30.7, 33.7, 64.9 (x2), 72.0, 73.7, 80.4, 87.3, 104.1, 109.0, 124.7, 127.7, 128.0, 128.3, 128.6, 129.2, 129.9, 135.6, 145.2; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 $[M+Na]^+$, found 637.4080.

Complex 2-28b. [TG-II-118] $Co_2(CO)_8$ (213 mg, 0.623 mmol) was added to a solution of **2-2b** (38.3 mg, 62.8 μmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 4 h and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1) to afford **2-28b** (104 mg, 59.4 μmol) in 94% yield: brown oil. Because signals in the ^{1}H NMR spectrum of **2-28b** were broaden, the formation was confirmed by the MS analysis: LRMS (ESI) calcd for $C_{60}H_{56}Co_8O_{28}Si_2Na$ 1774.7 $[M+Na]^+$, found 1774.7.

Complex 2-29b. [TG-III-039] $Co_2(CO)_8$ (69 mg, 0.20 mmol) was added to a solution of **2-23b** (31.1 mg, 50.5 μmol) in CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1) to afford **2-29b** (42.2 mg, 46.8 μmol) in 93% yield: brown oil; IR (neat) ν 2956, 2930, 2858, 2088, 2048, 2018, 1255, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.89 (3H, t, *J* = 7.8 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.54 (2H, m, H21), 1.72 (2H, m, H2), 2.20 (2H, td, *J* = 7.3, 7.3 Hz, H3), 2.82 (2H, t, *J* = 6.4 Hz, H6), 2.89-3.00 (2H, m, H9), 3.15-3.26 (2H, m, H15), 3.80-3.90 (2H, m, acetal), 3.91-4.01 (2H, m, acetal), 4.13 (1H, td, *J* = 6.4, 6.0 Hz, H20), 4.44 (1H, td, *J* = 6.0, 5.0 Hz, H14), 4.87 (1H, t, *J* = 4.6 Hz, H1), 5.30-5.47 (5H, m, H4, H5, H7, H8 and H10), 5.74 (1H, dd, *J* = 15.6, 6.0 Hz, H13), 5.99 (1H, dd, *J* = 15.6, 6.0 Hz, H19), 6.00 (1H, dd, *J* = 11.5, 11.5 Hz, H11), 6.58 (1H, dd, *J* = 15.6, 11.5 Hz, H12), 6.62 (1H, d, *J* = 15.6 Hz, H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.54, -4.46, 9.6, 18.26, 18.34, 21.9, 25.5, 25.8 (x3), 25.9 (x3), 26.0, 31.0, 33.7, 44.0, 64.9 (x2), 73.6, 74.4, 93.8, 104.1, 125.9, 126.4, 127.6, 128.0, 128.3, 128.7, 129.2, 130.5, 135.3, 140.4, some of the ^{13}C peaks

were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 $[M+Na]^+$, found 923.2457.

Hexaene 2-24b. [TG-III-040] *n*-Bu_3SnH (0.19 mL, 0.71 mmol) and *N*-methylmorpholine oxide (54.9 mg, 0.469 mmol) were successively added to a solution of **2-29b** (42.2 mg, 46.9 μmol) in toluene (45 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and was directly subjected to flash column chromatography [a column consecutively packed with silica gel 4 g and 10% (w/w) KF contained silica gel 4 g, hexane to hexane/EtOAc 20/1] to afford **2-24b** (25.2 mg, 40.8 μmol) in 87% yield: colorless oil; $[\alpha]_D^{27}$ +10 (*c* 0.93, $CHCl_3$); IR (neat) ν 2955, 2928, 2856, 1471, 1463, 1361, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.87 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.52 (2H, m, H21), 1.72 (2H, m, H2), 2.21 (2H, td, *J* = 8.2, 6.9 Hz, H3), 2.40 (2H, m, H15), 2.83 (2H, t, *J* = 6.4 Hz, H6), 2.94 (2H, t, *J* = 6.4 Hz, H9), 3.80-3.90 (2H, m, acetal), 3.91-4.02 (2H, m, acetal), 4.07 (1H, dt, *J* = 6.4, 6.0 Hz, H20), 4.22 (1H, td, *J* = 6.0, 6.0 Hz, H14), 4.87 (1H, t, *J* = 5.0 Hz, H1), 5.32-5.48 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.6, 6.0 Hz, H13 or H19), 5.66 (1H, dd, *J* = 15.6, 6.0 Hz, H13 or H19), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, dd, *J* = 11.4, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.6, 11.0 Hz, H12 or H18), 6.48 (1H, dd, *J* = 15.6, 11.4 Hz, H12 or H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 21.9, 25.6, 25.87 (x3), 25.90 (x3), 26.0, 31.1, 33.7, 36.8, 64.9 (x2), 72.9, 74.4, 104.1, 124.5, 124.6, 126.9, 127.7, 128.2, 128.3, 128.6, 129.2, 129.5, 129.8, 136.6, 137.2; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 $[M+Na]^+$, found 639.4233.

Complex 2-29c. [TG-IV-182] According to the synthetic procedure of **2-29b**, **2-29c** (41.3 mg, 45.9 μmol) was synthesized from **2-23c** (30.5 mg, 49.6 μmol) in 92% yield by using $Co_2(CO)_8$ (69 mg, 0.20 mmol) in CH_2Cl_2 (4.4 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 20/1): brown oil; IR (neat) ν 2955, 2929, 2857, 2088, 2048, 2018, 1472, 1255, 1062 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.88 (3H, t, *J* = 7.8 Hz, H22), 0.90 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.54 (2H, m, H21), 1.72 (2H, m, H2), 2.20 (2H, td, *J* = 7.3, 7.3 Hz, H3), 2.81 (2H, t, *J* = 6.4 Hz, H6), 2.89-3.00 (2H, m, H9), 3.15-3.26 (2H, m, H15),

3.80-3.90 (2H, m, acetal), 3.91-4.01 (2H, m, acetal), 4.13 (1H, td, *J* = 6.4, 6.0 Hz, H20), 4.44 (1H, td, *J* = 6.0, 5.0 Hz, H14), 4.87 (1H, t, *J* = 4.6 Hz, H1), 5.30-5.47 (5H, m, H4, H5, H7, H8 and H10), 5.75 (1H, dd, *J* = 15.6, 6.0 Hz, H13), 5.99 (1H, dd, *J* = 15.6, 6.0 Hz, H19), 6.00 (1H, dd, *J* = 11.5, 11.5 Hz, H11), 6.59 (1H, dd, *J* = 15.6, 11.5 Hz, H12), 6.62 (1H, d, *J* = 15.6 Hz, H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.80, -4.78, -4.6, -4.5, 9.6, 18.26, 18.33, 21.9, 25.5, 25.8 (x3), 25.9 (x3), 26.0, 31.0, 33.7, 44.0, 64.9 (x2), 73.5, 74.3, 91.8, 93.7, 104.1, 125.8, 126.4, 127.6, 128.0, 128.3, 128.7, 129.2, 130.4, 135.3, 140.5, 199.7, some of the ^{13}C peaks were missing due to broadening of the spectrum; $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 $[M+Na]^+$, found 923.2425.

Hexaene 2-24c. [TG-IV-183] According to the synthetic procedure of **2-24b**, **2-24c** (25 mg, 41 μmol) was synthesized from **2-29c** (41.3 mg, 45.9 μmol) in 86% yield by using *n*-Bu_3SnH (0.19 mL, 0.71 mmol) and *N*-methylmorpholine oxide (54 mg, 0.46 mmol) in toluene (40 mL). Purification was performed by flash column chromatography [a column consecutively packed with silica gel 3 g and 10% (w/w) KF contained silica gel 1 g, hexane to hexane/EtOAc 20/1]: colorless oil; $[\alpha]_D^{23}$ -24 (*c* 0.85, $CHCl_3$); IR (neat) ν 2956, 2927, 2856, 1471, 1462, 1362, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (6H, s, C*H*$_3$ of TBS x2), 0.87 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.52 (2H, m, H21), 1.72 (2H, m, H2), 2.21 (2H, td, *J* = 8.2, 6.9 Hz, H3), 2.40 (2H, m, H15), 2.83 (2H, t, *J* = 6.4 Hz, H6), 2.95 (2H, t, *J* = 6.4 Hz, H9), 3.80-3.90 (2H, m, acetal), 3.91-4.02 (2H, m, acetal), 4.07 (1H, dt, *J* = 6.4, 6.0 Hz, H20), 4.22 (1H, td, *J* = 6.0, 6.0 Hz, H14), 4.87 (1H, t, *J* = 5.0 Hz, H1), 5.32-5.48 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.6, 6.0 Hz, H13 or H19), 5.66 (1H, dd, *J* = 15.6, 6.0 Hz, H13 or H19), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, dd, *J* = 11.4, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.6, 11.0 Hz, H12 or H18), 6.48 (1H, dd, *J* = 15.6, 11.4 Hz, H12 or H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 21.9, 25.6, 25.86 (x3), 25.90 (x3), 26.0, 31.1, 33.7, 36.8, 64.8 (x2), 72.9, 74.5, 104.1, 124.5, 124.7, 127.0, 127.7, 128.2, 128.3, 128.6, 129.1, 129.5, 129.8, 136.6, 137.2; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 $[M+Na]^+$, found 639.4247.

(14*S*,20*R*)-2-1b. [TG-IV-170, 171, 172] TMSOTf (0.15 mL, 0.83 mmol) was added to a solution of **2-24b** (34.1 mg, 55.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (3.5 mL) at -10 °C. The reaction mixture was stirred at -10 °C for 45 min, and then H_2O (1.0 mL) was added. The resultant mixture was warmed to room

temperature and stirred for 30 min. Then the mixture was extracted with EtOAc (8 mL x2), and the combined organic layers were washed with aqueous 0.1 M HCl (4 mL), H_2O (4 mL) and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 20/1) to afford the crude aldehyde **2-30b**, which was used in the next reaction without further purification. Aldehyde **2-30b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (6H, s, C*H*$_3$ of TBS x2), 0.87 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.50 (2H, m, H21), 2.40 (4H, m, H3 and H15), 2.50 (2H, t, *J* = 6.8 Hz, H2), 2.84 (2H, t, *J* = 5.9 Hz, H6), 2.95 (2H, t, *J* = 6.4 Hz, H9), 4.07 (2H, dt, *J* = 6.4, 6.0 Hz, H20), 4.23 (2H, q, *J* = 6.0 Hz, H14), 5.30-5.46 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.1, 6.4 Hz, H13 or H19), 5.67 (1H, dd, *J* = 15.1, 6.0 Hz, H13 or H19), 5.91 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18), 6.47 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18), 9.77 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 20.1, 25.6, 25.87 (x3), 25.90 (x3), 26.1, 31.1, 36.8, 43.7, 72.9, 74.4, 124.3, 124.5, 126.9, 127.7, 128.0, 128.2, 128.3, 129.2, 129.3, 129.8, 136.7, 137.2, 201.9.

A solution of $NaClO_2$ (80% purity, 55.3 mg, 0.489 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (80.0 mg, 0.513 mmol) in H_2O (1.5 mL) were added to a solution of the above crude aldehyde **2-30b** in a mixture of *t*-BuOH (1.5 mL) and 2-methyl-2-butene (1.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Then the mixture was extracted with EtOAc (8 mL x2), and the combined organic layers were washed with H_2O (4 mL) and brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) to afford the crude carboxylic acid **2-31b**, which was used in the next reaction without further purification. Carboxylic acid **2-31b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (6H, s, C*H*$_3$ of TBS ×2), 0.87 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.44-1.55 (2H, m, H21), 2.35-2.42 (6H, m, H2, H3 and H15), 2.84 (2H, t, *J* = 6.0 Hz, H6), 2.95 (2H, t, *J* = 6.4 Hz, H9), 4.07 (2H, dt, *J* = 6.4, 6.4 Hz, H20), 4.23 (2H, dt, *J* = 6.0, 6.0 Hz, H14), 5.30-5.46 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.1, 6.4 Hz, H13 or H19), 5.67 (1H, dd, *J* = 15.1, 6.0 Hz, H13 or H19), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.1, 11.0 Hz, H18), 6.47 (1H, dd, *J* = 15.1, 11.0 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$) δ

-4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 22.5, 25.6, 25.87 (x3), 25.91 (x3), 26.0, 31.1, 33.9, 36.8, 72.9, 74.4, 124.4, 124.6, 126.9, 127.6, 128.0, 128.3 (x2), 129.3, 129.5, 129.8, 136.6, 137.2, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M-H]^-$, found 587.3951.

TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol) was added to a solution of the above crude carboxylic acid **2-31b** in THF (3.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, and then saturated aqueous NH_4Cl (4 mL) and 0.1 M HCl (10 mL) were successively added. The resultant mixture was extracted with EtOAc (10 mL and 5 mL), and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) to afford the crude (14*R*,20*S*)-**2-1b**. Then the crude **2-1b** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7:3:0.1 3 mL/min, t_R = 40 min) to afford **2-1b** (10.0 mg, 27.8 μmol) in 50% over 3 steps. **(14*S*,20*R*)-2-1b**: pale yellow oil; $[\alpha]_D^{18}$ -28 (*c* 0.42, MeOH); IR (neat) ν 3348, 3010, 2956, 2923, 2851, 1726, 1451, 1389, 1274 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.91 (3H, t, *J* = 7.8 Hz, H22), 1.53 (2H, m, H21), 2.27-2.52 (6H, m, H2, H3 and H15), 2.87 (2H, m, H6), 2.98 (2H, t, *J* = 6.4 Hz, H9), 4.01 (1H, dt, *J* = 6.4, 6.4 Hz, H20), 4.18 (1H, dt, *J* = 6.4, 6.4 Hz, H14), 5.32-5.50 (6H, m, H4, H5, H7, H8, H10 and H16), 5.65 (1H, dd, *J* = 15.1, 6.9 Hz, H19), 5.69 (1H, dd, *J* = 15.1, 6.9 Hz, H13), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11), 6.08 (1H, dd, *J* = 11.0, 11.0 Hz, H17), 6.50 (1H, dd, *J* = 15.1, 11.0 Hz, H18), 6.57 (1H, dd, *J* = 15.1, 11.0 Hz, H12); ^{13}C NMR (100 MHz, CD_3OD) δ 10.2, 26.6, 27.0, 31.2, 36.8, 73.1, 74.8, 126.5, 126.7, 128.1, 128.7, 129.3, 129.5, 129.7, 130.2, 130.8, 131.1, 137.2, 137.8, the C1, C2, and C3 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M-H]^-$, found 359.2222; UV (MeOH) λ_{max} 237 nm (ε 2.82×10^4).

(14*R*,20*R*)-2-1c. [TG-IV-184, 185, 186] According to the synthetic procedure of **2-1b**, **2-1c** (5.60 mg, 15.6 μmol) was synthesized from **2-24c** (40.7 mg, 66.0 μmol) in 24% yield over 3 steps by using TMSOTf (0.18 mL, 0.99 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) in CH_2Cl_2 (4.2 mL) for the first step, $NaClO_2$ (80% purity, 68.2 mg, 0.603 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (99.2 mg, 0.636 mmol) in a 1 : 1 : 1 mixture of *t*-BuOH, 2-methyl-2-butene and H_2O (4.5 mL) for the second, and TBAF (1.0 M in THF, 0.66 mL, 0.66 mmol) in THF (4.2 mL) for the third.

Purification was performed by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) for the second step, and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7:3:0.1 3 mL/min, t_R = 33 min) for the third. Aldehyde **2-30c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (6H, s, C*H*$_3$ of TBS x2), 0.87 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.50 (2H, m, H21), 2.40 (4H, m, H3 and H15), 2.50 (2H, t, *J* = 6.8 Hz, H2), 2.84 (2H, t, *J* = 5.9 Hz, H6), 2.95 (2H, t, *J* = 6.4 Hz, H9), 4.07 (2H, dt, *J* = 6.4, 6.0 Hz, H20), 4.23 (2H, m, H14), 5.30-5.46 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.1, 6.4 Hz, H13 or H19), 5.67 (1H, dd, *J* = 15.1, 6.0 Hz, H13 or H19), 5.91 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18), 6.47 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18), 9.78 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 20.1, 25.6, 25.86 (x3), 25.91 (x3), 26.0, 31.1, 36.8, 43.7, 72.8, 74.5, 124.4, 124.6, 127.0, 127.4, 128.0, 128.2, 128.3, 129.2, 129.3, 129.8, 136.7, 137.2, 201.9. Carboxylic acid **2-31c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (6H, s, C*H*$_3$ of TBS x2), 0.86 (3H, t, *J* = 7.3 Hz, H22), 0.90 (18H, s, *t*-Bu of TBS x2), 1.44-1.55 (2H, m, H21), 2.35-2.42 (6H, m, H2, H3 and H15), 2.84 (2H, t, *J* = 6.0 Hz, H6), 2.95 (2H, t, *J* = 6.4 Hz, H9), 4.07 (2H, dt, *J* = 6.4, 6.4 Hz, H20), 4.23 (2H, dt, *J* = 6.0, 6.0 Hz, H14), 5.30-5.46 (6H, m, H4, H5, H7, H8, H10 and H16), 5.62 (1H, dd, *J* = 15.1, 6.4 Hz, H13 or H19), 5.67 (1H, dd, *J* = 15.1, 6.0 Hz, H13 or H19), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11 or H17), 6.04 (1H, d, *J* = 11.0, 11.0 Hz, H11 or H17), 6.38 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18), 6.47 (1H, dd, *J* = 15.1, 11.0 Hz, H12 or H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 9.7, 18.2, 18.3, 22.5, 25.6, 25.87 (x3), 25.91 (x3), 26.0, 31.1, 33.9, 36.8, 72.9, 74.5, 124.4, 124.7, 127.0, 127.6, 128.0, 128.2, 128.3, 129.3, 129.5, 129.8, 136.6, 137.2, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M-H]^-$, found 587.3974. **(14*R*,20*R*)-2-1c**: pale yellow oil; $[\alpha]_D^{27}$ -16 (*c* 0.28, MeOH); IR (neat) ν 3380, 3011, 2958, 2925, 2855, 1713, 1556, 1415, 1260 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (3H, t, *J* = 7.3 Hz, H22), 1.53 (2H, m, H21), 2.27-2.52 (6H, m, H2, H3 and H15), 2.87 (2H, t, *J* = 5.5 Hz, H6), 2.98 (2H, t, *J* = 6.0 Hz, H9), 4.01 (1H, dt, *J* = 6.4, 6.4 Hz, H20), 4.18 (1H, dt, *J* = 6.4, 6.4 Hz, H14), 5.32-5.50 (6H, m, H4, H5, H7, H8, H10 and H16), 5.66 (1H, dd, *J* = 15.5, 6.4 Hz, H19), 5.69 (1H, dd, *J* = 15.5, 6.4 Hz, H13), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H11), 6.08 (1H, dd, *J* = 11.0, 11.0 Hz, H17), 6.51 (1H, ddt, *J* = 15.1, 11.0. 1.4 Hz, H18),

6.58 (1H, dd, J = 15.6, 11.0 Hz, H12); ^{13}C NMR (100 MHz, CD_3OD) δ 10.2, 26.5, 27.0, 31.2, 36.7, 73.1, 74.7, 126.5, 126.6, 128.1, 128.7, 129.3, 129.4, 129.6, 130.1, 130.8, 131.1, 137.1, 137.8, the C1, C2 and C3 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M-H]^-$, found 359.2243.

C16-22 fragment 2-8b. [TG-III-091, 092] According to the synthetic procedure of **2-8a**, **2-8b** (1.73 g, 7.72 mmol) was synthesized from **2-15b** (1.71 g, 9.40 mmol) in 82% yield over 2 steps by using TBSCl (2.84 g, 18.8 mmol) and imidazole (2.55 g, 37.5 mmol) in DMF (100 mL) for the first step, and K_2CO_3 (1.94 g, 14.1 mmol) in MeOH (100 mL) for the second. Purification was performed twice by medium pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 30/1 to 20/1; 45 g, hexane to hexane/EtOAc 30/1 to 20/1): colorless oil; $[\alpha]_D^{24}$ -18 (*c* 1.3, $CHCl_3$); Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78; found: C, 69.39 H, 10.48. The other analytical data of **2-8b** were identical to those of **2-8a**.

Alcohol 2-18a. [TG-III-107] According to the synthetic procedure of **2-18b**, **2-18a** (777 mg, 1.88 mmol) was synthesized from C16-22 fragment **2-8b** (867 mg, 3.87 mmol) and glycidol derivative **2-7a** (624 mg, 3.32 mmol) in 57% yield by using *n*-BuLi (1.6 M in hexane, 2.6 mL, 4.2 mmol) and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.5 mmol) in THF (37 mL). Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{24}$ -32 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3SiNa$ 435.2721 $[M+Na]^+$, found 435.2713. The other analytical data of **2-18a** were identical to those of **2-18b**.

Alcohol 2-20a. [TG-III-109, 110] According to the synthetic procedure of **2-20b**, **2-20a** (480 mg, 1.16 mmol) was synthesized from alcohol **2-18a** (766 mg, 1.86 mmol) in 62% yield over 2 steps by using Et_3N (0.65 mL, 4.7 mmol), TBSOTf (0.47 mL, 2.0 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (41 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step, and twice on silica gel (30 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{23}$ -20 (*c* 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M+Na]^+$, found 435.2738. The other analytical data of **2-20a** were identical to those of **2-20b**.

Aldehyde 2-21a. [TG-III-114] According to the synthetic procedure of **2-21b**, **2-21a** (378 mg, 0.920 mmol) was synthesized from alcohol **2-20a** (472 mg, 1.15 mmol) in 80% yield by using $NaHCO_3$ (904 mg, 10.8 mmol) and Dess-Martin periodinane (1.20 g, 2.83 mmol) in CH_2Cl_2 (24 mL). Purification was performed twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1; 30 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{22}$ +12 (*c* 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 $[M+MeOH+Na]^+$, found 465.2825. The other analytical data of **2-21a** were identical to those of **2-21b**.

C12-22 fragment 2-4a. [TG-III-115] According to the synthetic procedure of **2-4b**, **2-4a** (213 mg, 0.391 mmol) was synthesized from aldehyde **2-21a** (370 mg, 0.900 mmol) in 43% yield by using iodoform (571 mg, 1.45 mmol) and $CrCl_2$ (657 mg, 5.34 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/CH_2Cl_2 20/1 to 12/1): colorless oil; $[\alpha]_D^{22}$ -50 (*c* 0.77, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 $[M+Na]^+$, found 557.1719. The other analytical data of **2-4a** were identical to those of **2-4b**.

Tetrayne 2-2a. [TG-III-119] According to the synthetic procedure of **2-2b**, **2-2a** (144 mg, 0.236 mmol) was synthesized from **2-4a** (203 mg, 0.380 mmol) and **2-3** (92.9 mg, 0.459 mmol) in 62% yield by using $Pd(PPh_3)_4$ (64.8 mg, 56.1 μmol), CuI (21.6 mg, 0.113 mmol), and piperidine (0.12 mL, 1.20 mmol) in benzene (13 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil. The ^1H NMR spectrum of **2-2a** was identical to that of **2-2b**.

Allkyne 2-23a. [TG-III-122] According to the synthetic procedure of **2-23b**, **2-23a** (51.7 mg, 84.1 μmol) was synthesized from **2-2a** (68.4 mg, 0.112 mmol) in 75% yield by using Lindlar catalyst (173 mg) and quinoline (0.16 mL, 1.4 mmol) in hexane (7.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1), and twice on Chromatorex-ACD (20 g, hexane/EtOAc 500/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{21}$ -43 (*c* 0.69, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 $[M+Na]^+$, found 637.4128. The other analytical data of **2-23a** were identical to those of **2-23b**.

Complex 2-29a. [TG-III-128] According to the synthetic procedure of **2-29b**, **2-29a** (92.0 mg, 0.102 mmol) was synthesized from **2-23a** (66.0 mg, 0.107 mmol) in 95% yield by using $Co_2(CO)_8$ (149 mg, 0.436 mmol) in CH_2Cl_2

(10 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 $[M+Na]^+$, found 923.2449. The ^1H NMR spectrum of **2-29a** were identical to those of complex **2-29b**.

Hexaene 2-24a. [TG-III-129] According to the synthetic procedure of **2-24b**, **2-24a** (52.4 mg, 84.9 μmol) was synthesized from **2-29a** (92.0 mg, 0.102 mmol) in 85% yield by using *n*-Bu_3SnH (0.40 mL, 1.50 mmol) and *N*-methylmorpholine oxide (119 mg, 1.02 mmol) in toluene (50 mL). Purification was performed twice by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{21}$ -10 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 $[M+Na]^+$, found 639.4240. The other analytical data of **2-24a** were identical to those of **2-24b**.

(14*R*,20*S*)-2-1a. [TG-III-160, 161, 166] According to the synthetic procedure of **2-1b**, **2-1a** (4.59 mg, 12.8 μmol) was synthesized from **2-24a** (22.0 mg, 35.6 μmol) in 36% yield over 3 steps by using TMSOTf (95 μL, 0.52 mmol) and 2,6-lutidine (95 μL, 0.82 mmol) in CH_2Cl_2 (2.2 mL) for the first step, $NaClO_2$ (80% purity, 35.4 mg, 0.313 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (53.9 mg, 0.345 mmol) in a 1 : 1 : 1 mixture of *t*-BuOH, 2-methyl-2-butene and H_2O (3.0 mL) for the second, and TBAF (1.0 M in THF, 0.36 mL, 0.36 mmol) in THF (2.3 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 3/1) for the second step, and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7:3:0.1 3 mL/min, t_R = 42 min) for the third: pale yellow oil; $[\alpha]_D^{17}$ +22 (*c* 0.21, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M-H]^-$, found 359.2224. The other analytical data of **2-1a** were identical to those of **2-1b**.

Alcohol 2-18d. [TG-III-101] According to the synthetic procedure of **2-18b**, **2-18d** (791 mg, 1.92 mmol) was synthesized from C16-22 fragment **2-8b** (833 mg, 3.72 mmol) and glycidol derivative **2-7b** (596 mg, 3.17 mmol) in 61% yield by using *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol) and $BF_3{\cdot}OEt_2$ (0.41 mL, 3.3 mmol) in THF (31 mL). Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ -5.9 (*c* 0.98, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3SiNa$ 435.2721 $[M+Na]^+$, found 435.2716. The other analytical data of **2-18d** were identical to those of **2-18c**.

Alcohol 2-20d. [TG-III-103, 104] According to the synthetic procedure of **2-20b**, **2-20d** (453 mg, 1.10 mmol) was synthesized from alcohol **2-18d** (780 mg, 1.89 mmol) in 58% yield over 2 steps by using Et_3N (0.66 mL, 4.7 mmol), TBSOTf (0.48 mL, 2.1 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (40 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 20/1) for the first step, and on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{25}$ -17 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M+Na]^+$, found 435.2721. The other analytical data of **2-20d** were identical to those of **2-20c**.

Aldehyde 2-21d. [TG-III-105] According to the synthetic procedure of **2-21b**, **2-21d** (393 mg, 0.956 mmol) was synthesized from alcohol **2-20d** (437 mg, 1.06 mmol) in 90% yield by using $NaHCO_3$ (861 mg, 10.3 mmol) and Dess-Martin periodinane (677 mg, 1.60 mmol) in CH_2Cl_2 (22 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ -52 (*c* 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 $[M+MeOH+Na]^+$, found 465.2832. The other analytical data of **2-21d** were identical to those of **2-21c**.

C12-22 fragment 2-4d. [TG-III-106] According to the synthetic procedure of **2-4b**, **2-4d** (218 mg, 0.407 mmol) was synthesized from aldehyde **2-21d** (384 mg, 0.934 mmol) in 44% yield by using iodoform (739 mg, 1.88 mmol) and $CrCl_2$ (687 mg, 5.58 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15.5 mL). Purification was performed three times by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1; 30 g, hexane to hexane/EtOAc 20/1; 30 g, hexane/CH_2Cl_2 100/1 to 20/1): colorless oil; $[\alpha]_D^{23}$ +25 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 $[M+Na]^+$, found 557.1728. The other analytical data of **2-4d** were identical to those of **2-4c**.

Tetrayne 2-2d. [TG-III-124] According to the synthetic procedure of **2-2b**, **2-2d** (175 mg, 0.287 mmol) was synthesized from **2-4d** (218 mg, 0.407 mmol) and **2-3** (98.2 mg, 0.486 mmol) in 71% yield by using $Pd(PPh_3)_4$ (69.0 mg, 59.7 μmol), CuI (23.3 mg, 0.122 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil. The ^1H NMR spectrum of **2-2d** was identical to that of **2-2c**.

Alkyne 2-23d. [TG-III-127] According to the synthetic procedure of **2-23b**, **2-23d** (87.8 mg, 0.143 mmol) was synthesized from **2-2d** (86.9 mg, 0.143 mmol) in 100% yield by using Lindlar catalyst (180 mg) and quinoline (0.20 mL, 1.4 mmol) in hexane (8.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 30/1): colorless oil; $[\alpha]_D^{19}$ +16 (*c* 1.4, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 $[M+Na]^+$, found 637.4083. The other analytical data of **2-23d** were identical to those of **2-23c**.

Complex 2-29d. [TG-III-157] According to the synthetic procedure of **2-29b**, **2-29d** (80.2 mg, 89.1 μmol) was synthesized from **2-23d** (54.2 mg, 88.1 μmol) in 100% yield by using $Co_2(CO)_8$ (119 mg, 0.348 mmol) in CH_2Cl_2 (6.0 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 $[M+Na]^+$, found 923.2507. The ^1H NMR spectrum of **2-29d** were identical to those of cobalt complex **2-29c**.

Hexaene 2-24d. [TG-III-159] According to the synthetic procedure of **2-24b**, **2-24d** (47.2 mg, 76.5 μmol) was synthesized from **2-29d** (80.2 mg, 89.1 μmol) in 87% yield by using *n*-Bu_3SnH (0.34 mL, 1.3 mmol) and *N*-methylmorpholine oxide (101 mg, 0.86 mmol) in toluene (45 mL). Purification was performed twice by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1; 8 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{22}$ +21 (*c* 0.96, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 $[M+Na]^+$, found 639.4246. The other analytical data of **2-24d** were identical to those of **23ba**.

(14*S*,20*S*)-2-1d. [TG-III-162, 163, 165] According to the synthetic procedure of **2-1b**, **2-1d** (8.64 mg, 24.1 μmol) was synthesized from **2-24d** (47.2 mg, 76.4 μmol) in 32% yield over 3 steps by using TMSOTf (0.21 mL, 1.2 mmol) and 2,6-lutidine (0.20 mL, 1.7 mmol) in CH_2Cl_2 (4.7 mL) for the first step, $NaClO_2$ (80% purity, 76.0 mg, 0.672 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (113 mg, 0.73 mmol) in a 1 : 1 : 1 mixture of *t*-BuOH, 2-methyl-2-butene and H_2O (6.0 mL) for the second, and TBAF (1.0 M in THF, 0.76 mL, 0.76 mmol) in THF (5.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (8 g, hexane/EtOAc 4/1 to 3/1 to 3/2) for the second step, and by flash column chromatography on silica gel (6 g, hexane/EtOAc/AcOH 40/60/0.05 to 30/70/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 36 min) for the third: pale

yellow oil; $[\alpha]_D^{19}$ +13 (*c* 0.41, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M-H]^-$, found 359.2223; UV (MeOH) λ_{max} 236 nm (ε 2.60×10^4). The other analytical data of **2-1d** were identical to those of **2-1c**.

C1-9 fragment 3-3. [TG-V-108, 109] A mixture of CuI (287 mg, 1.51 mmol), NaI (227 mg, 1.51 mmol) and Cs_2CO_3 (491 mg, 1.51 mmol) was dried in vacuo at room temperature. After the mixture was cooled to 0 °C, a solution of propargy bromide **3-5** (0.27 mL, 1.7 mmol) in DMF (2.6 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **3-6** (332 mg, 1.80 mmol, a 1:0.3:0.3 mixture of **3-6**, Et_2O and pentane) in DMF (2.6 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 h, and then saturated aqueous NH_4Cl (5 mL) was added. The resultant mixture was filtered through a pad of Celite with Et_2O. The filtrate was extracted with Et_2O (20 mL and 10 mL x3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 20/1) to afford the crude **3-10**, which was used in the next reaction without further purification.

AcOH (0.21 mL, 3.7 mmol) and TBAF (1.0 M in THF, 3.7 mL, 3.7 mmol) were successively added to a solution of the above crude **3-10** in THF (50 mL) at -5 ºC. The reaction mixture was stirred at -5 ºC for 1 h, warmed to room temperature, and stirred for 2 h. Then saturated aqueous NH_4Cl (15 mL) was added. The resultant mixture was extracted Et_2O (50 mL), and the organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 20/1) to afford C1-9 fragment **3-3** (165 mg, 0.927 mmol) in 56% over 2 steps based on **3-5**: colorless oil; IR (neat) ν 3288, 2953, 2882, 2233, 2124, 1473, 1455, 1435, 1414, 1312, 1135, 1033, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59-1.67 (2H, m, H3), 1.73-1.80 (2H, m, H2), 2.05 (1H, t, *J* = 2.7 Hz, H9), 2.23 (2H, tt, *J* = 7.3, 2.7 Hz, H4), 3.14 (2H, dt, *J* = 2.7, 2.7 Hz, H7), 3.81-4.01 (4H, m, acetal), 4.87 (1H, t, *J* = 4.6 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 18.4, 22.9, 32.7, 64.7 (x2), 68.4, 73.4, 78.7, 80.5, 104.0; HRMS (DART) calcd for $C_{11}H_{15}O_2$ 179.1067 $[M+H]^+$, found 179.1073.

C11-15 fragment 3-22a. [TG-V-056, 058, 059] According to the synthetic procedure of **3-22b**, C11-15 fragment **3-22a** (1.58 g, 4.73 mmol) was synthesized from **3-24a** (970 mg, 5.00 mmol) and trimethylsilyl acetylene (1.4 mL, 9.9 mmol) in 95% yield over 3 steps by using *n*-BuLi (1.6 M in hexane, 6.6 mL, 11 mmol) and $BF_3{\cdot}OEt_2$ (1.2 mL,

9.7 mmol) in THF (25 mL) for the first reaction, K_2CO_3 (899 mg, 6.51 mmol) in MeOH (40 mL) for the second, and TBSOTf (1.3 mL, 5.7 mmol) and 2,6-lutidine (1.4 mL, 12 mmol) in CH_2Cl_2 (45 mL) for the third. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 5/1) for the first reaction, on silica gel (45 g, hexane/EtOAc 6/1 to 2/1) for the second and on silica gel (45 g, hexane to hexane/EtOAc 30/1) for the third: colorless oil; $[\alpha]_D^{27}$ +0.51 (*c* 1.1, $CHCl_3$); IR (neat) ν 3310, 2953, 2929, 2856, 2121, 1613, 1514, 1464, 1249, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.95 (1H, t, *J* = 2.7 Hz, H15), 2.35 (1H, ddd, *J* = 16.9, 6.0, 2.7 Hz, H13a), 2.47 (1H, ddd, *J* = 16.9, 6.0, 2.7 Hz, H13b), 3.45 (1H, dd, *J* = 14.2, 5.5 Hz, H11a), 3.47 (1H, dd, *J* = 14.2, 5.5 Hz, H11b), 3.81 (3H, s, OMe), 3.96 (1H, tt, *J* = 6.0, 5.5 Hz, H12), 4.47 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J* = 8.7 Hz, aromatic), 7.26 (2H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.7, -4.6, 18.1, 24.7, 25.8 (x3), 55.3, 69.8, 70.2, 73.0, 73.3, 81.4, 113.7 (x2), 129.2 (x2), 130.4, 159.1; HRMS (ESI) calcd for $C_{19}H_{30}O_3SiNa$ 357.1856 $[M+Na]^+$, found 357.1862.

C11-15 fragment 3-22b. [TG-V-183, 184, 185] *n*-BuLi (1.35 M in hexane, 12.5 mL, 16.9 mmol) was added to a solution of trimethylsilyl acetylene (2.3 mL, 16 mmol) in THF (34 mL) at -78 ºC. The solution was stirred at -78 ºC for 10 min, warmed to 0 ºC and stirred for 50 min. After the mixture was cooled to -78 °C, $BF_3{\cdot}OEt_2$ (2.0 mL, 16 mmol) and a solution of **3-24b** (1.56 g, 8.04 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at -78 ºC for 30 min and warmed to -40 ºC over 1 h, and then saturated aqueous NH_4Cl (30 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 4/1) to afford the crude alcohol **3-25b**, which was used in the next reaction without further purification.

K_2CO_3 (1.44 g, 10.4 mmol) was added to a solution of the above crude alcohol **3-25b** in MeOH (62 mL) at room temperature. The reaction mixture was stirred at room temperature for 11 h. After the mixture was cooled to 0 ºC, saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with Et_2O (60 mL x4), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g,

hexane/EtOAc 4/1 to 1/1) to afford the crude alcohol, which was used in the next reaction without further purification.

TBSOTf (0.28 mL, 1.2 mmol) was added to a solution of the above crude alcohol and 2,6-lutidine (0.32 mL, 2.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to room temperature and stirred for 1.5 h, and then TBSOTf (0.40 mL, 1.7 mmol) and 2,6-lutidine (0.68 mL, 5.8 mmol) were added. After 20 min, TBSOTf (1.4 mL, 5.9 mmol) and 2,6-lutidine (1.3 mL, 11 mmol) were added. After further 40 min, TBSOTf (1.0 mL, 4.4 mmol) and 2,6-lutidine (0.70 mL, 6.0 mmol) were added again. The mixture was stirred for 10 min and cooled to 0 ºC, and then saturated aqueous $NaHCO_3$ (10 mL) was added. The resultant mixture was extracted Et_2O (60 mL x3), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 7/1) to afford C11-15 fragment **3-22b** (2.61 g, 7.79 mmol) in 97% yield over 3 steps: colorless oil: $[\alpha]_D^{28}$ -0.60 (*c* 0.90, $CHCl_3$). The other analytical data of **3-22b** were identical to those of **3-22a**.

Triol 3-28a. [TG-VI-083] According to the synthetic procedure of **3-28b**, triol **3-28a** (390 mg, 3.25 mmol) was synthesized from **3-35a** (1.00 g, 3.39 mmol, a 2.5 : 2 : 1 : 2 mixture of **3-35a**, *t*-BuOH, Et_2O and pentane) in 96% yield by using $LiAlH_4$ (520 mg, 13.7 mmol) in THF (36 mL). Purification was performed by flash column chromatography on silica gel (20 g, $CHCl_3$/MeOH 5/1): colorless oil. The other analytical data of **3-28a** were identical to those reported previously [ref. 6b in chapter 3].

Triol 3-28b. [TG-V-170] A solution of **3-35b** (3.71 g, 8.38 mmol, a 1.8 : 4.5 : 1 : 1.6 mixture of **3-35b**, *t*-BuOH, Et_2O and pentane) in THF (20 mL) was added to a solution of $LiAlH_4$ (1.28 g, 33.7 mmol) in THF (65 mL) at 0 ºC over 25 min. The reaction mixture was warmed to room temperature and stirred for 5 h. After the mixture was cooled to 0 ºC, saturated aqueous potassium sodium tartrate (50 mL) and *n*-BuOH (100 mL) were added. The resultant mixture was warmed to room temperature and stirred for 19 h. After separation, the aqueous layer was extracted with *n*-BuOH (20 mL x4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was performed by flash column chromatography on silica gel (30 g, $CHCl_3$/MeOH 9/1

to 5/1) to afford triol **3-28b** (783 mg, 6.51 mmol) in 78% yield: colorless oil. The analytical data of **3-28b** were identical to those reported previously [ref. 6b in chapter 3].

C16-20 fragment 3-9a. [TG-VI-089] According to the synthetic procedure of **3-9b**, C16-20 fragment **3-9a** (549 mg, 2.14 mmol) was synthesized from **3-28a** (393 mg, 3.28 mmol) in 65% yield by using NaH (60 wt% in mineral oil, 789 mg, 19.7 mmol) and tosyl imidazole (2.97 g, 13.4 mmol) in THF (65 mL). Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1): white solid; mp 61-62 ºC; $[\alpha]_D^{18}$ +16 (*c* 1.0, $CHCl_3$). The other analytical data of **3-9a** were identical to those of **3-9b** and the previously reported data [ref. 11 in chapter 3].

C16-20 fragment 3-9b. [TG-V-173] NaH (60 wt% in mineral oil, 784 mg, 19.6 mmol) was added to a solution of **3-28b** (783 mg, 6.53 mmol) in THF (130 mL) at 0 °C. The mixture was stirred at 0 ºC for 1 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at 0 ºC for 50 min, warmed to room temperature, and stirred for 40 min. After the mixture was cooled to 0 °C, NaH (60 wt% in mineral oil, 392 mg, 9.80 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1.5 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at room temperature for 17 h. After the mixture was cooled to 0 ºC, pH 7 phosphate buffer (20 mL) was added. The resultant mixture was extracted with EtOAc (150 mL and 100 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 9/1) to afford C16-20 fragment **3-9b** (1.16 g, 4.53 mmol) in 69% yield: white solid; mp 61 ºC; $[\alpha]_D^{18}$ -16 (*c* 1.0, $CHCl_3$); IR (neat) ν 2976, 2935, 2886, 1598, 1459, 1358, 1189, 1174, 1097, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.4 Hz, H20), 1.76 (2H, qd, *J* = 7.4, 6.4 Hz, H19), 2.44 (3H, s, C*H*$_3$ of Ts), 2.63 (1H, dd, *J* = 4.6, 2.3 Hz, H16a), 2.78 (1H, dd, *J* = 4.6, 4.6 Hz, H16b), 3.05 (1H, ddd, *J* = 6.4, 4.6, 2.3 Hz, H17), 4.28 (1H, dt, *J* = 6.4, 6.4 Hz, H18), 7.33 (2H, d, *J* = 7.8 Hz, aromatic), 7.82 (2H, d, *J* = 7.8 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 21.5, 25.0, 44.6, 52.3, 84.6, 127.7 (x2), 129.5 (x2), 134.0, 144.5; HRMS (ESI) calcd for $C_{12}H_{16}O_4SNa$ 279.0662 $[M+Na]^+$, found 279.0661.

TBS ether 3-44a. [TG-V-130, 132] According to the synthetic procedure of **3-44c**, **3-44a** (781 mg, 1.11 mmol) was synthesized from **3-22a** (988 mg, 2.95 mmol) and **3-9a** (306 mg, 1.20 mmol) in 93% yield over 2 steps by using *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) and $BF_3{\cdot}OEt_2$ (0.37 mL, 3.0 mmol) in THF (5.9 mL) for the first reaction, and TBSOTf (0.95 mL, 4.1 mmol) and Et_3N (1.4 mL, 10 mmol) in 1,2-dichloroethane (12 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1 to 3/1) for the first reaction, and on silica gel (10 g, hexane to hexane/EtOAc 20/1) for the second: colorless oil; $[\alpha]_D^{26}$ -15 (*c* 1.4, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1920, 1613, 1514, 1463, 1364, 1250, 1177, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (6H, s, C*H*$_3$ of TBS x2), 0.08 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J* = 7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.88 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.76 (1H, m, H19b), 2.13-2.37 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.41 (1H, dd, *J* = 10.0, 6.0 Hz, H11a), 3.49 (1H, dd, *J* = 10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.86-3.94 (2H, m, H12 and 17), 4.35 (1H, ddd, *J* = 8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.86 (2H, d, *J* = 8.2 Hz, aromatic), 7.26 (2H, d, *J* = 8.2 Hz, aromatic), 7.32 (2H, d, *J* = 8.2 Hz, aromatic), 7.79 (2H, d, *J* = 8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.64, -4.59, 10.1, 17.9, 18.1, 21.4, 21.6, 22.2, 25.0, 25.7 (x3), 25.8 (x3), 55.2, 70.8, 71.5, 72.9, 73.5, 78.4, 78.7, 85.5, 113.6 (x2), 127.8 (x2), 129.1 (x2), 129.7 (x2), 130.5, 134.2, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3469.

Alcohol 3-45a. [TG-V-135] According to the synthetic procedure of **3-45c**, alcohol **3-45a** (606 mg, 1.04 mmol) was synthesized from **3-44a** (781 mg, 1.11 mmol) in 94% yield by using DDQ (279 mg, 1.23 mmol) in a mixture of CH_2Cl_2 (10 mL) and pH 7 phosphate buffer (1.0 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1), and three times by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 4/1; 45 g, hexane to hexane/EtOAc 4/1; 14 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{27}$ -24 (*c* 0.91, $CHCl_3$); IR (neat) ν 3465, 2954, 2929, 2857, 1644, 1463, 1363, 1255, 1189, 1177, 1100, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J* = 7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 1.93 (1H, dd, *J* = 7.3, 5.9 Hz, O*H*),

2.15-2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.57 (1H, ddd, *J* = 11.9, 7.3, 5.0 Hz, H11a), 3.68 (1H, ddd, *J* = 11.9, 5.9, 3.6 Hz, H11b), 3.85 (1H, m, H17), 3.91 (1H, m, H12), 4.35 (1H, ddd, *J* = 8.2, 8.2, 4.1 Hz, H18), 7.34 (2H, d, *J* = 8.7 Hz, aromatic), 7.79 (2H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.94, -4.86, -4.69, -4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (x3), 25.7 (x3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.5, 127.7 (x2), 129.7 (x2), 134.1, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2897.

Aldehyde 3-46a. [TG-V-136] According to the synthetic procedure of aldehyde **3-46c**, **3-46a** (577 mg, 0.990 mmol) was synthesized from **3-45a** (606 mg, 1.04 mmol) in 95% yield by using Dess-Martin periodinane (887 mg, 2.09 mmol) and $NaHCO_3$ (832 mg, 9.90 mmol) in CH_2Cl_2 (10 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$ -13 (*c* 0.83, $CHCl_3$); IR (neat) ν 2953, 2930, 2857, 1741, 1463, 1365, 1254, 1177, 1119, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.12 (6H, s, C*H*$_3$ of TBS x2), 0.75 (3H, t, *J* = 7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 2.19 (1H, ddt, *J* = 16.5, 8.2, 2.3 Hz, H16a), 2.35 (1H, m, H16b), 2.45-2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.92 (1H, dt, *J* = 7.3, 4.6 Hz, H17), 4.07 (1H, td, *J* = 6.8, 1.4 Hz, H12), 4.34 (1H, dt, *J* = 9.2, 3.7 Hz, H18), 7.34 (2H, d, *J* = 8.2 Hz, aromatic), 7.79 (2H, d, *J* = 8.2 Hz, aromatic), 9.63 (1H, t, *J* = 1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.92, -4.87, -4.82, -4.6, 10.1, 17.9, 18.2, 21.3, 21.6, 22.2, 23.4, 25.6 (x3), 25.7 (x3), 71.3, 76.0, 76.5, 79.7, 85.4, 127.8 (x2), 129.7 (x2), 134.1, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3020.

C10-20 fragment 3-43a. [TG-V-137] According to the synthetic procedure of C10-20 fragment **3-43c**, **3-43a** (613 mg, 0.868 mmol) was synthesized from aldehyde **3-46a** (577 mg, 0.990 mmol) in 88% yield by using $CrCl_2$ (836 mg, 6.80 mmol) and iodoform (903 mg, 2.29 mmol) in a mixture of THF (4.0 mL) and 1,4-dioxane (12.4 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{24}$ -41 (*c* 1.0, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1917, 1600, 1463, 1363, 1255, 1188, 1177, 1098, 931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.08 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J* = 7.4 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.16-2.40 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H,

dt, *J* = 8.7, 4.5 Hz, H17), 4.19 (1H, m, H12), 4.35 (1H, dt, *J* = 8.7, 4.1 Hz, H18), 6.31 (1H, dd, *J* = 14.6, 1.4 Hz, H10), 6.66 (1H, dd, *J* = 14.6, 5.5 Hz, H11), 7.34 (2H, d, *J* = 8.7 Hz, aromatic), 7.80 (2H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.94, -4.88, -4.81, -4.6, 10.2, 17.9, 18.2, 21.3, 21.6, 22.2, 25.68 (x3), 25.73 (x3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.5, 127.8 (x2), 129.7 (x2), 134.1, 144.6, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1923.

TBS ether 3-44b. [TG-VI-092, 093] According to the synthetic procedure of **3-44c**, **3-44b** (319 mg, 0.452 mmol) was synthesized from **3-22b** (504 mg, 1.50 mmol) and **3-9a** (155 mg, 0.605 mmol) in 75% yield over 2 steps by using *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.6 mmol) and $BF_3{\cdot}OEt_2$ (0.19 mL, 1.5 mmol) in THF (3.0 mL) for the first reaction, and TBSOTf (0.23 mL, 1.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in 1,2-dichloroethane (5.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{26}$ -7.5 (*c* 1.1, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1614, 1514, 1463, 1363, 1250, 1177, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.065 (3H, s, C*H*$_3$ of TBS), 0.067 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J* = 7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.76 (1H, m, H19b), 2.14-2.43 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.42 (1H, dd, *J* = 10.0, 5.5 Hz, H11a), 3.50 (1H, dd, *J* = 10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.87-3.94 (2H, m, H12 and 17), 4.38 (1H, ddd, *J* = 8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J* = 8.7 Hz, aromatic), 7.26 (2H, d, *J* = 8.7 Hz, aromatic), 7.32 (2H, d, *J* = 8.7 Hz, aromatic), 7.80 (2H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.61, -4.56, 10.1, 17.9, 18.2, 21.5, 21.6, 22.3, 25.0, 25.7 (x3), 25.8 (x3), 55.2, 70.8, 71.5, 73.0, 73.6, 78.4, 78.7, 85.5, 113.7 (x2), 127.8 (x2), 129.1 (x2), 129.7 (x2), 130.6, 134.3, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3470.

Alcohol 3-45b. [TG-V-079] According to the synthetic procedure of alcohol **3-45c**, **3-45b** (452 mg, 0.773 mmol) was synthesized from **3-44b** (736 mg, 1.04 mmol) in 74% yield by using DDQ (402 mg, 1.81 mmol) in a mixture of CH_2Cl_2 (80 mL) and pH 7 phosphate buffer (8 mL). The residue was purified twice by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) and flash column chromatography on silica gel (15 g, hexane/EtOAc 20/1 to 6/1): colorless oil; $[\alpha]_D^{28}$ -6.6 (*c* 2.0, $CHCl_3$); IR (neat) ν 3571, 2953, 2929, 2857, 1923, 1599,

1463, 1363, 1255, 1189, 1176, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J* = 7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 1.92 (1H, dd, *J* = 6.4, 6.4 Hz, O*H*), 2.14-2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.58 (1H, ddd, *J* = 11.0, 7.3, 5.0 Hz, H11a), 3.67 (1H, ddd, *J* = 11.0, 5.5, 3.6 Hz, H11b), 3.85 (1H, m, H12), 3.90 (1H, m, H17), 4.37 (1H, ddd, *J* = 8.3, 8.3, 3.7 Hz, H18), 7.34 (2H, d, *J* = 8.2 Hz, aromatic), 7.80 (2H, d, *J* = 8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.93, -4.85, -4.68, -4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (x3), 25.7 (x3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.4, 127.7 (x2), 129.7 (x2), 134.2, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2919.

Aldehyde 3-46b. [TG-V-083] According to the synthetic procedure of aldehyde **3-46c**, **3-46b** (303 mg, 0.520 mmol) was synthesized from **3-45b** (320 mg, 0.547 mmol) in 95% yield by using Dess-Martin periodinane (471 mg, 1.11 mmol) and $NaHCO_3$ (449 mg, 5.35 mmol) in CH_2Cl_2 (32 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 10 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{27}$ -22 (*c* 1.6, $CHCl_3$); IR (neat) ν 2953, 2929, 2857, 1741, 1600, 1471, 1463, 1363, 1255, 1177, 1120, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.117 (3H, s, C*H*$_3$ of TBS), 0.122 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J* = 7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.20 (1H, dd, *J* = 16.0, 7.8 Hz, H16a), 2.37 (1H, m, H16b), 2.45-2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J* = 7.8, 4.6 Hz, H17), 4.08 (1H, td, *J* = 6.4, 1.4 Hz, H12), 4.36 (1H, dt, *J* = 9.2, 3.7 Hz, H18), 7.34 (2H, d, *J* = 8.2 Hz, aromatic), 7.80 (2H, d, *J* = 8.2 Hz, aromatic), 9.63 (1H, t, *J* = 1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.85, -4.78, -4.6, 10.1, 17.9, 18.2, 21.4, 21.6, 22.2, 23.5, 25.67 (x3), 25.69 (x3), 71.3, 76.1, 76.6, 79.8, 85.4, 127.8 (x2), 129.7 (x2), 134.2, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3011.

C10-20 fragment 3-43b. [TG-V-084] According to the synthetic procedure of C10-20 fragment **3-43c**, **3-43b** (244 mg, 0.346 mmol) was synthesized from aldehyde **3-46b** (291 mg, 0.499 mmol) in 69% yield by using $CrCl_2$ (434 mg, 3.53 mmol) and iodoform (469 mg, 1.19 mmol) in a mixture of THF (2.0 mL) and 1,4-dioxane (6.2 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{27}$ +12 (*c* 1.1, $CHCl_3$); IR (neat) ν 2954, 2929, 2857, 1600, 1463, 1363, 1255, 1189, 1177, 1098,

931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s, CH_3 of TBS x2), 0.07 (6H, s, CH_3 of TBS x2), 0.77 (3H, t, *J* = 7.5 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.50 (1H, m, H19a), 1.76 (1H, m, H19b), 2.17-2.42 (4H, m, H13 and H16), 2.45 (3H, s, CH_3 of Ts), 3.91 (1H, dt, *J* = 6.9, 4.5 Hz, H17), 4.18 (1H, m, H12), 4.37 (1H, dt, *J* = 8.0, 4.0 Hz, H18), 6.32 (1H, dd, *J* = 14.3, 1.8 Hz, H10), 6.66 (1H, dd, *J* = 14.3, 5.2 Hz, H11), 7.34 (2H, d, *J* = 8.6 Hz, aromatic), 7.80 (2H, d, *J* = 8.6 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.95, -4.86, -4.81, -4.6, 10.2, 17.9, 18.1, 21.4, 21.6, 22.2, 25.68 (x3), 25.72 (x3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.4, 127.8 (x2), 129.7 (x2), 134.2, 144.5, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1952.

Triyne 3-42a. [TG-V-139] According to the synthetic procedure of triyne **3-42c**, **3-42a** (181 mg, 0.240 mmol) was synthesized from **3-43a** (242 mg, 0.342 mmol) and **3-3** (91.2 mg, 0.512 mmol) in 70% yield by using $Pd(PPh_3)_4$ (59.4 mg, 51.4 μmol), CuI (19.6 mg, 0.103 mmol) and piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 30 g, hexane to hexane/EtOAc 9/1). Triyne **3-42a** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 0.03 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.81 (3H, t, *J* = 7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.58-1.65 (2H, m, H3), 1.75-1.81 (3H, m, H2 and H19b), 1.86 (3H, s, CH_3 of Ts), 2.03 (2H, tt, *J* = 6.9, 2.3 Hz, H4), 2.24-2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, *J* = 1.8, 1.8 Hz, H7), 3.29-3.38 (2H, m, acetal), 3.45-3.54 (2H, m, acetal), 4.17 (1H, dt, *J* = 6.8, 4.6 H, H17), 4.27 (1H, dt, *J* = 5.5, 5.0 H, H12), 4.69 (1H, ddd, *J* = 8.7, 4.6 Hz, H18), 4.73 (1H, t, *J* = 5.0 Hz, H1), 5.93 (1H, ddt, *J* = 16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, *J* = 16.0, 5.0 Hz, H11), 6.75 (2H, d, *J* = 8.2 Hz, aromatic), 7.83 (2H, d, *J* = 8.2 Hz, aromatic); HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3819.

Triyne 3-42b. [TG-V-110] According to the synthetic procedure of triyne **3-42c**, **3-42b** (152 mg, 0.201 mmol) was synthesized from **3-43b** (166 mg, 0.235 mmol) and **3-3** (63.4 mg, 0.356 mmol) in 86% yield by using $Pd(PPh_3)_4$ (41.0 mg, 35.5 μmol), CuI (13.5 mg, 70.9 mmol) and piperidine (70 μL, 0.71 mmol) in benzene (3.6 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 6/1).

Triyne **3-42b** was immediately used in the next reaction due to its instability under air: pale yellow oil; HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3828. The ^1H NMR spectrum of **3-42b** was identical to that of **3-42d**.

Alkyne 3-53a. [TG-V-143] According to the synthetic procedure of **3-53c**, **3-53a** (96.0 mg, 0.126 mmol) was synthesized from **3-42a** (98.1 mg, 0.130 mmol) in 97% by using quinoline (0.18 mL, 1.6 mmol) and Lindlar catalyst (800 mg) in hexane (10 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{24}$ -37 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1461, 1364, 1254, 1177, 931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.066 (3H, s, C*H*$_3$ of TBS), 0.071 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J* = 7.5 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45-1.55 (3H, m, H3 and H19a), 1.64-1.70 (2H, m, H2), 1.75 (1H, m, H19b), 2.11 (2H, dt, *J* = 7.4 Hz, H4), 2.15-2.29 (2H, m, H13a and H16a), 2.32-2.39 (2H, m, H13b and H16b), 2.44 (3H, s, C*H*$_3$ of Ts), 2.92 (2H, m, H7), 3.83-3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.94-3.98 (2H, m, acetal), 4.30 (1H, dt, *J* = 6.0, 5.7 Hz, H12), 4.36 (1H, dt, *J* = 9.0, 4.0 Hz, H18), 4.85 (1H, t, *J* = 5.0 Hz, H1), 5.33-5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, *J* = 15.0, 5.5 Hz, H11), 6.00 (1H, dd, *J* = 11.0, 11.0 Hz, H9), 6.54 (1H, dd, *J* = 15.0, 11.0 Hz, H10), 7.33 (2H, d, *J* = 8.5 Hz, aromatic), 7.80 (2H, d, *J* = 8.5 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.9, -4.8, -4.64, -4.59, 10.1, 17.9, 18.2, 21.4, 21.6, 22.3, 23.9, 25.7 (x3), 25.8 (x3), 26.0, 27.0, 29.0, 33.3, 64.8 (x2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (x2), 127.9, 129.7 (x2), 129.9, 130.0, 134.2, 135.5, 144.5; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4117.

Alkyne 3-53b. [TG-V-113] According to the synthetic procedure of **3-53c**, **3-53b** (64.0 mg, 84.2 μmol) was synthesized from **3-42b** (75.3 mg, 99.6 μmol) in 85% by using quinoline (0.14 mL, 1.2 mmol) and Lindlar catalyst (330 mg) in hexane (7.5 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$ +15 (*c* 0.93, $CHCl_3$); IR (neat) ν 2953, 2928, 2856, 1599, 1471, 1462, 1364, 1257, 1177, 1099, 932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.07 (6H, s, C*H*$_3$ of TBS x2), 0.08 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J* = 7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.45-1.55 (3H, m, H3 and H19a), 1.63-1.70 (2H, m, H2), 1.76 (1H, m, H19b), 2.11 (2H, dt, *J* = 7.3, 7.3 Hz,

H4), 2.20-2.28 (2H, m, H13a and H16a), 2.33-2.41 (2H, m, H13b and H16b), 2.44 (3H, s, CH_3 of Ts), 2.92 (2H, m, H7), 3.82-3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.93-3.98 (2H, m, acetal), 4.30 (1H, dt, *J* = 6.0, 6.0 Hz, H12), 4.37 (1H, ddd, *J* = 8.7, 8.7, 3.6 Hz, H18), 4.85 (1H, t, *J* = 5.0 Hz, H1), 5.33-5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, *J* = 15.1, 5.0 Hz, H11), 6.00 (1H, dd, *J* = 11.0, 11.0 Hz, H9), 6.45 (1H, dd, *J* = 15.1, 11.0 Hz, H10), 7.33 (2H, d, *J* = 8.7 Hz, aromatic), 7.80 (2H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.8, -4.61, -4.56, 10.1, 18.0, 18.3, 21.4, 21.6, 22.3, 23.9, 25.7 (x3), 25.8 (x3), 26.1, 27.0, 29.0, 33.4, 64.8 (x2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (x2), 128.0, 129.7 (x2), 129.9, 130.0, 134.3, 135.5, 144.5; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4099.

Complex 3-54a. [TG-V-145] According to the synthetic procedure of complex **3-54c**, **3-54a** (118 mg, 0.113 mmol) was synthesized from **3-53a** (96 mg, 0.13 mmol) in 87% yield by using $Co_2(CO)_8$ (185 mg, 0.541 mmol) in CH_2Cl_2 (2.5 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 20/1 to 9/1): brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3 of TBS), 0.09 (3H, s, CH_3 of TBS), 0.10 (6H, s, CH_3 of TBS x2), 0.79 (3H, t, *J* = 7.5 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.49 (2H, dq, *J* = 7.5, 7.5 Hz, H19), 1.57-1.77 (4H, m, H2 and H3), 2.08 (2H, dt, *J* = 7.4, 7.4 Hz, H4), 2.44 (3H, s, CH_3 of Ts), 2.80-2.92 (3H, m, H7 and H16a), 3.12 (1H, dd, *J* = 16.0, 8.6 Hz, H13a), 3.28 (1H, dd, *J* = 16.0, 2.9 Hz, H13b), 3.37 (1H, dd, *J* = 16.6, 6.9 Hz, H16b), 3.80-3.86 (2H, m, acetal), 3.90-3.96 (2H, m, acetal), 3.97 (1H, m, H17), 4.44 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J* = 4.6 Hz, H1), 5.30-5.42 (3H, m, H5, H6 and H8), 5.74 (1H, dd, *J* = 15.5, 6.9 Hz, H11), 5.97 (1H, dd, *J* = 11.5, 11.5 Hz, H9), 6.58 (1H, dd, *J* = 15.5, 11.5 Hz, H10), 7.32 (2H, d, *J* = 8.6 Hz, aromatic), 7.79 (2H, d, *J* = 8.6 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2445.

Tetraene 3-49a. [TG-V-146] According to the synthetic procedure of tetraene **3-49c**, **3-49a** (45.1 mg, 59.2 μmol) was synthesized from **3-54a** (118 mg, 0.113 mmol) in 52% yield by using *n*-Bu_3SnH (0.45 mL, 1.7 mmol) and *N*-methylmorpholine oxide (133 mg, 1.14 mmol) in toluene (55 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g,

hexane to hexane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{25}$ -26 (*c* 0.83, $CHCl_3$); HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4259. The other analytical data of **3-50a** were identical to those of **3-50c**.

Complex 3-54b. [TG-V-115] According to the synthetic procedure of complex **3-54c**, **3-54b** (146 mg, 0.139 mmol) was synthesized from **3-53b** (117 mg, 0.154 mmol) in 90% yield by using $Co_2(CO)_8$ (342 mg, 1.00 mmol) in CH_2Cl_2 (3.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s, C*H*$_3$ of TBS), 0.10 (6H, s, C*H*$_3$ of TBS x2), 0.11 (3H, s, C*H*$_3$ of TBS), 0.79 (3H, t, *J* = 7.3 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45-1.55 (1H, m, H19a), 1.58-1.70 (4H, m, H2 and H3), 1.73 (1H, qd, *J* = 7.4, 5.9 Hz, H19b), 2.09 (2H, dt, *J* = 7.3, 6.8 Hz, H4), 2.44 (3H, s, C*H*$_3$ of Ts), 2.83 (1H, dd, *J* = 16.5, 4.6 Hz, H16a), 2.88 (2H, m, H7), 3.14 (1H, dd, *J* = 15.5, 3.2 Hz, H13a), 3.22 (1H, dd, *J* = 15.5, 8.2 Hz, H13b), 3.35 (1H, dd, *J* = 16.5, 6.4 Hz, H16b), 3.80-3.89 (2H, m, acetal), 3.92-3.99 (2H, m, acetal), 4.01 (1H, m, H17), 4.42 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J* = 5.0 Hz, H1), 5.29-5.43 (3H, m, H5, H6 and H8), 5.73 (1H, dd, *J* = 15.6, 6.9 Hz, H11), 5.99 (1H, dd, *J* = 11.4, 11.4 Hz, H9), 6.56 (1H, dd, *J* = 15.6, 11.4 Hz, H10), 7.31 (2H, d, *J* = 8.3 Hz, aromatic), 7.79 (2H, d, *J* = 8.3 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2482.

Tetraene 3-49b. [TG-V-116] According to the synthetic procedure of tetraene **3-49c**, **3-49b** (81.4 mg, 0.107 mmol) was synthesized from **3-54b** (146 mg, 0.139 mmol) in 77% yield by using *n*-Bu_3SnH (0.56 mL, 2.1 mmol) and *N*-methylmorpholine oxide (164 mg, 1.40 mmol) in toluene (68 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g, hexane to hexane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{27}$ -4.2 (*c* 0.85, $CHCl_3$); IR (neat) ν 2955, 2929, 2857, 1921, 1599, 1471, 1463, 1366, 1258, 1189, 1177, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J* = 7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45-1.55 (3H, m, H3 and H19a), 1.63-1.70 (2H, m, H2), 1.77 (1H, m, H19b), 1.98-2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.91 (2H, t, *J* = 6.3 Hz, H7), 3.78 (1H, ddd, *J* = 8.6, 4.0, 4.0 Hz, H17), 3.82-3.86 (2H, m, acetal), 3.92-3.99 (2H, m, acetal), 4.18 (1H, dt, *J* = 6.9, 5.8 Hz, H12), 4.31 (1H, dt, *J* = 8.6, 4.0 Hz, H18), 4.85 (1H, t, *J* = 4.5 Hz, H1), 5.31-5.48 (5H, m, H5, H6, H8, H14 and H15), 5.64

(1H, dd, *J* = 14.9, 5.8 Hz, H11), 5.97 (1H, dd, *J* = 10.9, 10.9 Hz, H9), 6.46 (1H, dd, *J* = 14.9, 10.9 Hz, H10), 7.33 (2H, d, *J* = 8.0 Hz, aromatic), 7.79 (2H, d, *J* = 8.0 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.75, -4.71, -4.6, -4.4, 10.3, 17.8, 18.2, 21.0, 21.6, 23.9, 25.7 (x3), 25.9 (x3), 26.0, 27.0, 29.2, 33.4, 36.5, 64.8 (x2), 72.2, 72.7, 86.2, 104.5, 124.3, 127.5, 127.6, 127.8 (x2), 127.9, 128.1, 129.6, 129.7 (x2), 130.0, 134.3, 136.6, 144.5; HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4254.

(12*R*,17*S*,18*R*)-3-1a. [TG-V-149, 150, 151] According to the synthetic procedure of **3-1c**, **3-1a** (6.64 mg, 19.9 μmol) was synthesized from **3-49a** (45.1 mg, 59.2 mmol) in 34% yield over 3 steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first raction, $NaClO_2$ (80 wt%, 60.9 mg, 0.539 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (85.7 mg, 0.549 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R = 35 min) for the third. Aldehyde **3-50a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.73 (3H, t, *J* = 7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.44-1.60 (3H, m, H3 and H19a), 1.70-1.80 (3H, m, H2 and H19b), 2.00-2.28 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.90 (2H, m, H7), 3.79 (1H, m, H17), 4.19 (1H, dt, *J* = 6.3, 5.8 Hz, H12), 4.29 (1H, m, H18), 5.29-5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J* = 15.5, 5.8 Hz, H11), 5.98 (1H, dd, *J* = 11.5, 10.9 Hz, H9), 6.47 (1H, dd, *J* = 15.5, 11.5 Hz, H10), 7.32 (2H, d, *J* = 8.0 Hz, aromatic), 7.79 (2H, d, *J* = 8.0 Hz, aromatic), 9.77 (1H, s, H1). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.73, -4.69, -4.63, -4.4, 10.3, 17.9, 18.2, 20.9, 21.6, 21.9, 25.7 (x3), 25.9 (x3), 26.0, 26.5, 29.1, 36.5, 43.3, 72.3, 72.9, 86.2, 124.3, 127.4, 127.7, 127.8 (x2), 128.2, 128.7, 129.1, 129.2, 129.7 (x2), 134.3, 136.8, 144.6, 202.4; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.3996. **(12*R*,17*S*,18*R*)-3-1a**: colorless oil; $[\alpha]_D^{24}$ -4.1 (*c* 0.36, MeOH); IR (neat) ν 3416, 3010, 2966, 2927, 2875, 2854, 1714, 1565, 1437, 1409, 1260, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J* = 7.5 Hz, H20), 1.57 (2H, qd, *J* = 7.5, 6.3 Hz, H19), 1.68 (2H, br s, H3), 2.15 (2H, m, H4), 2.20-2.40 (6H, m, H2, H13 and H16), 2.90-3.00 (4H,

m, H7, H17 and H18), 4.18 (1H, dt, *J* = 6.3, 6.3 Hz, H12), 5.34-5.41 (3H, m, H5, H6 and H8), 5.53-5.61 (2H, m, H14 and H15), 5.69 (1H, dd, *J* = 15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J* = 10.9, 10.9 Hz, H9), 6.57 (1H, ddt, *J* = 15.5, 10.9, 1.2 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 26.1, 27.0, 27.3, 27.6, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.4, 130.4, 130.9, 137.1, the C1 and C2 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$, found 333.2059; UV (MeOH) λ_{max} 236 nm (ε 2.35×10^4).

(12*S*,17*S*,18*R*)-3-1b. [TG-V-117, 118, 119] According to the synthetic procedure of **3-1c**, **3-1b** (12.3 mg, 36.8 μmol) was synthesized from **3-49b** (78 mg, 0.102 mmol) in 36% yield over 3 steps by using TMSOTf (0.28 mL, 1.6 mmol) and 2,6-lutidine (0.27 mL, 2.3 mmol) in CH_2Cl_2 (2.0 mL) for the first reaction, $NaClO_2$ (80 wt%, 107 mg, 0.946 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (152 mg, 0.974 mmol) in a mixture of *t*-BuOH (1.0 mL), 2-methyl-2-butene (1.0 mL) and H_2O (1.0 mL) for the second, and TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) in THF (2.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R = 34 min) for the third. Aldehyde **3-50b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J* = 7.3 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.43-1.82 (3H, m, H3 and H19a), 1.65-1.80 (3H, m, H2 and H19b), 2.00-2.24 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.91 (2H, t, *J* = 7.8 Hz, H7), 3.78 (1H, m, H17), 4.19 (1H, dt, *J* = 6.0, 5.5 Hz, H12), 4.30 (1H, dt, *J* = 8.7, 4.1 Hz, H18), 5.29-5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J* = 15.1, 6.0 Hz, H11), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H9), 6.46 (1H, dd, *J* = 15.1, 11.0 Hz, H10), 7.33 (2H, d, *J* = 8.2 Hz, aromatic), 7.79 (2H, d, *J* = 8.2 Hz, aromatic), 9.77 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.73, -4.66, -4.5, 10.3, 17.8, 18.2, 21.0, 21.6, 21.9, 25.7 (x3), 25.8 (x3), 26.0, 26.4, 29.1, 36.4, 43.2, 72.1, 72.7, 86.2, 124.2, 127.4, 127.6, 127.7 (x2), 128.2, 128.7, 129.0, 129.2, 129.7 (x2), 134.3, 136.8, 144.5, 202.3; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.4034. **(12*S*,17*S*,18*R*)-3-1b**: colorless oil; $[\alpha]_D^{25}$ -4.7 (*c* 0.18, $CHCl_3$); IR (neat) ν 3424, 3009, 2968, 2931, 2877, 2856, 1714, 1438, 1409, 1236, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J* = 7.5 Hz,

H20), 1.57 (2H, qd, *J* = 7.5, 6.3 Hz, H19), 1.73 (2H, br s, H3), 2.18 (2H, br s, H4), 2.21-2.38 (6H, m, H2, H13 and H16), 2.91 (1H, td, *J* = 6.3, 4.6 Hz, H18), 2.93-3.00 (2H, m, H7 and H17), 4.18 (1H, dt, *J* = 6.3, 6.3 Hz, H12), 5.34-5.46 (3H, m, H5, H6 and H8), 5.53-5.62 (2H, m, H14 and H15), 5.69 (1H, dd, *J* = 15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J* = 11.0, 11.0 Hz, H9), 6.57 (1H, dd, *J* = 15.5, 11.0 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 27.0, 27.3, 27.8, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.3, 130.5, 130.9, 137.1, the C1, C2 and C3 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074; UV (MeOH) λ_{max} 236 nm (ε 2.17×10^4).

TBS ether 3-44c. [TG-V-200, VI-002] *n*-BuLi (1.35 M in hexane, 1.7 mL, 2.3 mmol) was added to a solution of **3-22b** (722 mg, 2.16 mmol) in THF (3.0 mL) at -78 ºC. The solution was stirred at -78 °C for 15 min, warmed to 0 ºC and stirred for 30 min. After the mixture was cooled to -78 ºC, $BF_3{\cdot}OEt_2$ (0.27 mL, 2.2 mmol) and a solution of **3-9b** (221 mg, 0.863 mmol) in THF (1.3 mL) were successively added. The reaction mixture was stirred at -78 ºC for 30 min, warmed to 0 ºC and stirred for 2 h, and then saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1 to 6/1 to 4/1 to 2/1) to afford the crude secondary alcohol, which was used in the next reaction without further purification.

TBSOTf (0.29 mL, 1.3 mmol) was added to a solution of the above crude secondary alcohol and Et_3N (0.44 mL, 3.1 mmol) in 1,2-dichloroethane (6.0 mL) at 0 ºC. The reaction mixture was warmed to 30 ºC and stirred for 1 h, and then TBSOTf (0.14 mL, 0.61 mmol) and Et_3N (0.13 mL, 0.93 mmol) were added. The reaction mixture was stirred for 20 min, and then was poured into saturated aqueous $NaHCO_3$ (15 mL). The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) to afford TBS ether **3-44c** (401 mg, 0.570 mmol) in 66% over 2 steps: colorless oil; $[\alpha]_D^{24}$ +17 (*c* 0.97, $CHCl_3$). The other analytical data of **3-44c** were identical to those of **3-44a**.

Alcohol 3-45c. [TG-VI-003] DDQ (284 mg, 1.28 mmol) was added to a solution of **3-44c** (584 mg, 0.828 mmol) in a mixture of CH_2Cl_2 (8.0 mL) and pH 7 phosphate buffer (0.8 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 1 h. After the mixture was cooled to 0 ºC, saturated aqueous $NaHCO_3$ (10 mL) was added. The resultant mixture was extracted EtOAc (50 mL and 40 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) to afford alcohol **3-45c** (449 mg, 0.767 mmol) in 93% yield: colorless oil; $[\alpha]_D^{25}$ +25 (*c* 1.2, $CHCl_3$). The other analytical data of **3-45c** were identical to those of **3-45a**.

Aldehyde 3-46c. [TG-VI-004] Dess-Martin periodinane (493 mg, 1.16 mmol) was added to a suspension of alcohol **3-45c** (445 mg, 0.761 mmol) and $NaHCO_3$ (625 mg, 7.44 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then H_2O (10 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 4/1) to afford aldehyde **3-46c** (431 mg, 0.739 mmol) in 97% yield: colorless oil; $[\alpha]_D^{24}$ +12 (*c* 1.0, $CHCl_3$). The other analytical data of **3-46c** were identical to those of **3-46a**.

C10-20 fragment 3-43c. [TG-VI-005] A solution of iodoform (676 mg, 1.72 mmol) and aldehyde **3-46c** (431 mg, 0.739 mmol) in 1,4-dioxane (4.4 mL) was added to a suspension of $CrCl_2$ (629 mg, 5.11 mmol) in a mixture of THF (2.9 mL) and 1,4-dioxane (4.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then H_2O (5 mL) was added. The resultant mixture was extracted with Et_2O (15 mL x3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified flash column chromatography on silica gel (25 g, hexane to hexane/CH_2Cl_2 1/1) to afford C10-20 fragment **3-43c** (389 mg, 0.551 mmol) in 75% yield: colorless oil; $[\alpha]_D^{24}$ +40 (*c* 1.3, $CHCl_3$). The other analytical data of **3-43c** were identical to those of **3-43a**.

Triyne 3-42c. [TG-VI-007] A mixture of $Pd(PPh_3)_4$ (58.5 mg, 50.6 μmol), CuI (19.3 mg, 0.101 mmol), piperidine (0.10 mL, 1.0 mmol), and C10-20 fragment **3-43c** (237 mg, 0.336 mmol) in benzene (2.5 mL) was added to a

solution of **3-3** (90.6 mg, 0.509 mmol) in benzene (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then saturated aqueous NH_4Cl (5 mL) was added. The resultant mixture was extracted with Et_2O (10 mL x2) and EtOAc (10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1) to afford **3-42c** (192 mg, 0.254 mmol) in 76% yield: pale yellow oil. Triyne **3-42c** was immediately used in the next reaction due to its instability under air. The ^{1}H NMR spectrum of **3-42c** was identical to that of **3-42a**.

Alkyne 3-53c. [TG-VI-008] A suspension of triyne **3-42c** (108 mg, 0.143 mmol), quinoline (0.20 mL, 1.7 mmol) and Lindlar catalyst (222 mg) in hexane (10 mL) was stirred at room temperature for 15 min under H_2 atmosphere (1 atm). Lindlar catalyst (50-100 wt%) was added in every 5-10 min until triyne **3-42c** and the diyne intermediate were disappeared on TLC (540 mg of Lindlar catalyst was added in total). The reaction mixture was filtered through a pad of Celite with hexane, and the filtrate was concentrated. The residue was dissolved in EtOAc (15 mL). The resultant solution was washed with aqueous 0.2 M HCl (10 mL x2), aqueous saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1) to afford alkyne **3-53c** (88.2 mg, 0.116 mmol) in 81% yield: colorless oil; $[\alpha]_D^{25}$ +38 (*c* 0.97, $CHCl_3$). The other analytical data of **3-53c** were identical to those of **3-53a**.

Complex 3-54c. [TG-VI-010] $Co_2(CO)_8$ (175 mg, 0.512 mmol) was added to a solution of **3-53c** (98.2 mg, 0.129 mmol) in CH_2Cl_2 (2.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1) to afford alkyne-dicobalt hexacarbonyl complex **3-54c** (130 mg, 0.124 mmol) in 96% yield: brown oil. The ^{1}H NMR spectrum of **3-54c** was identical of that of **3-54a**.

Tetraene 3-49c. [TG-VI-012] *n*-Bu_3SnH (505 μL, 1.88 mmol) and *N*-methylmorpholine oxide (146 mg, 1.25 mmol) were successively added to a solution of alkyne dicobalt hexacarbonyl complex **3-54c** (130 mg, 0.124 mmol) in toluene (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then aqueous saturated KF (10

mL) was added. The resultant mixture was extracted with Et_2O (30 mL x2), and the combined organic layer were washed with aqueous saturated KF (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography [a column consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 5 g, hexane to hexane/EtOAc 9/1] to afford tetraene **3-49c** (45.4 mg, 0.0596 mmol) in 48% yield: colorless oil; $[\alpha]_D^{24}$ +24 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2928, 2956, 1462, 1366, 1254, 1189, 1177, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J* = 7.8 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45-1.56 (3H, m, H3 and H19a), 1.63-1.71 (2H, m, H2), 1.77 (1H, m, H19b), 1.98-2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.91 (2H, m, H7), 3.79 (1H, ddd, *J* = 9.2, 4.1, 4.1 Hz, H17), 3.82-3.89 (2H, m, acetal), 3.91-3.99 (2H, m, acetal), 4.18 (1H, dt, *J* = 6.4, 6.4 Hz, H12), 4.30 (1H, dt, *J* = 9.2, 4.1 Hz, H18), 4.85 (1H, t, *J* = 4.6 Hz, H1), 5.30-5.51 (5H, m, H5, H6, H8, H14 and H15), 5.64 (1H, dd, *J* = 15.1, 6.4 Hz, H11), 5.97 (1H, dd, *J* = 11.0, 11.0 Hz, H9), 6.47 (1H, dd, *J* = 15.1, 11.0 Hz, H10), 7.33 (2H, d, *J* = 8.3 Hz, aromatic), 7.79 (2H, d, *J* = 8.3 Hz, aromatic). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.75, -4.71, -4.6, -4.4, 10.3, 17.9, 18.2, 21.0, 21.6, 23.9, 25.7 (x3), 25.9 (x3), 26.0, 27.0, 29.1, 33.4, 36.5, 64.8 (x2), 72.3, 72.9, 86.2, 104.5, 124.4, 127.5, 127.6, 127.8 (x2), 127.9, 128.1, 129.6, 129.7 (x2), 130.0, 134.3, 136.6, 144.5.

(12*S*,17*R*,18*S*)-3-1c. [TG-VI-013, 014, 015] TMSOTf (0.16 mL, 0.86 mmol) was added to a solution of **3-49c** (42.9 mg, 56.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) at -15 ºC. The reaction mixture was stirred at -15 ºC for 15 min, and then H_2O (2.0 mL) and EtOAc (2.0 mL) were successively added. The resultant solution was warmed to room temperature and stirred for 30 min. After separation, the organic layer was washed with aqueous 0.1 M HCl (10 mL x2), aqueous saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude aldehyde, which was used in the next reaction without further purification.

A solution of $NaClO_2$ (80 wt%, 56.3 mg, 0.498 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (82.5 mg, 0.529 mmol) in H_2O (0.6 mL) was added to a solution of the above crude aldehyde **3-50c** in a mixture of *t*-BuOH (0.6 mL) and 2-methyl-2-butene (0.6 mL) at 0 ºC. The reaction mixture was warmed to room temperature, stirred for 1 h, and

then diluted with H_2O (5 mL). The resultant solution was extracted with EtOAc (10 mL), and the organic layer was washed with H_2O (4 mL) and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) to afford the crude carboxylic acid **3-51c**, which was used in the next reaction without further purification.

TBAF (1.0 M in THF, 0.56 mL, 0.56 mmol) was added to a solution of the above crude carboxylic acid **3-51c** in THF (1.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then saturated aqueous NH_4Cl (5 mL) was added. After 0.1 M HCl (4 mL) was added, the mixture was extracted with EtOAc (10 mL and 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) to afford the crude **3-1c**. The crude **3-1c** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R = 36 min) to afford **3-1c** (3.5 mg, 10 μmol) in 18% yield over 3 steps: colorless oil; $[\alpha]_D^{25}$ +3.4 (*c* 0.18, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074. The other analytical data of **3-1c** were identical to those of **3-1a**.

TBS ether 3-44d. [TG-V-177, 178] According to the synthetic procedure of **3-44c**, **3-44d** (444 mg, 0.629 mmol) was synthesized from **3-22a** (711 mg, 2.12 mmol) and **3-9b** (219 mg, 0.855 mmol) in 74% yield over 2 steps by using *n*-BuLi (1.6 M in hexane, 1.4 mL, 2.2 mmol) and $BF_3{\cdot}OEt_2$ (0.26 mL, 2.1 mmol) in THF (4.3 mL) for the first reaction, and TBSOTf (0.38 mL, 1.66 mmol) and Et_3N (0.51 mL, 3.7 mmol) in 1,2-dichloroethane (6.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{24}$ +7.4 (*c* 1.0, $CHCl_3$). The other analytical data of **3-44d** were identical to those of **3-44b**.

Alcohol 3-45d. [TG-V-179] According to the synthetic procedure of alcohol **3-45c**, **3-45d** (420 mg, 0.718 mmol) was synthesized from **3-44d** (523 mg, 0.742 mmol) in 97% yield by using DDQ (254 mg, 1.12 mmol) in a mixture of CH_2Cl_2 (7.0 mL) and pH 7 phosphate buffer (0.7 mL). The residue was purified by medium pressure liquid

chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$ +8.9 (*c* 1.1, $CHCl_3$). The other analytical data of **3-45d** were identical to those of **3-45b**.

Aldehyde 3-46d. [TG-V-180] According to the synthetic procedure of aldehyde **3-46c**, **3-46d** (395 mg, 0.679 mmol) was synthesized from **3-45d** (420 mg, 0.718 mmol) in 95% yield by using Dess-Martin periodinane (461 mg, 1.09 mmol) and $NaHCO_3$ (593 mg, 7.06 mmol) in CH_2Cl_2 (7.2 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 20 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{24}$ +22 (*c* 1.7, $CHCl_3$). The other analytical data of **3-46d** were identical to those of **3-46b**.

C10-20 fragment 3-43d. [TG-V-181] According to the synthetic procedure of C10-20 fragment **3-43c**, **3-43d** (388 mg, 0.550 mmol) was synthesized from aldehyde **3-46d** (395 mg, 0.677 mmol) in 81% yield by using $CrCl_2$ (591 mg, 4.84 mmol) and iodoform (636 mg, 1.61 mmol) in a mixture of THF (2.7 mL) and 1,4-dioxane (4.0 mL). Purification was performed by flash column chromatography on silica gel (20 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{26}$ -7.9 (*c* 1.1, $CHCl_3$). The other analytical data of **3-43d** were identical to those of **3-43b**.

Triyne 3-42d. [TG-V-188] According to the synthetic procedure of triyne **3-42c**, **3-42d** (179 mg, 0.236 mmol) was synthesized from **3-43d** (243 mg, 0.344 mmol) and **3-3** (92.2 mg, 0.518 mmol) in 69% yield by using $Pd(PPh_3)_4$ (60.0 mg, 51.9 μmol), CuI (20.3 mg, 0.106 mmol) and piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 8 g, hexane to hexane/EtOAc 9/1). Triyne **3-42d** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.03 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.15 (3H, s, C*H*$_3$ of TBS), 0.16 (3H, s, C*H*$_3$ of TBS), 0.82 (3H, t, *J* = 7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.53 (1H, m, H19a), 1.58-1.65 (2H, m, H3), 1.75-1.81 (3H, m, H2 and H19b), 1.86 (3H, s, C*H*$_3$ of Ts), 2.03 (2H, tt, *J* = 6.9, 2.3 Hz, H4), 2.24-2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, *J* = 1.8, 1.8 Hz, H7), 3.29-3.38 (2H, m, acetal), 3.45-3.54 (2H, m, acetal), 4.17 (1H, dt, *J* = 6.8, 4.6 H, H17), 4.27 (1H, dt, *J* = 5.5, 5.0 H, H12), 4.69 (1H, ddd, *J* = 8.7, 4.6 Hz, H18), 4.73 (1H, t, *J* = 5.0 Hz, H1), 5.94 (1H, ddt, *J* = 16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, *J* = 16.0, 5.0 Hz, H11), 6.75 (2H, d, *J* = 8.2 Hz, aromatic), 7.83 (2H, d, *J* = 8.2 Hz, aromatic).

Alkyne 3-53d. [TG-V-189] According to the synthetic procedure of **3-53c**, **3-53d** (84.3 mg, 0.111 mmol) was synthesized from **3-42d** (91.1 mg, 0.120 mmol) in 92% by using quinoline (0.17 mL, 1.4 mmol) and Lindlar catalyst (462 mg) in hexane (9.0 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$ -15 (*c* 1.4, $CHCl_3$). The other analytical data of **3-53d** were identical to those of **3-53b**.

Complex 3-54d. [TG-V-193] According to the synthetic procedure of complex **3-54c**, **3-54d** (129 mg, 0.123 mmol) was synthesized from **3-53d** (99 mg, 0.130 mmol) in 95% yield by using $Co_2(CO)_8$ (192 mg, 0.561 mmol) in CH_2Cl_2 (2.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil. The ^{1}H NMR spectrum of **3-54d** was identical of that of **3-54b**.

Tetraene 3-49d. [TG-V-195] According to the synthetic procedure of tetraene **3-49c**, **3-49d** (45.0 mg, 59.1 μmol) was synthesized from **3-54d** (129 mg, 0.123 mmol) in 48% yield by using *n*-Bu_3SnH (0.49 mL, 1.8 mmol) and *N*-methylmorpholine oxide (141 mg, 1.21 mmol) in toluene (60 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 6 g and 10% (w/w) KF contained silica gel 2 g, hexane to hexane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{23}$ +2.9 (*c* 1.2, $CHCl_3$). The other analytical data of **3-49d** were identical to those of **3-49b**.

(12*R*,17*R*,18*S*)-3-1d. [TG-V-196, 197, 198] According to the synthetic procedure of **3-1c**, **3-1d** (6.25 mg, 18.7 μmol) was synthesized from **3-49d** (45.0 mg, 59.0 mmol) in 32%yield over 3 steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first reaction, $NaClO_2$ (80 wt%, 61.0 mg, 0.540 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (88.0 mg, 0.564 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R = 35 min) for the third: colorless oil; $[\alpha]_D^{24}$ +7.6 (*c* 0.31, MeOH); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2046. The other analytical data of **3-1d** were identical to those of **3-1b**.

^{1}H and ^{13}C NMR spectra

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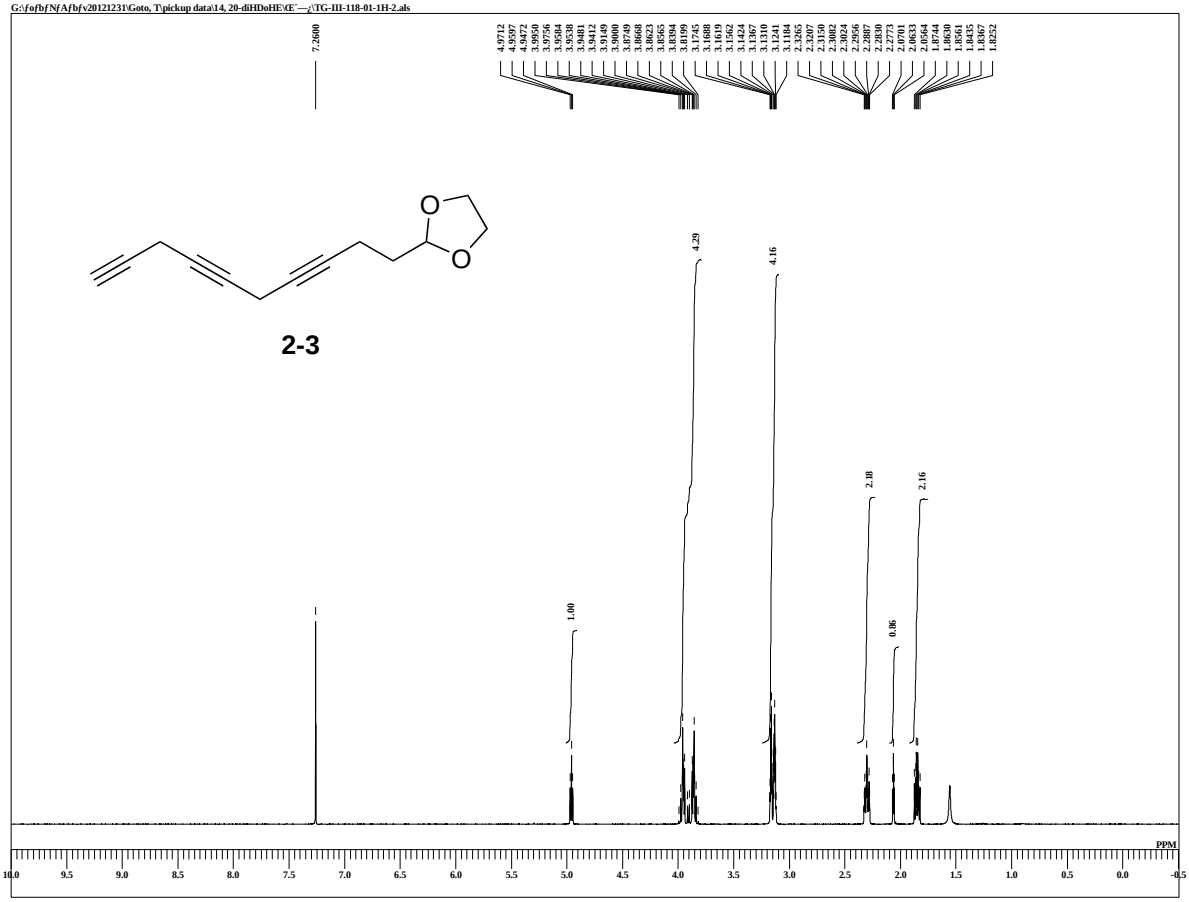

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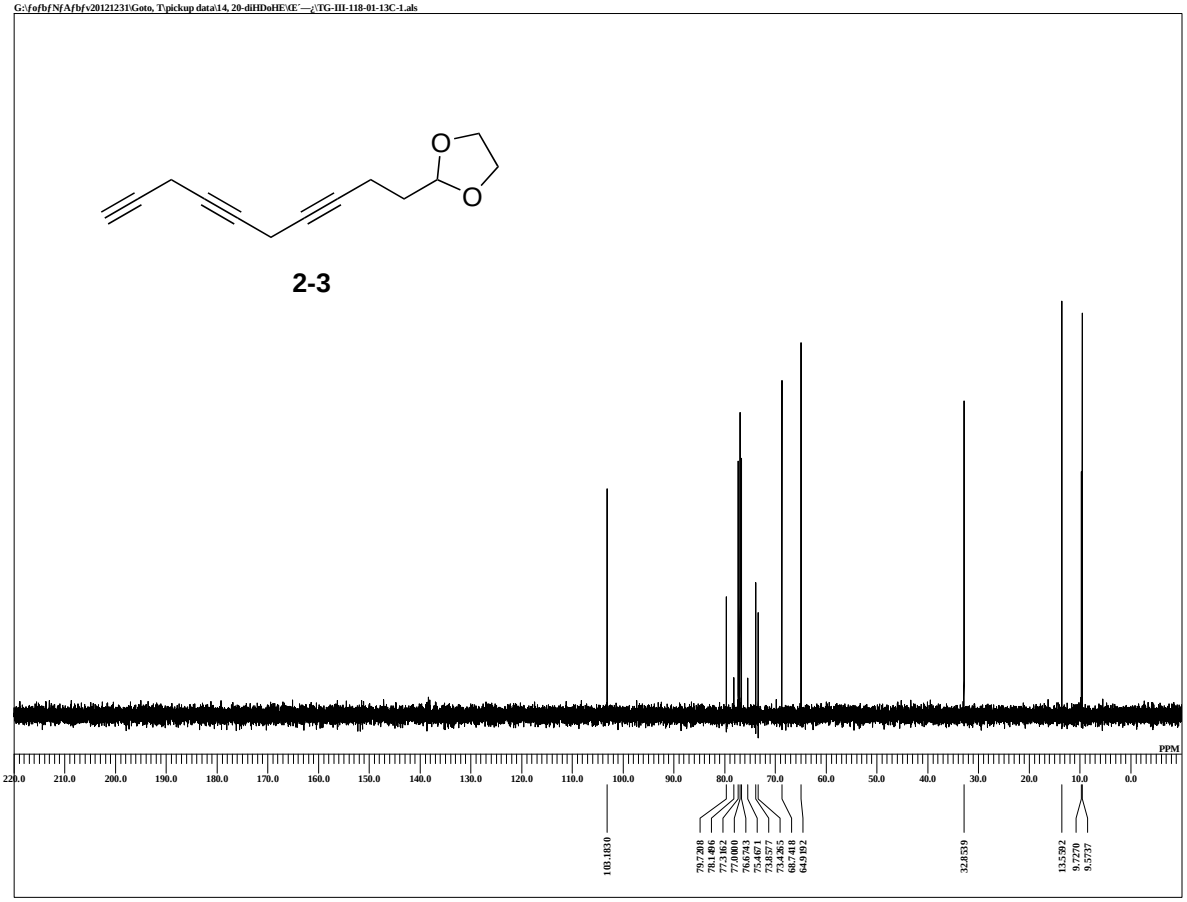

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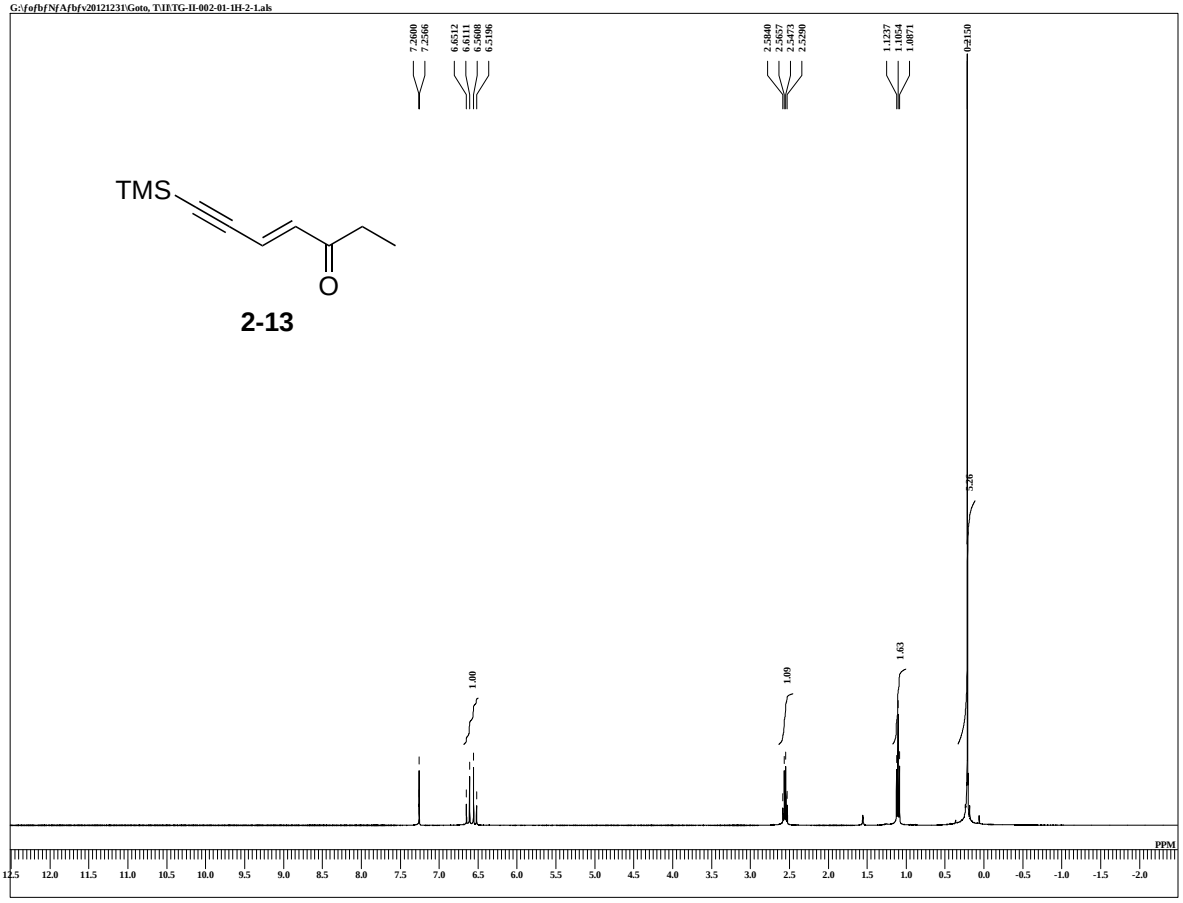

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TG-II-002-01-13C

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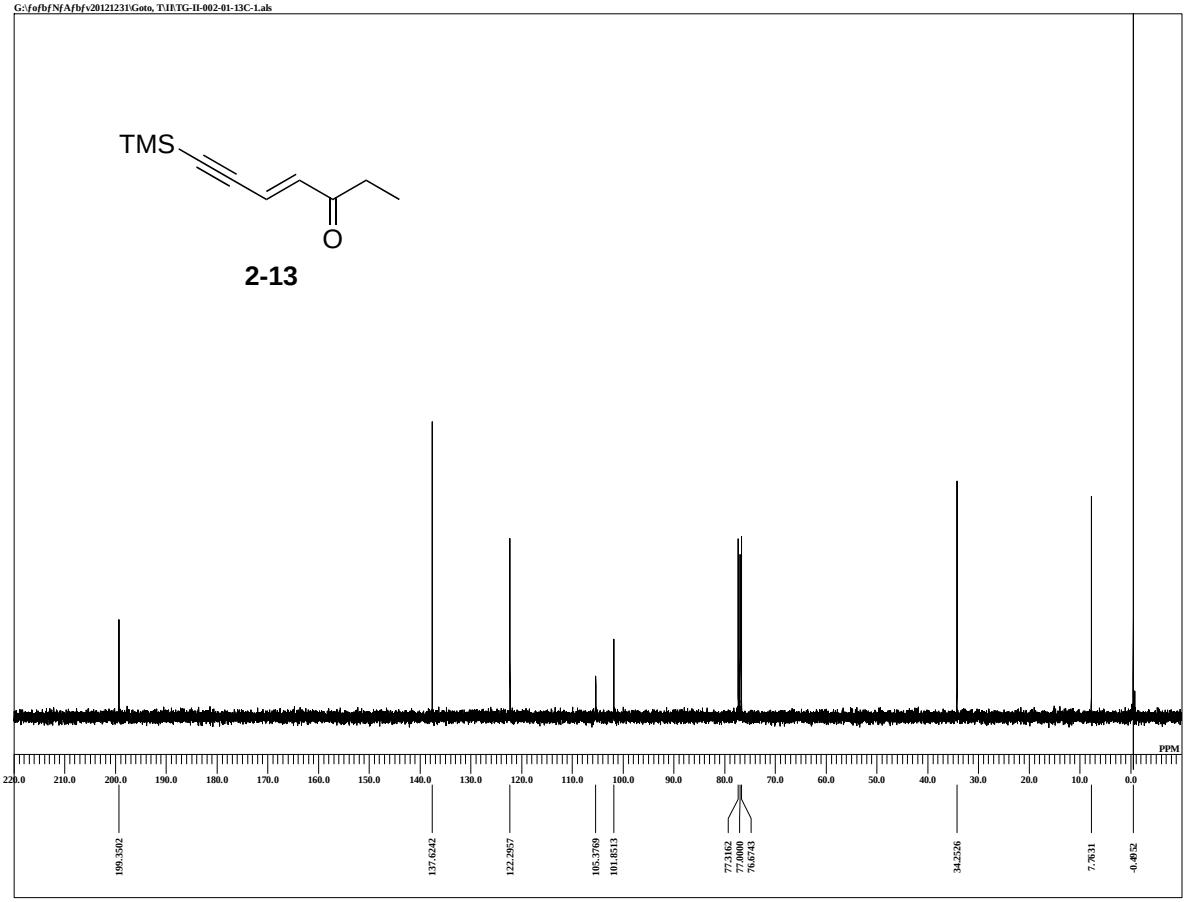
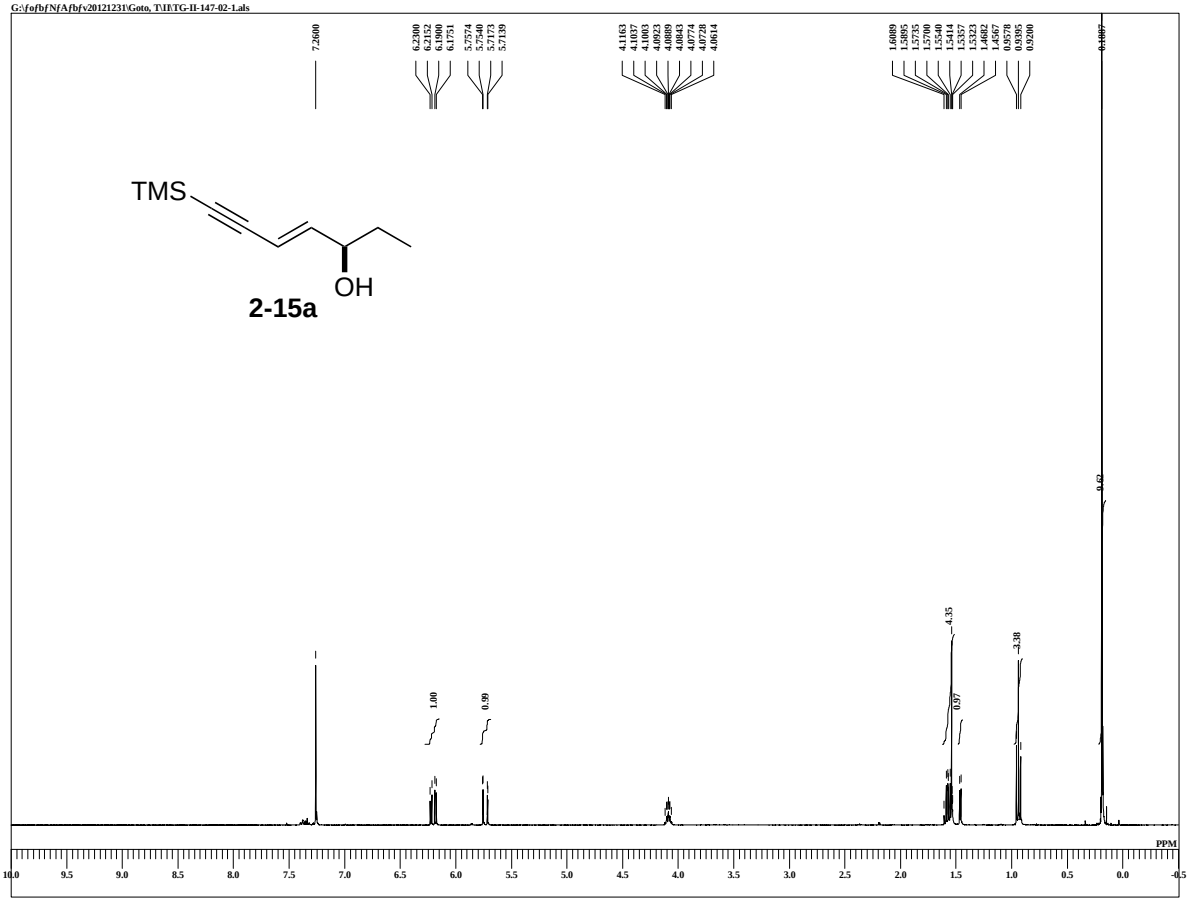


DFILE TG-II-002-01-13C-1.als
COMNT TG-II-002-01-13C
DATIM 03-12-2012 14:41:00
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 3.25 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 17
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 8.0000 sec
SCANS 17
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-002-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 20.8 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-147-02

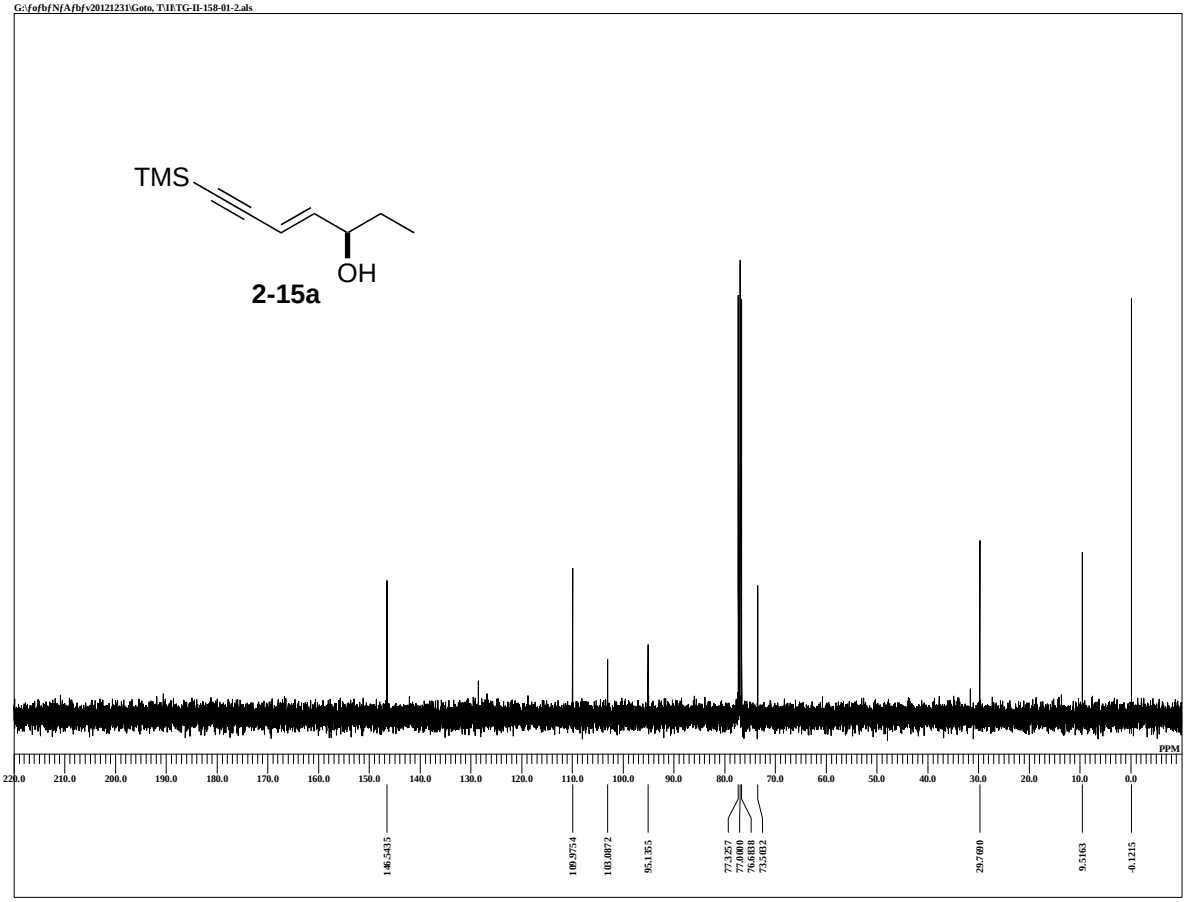
G:\fofbfNfAfbfv20121231\Goto, T\II\TG-II-147-02-1.als



DFILE TG-II-147-02-1.als
COMNT TG-II-147-02
DATIM 25-07-2011 20:50:43
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 50
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-147-02-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.1 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-II-158-01

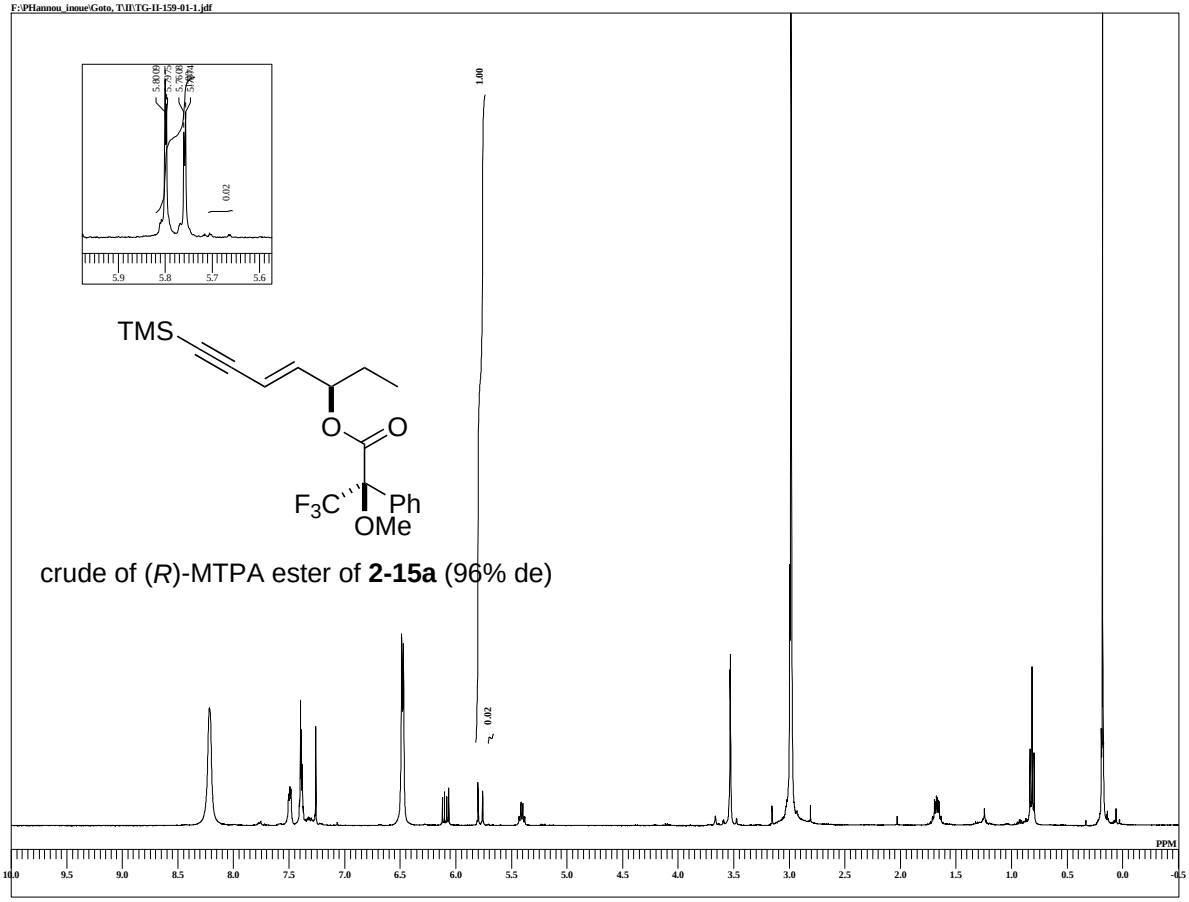
G:\fofbfNfAfbfv20121231\Goto, T\II\TG-II-158-01-2.als



DFILE TG-II-158-01-2.als
COMNT TG-II-158-01
DATIM 01-08-2011 09:12:44
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 104
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 104
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-158-01-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.2 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-159-01

F:\PHannou_inoue\Goto, T\II\TG-II-159-01-1.jdf

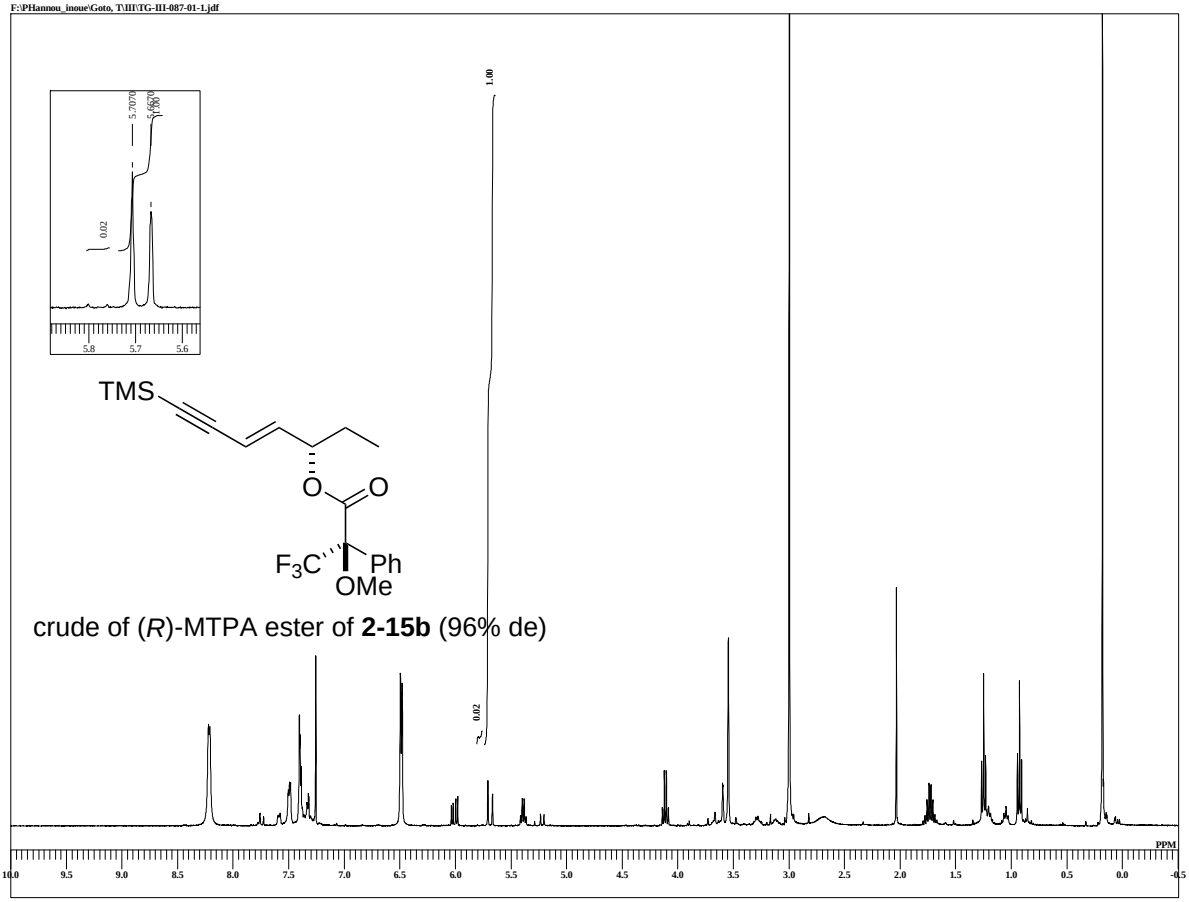


crude of (*R*)-MTPA ester of **2-15a** (96% de)

```
DFILE     TG-II-159-01-1.jdf
COMNT     TG-II-159-01
DATIM     01-08-2011 18:40:25
MENUF
OBNUC     1H
OFR       395.88 MHz
OBFRQ     395.88 MHz
OBSET     6.28 KHz
OBFIN     0.87 Hz
PW1       6.62 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     16384
SPO       16384
TIMES     8
DUMMY     1
FREQU     7422.80 Hz
FLT       30000 Hz
DELAY     16.68 usec
ACQTM     2.2073 sec
PD        2.0000 sec
SCANS     8
ADBIT     16
RGAIN     34
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse.ex2
EXPCM
IRNUC     1H
IFR       395.88 MHz
IRSET     6.28 KHz
IRFIN     0.87 Hz
IRRPW     115 usec
IRATN     79
DFILE     TG-II-159-01-1.jdf
SF
LKSET     13.20 KHz
LKFIN     75.7 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     25.0 c
SLVNT     CDCL3
EXREF     7.26 ppm
```

TG-III-087-01

F:\PHannou_inoue\Goto, T\III\TG-III-087-01-1.jdf

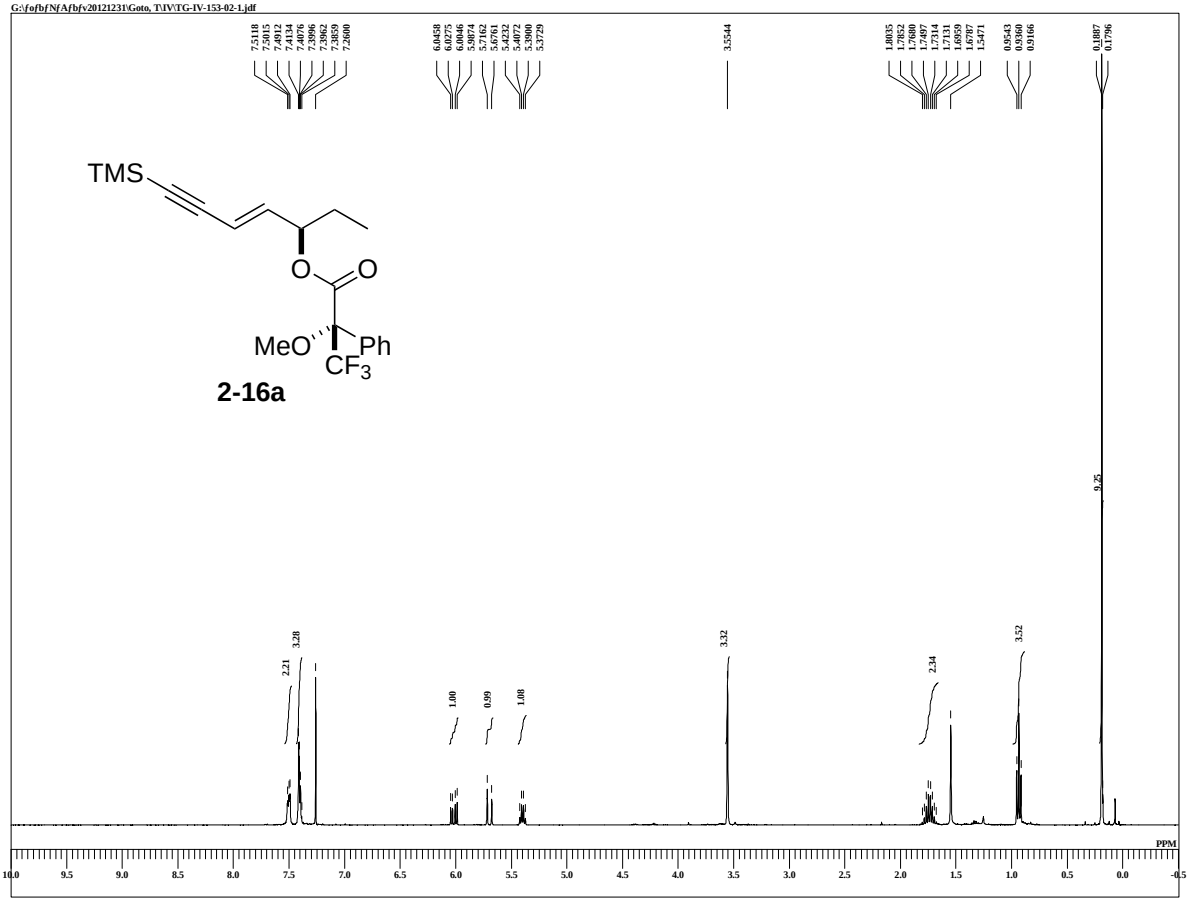


crude of (*R*)-MTPA ester of **2-15b** (96% de)

```
DFILE     TG-III-087-01-1.jdf
COMNT     TG-III-087-01
DATIM     18-10-2011 16:44:13
MENUF
OBNUC     1H
OFR       395.88 MHz
OBFRQ     395.88 MHz
OBSET     6.28 KHz
OBFIN     0.87 Hz
PW1       6.62 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     16384
SPO       16384
TIMES     8
DUMMY     1
FREQU     7422.80 Hz
FLT       30000 Hz
DELAY     16.68 usec
ACQTM     2.2073 sec
PD        2.0000 sec
SCANS     8
ADBIT     16
RGAIN     38
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse.ex2
EXPCM
IRNUC     1H
IFR       395.88 MHz
IRSET     6.28 KHz
IRFIN     0.87 Hz
IRRPW     115 usec
IRATN     79
DFILE     TG-III-087-01-1.jdf
SF
LKSET     13.20 KHz
LKFIN     75.7 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     24.8 c
SLVNT     CDCL3
EXREF     7.26 ppm
```

TG-IV-153-02

G:*fofbf*NfA*fbfv20121231\Goto, T\IV\TG-IV-153-02-1.jdf



TMS

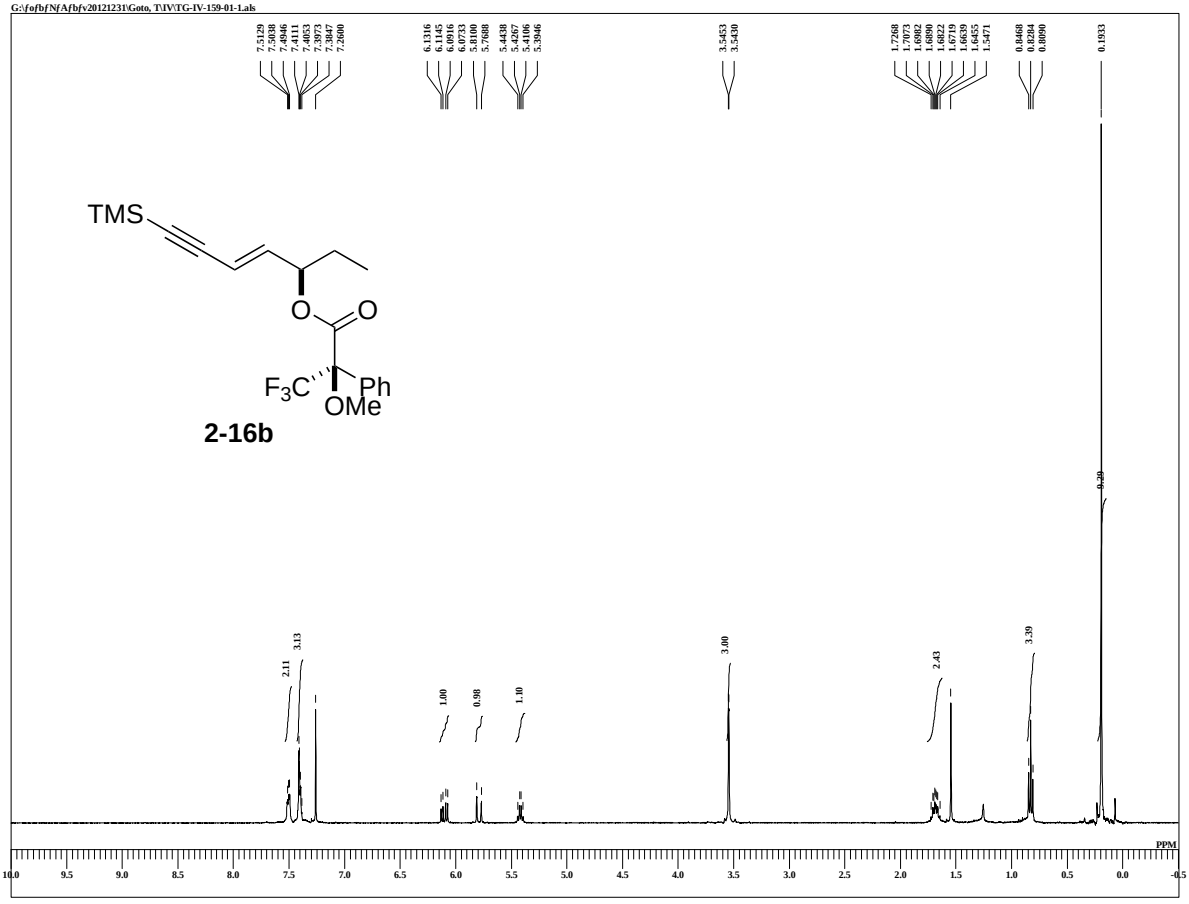
MeO Ph CF_3

2-16a

DFILE TG-IV-153-02-1.jdf
COMNT TG-IV-153-02
DATIM 11-04-2012 10:54:44
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 16
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 16
ADBIT 16
RGAIN 44
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-153-02-1.jdf
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.6 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-IV-159-01

G:*fofbf*NfA*fbfv20121231\Goto, T\IV\TG-IV-159-01-1.als



TMS

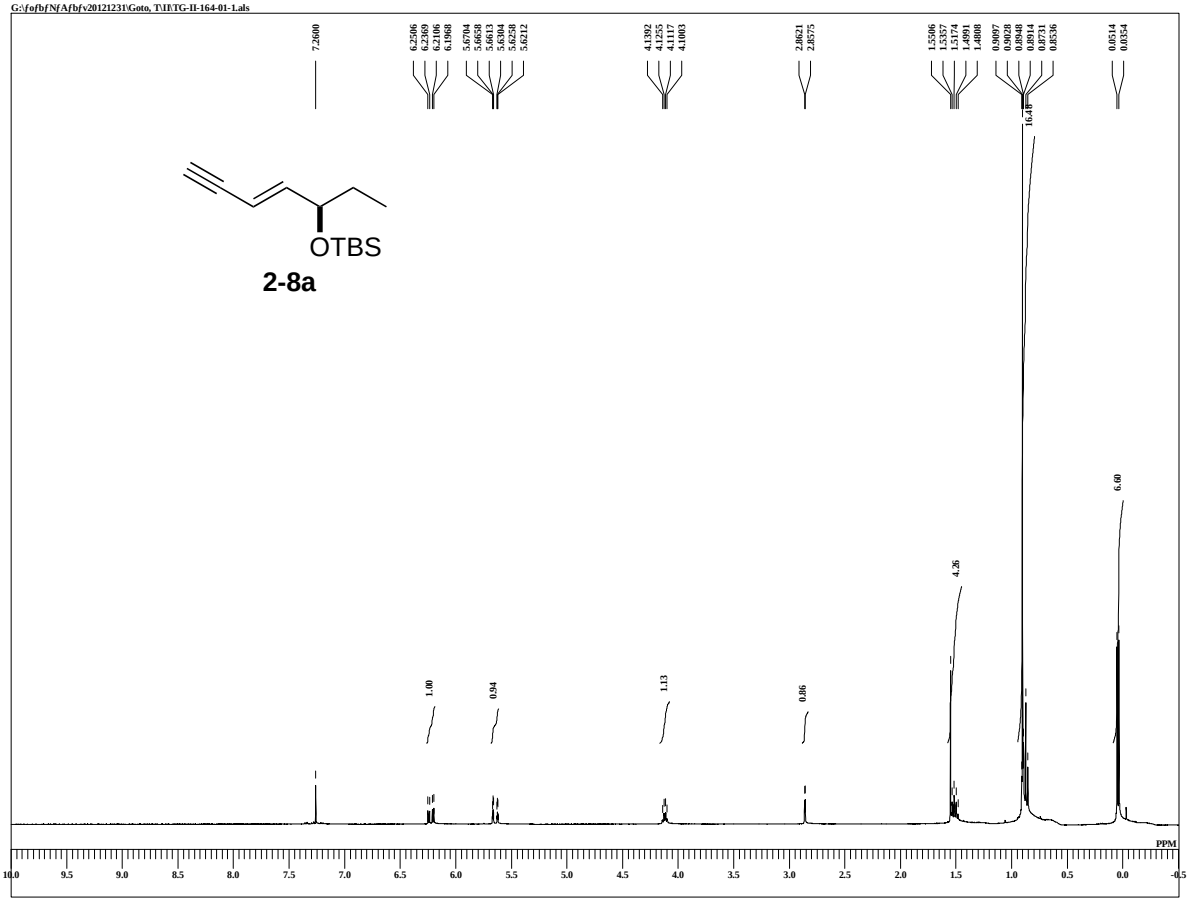
F_3C Ph OMe

2-16b

DFILE TG-IV-159-01-1.als
COMNT TG-IV-159-01
DATIM 12-04-2012 17:30:04
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 44
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-159-01-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.4 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-II-164-01

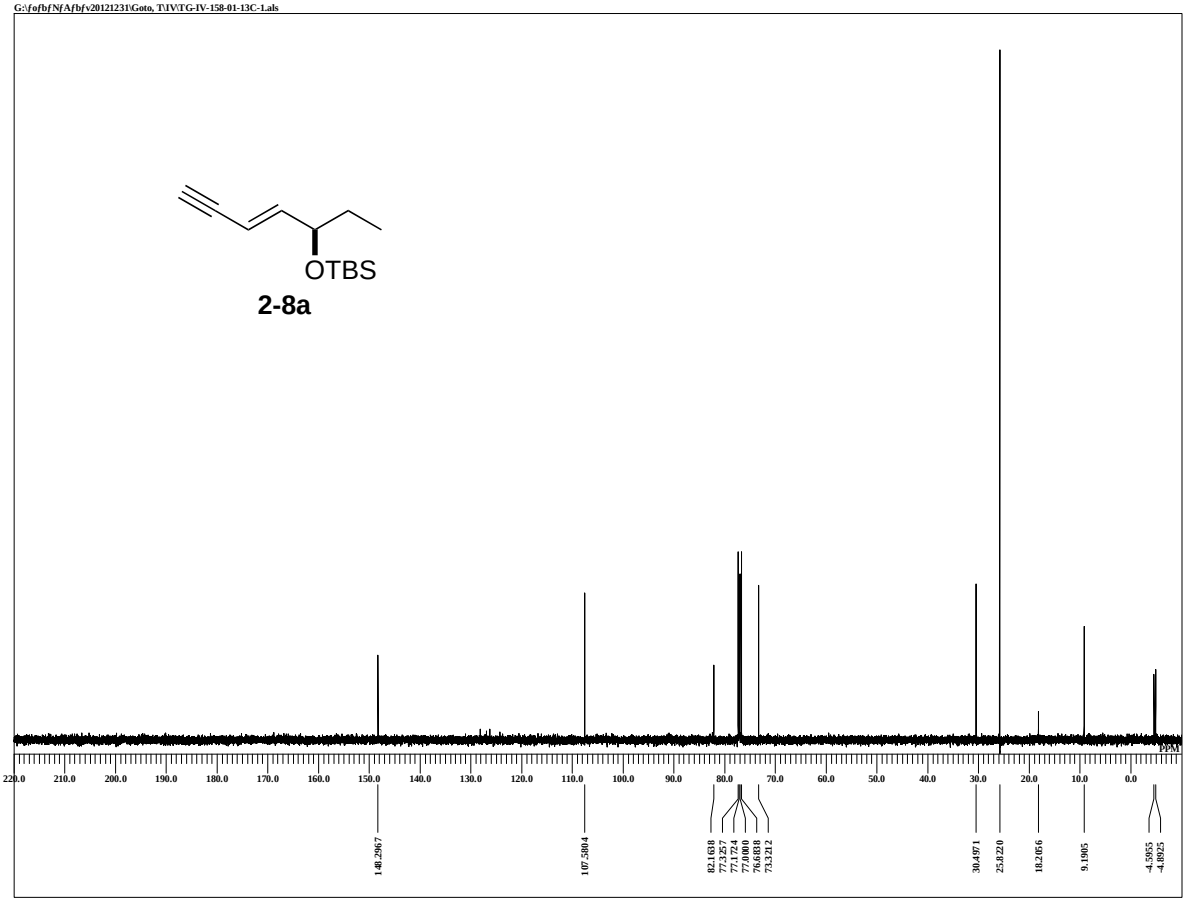
G:\fofbf\NfA\fbfv20121231\Goto, T\II\TG-II-164-01-1.als



DFILE TG-II-164-01-1.als
COMNT TG-II-164-01
DATIM 06-08-2011 10:17:58
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 40
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-164-01-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-IV-158-01-13C

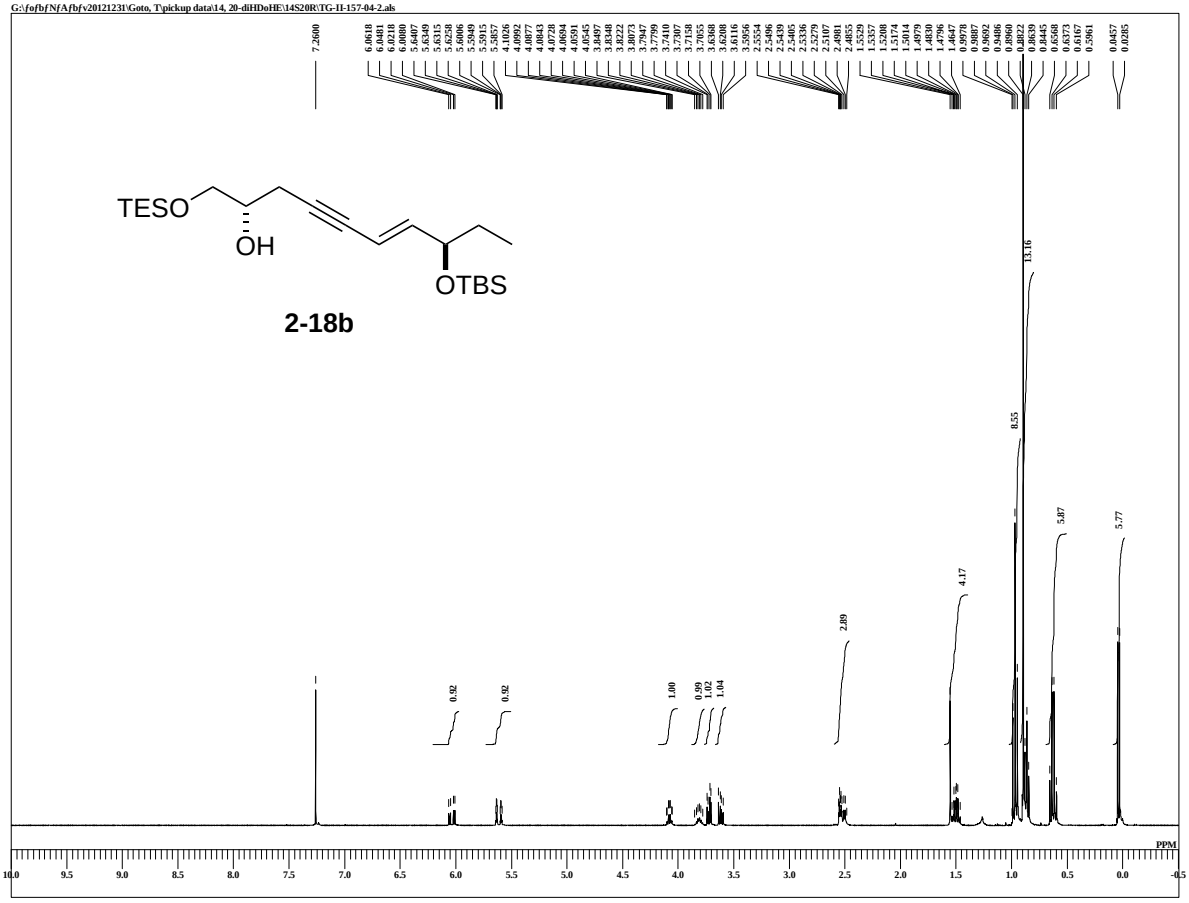
G:\fofbf\NfA\fbfv20121231\Goto, T\IV\TG-IV-158-01-13C-1.als



DFILE TG-IV-158-01-13C-1.als
COMNT TG-IV-158-01-13C
DATIM 12-04-2012 20:31:47
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 102
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 102
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-158-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.7 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-157-04

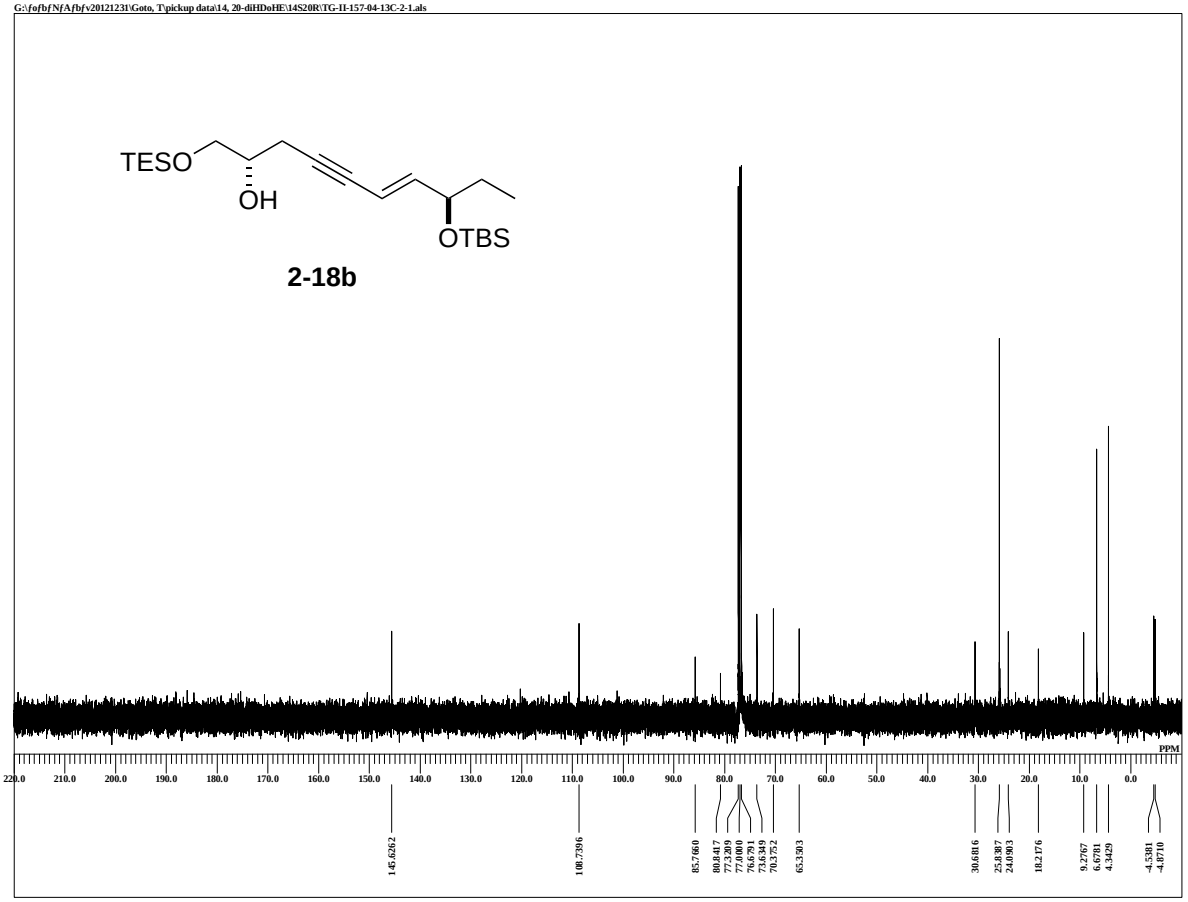
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-157-04-2.als



DFILE TG-II-157-04-2.als
COMNT TG-II-157-04
DATIM 01-08-2011 11:58:34
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
1WT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 50
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-157-04-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-II-157-04-13C-2

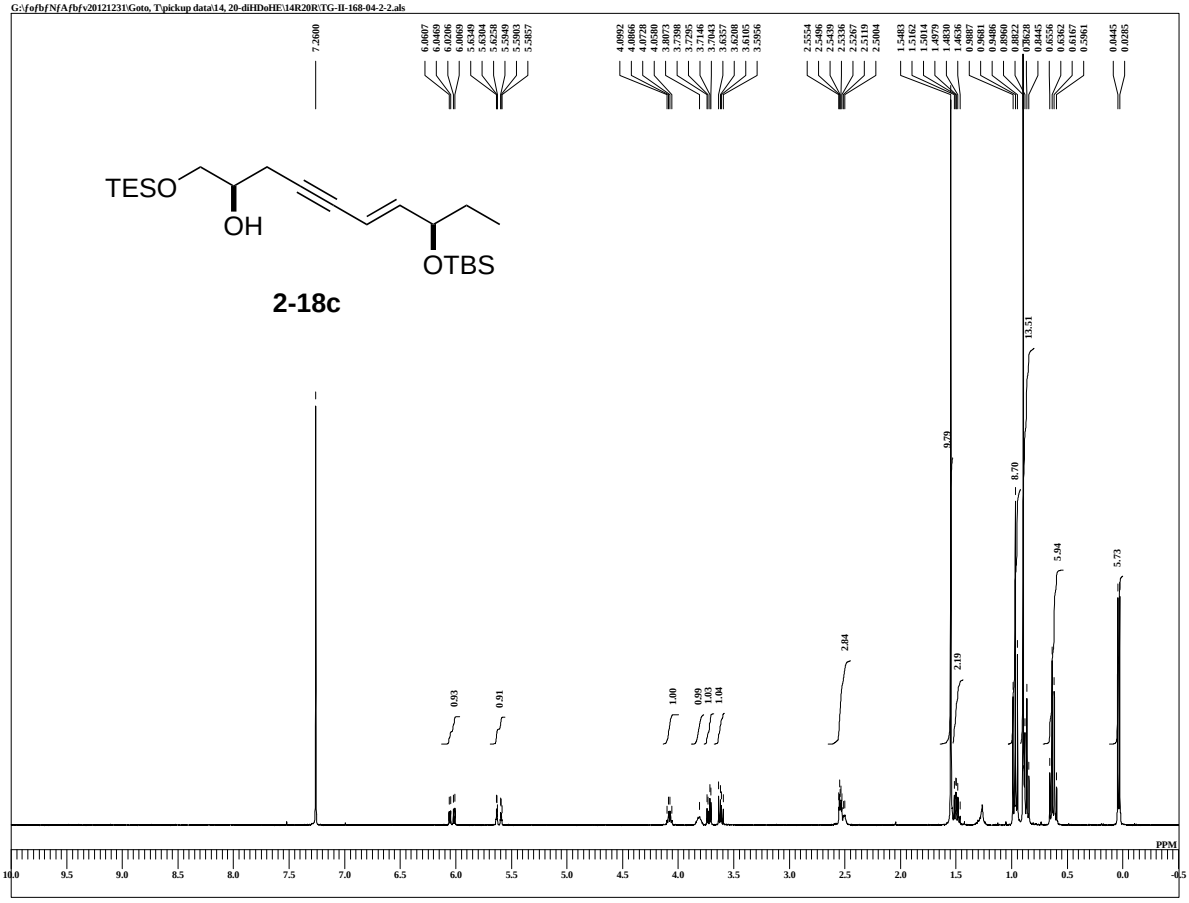
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-157-04-13C-2-1.als



DFILE TG-II-157-04-13C-2-1.als
COMNT TG-II-157-04-13C-2
DATIM 01-08-2011 12:32:28
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
1WT 1.0000 sec
POINT 104856
SPO 104856
TIMES 183
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 183
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-157-04-13C-2-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.1 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-168-04

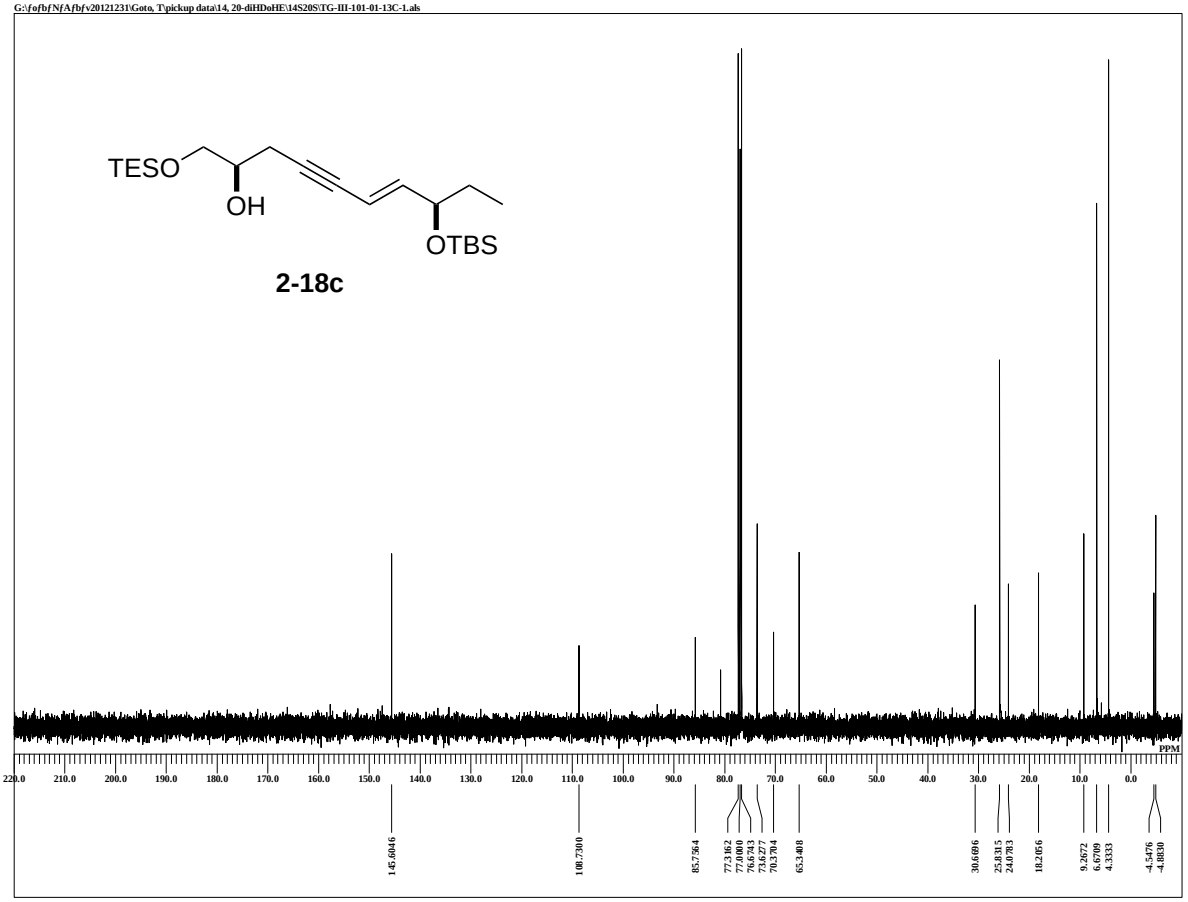
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-168-04-2-2.als



DFILE TG-II-168-04-2-2.als
COMNT TG-II-168-04
DATIM 07-08-2011 11:31:02
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 23
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 23
ADBIT 16
RGAIN 50
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-168-04-2-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.1 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-III-101-01-13C

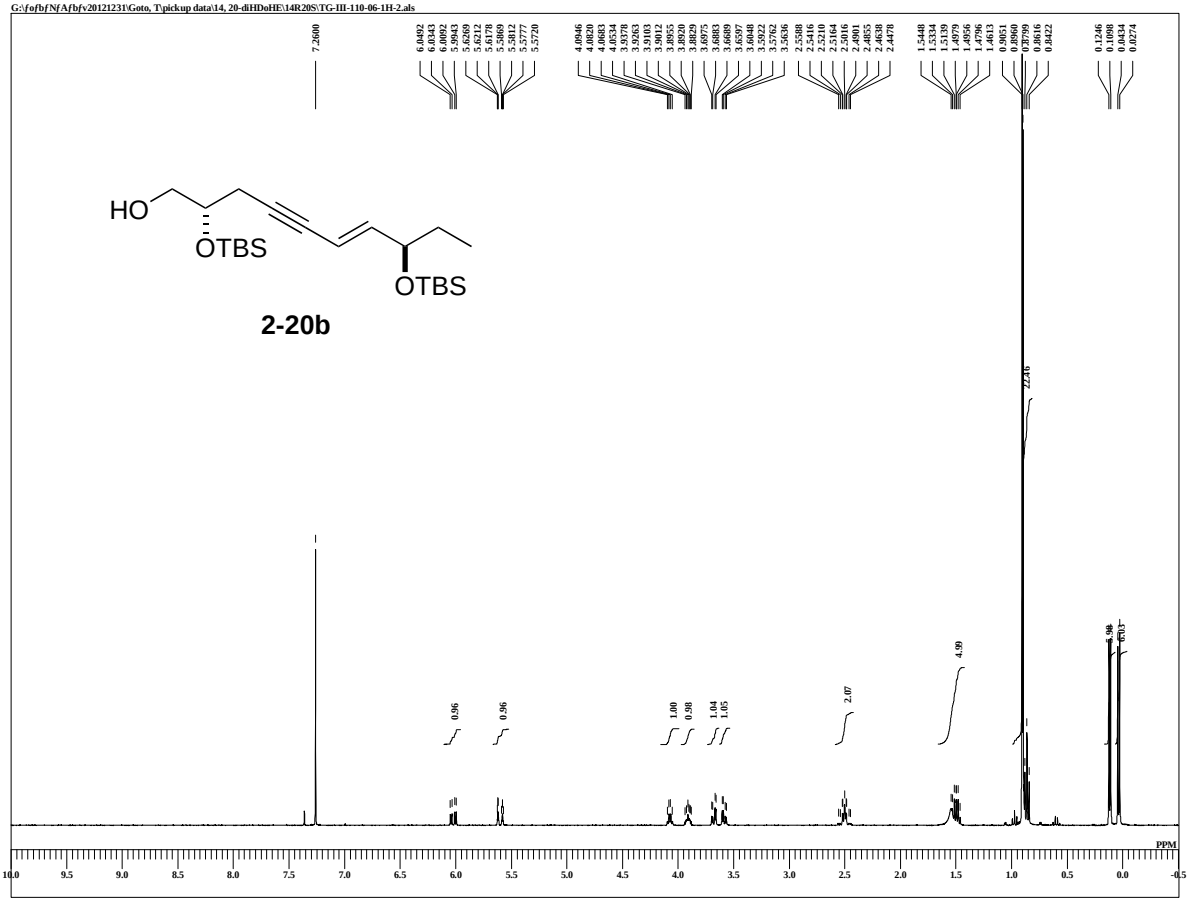
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20S\TG-III-101-01-13C-1.als



DFILE TG-III-101-01-13C-1.als
COMNT TG-III-101-01-13C
DATIM 24-10-2011 18:24:57
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 148
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 148
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-III-101-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.2 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-III-110-06-1H

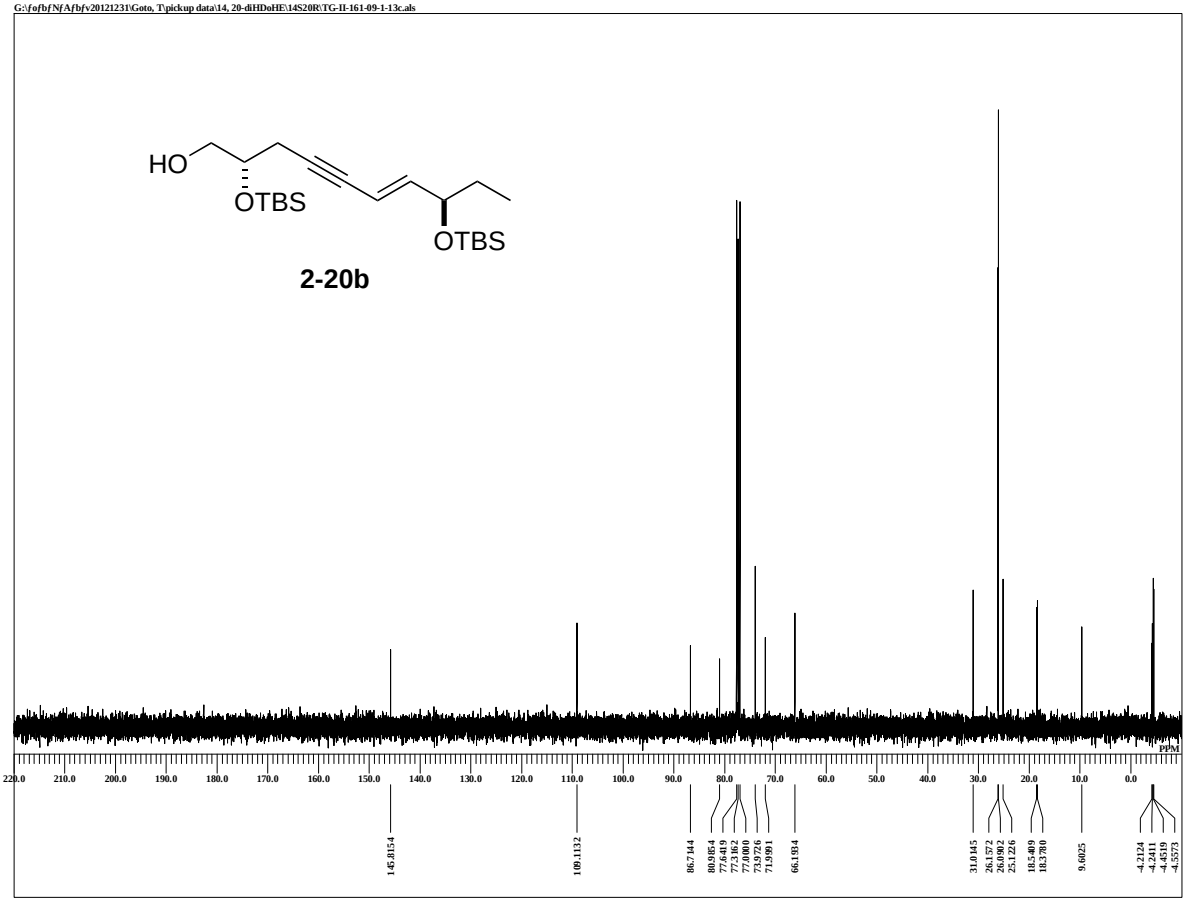
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20S\TG-III-110-06-1H-2.als




```
DFILE    TG-III-110-06-1H-2.als
COMNT    TG-III-110-06-1H
DATIM    09-11-2011 13:25:00
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.62 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    8
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    48
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    147 usec
IRATN    79
DFILE    TG-III-110-06-1H-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    24.8 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-II-161-09

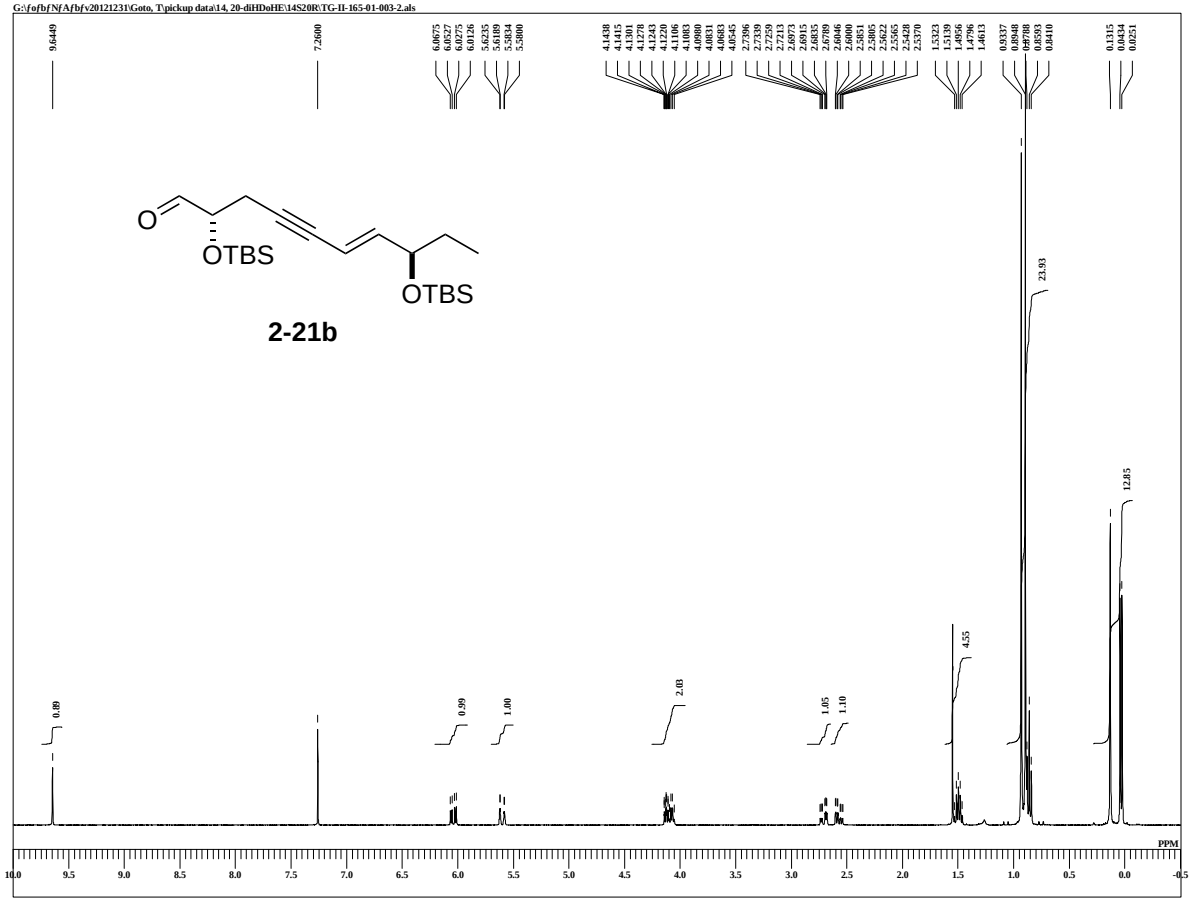
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-161-09-1-13c.als




```
DFILE    TG-II-161-09-1-13c.als
COMNT    TG-II-161-09
DATIM    03-08-2011 10:29:09
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      2.92 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    26214
SPO      26214
TIMES    92
DUMMY    4
FREQU    24999.62 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       2.0000 sec
SCANS    92
ADBIT    16
RGAIN    60
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-II-161-09-1-13c.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    25.0 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-II-165-01-003

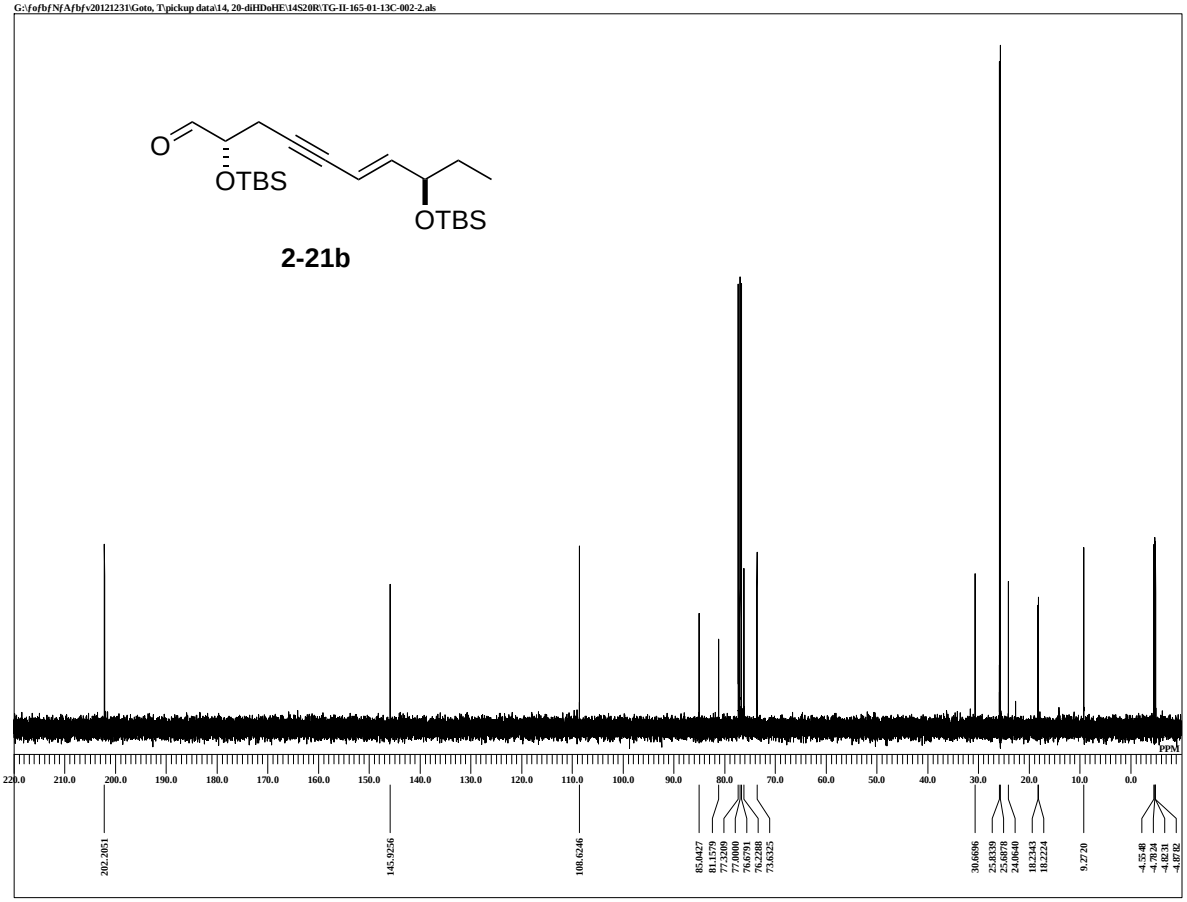
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-165-01-003-2.als




```
DFILE    TG-II-165-01-003-2.als
COMNT    TG-II-165-01-003
DATIM    05-08-2011 20:13:18
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.62 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    8
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    42
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-II-165-01-003-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    25.2 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-II-165-01-13C-002

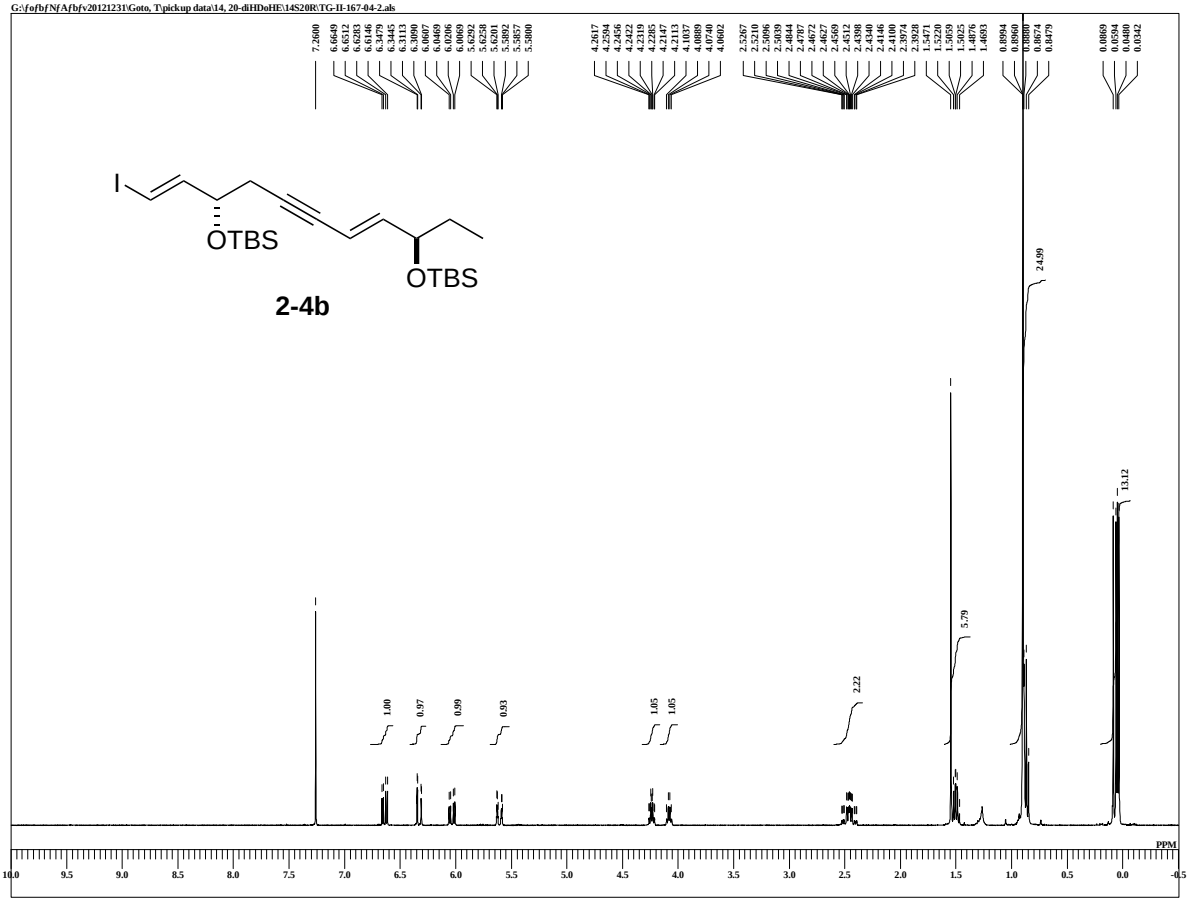
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-165-01-13C-002-2.als




```
DFILE    TG-II-165-01-13C-002-2.a
COMNT    TG-II-165-01-13C-002
DATIM    05-08-2011 20:38:13
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      2.92 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    104856
SPO      104856
TIMES    130
DUMMY    4
FREQU    24999.62 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       2.0000 sec
SCANS    130
ADBIT    16
RGAIN    60
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-II-165-01-13C-002-2.a
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    25.3 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-II-167-04

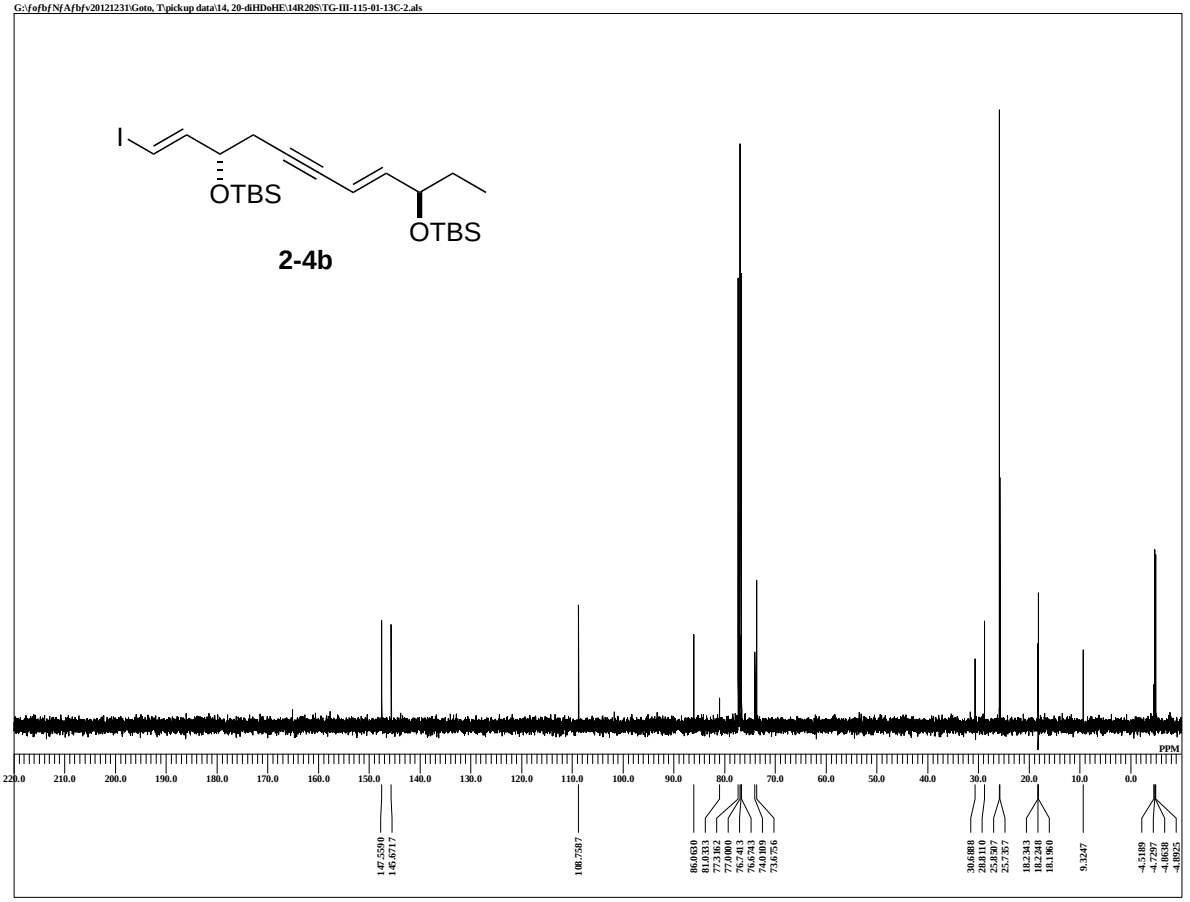
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-II-167-04-2.als



DFILE TG-II-167-04-2.als
COMNT TG-II-167-04
DATIM 07-08-2011 16:59:38
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 44
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-167-04-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.1 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-III-115-01-13C

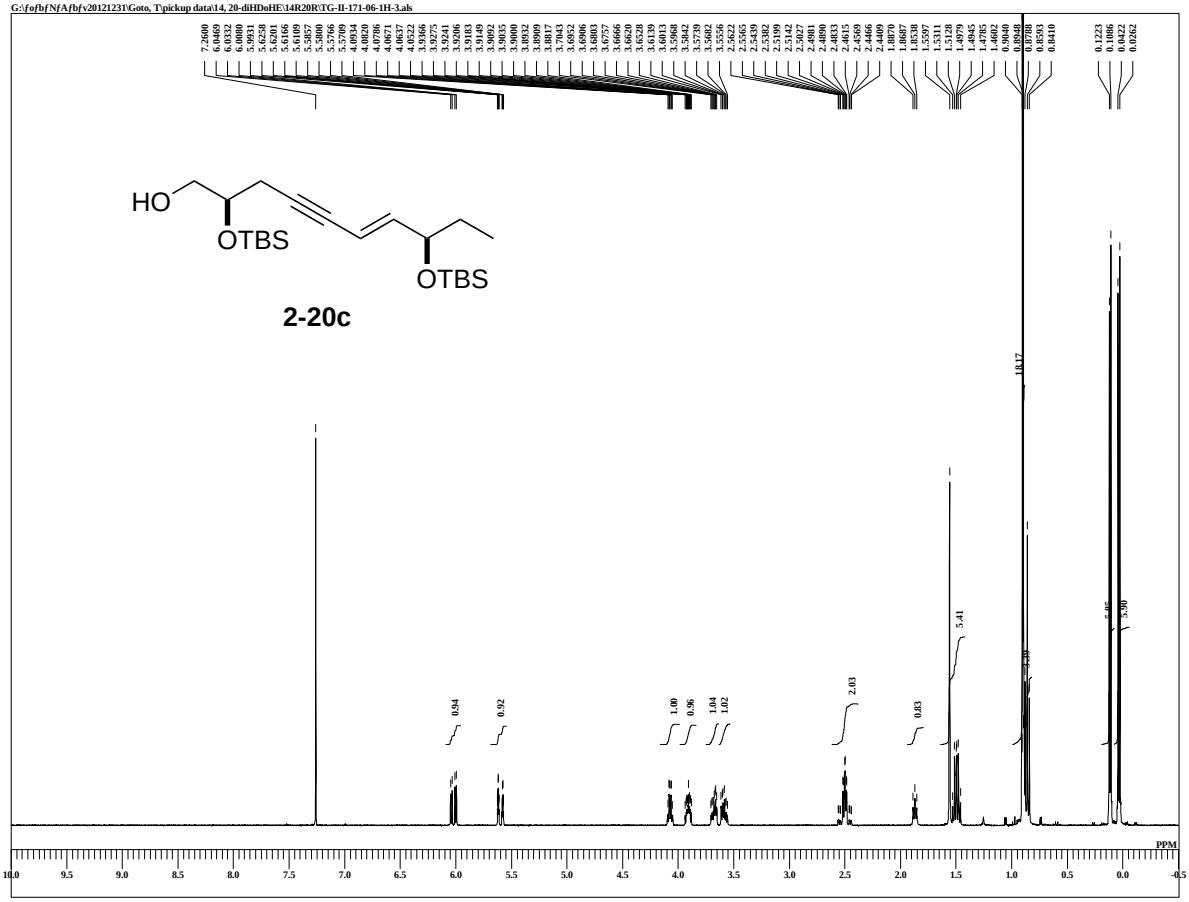
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20S\TG-III-115-01-13C-2.als



DFILE TG-III-115-01-13C-2.als
COMNT TG-III-115-01-13C
DATIM 16-11-2011 15:19:54
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 252
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 252
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-III-115-01-13C-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.4 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-171-06-1H

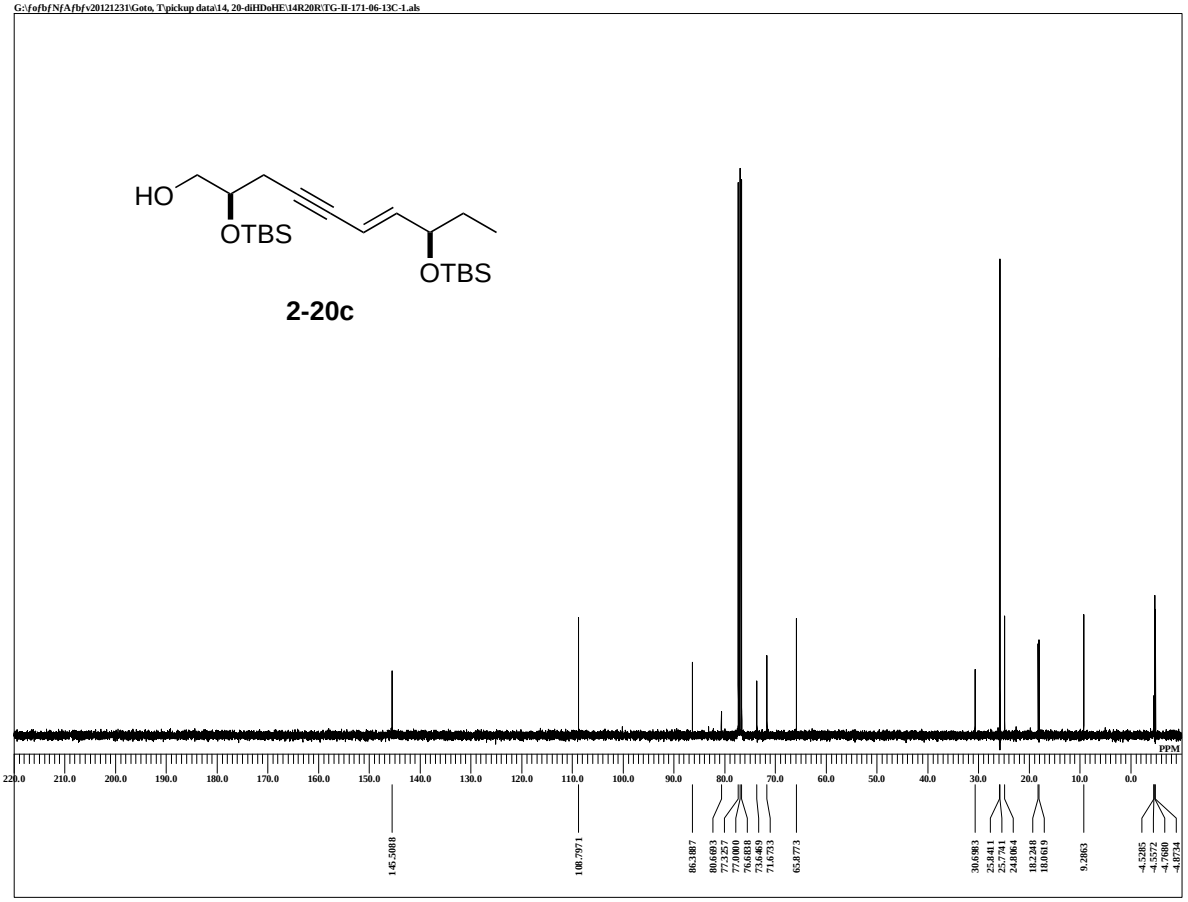
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-171-06-1H-3.als



DFILE TG-II-171-06-1H-3.als
COMNT TG-II-171-06-1H
DATIM 12-08-2011 15:08:09
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 44
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-171-06-1H-3.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-II-171-06-13C

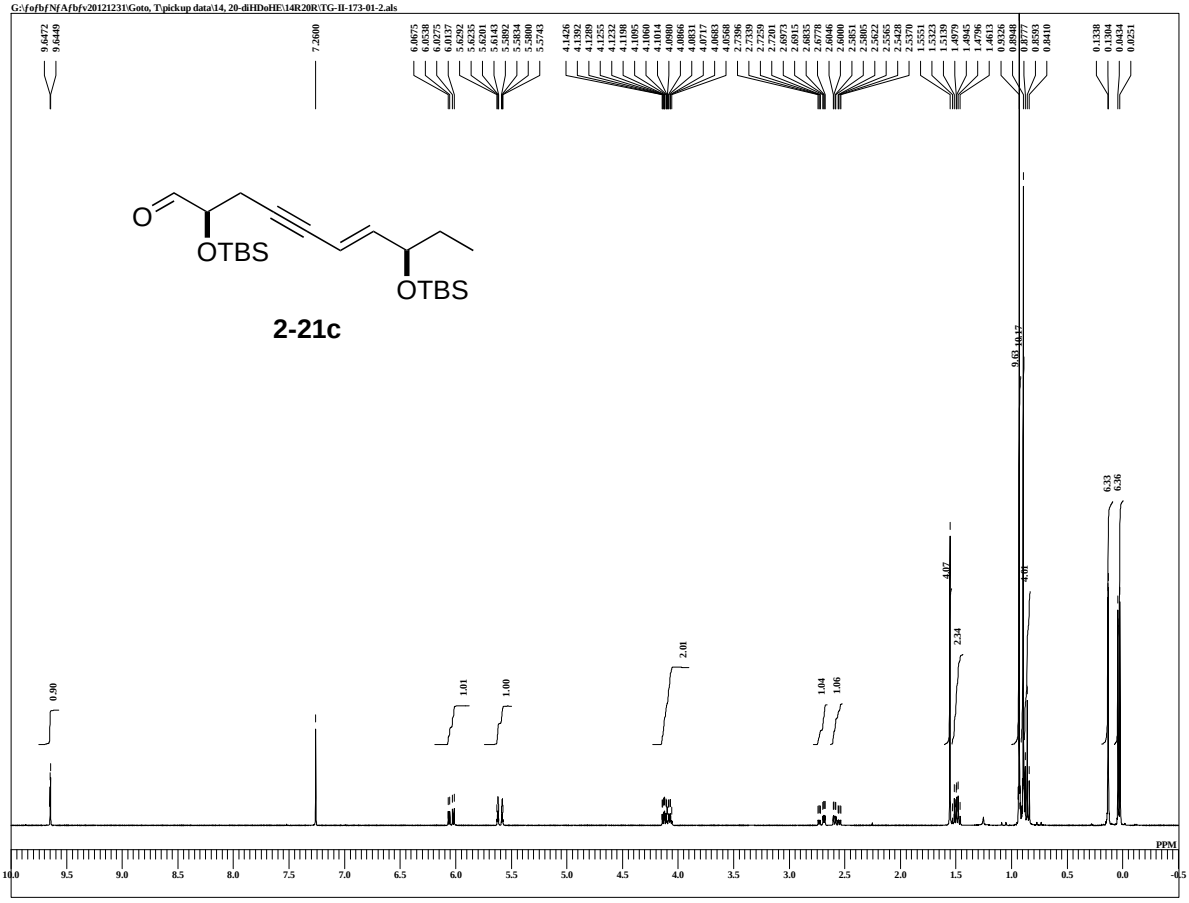
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-171-06-13C-1.als



DFILE TG-II-171-06-13C-1.als
COMNT TG-II-171-06-13C
DATIM 12-08-2011 16:03:56
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 1000
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 1000
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-171-06-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-173-01

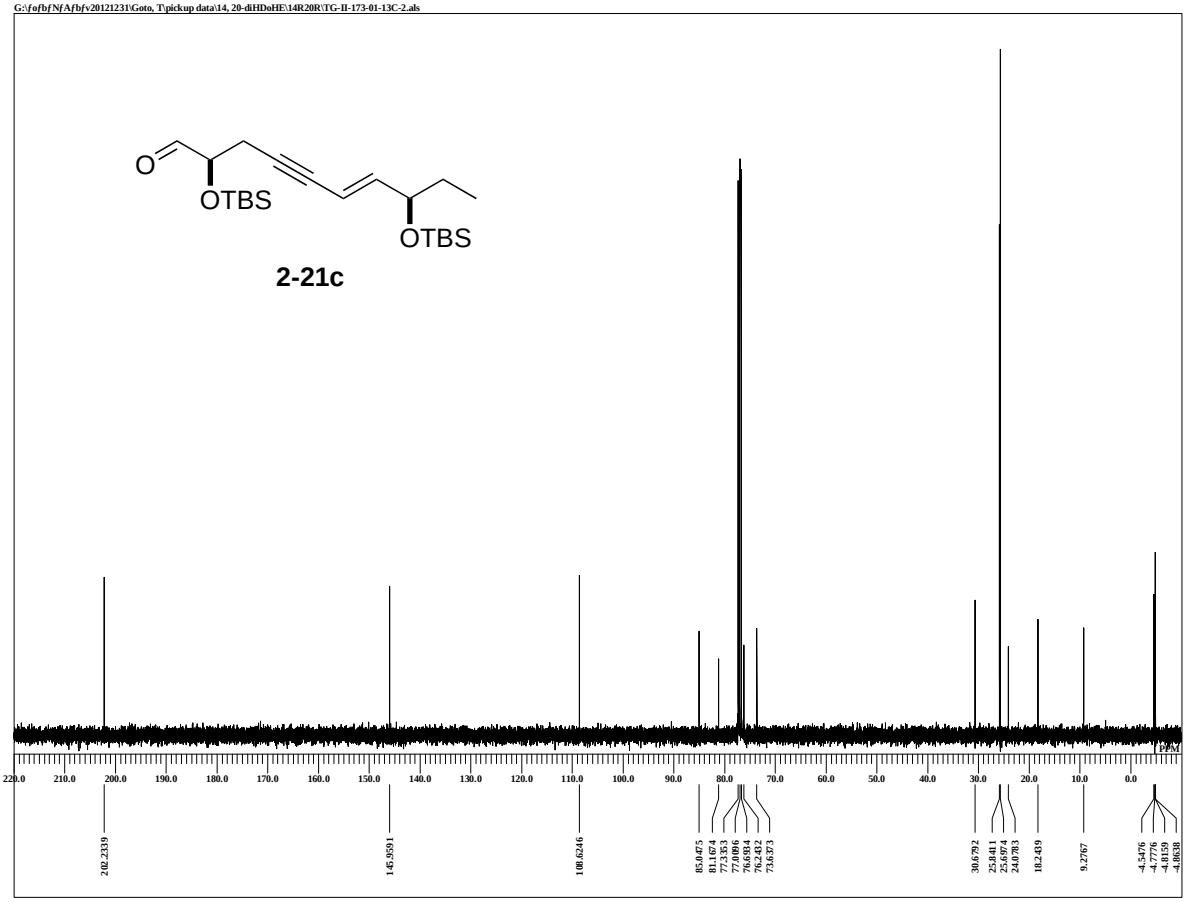
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-173-01-2.als



DFILE TG-II-173-01-2.als
COMNT TG-II-173-01
DATIM 13-08-2011 16:20:19
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.62 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 44
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-173-01-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-II-173-01-13C

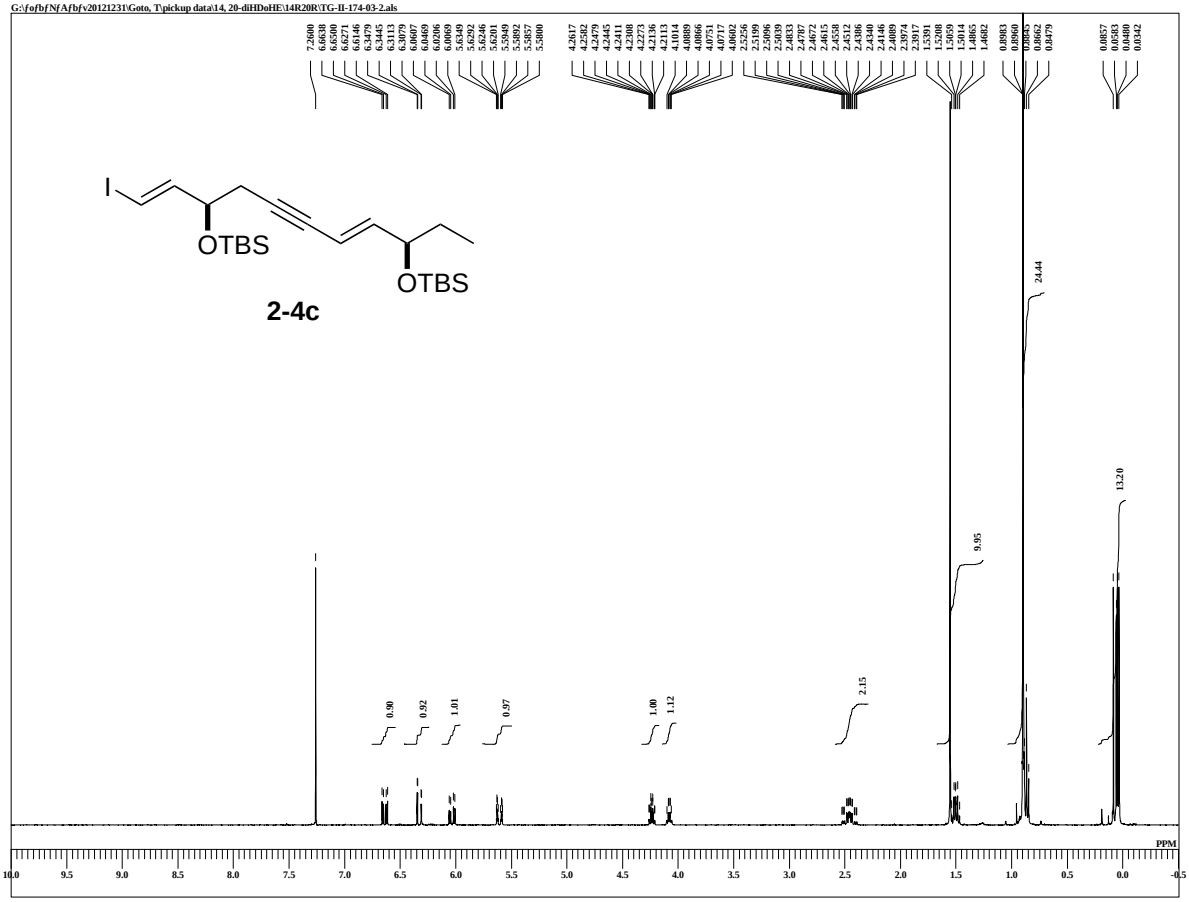
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-173-01-13C-2.als



DFILE TG-II-173-01-13C-2.als
COMNT TG-II-173-01-13C
DATIM 13-08-2011 16:40:01
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 2.92 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 288
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 288
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-II-173-01-13C-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.1 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-174-03

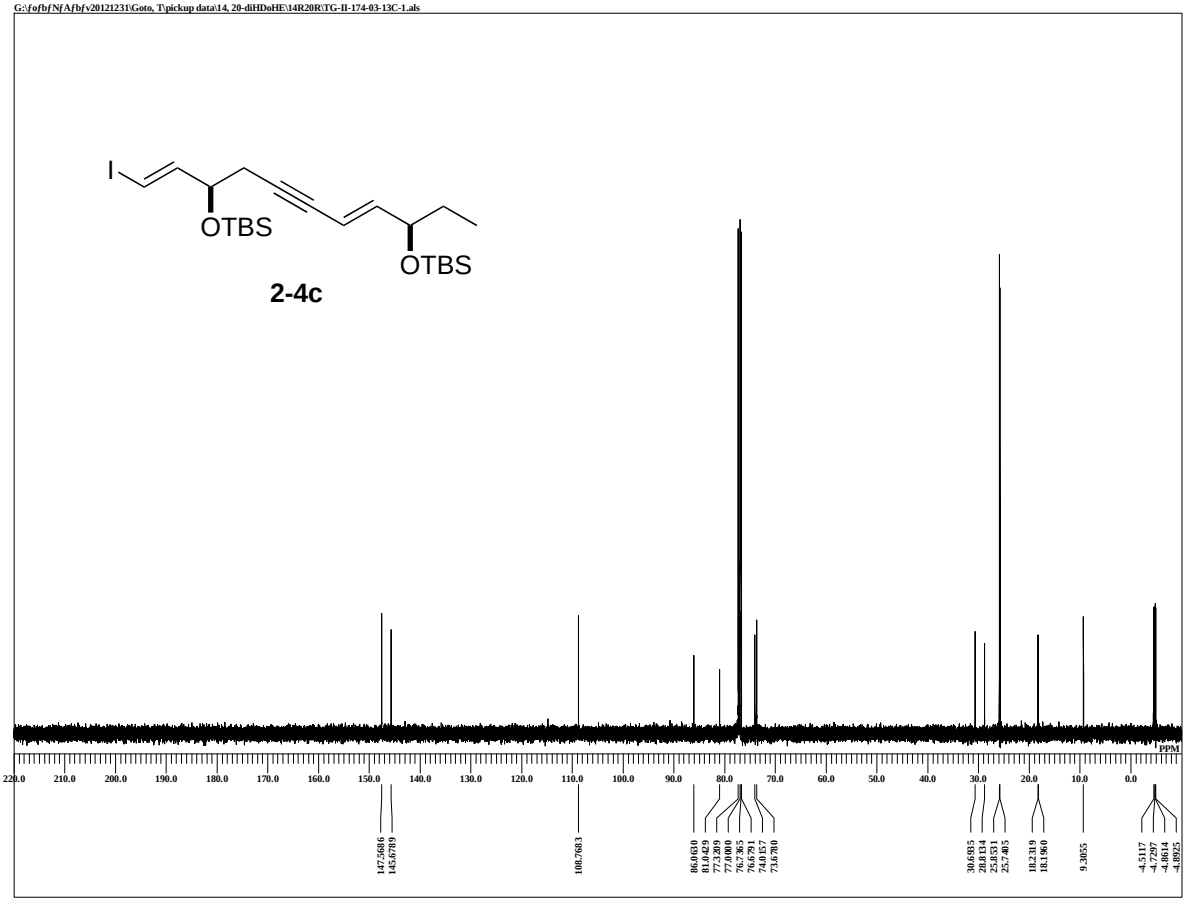
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-174-03-2.als




```
DFILE   TG-II-174-03-2.als
COMNT   TG-II-174-03
DATIM   14-08-2011 15:52:23
MENUF
OBNUC   1H
OFR     395.88 MHz
OBFRQ   395.88 MHz
OBSET   6.28 KHz
OBFIN   0.87 Hz
PW1     6.62 usec
DEADT   0.00 usec
PREDL   0.00000 msec
IWT     1.0000 sec
POINT   13107
SPO     13107
TIMES   8
DUMMY   1
FREQU   5938.15 Hz
FLT     30000 Hz
DELAY   16.68 usec
ACQTM   2.2073 sec
PD      2.0000 sec
SCANS   8
ADBIT   16
RGAIN   48
BF      0.01 Hz
T1      0.00
T2      0.00
T3      90.00
T4      100.00
EXMOD   single_pulse.ex2
EXPCM
IRNUC   1H
IFR     395.88 MHz
IRSET   6.28 KHz
IRFIN   0.87 Hz
IRRPW   115 usec
IRATN   79
DFILE   TG-II-174-03-2.als
SF
LKSET   13.20 KHz
LKFIN   75.7 Hz
LKLEV   0
LGAIN   0
LKPHS   0
LKSIG   0
CSPED   0 Hz
FILDC
FILDF
CTEMP   25.0 c
SLVNT   CDCL3
EXREF   7.26 ppm
```

TG-II-174-03-13C

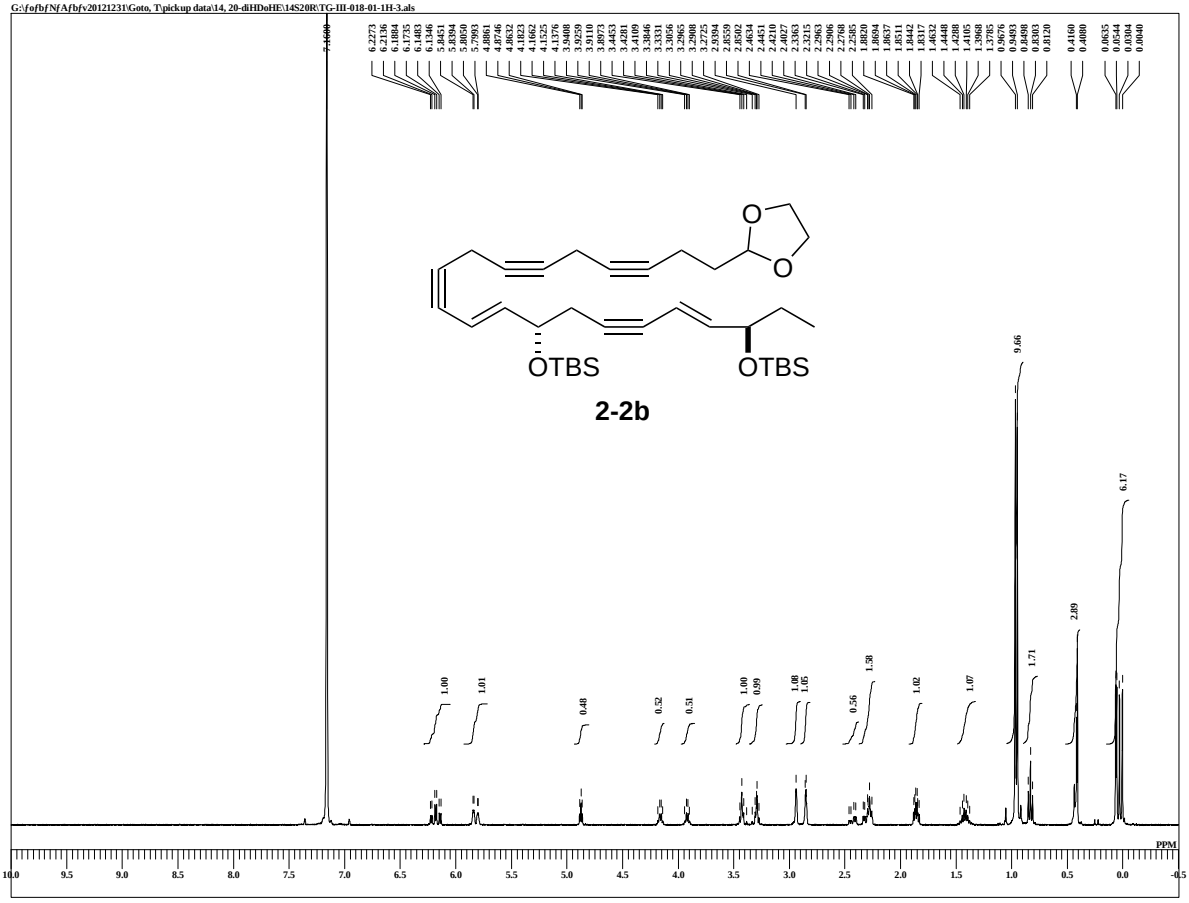
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-II-174-03-13C-1.als




```
DFILE   TG-II-174-03-13C-1.als
COMNT   TG-II-174-03-13C
DATIM   14-08-2011 16:19:03
MENUF
OBNUC   13C
OFR     99.55 MHz
OBFRQ   99.55 MHz
OBSET   5.13 KHz
OBFIN   0.98 Hz
PW1     2.92 usec
DEADT   0.00 usec
PREDL   0.00000 msec
IWT     1.0000 sec
POINT   104856
SPO     104856
TIMES   341
DUMMY   4
FREQU   24999.62 Hz
FLT     125000 Hz
DELAY   20.50 usec
ACQTM   1.0486 sec
PD      2.0000 sec
SCANS   341
ADBIT   16
RGAIN   60
BF      0.01 Hz
T1      0.00
T2      0.00
T3      90.00
T4      100.00
EXMOD   single_pulse_dec
EXPCM
IRNUC   1H
IFR     395.88 MHz
IRSET   6.28 KHz
IRFIN   0.87 Hz
IRRPW   115 usec
IRATN   79
DFILE   TG-II-174-03-13C-1.als
SF
LKSET   13.20 KHz
LKFIN   75.7 Hz
LKLEV   0
LGAIN   0
LKPHS   0
LKSIG   0
CSPED   0 Hz
FILDC
FILDF
CTEMP   25.1 c
SLVNT   CDCL3
EXREF   77.00 ppm
```

TG-III-018-01-1H

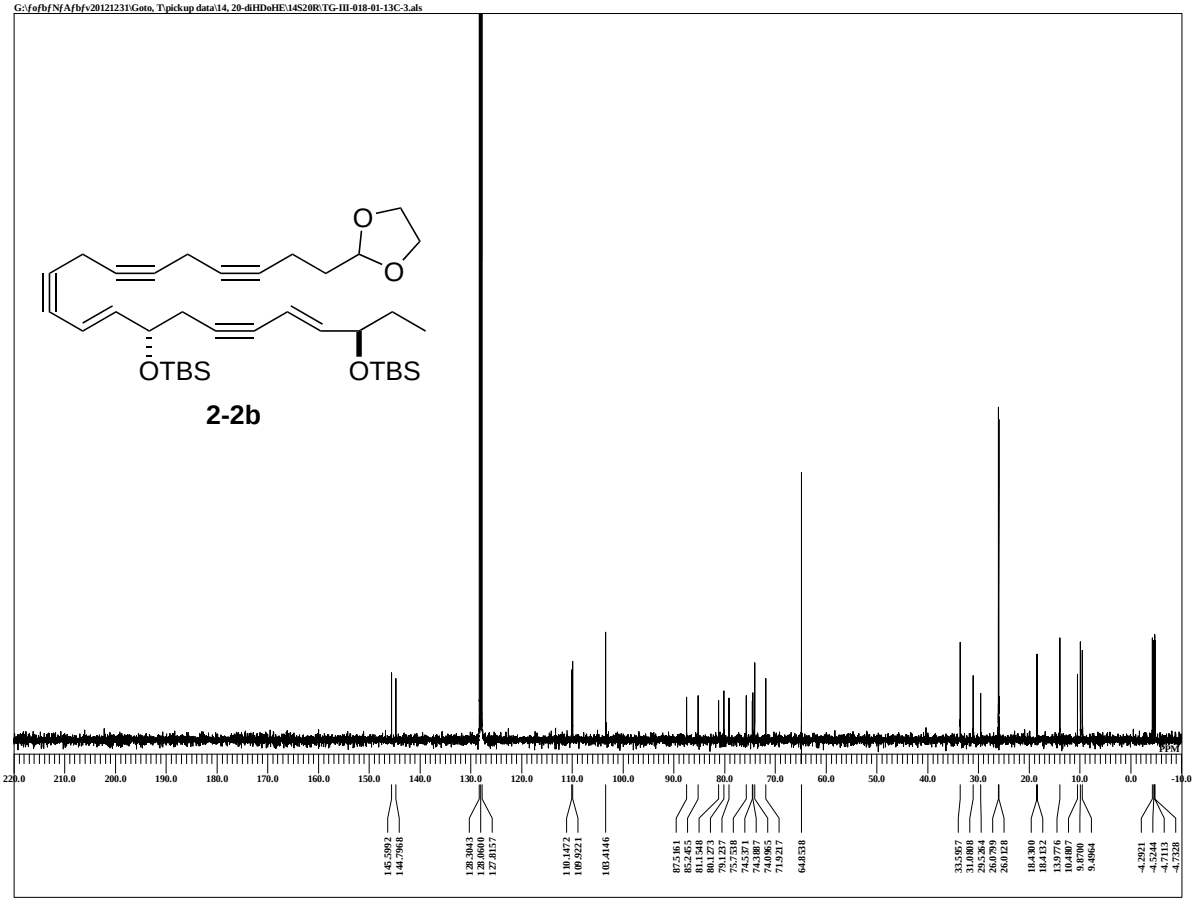
G:\fofbfNfA\bfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-III-018-01-1H-3.als



DFILE	TG-III-018-01-1H-3.als
COMNT	TG-III-018-01-1H
DATIM	14-09-2011 15:51:48
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.62 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	44
BF	0.01 Hz
T1	0.00
T2	0.00
T3	100.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-III-018-01-1H-3.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.2 c
SLVNT	C6D6
EXREF	7.16 ppm

TG-III-018-01-13C

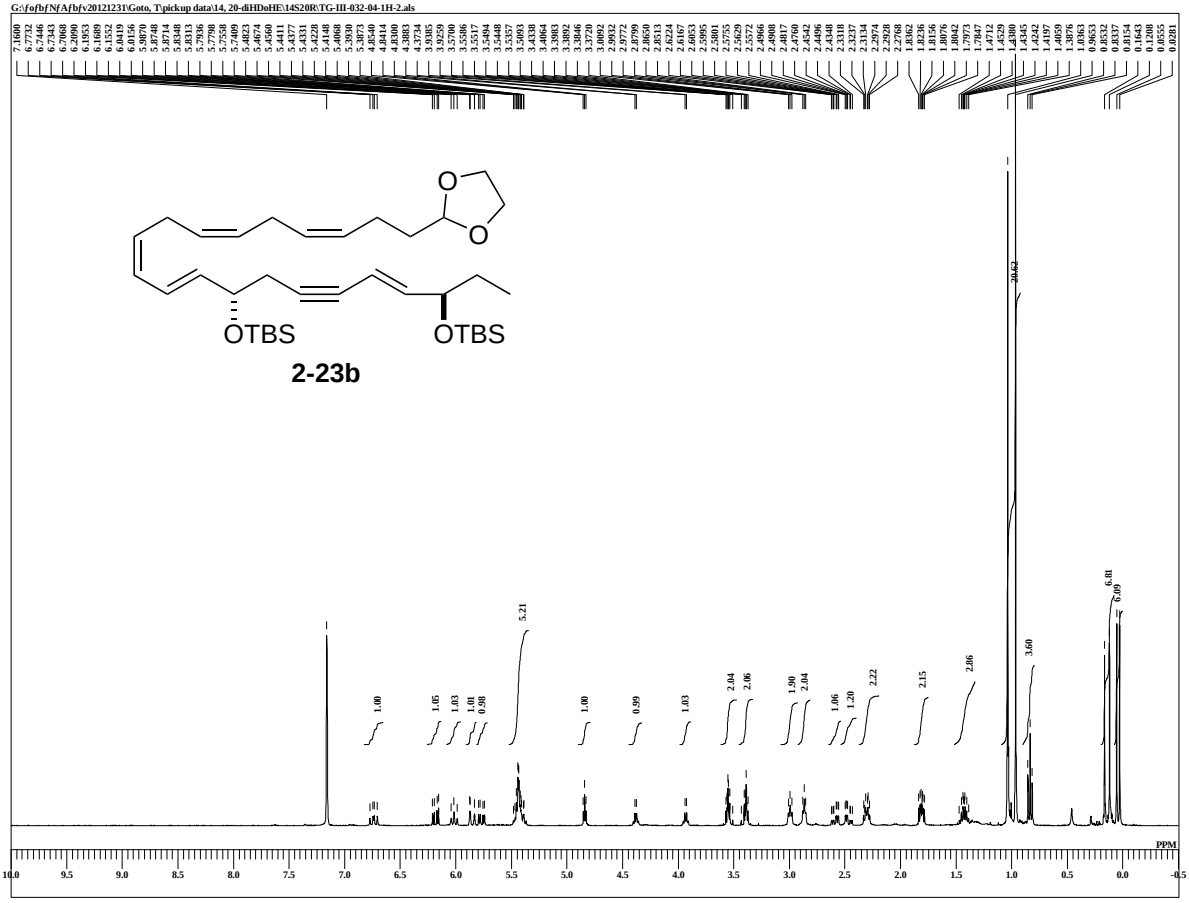
G:\fofbfNfA\bfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-III-018-01-13C-3.als



DFILE	TG-III-018-01-13C-3.als
COMNT	TG-III-018-01-13C
DATIM	14-09-2011 16:06:37
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	2.92 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	102
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	2.0000 sec
SCANS	102
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	100.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-III-018-01-13C-3.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.3 c
SLVNT	C6D6
EXREF	128.06 ppm

TG-III-032-04-1H

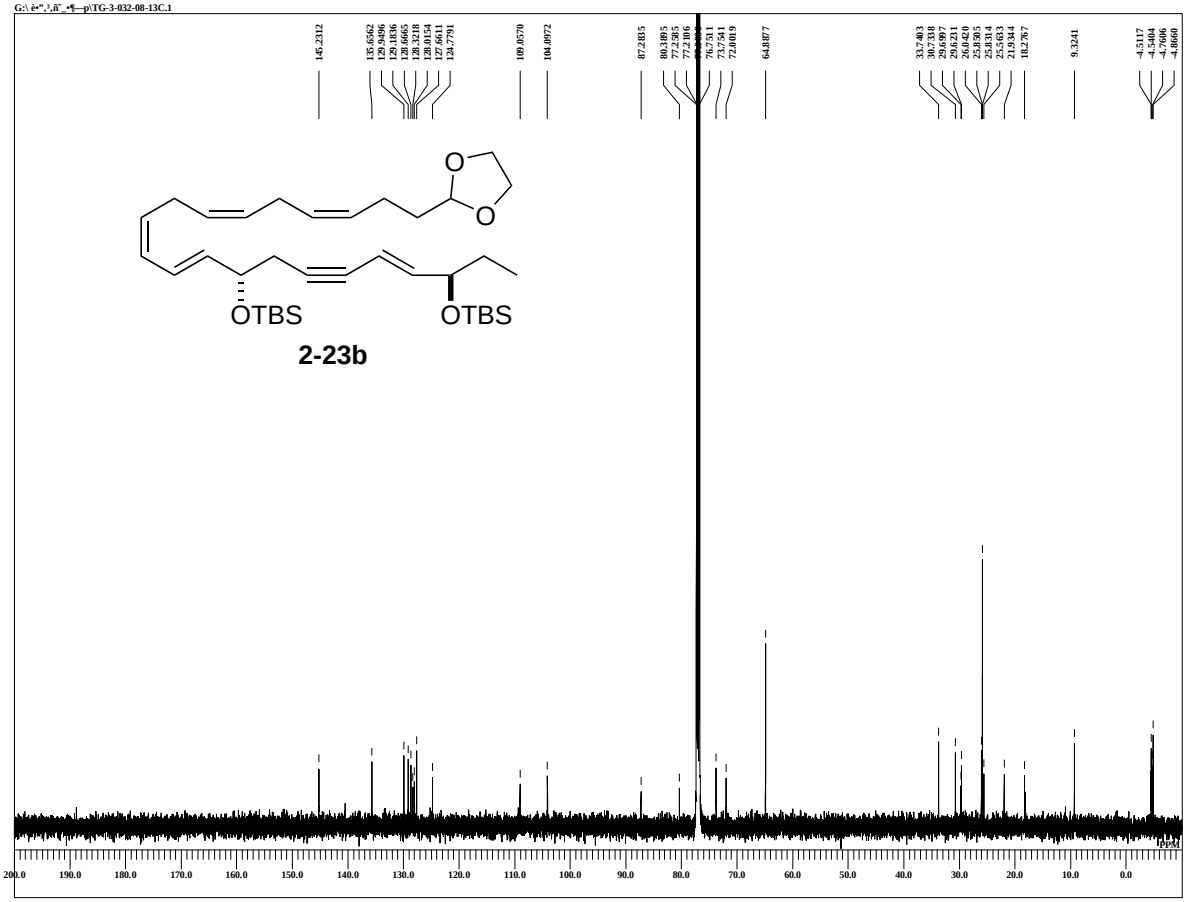
G:\fofbf\NfA\bfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-III-032-04-1H-2.als



DFILE	TG-III-032-04-1H-2.als
COMNT	TG-III-032-04-1H
DATIM	20-09-2011 16:42:02
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.62 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	34
BF	0.01 Hz
T1	0.00
T2	0.00
T3	100.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-III-032-04-1H-2.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.1 c
SLVNT	C6D6
EXREF	7.16 ppm

TG-3-032-08-13C

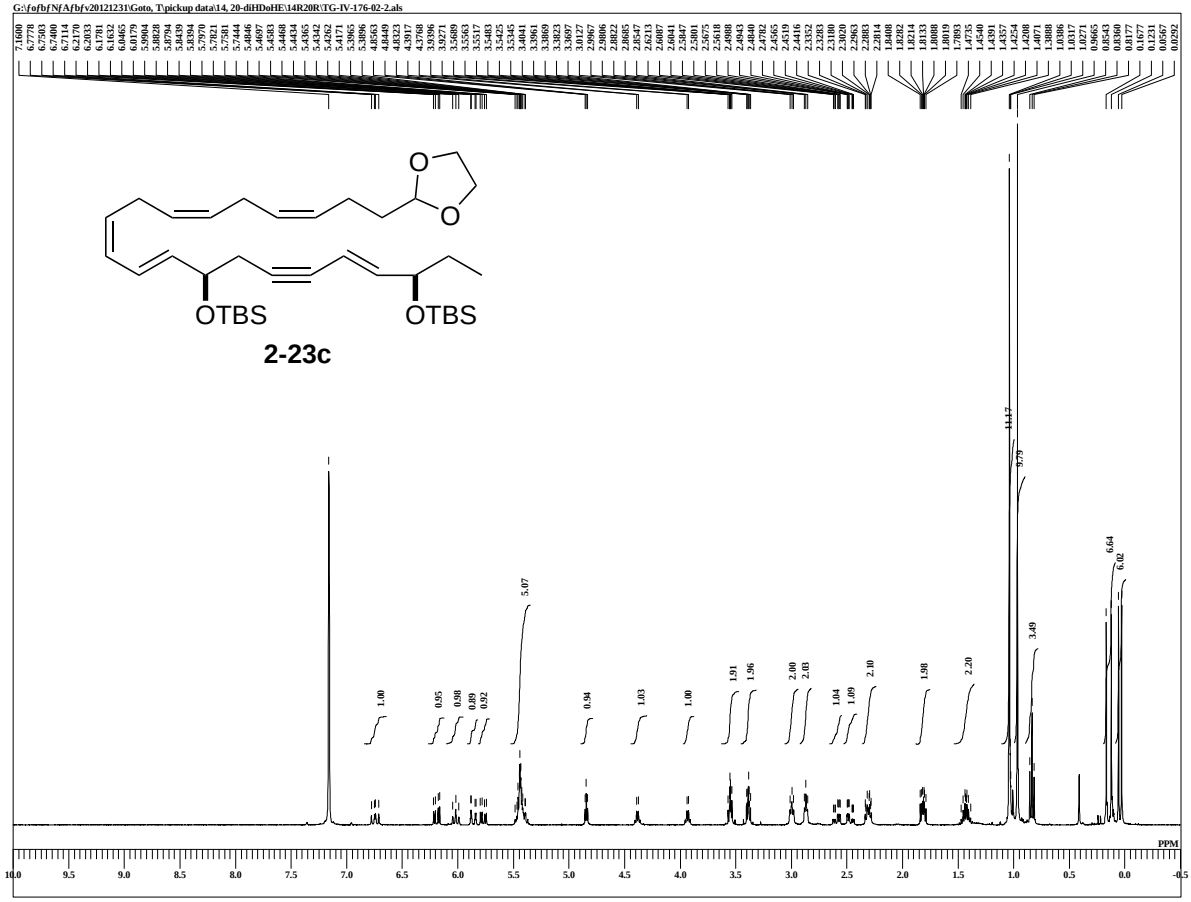
G:\ è*",³,ñ¯„•¶—p\TG-3-032-08-13C.1



DFILE	TG-3-032-08-13C.1
COMNT	TG-3-032-08-13C
DATIM	22-06-2015 08:41:54
MENUF	
OBNUC	13C
OFR	124.51 MHz
OBFRQ	124.51 MHz
OBSET	3.45 KHz
OBFIN	6.00 Hz
PW1	4.42 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	32768
SPO	32768
TIMES	40469
DUMMY	4
FREQU	39062.50 Hz
FLT	157000 Hz
DELAY	20.80 usec
ACQTM	0.8389 sec
PD	2.0000 sec
SCANS	40469
ADBIT	16
RGAIN	50
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-3-032-08-13C.1
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.0 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-IV-176-02

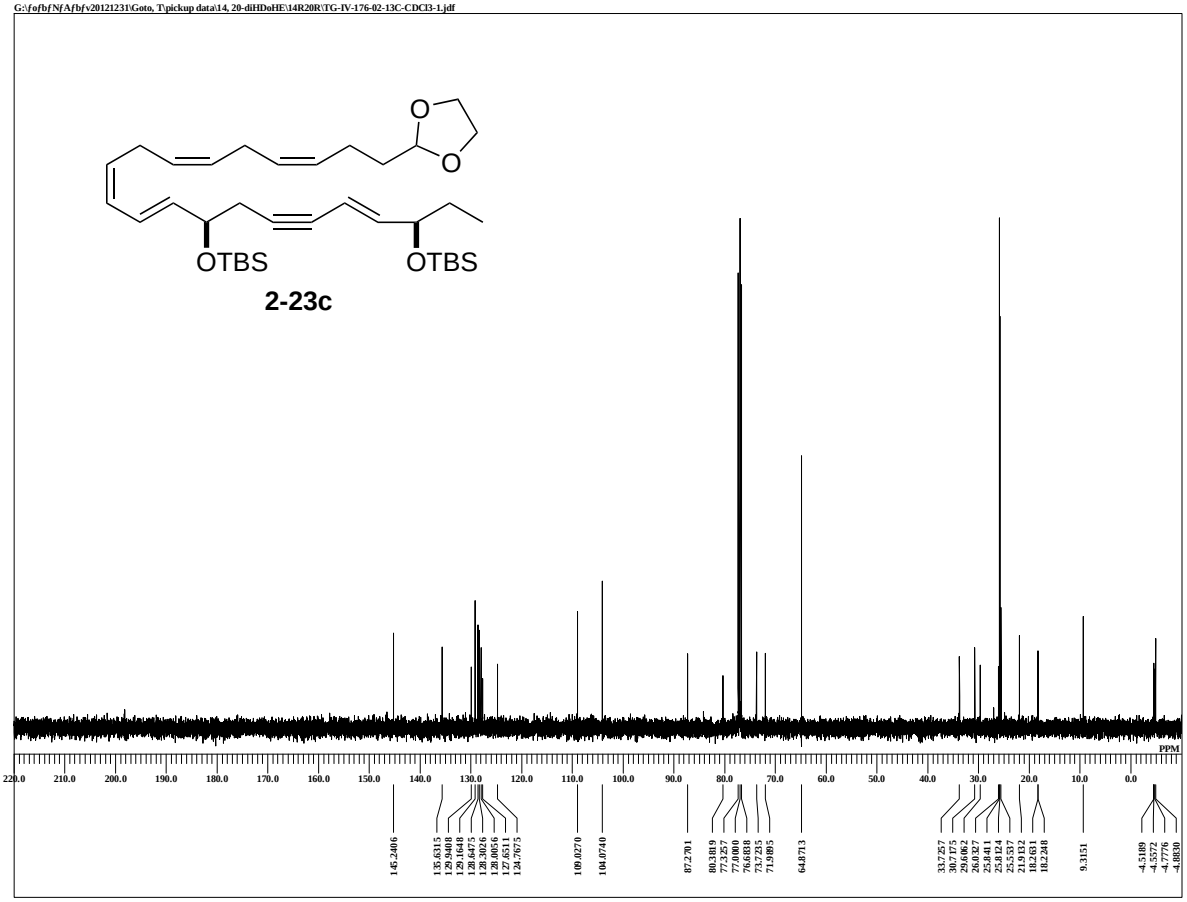
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-176-02-2.als



DFILE TG-IV-176-02-2.als
COMNT TG-IV-176-02
DATIM 26-04-2012 15:34:24
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.55 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 16
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 16
ADBIT 16
RGAIN 36
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-176-02-2.als
SF
LKSET 13.20 KHz
LKFIN 69.6 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.7 c
SLVNT C6D6
EXREF 7.16 ppm

TG-IV-176-02-13C-CDCl3

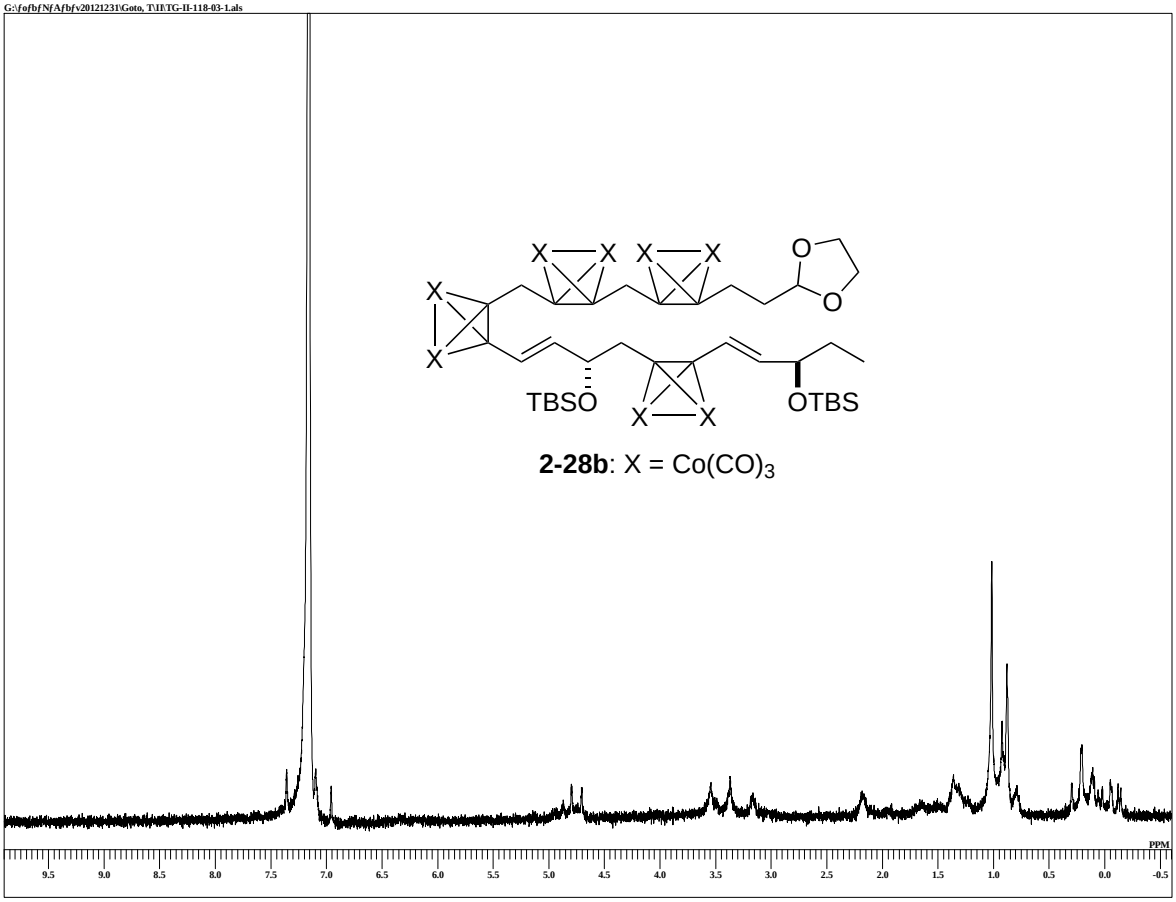
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-176-02-13C-CDCl3-1.jdf



DFILE TG-IV-176-02-13C-CDCl
COMNT TG-IV-176-02-13C-CDCl
DATIM 26-04-2012 18:34:31
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 3.67 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 185
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 185
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-176-02-13C-CDCl
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.0 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-II-118-03

G:\fofbf\NfA\fbfv20121231\Goto, T\II\TG-II-118-03-1.als



2-28b: X = $Co(CO)_3$

DFILE	TG-II-118-03-1.als
COMNT	TG-II-118-03
DATIM	23-07-2011 19:25:19
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.50 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	16384
SPO	16384
TIMES	12
DUMMY	1
FREQU	7422.80 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	12
ADBIT	16
RGAIN	50
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	147 usec
IRATN	79
DFILE	TG-II-118-03-1.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.2 c
SLVNT	C6D6
EXREF	7.16 ppm

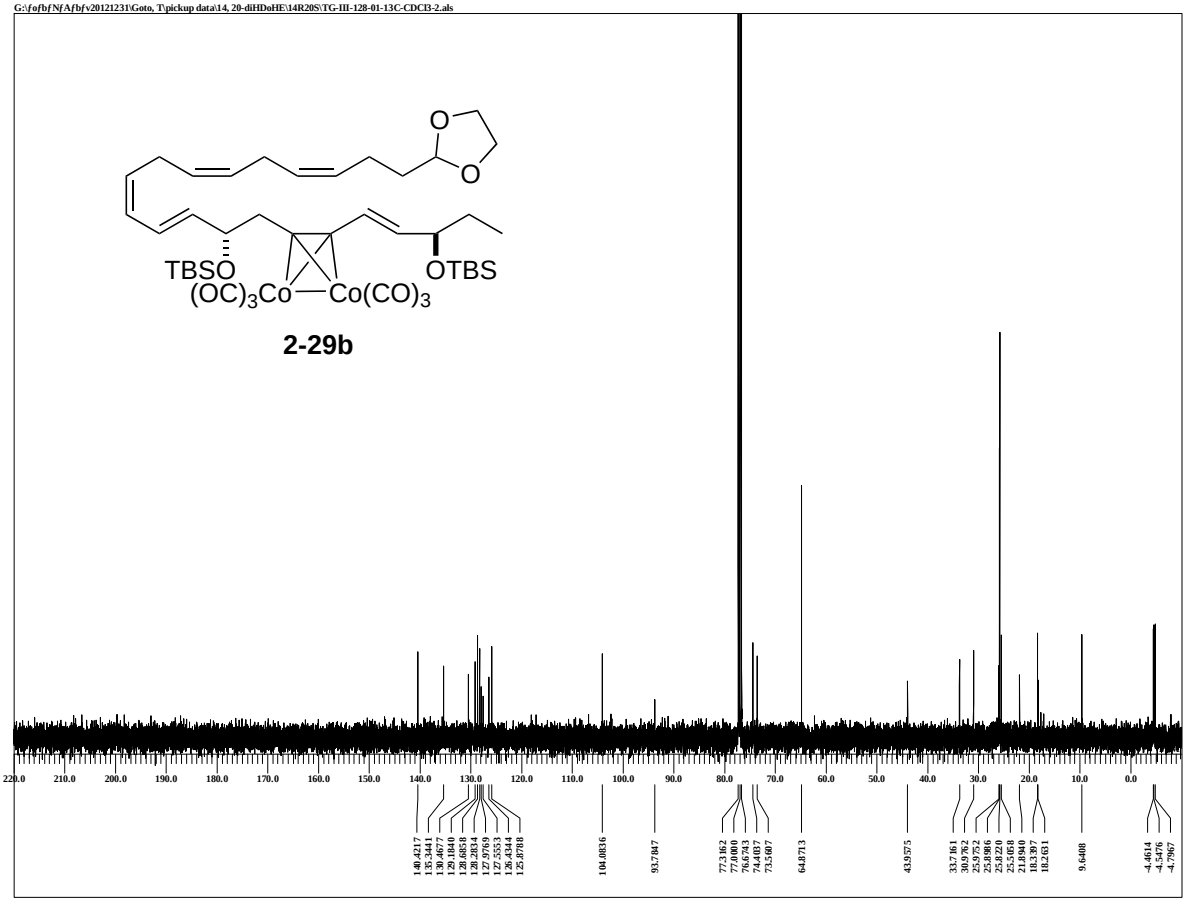
TG-IV-168-01

G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-IV-168-01-2.als


```
DFILE    TG-IV-168-01-2.als
COMNT    TG-IV-168-01
DATIM    19-04-2012 14:59:50
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.55 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    16
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    16
ADBIT    16
RGAIN    30
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    147 usec
IRATN    79
DFILE    TG-IV-168-01-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    23.6 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-III-128-01-13C-CDCl3

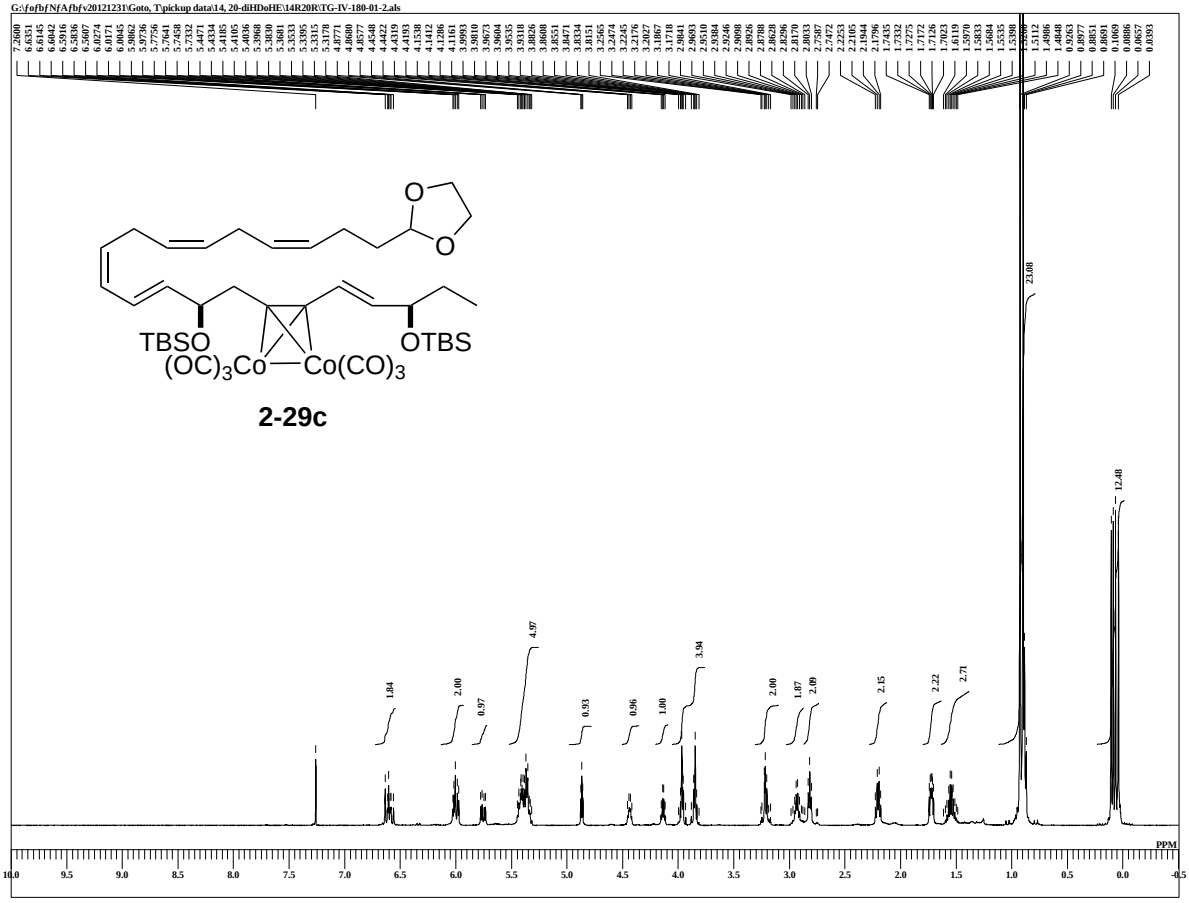
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20S\TG-III-128-01-13C-CDCl3-2.als




```
DFILE    TG-III-128-01-13C-CDCl
COMNT    TG-III-128-01-13C-CDCl
DATIM    29-11-2011 11:08:48
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      2.92 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    32768
SPO      32768
TIMES    308
DUMMY    4
FREQU    31250.00 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       2.0000 sec
SCANS    308
ADBIT    16
RGAIN    60
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-III-128-01-13C-CDCl
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    23.5 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-IV-180-01

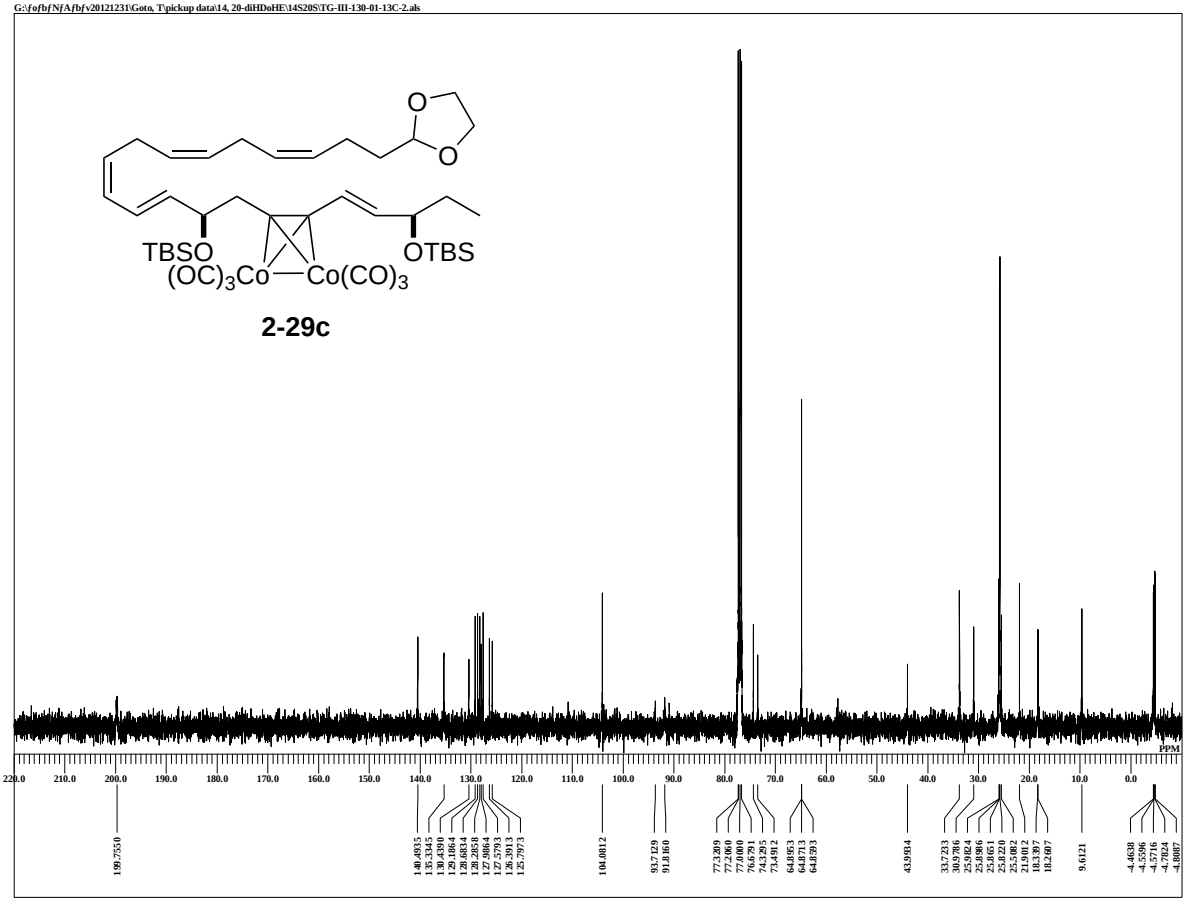
G:*fofbf*\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-180-01-2.als



DFILE	TG-IV-180-01-2.als
COMNT	TG-IV-180-01
DATIM	27-04-2012 11:23:16
MENUF	
OBNUC	1H
OFR	490.15 MHz
OBFRQ	490.15 MHz
OBSET	9.16 KHz
OBFIN	7.60 Hz
PW1	8.55 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	16
DUMMY	1
FREQU	7352.83 Hz
FLT	37000 Hz
DELAY	13.52 usec
ACQTM	1.7826 sec
PD	2.0000 sec
SCANS	16
ADBIT	16
RGAIN	36
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	490.15 MHz
IRSET	9.16 KHz
IRFIN	7.60 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-IV-180-01-2.als
SF	
LKSET	70.30 KHz
LKFIN	32.5 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.4 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-III-130-01-13C

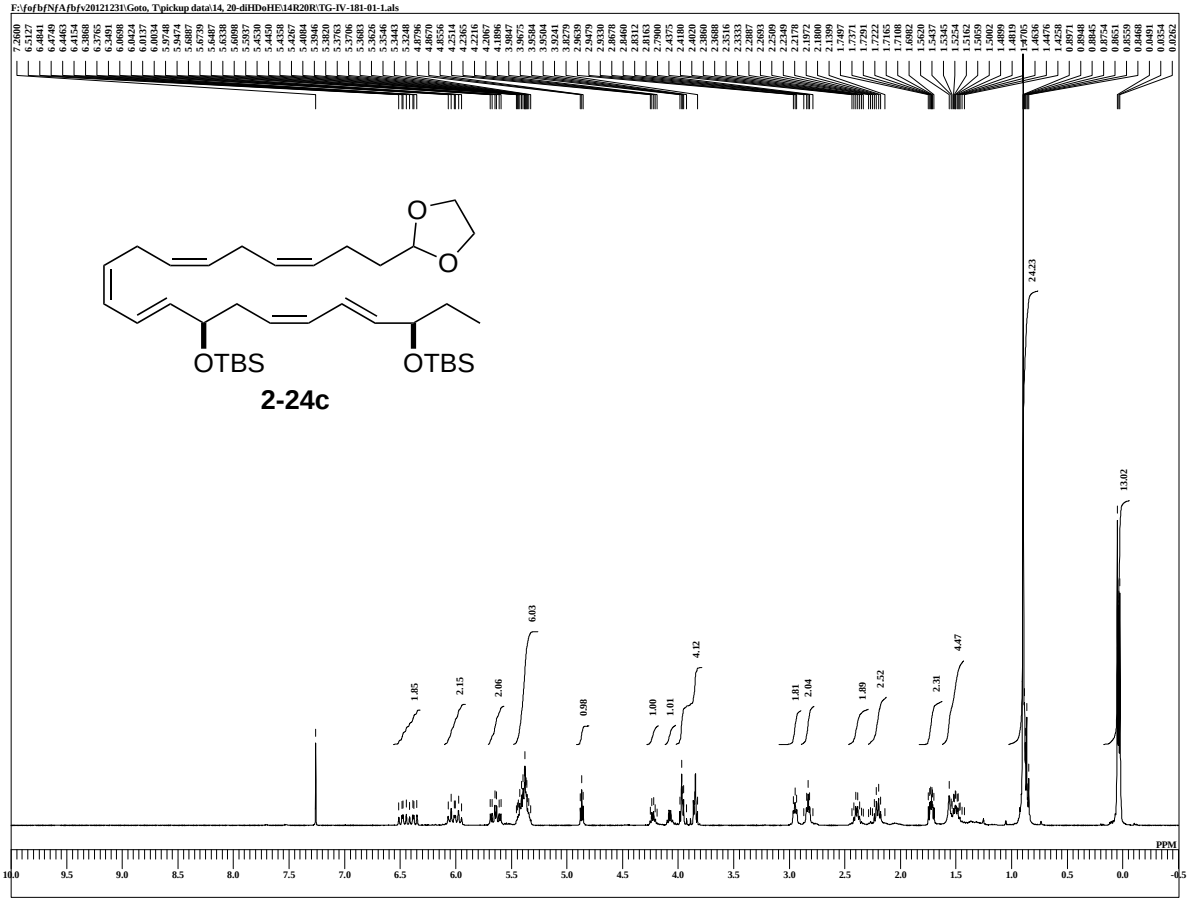
G:*fofbf*\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20S\TG-III-130-01-13C-2.als



DFILE	TG-III-130-01-13C-2.als
COMNT	TG-III-130-01-13C
DATIM	29-11-2011 21:12:47
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	2.92 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	591
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	2.0000 sec
SCANS	591
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-III-130-01-13C-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.3 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-IV-181-01

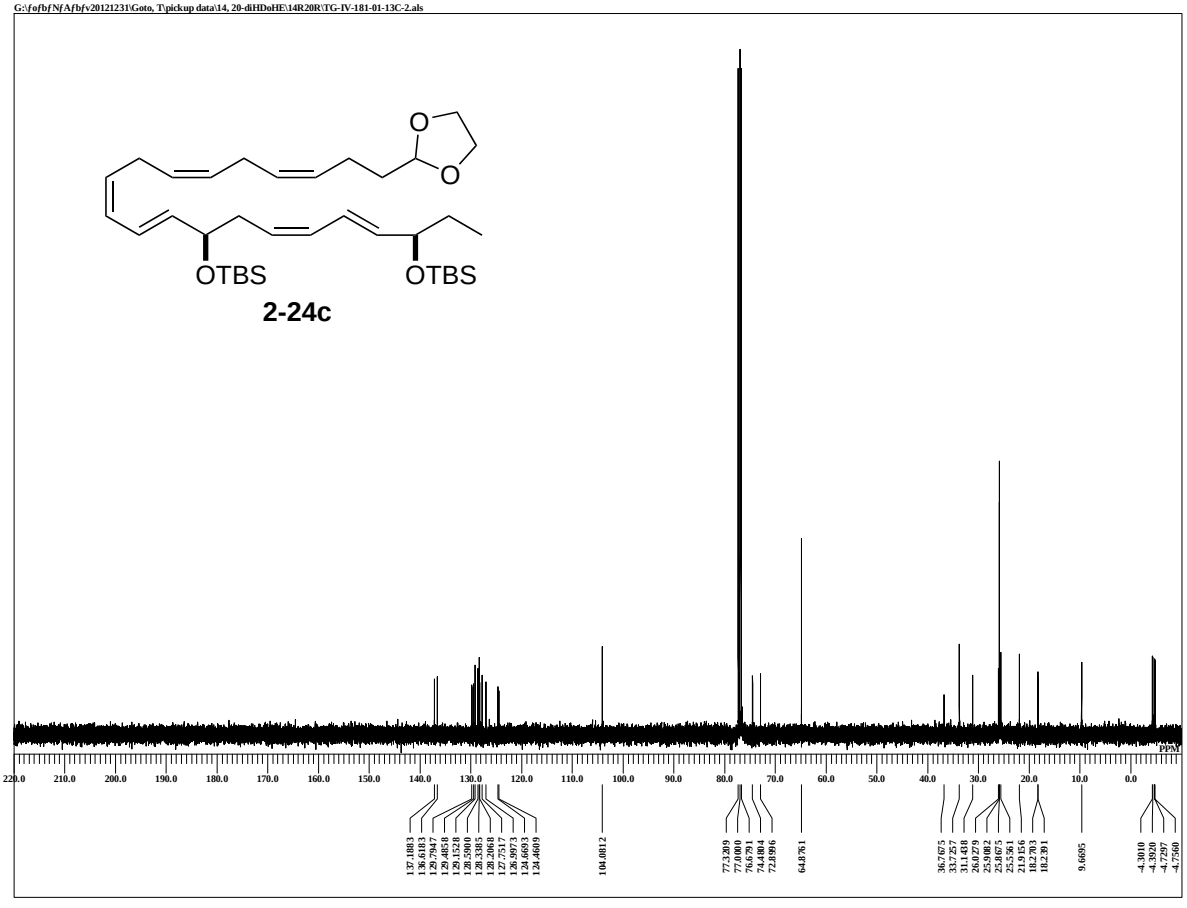
F:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-181-01-1.als



DFILE	TG-IV-181-01-1.als
COMNT	TG-IV-181-01
DATIM	27-04-2012 15:26:31
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.55 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	16
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	16
ADBIT	16
RGAIN	34
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-IV-181-01-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.7 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-IV-181-01-13C

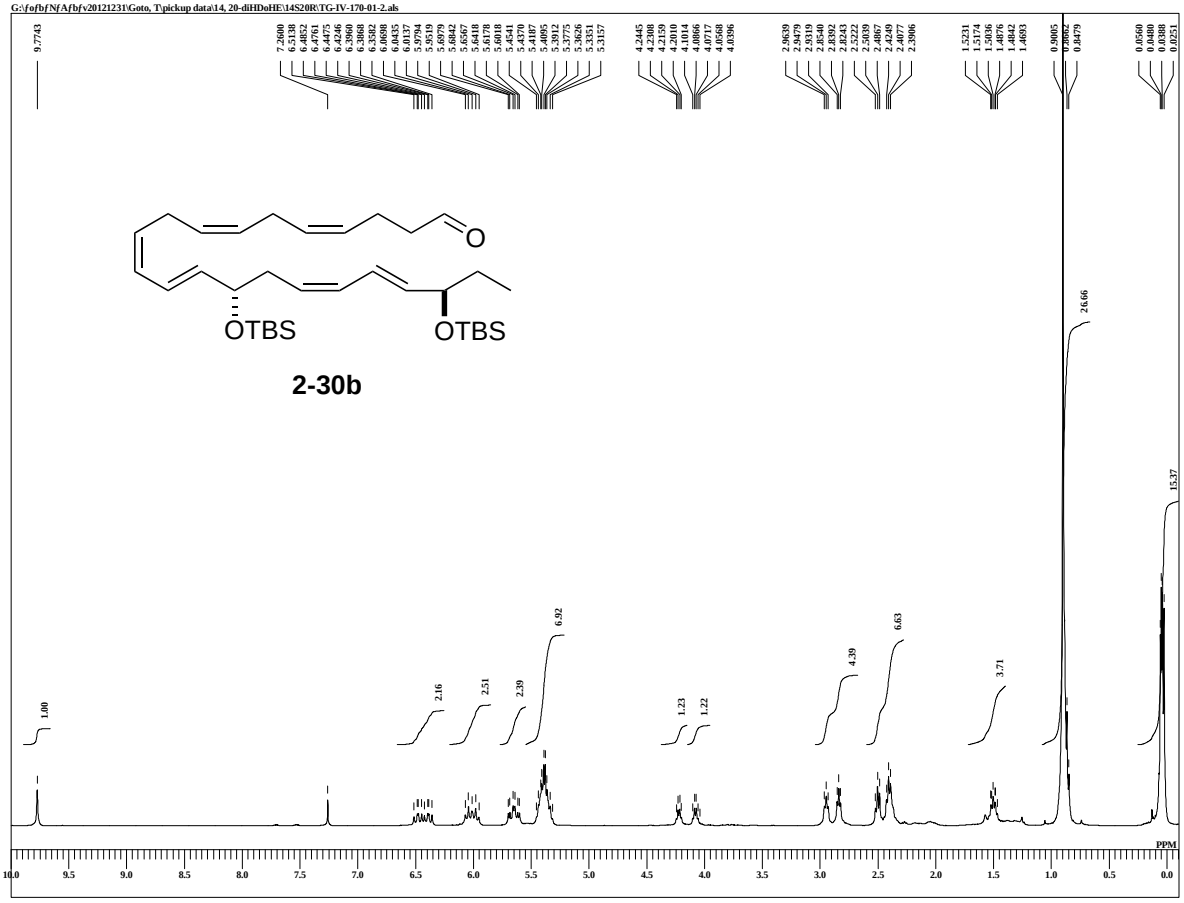
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-181-01-13C-2.als



DFILE	TG-IV-181-01-13C-2.als
COMNT	TG-IV-181-01-13C
DATIM	27-04-2012 15:49:44
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.67 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	446
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	2.0000 sec
SCANS	446
ADBIT	16
RGAIN	34
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-IV-181-01-13C-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.1 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-IV-160-01

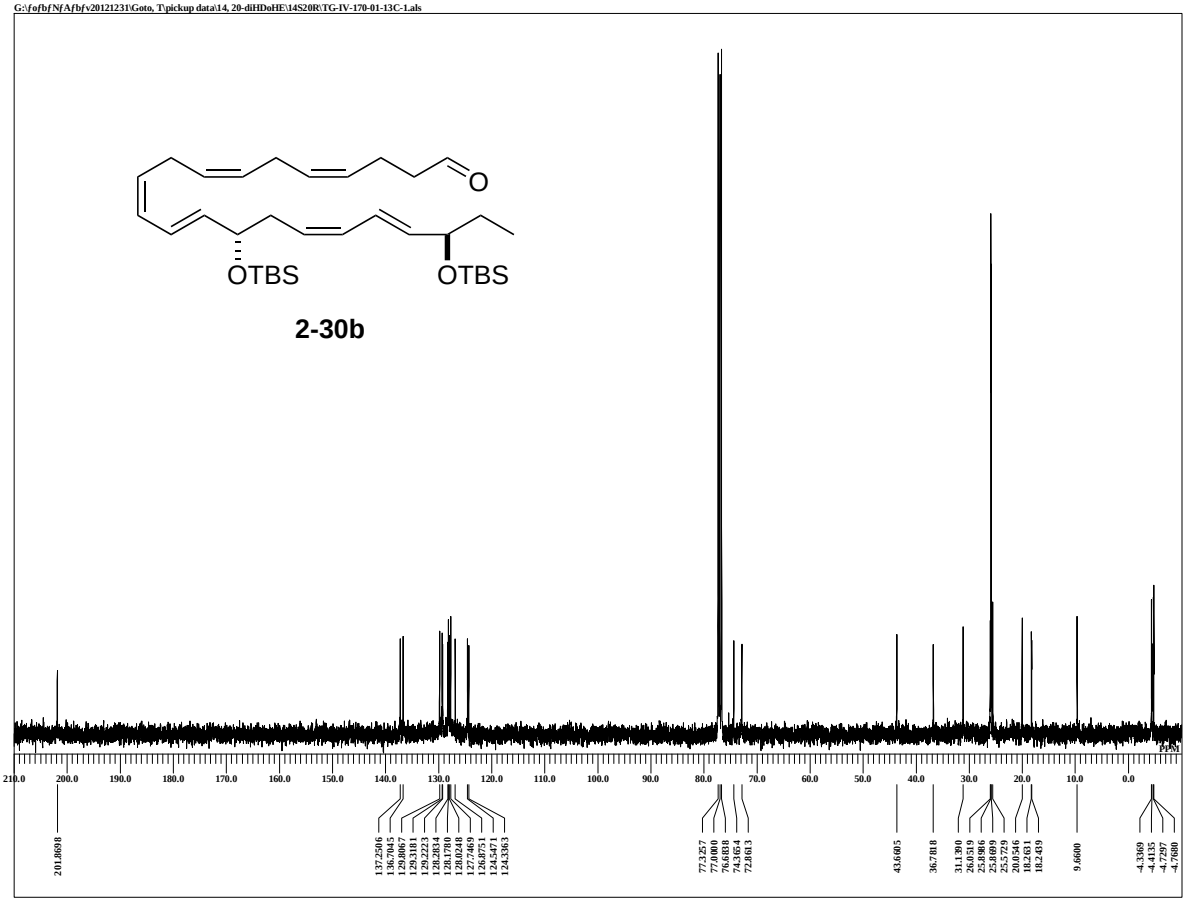
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-IV-170-01-2.als



DFILE TG-IV-170-01-2.als
COMNT TG-IV-160-01
DATIM 20-04-2012 11:11:36
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.55 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 24
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 24
ADBIT 16
RGAIN 30
BF 1.00 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-170-01-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.4 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-IV-170-01-13C

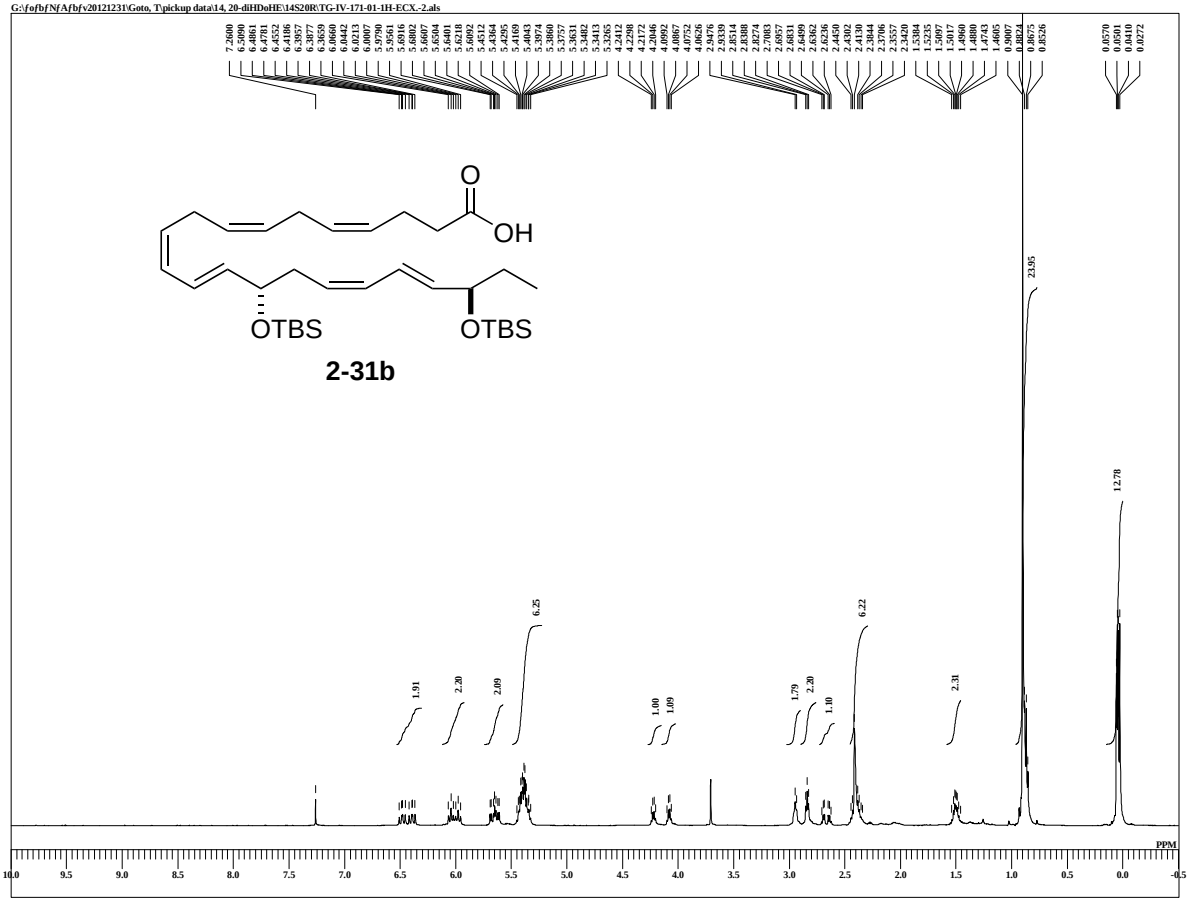
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-IV-170-01-13C-1.als



DFILE TG-IV-170-01-13C-1.als
COMNT TG-IV-170-01-13C
DATIM 20-04-2012 11:45:16
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 3.67 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 301
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 301
ADBIT 16
RGAIN 60
BF 1.00 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-IV-170-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 23.4 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-IV-171-01-1H-ECX

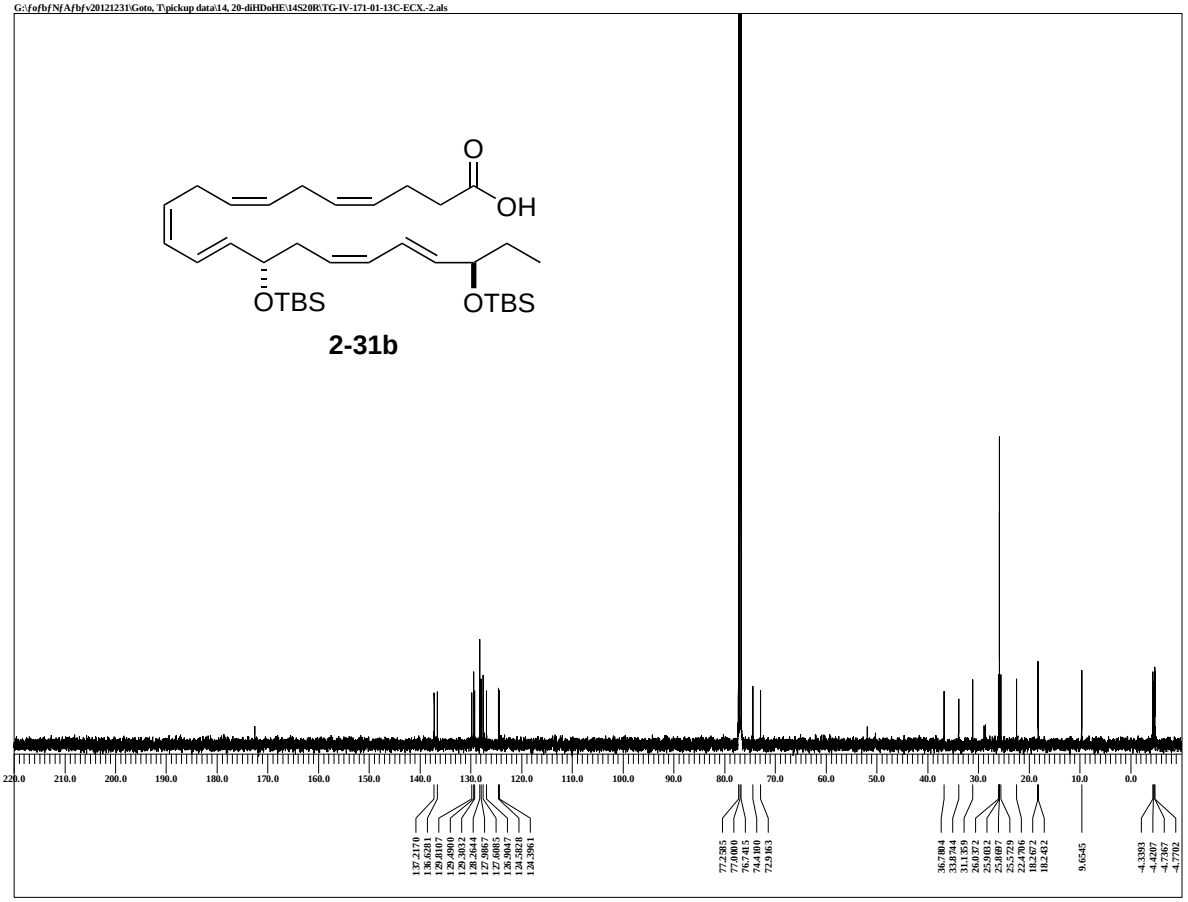
G:\fofbf\NfA\fbf\v20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-IV-171-01-1H-ECX.-2.als



DFILE	TG-IV-171-01-1H-ECX.-2
COMNT	TG-IV-171-01-1H-ECX
DATIM	20-04-2012 16:42:47
MENUF	
OBNUC	1H
OFR	495.13 MHz
OBFRQ	495.13 MHz
OBSET	4.38 KHz
OBFIN	9.64 Hz
PW1	5.75 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	7429.31 Hz
FLT	38000 Hz
DELAY	13.16 usec
ACQTM	1.7642 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	40
BF	1.00 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-IV-171-01-1H-ECX.-2
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.9 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-IV-171-01-13C-ECX

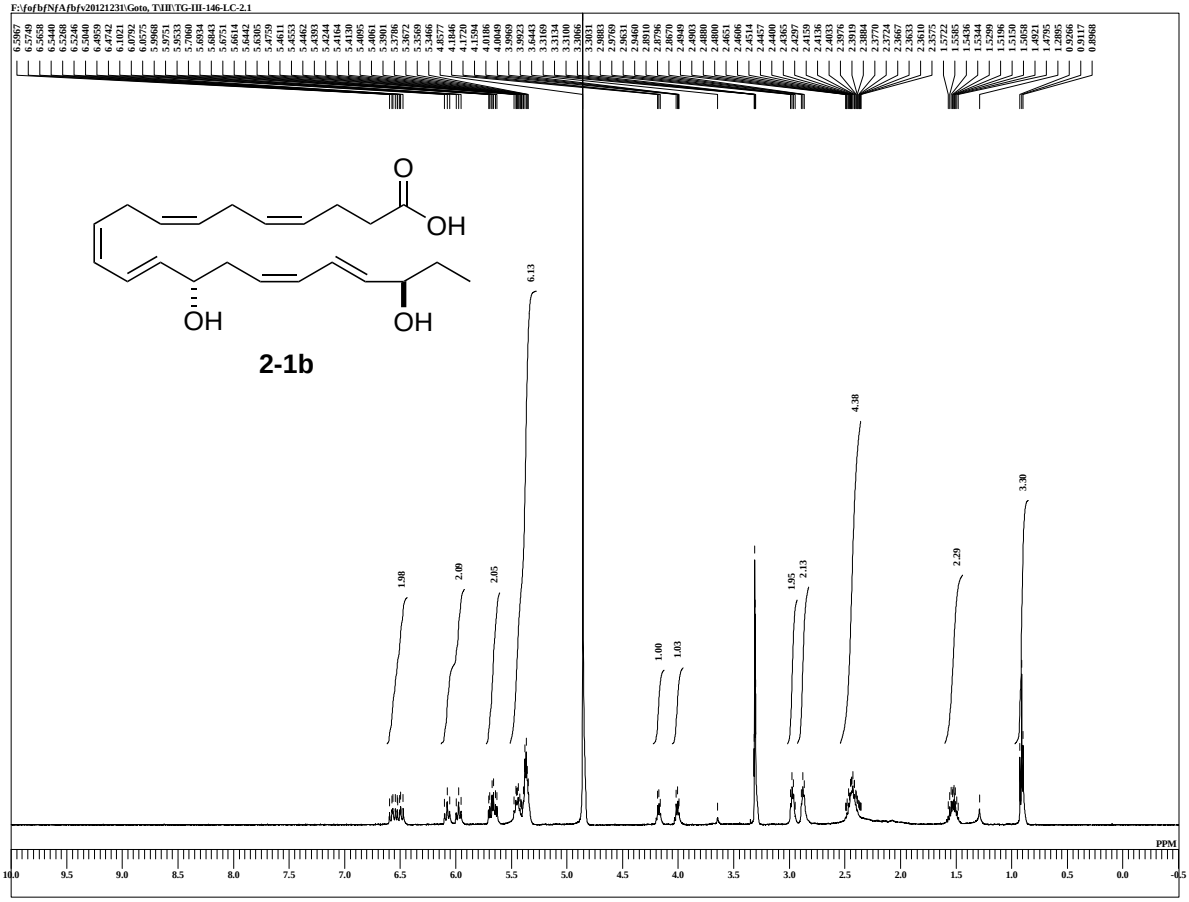
G:\fofbf\NfA\fbf\v20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-IV-171-01-13C-ECX.-2.als



DFILE	TG-IV-171-01-13C-ECX.-
COMNT	TG-IV-171-01-13C-ECX
DATIM	20-04-2012 17:16:08
MENUF	
OBNUC	13C
OFR	124.51 MHz
OBFRQ	124.51 MHz
OBSET	3.45 KHz
OBFIN	6.00 Hz
PW1	3.00 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	52428
SPO	52428
TIMES	243
DUMMY	4
FREQU	31249.52 Hz
FLT	157000 Hz
DELAY	20.80 usec
ACQTM	0.8389 sec
PD	7.0000 sec
SCANS	243
ADBIT	16
RGAIN	50
BF	1.00 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-IV-171-01-13C-ECX.-
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.7 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-III-146-LC-2

F:\fofbfNfAfbfv20121231\Goto, TIII\TG-III-146-LC-2.1

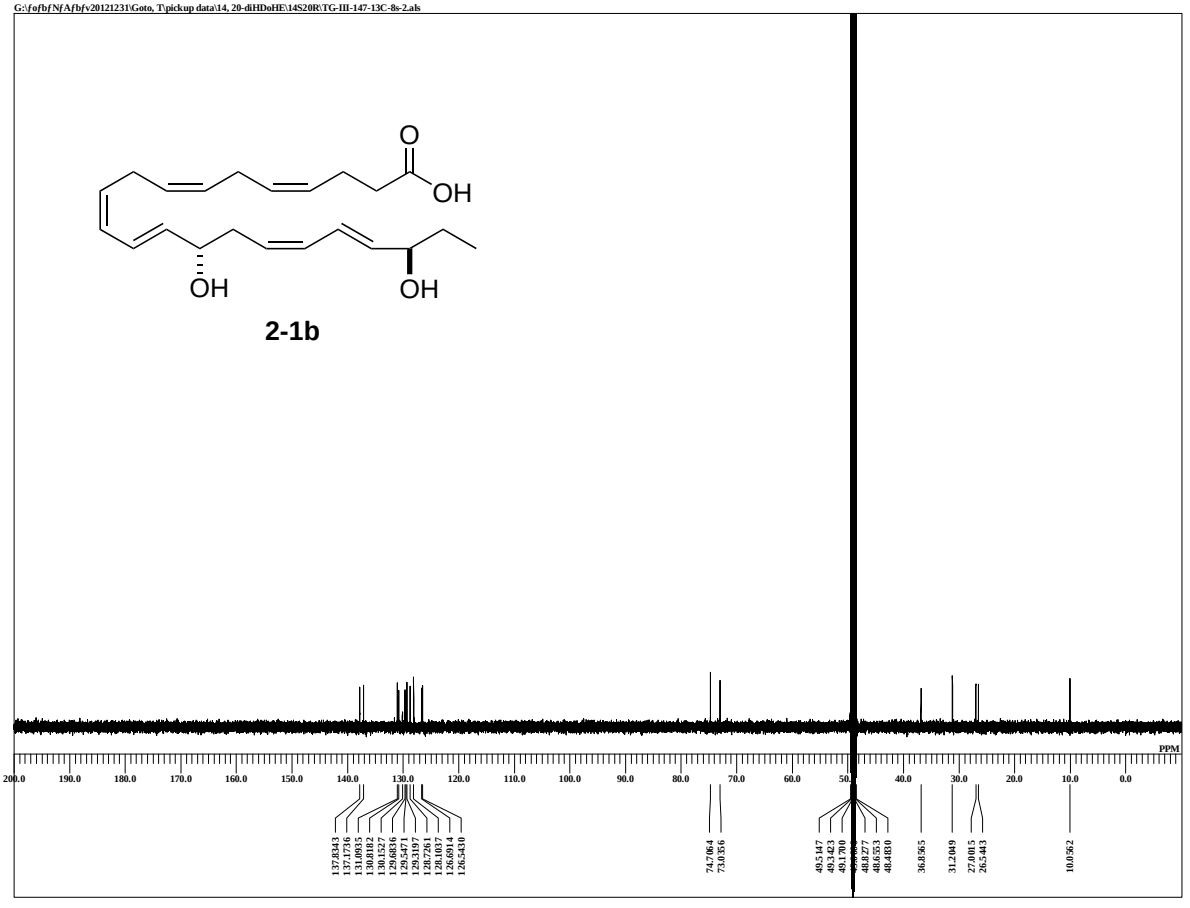


2-1b

```
DFILE    TG-III-146-LC-2.1
COMNT    TG-III-146-LC-2
DATIM    07-12-2011 20:23:48
MENUF
OBNUC    1H
OFR      495.13 MHz
OBFRQ    495.13 MHz
OBSET    4.38 KHz
OBFIN    9.64 Hz
PW1      6.60 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    16384
SPO      16384
TIMES    8
DUMMY    1
FREQU    9286.78 Hz
FLT      38000 Hz
DELAY    13.16 usec
ACQTM    1.7642 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    56
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      495.13 MHz
IRSET    4.38 KHz
IRFIN    9.64 Hz
IRRPW    75 usec
IRATN    79
DFILE    TG-III-146-LC-2.1
SF
LKSET    748.10 KHz
LKFIN    98.0 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    24.1 c
SLVNT    CD3OD
EXREF    3.31 ppm
```

TG-III-147-13C-8s

G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20R\TG-III-147-13C-8s-2.als

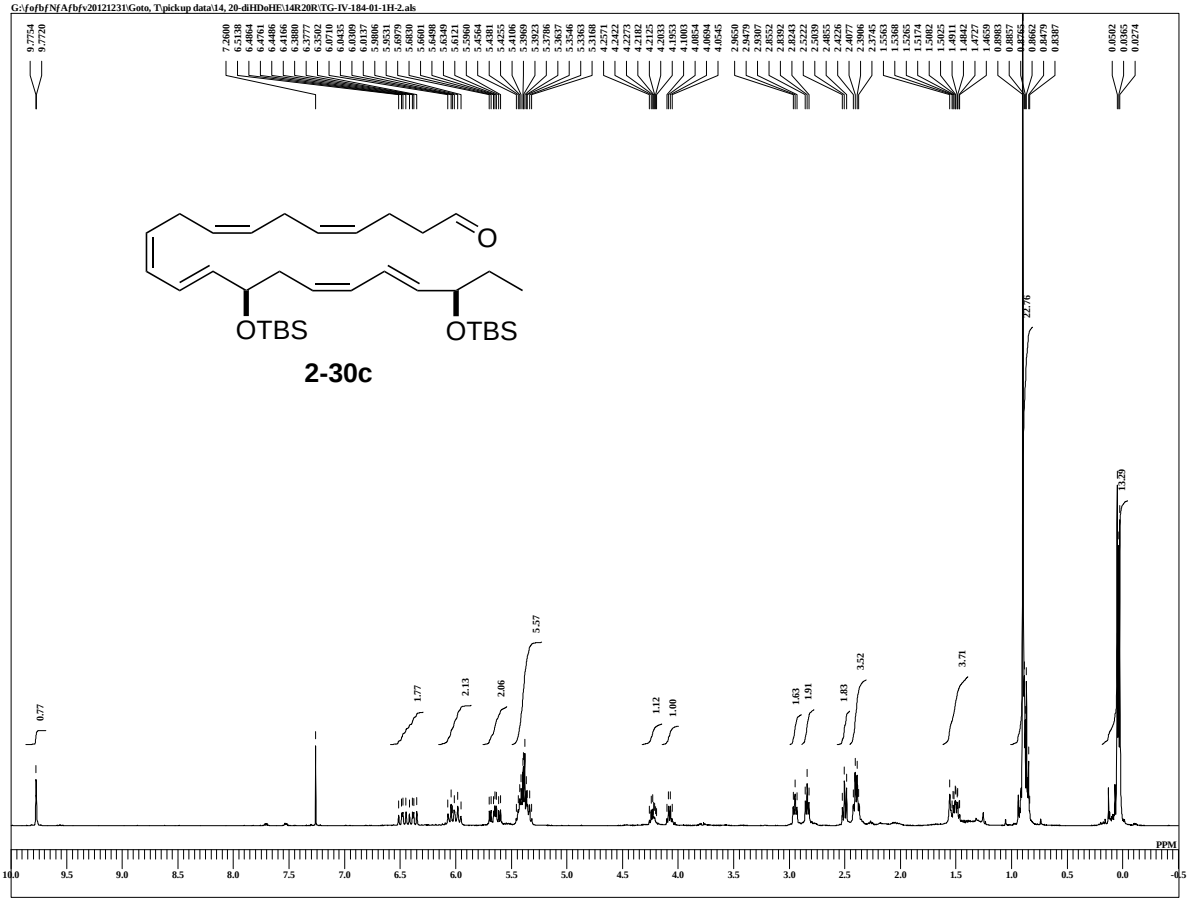


2-1b

```
DFILE    TG-III-147-13C-8s-2.als
COMNT    TG-III-147-13C-8s
DATIM    27-12-2011 04:33:31
MENUF
OBNUC    13C
OFR      124.51 MHz
OBFRQ    124.51 MHz
OBSET    3.45 KHz
OBFIN    6.00 Hz
PW1      3.13 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    104856
SPO      104856
TIMES    2800
DUMMY    4
FREQU    31249.52 Hz
FLT      157000 Hz
DELAY    20.80 usec
ACQTM    0.8389 sec
PD       8.0000 sec
SCANS    2800
ADBIT    16
RGAIN    54
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      495.13 MHz
IRSET    4.38 KHz
IRFIN    9.64 Hz
IRRPW    92 usec
IRATN    79
DFILE    TG-III-147-13C-8s-2.als
SF
LKSET    748.10 KHz
LKFIN    98.0 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    50.0 c
SLVNT    CD3OD
EXREF    49.00 ppm
```

TG-IV-184-01-1H

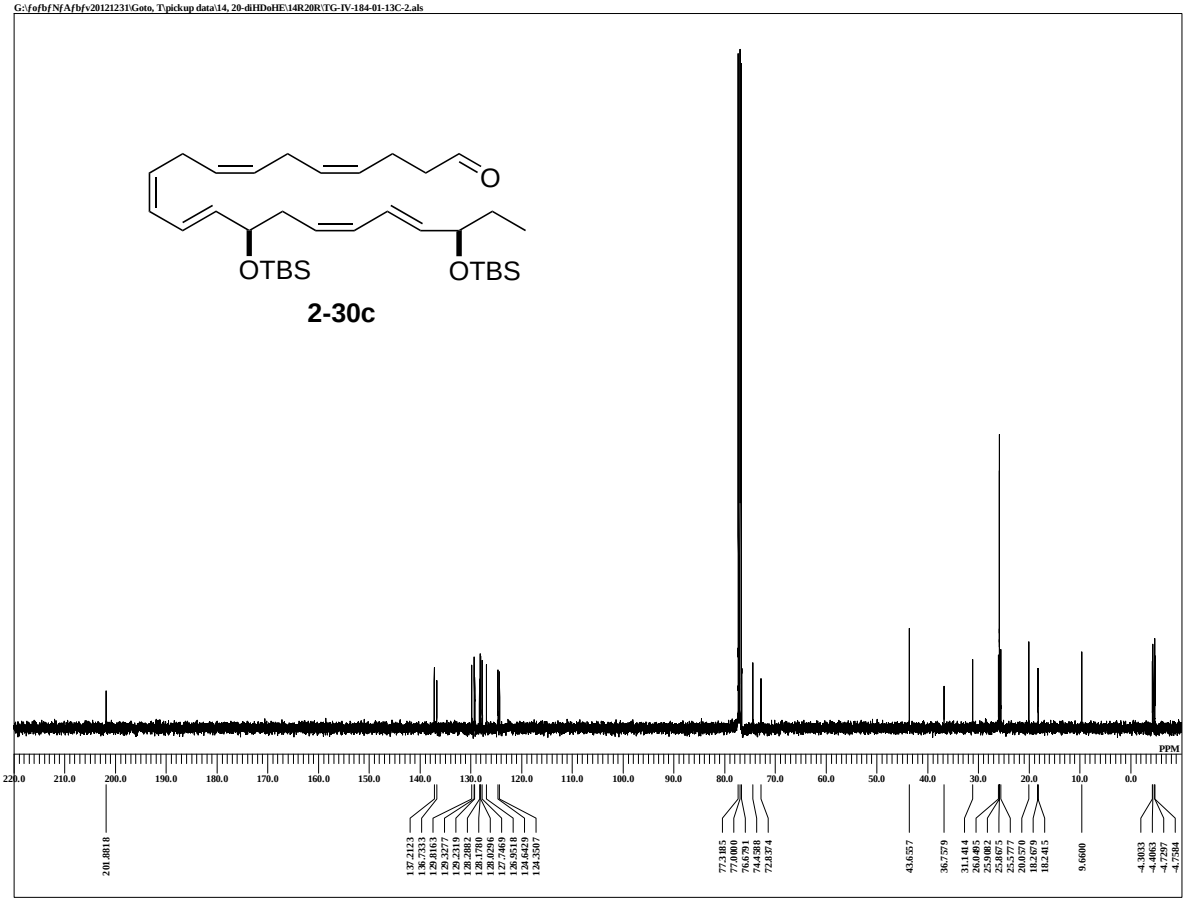
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-184-01-1H-2.als




```
DFILE    TG-IV-184-01-1H-2.als
COMNT    TG-IV-184-01-1H
DATIM    29-04-2012 14:50:33
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.55 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    16
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    16
ADBIT    16
RGAIN    32
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-IV-184-01-1H-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    25.0 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-IV-184-01-13C

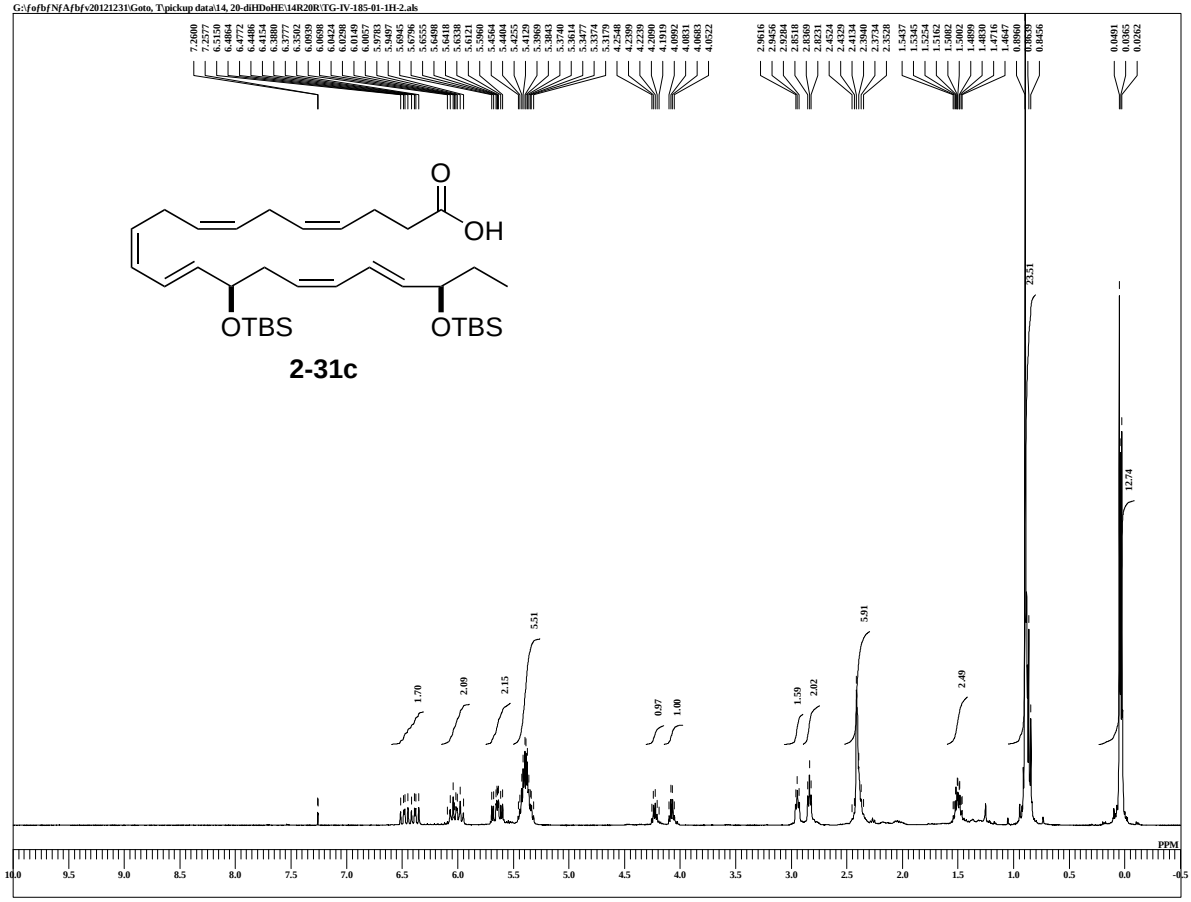
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-184-01-13C-2.als




```
DFILE    TG-IV-184-01-13C-2.als
COMNT    TG-IV-184-01-13C
DATIM    29-04-2012 15:08:20
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      3.67 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    104856
SPO      104856
TIMES    344
DUMMY    4
FREQU    24999.62 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       2.0000 sec
SCANS    344
ADBIT    16
RGAIN    32
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-IV-184-01-13C-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    24.0 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-IV-185-01-1H

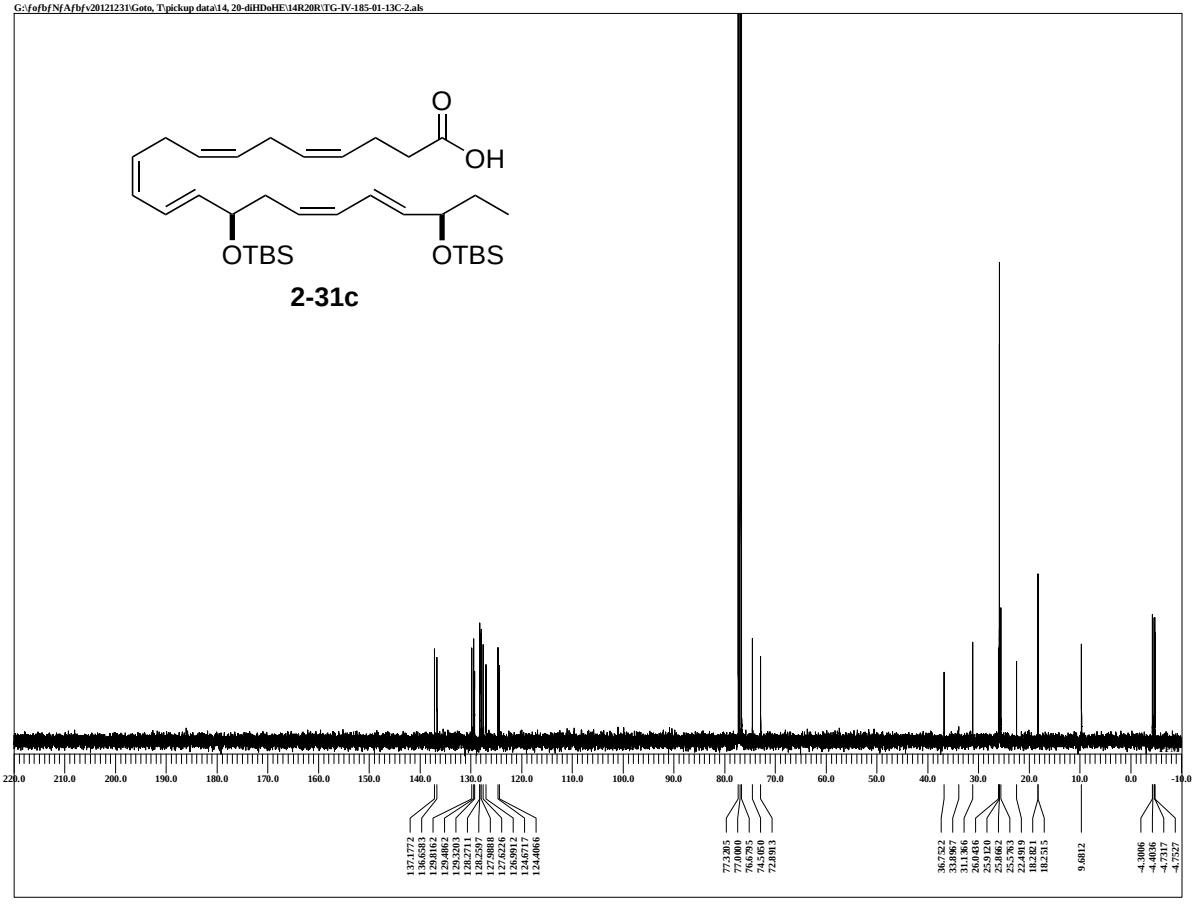
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-185-01-1H-2.als




```
DFILE     TG-IV-185-01-1H-2.als
COMNT     TG-IV-185-01-1H
DATIM     29-04-2012 18:40:20
MENUF
OBNUC     1H
OFR       395.88 MHz
OBFRQ     395.88 MHz
OBSET     6.28 KHz
OBFIN     0.87 Hz
PW1       6.55 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     13107
SPO       13107
TIMES     16
DUMMY     1
FREQU     5938.15 Hz
FLT       30000 Hz
DELAY     16.68 usec
ACQTM     2.2073 sec
PD        2.0000 sec
SCANS     16
ADBIT     16
RGAIN     30
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse.ex2
EXPCM
IRNUC     1H
IFR       395.88 MHz
IRSET     6.28 KHz
IRFIN     0.87 Hz
IRRPW     115 usec
IRATN     79
DFILE     TG-IV-185-01-1H-2.als
SF
LKSET     13.20 KHz
LKFIN     75.7 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     23.5 c
SLVNT     CDCL3
EXREF     7.26 ppm
```

TG-IV-185-01-13C

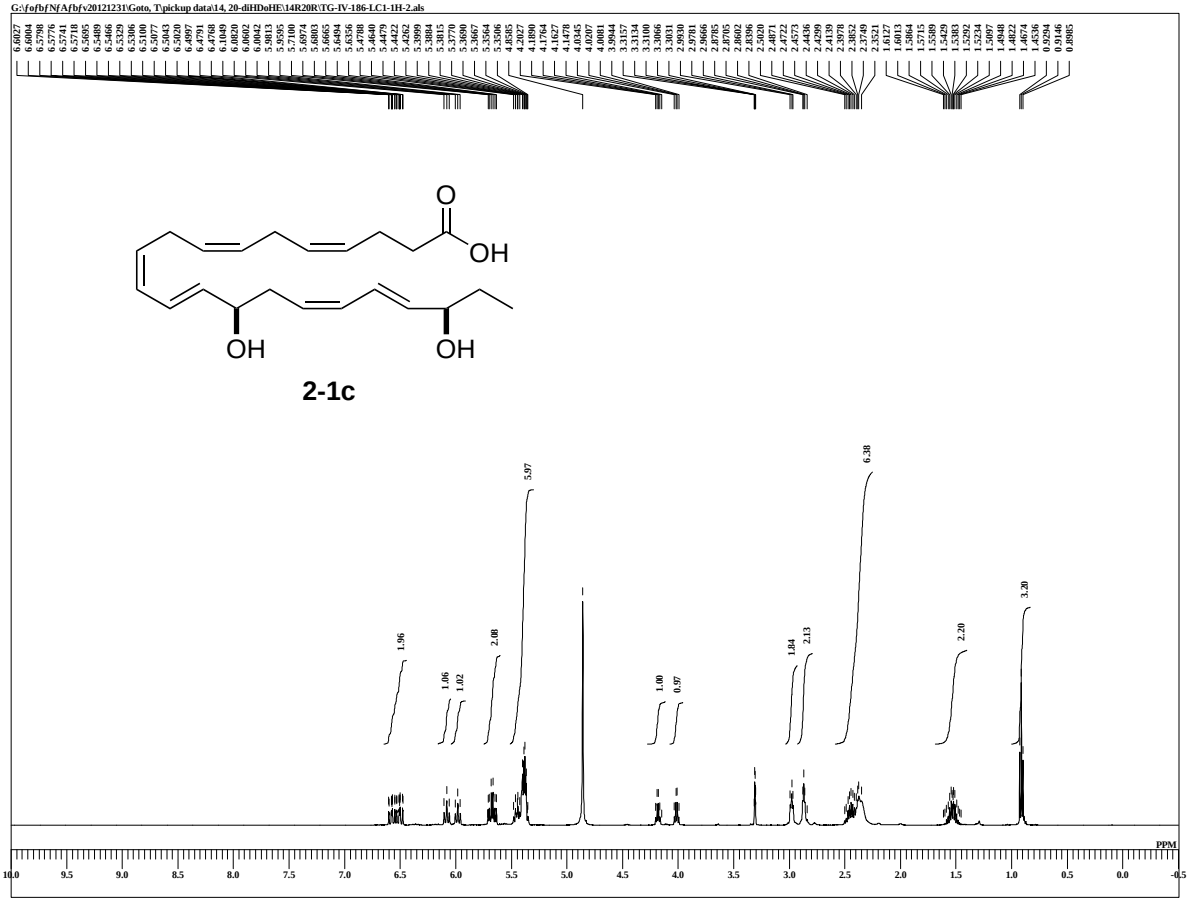
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-185-01-13C-2.als




```
DFILE     TG-IV-185-01-13C-2.als
COMNT     TG-IV-185-01-13C
DATIM     29-04-2012 18:54:52
MENUF
OBNUC     13C
OFR       99.55 MHz
OBFRQ     99.55 MHz
OBSET     5.13 KHz
OBFIN     0.98 Hz
PW1       3.67 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     131072
SPO       32768
TIMES     100
DUMMY     4
FREQU     24888.00 Hz
FLT       13000 Hz
DELAY     38.48 usec
ACQTM     1.3166 sec
PD        7.0000 sec
SCANS     100
ADBIT     16
RGAIN     30
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse_dec
EXPCM
IRNUC     1H
IFR       395.88 MHz
IRSET     6.28 KHz
IRFIN     0.87 Hz
IRRPW     115 usec
IRATN     79
DFILE     TG-IV-185-01-13C-2.als
SF
LKSET     13.20 KHz
LKFIN     75.7 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     23.8 c
SLVNT     CDCL3
EXREF     77.00 ppm
```

TG-IV-186-LC1-1H

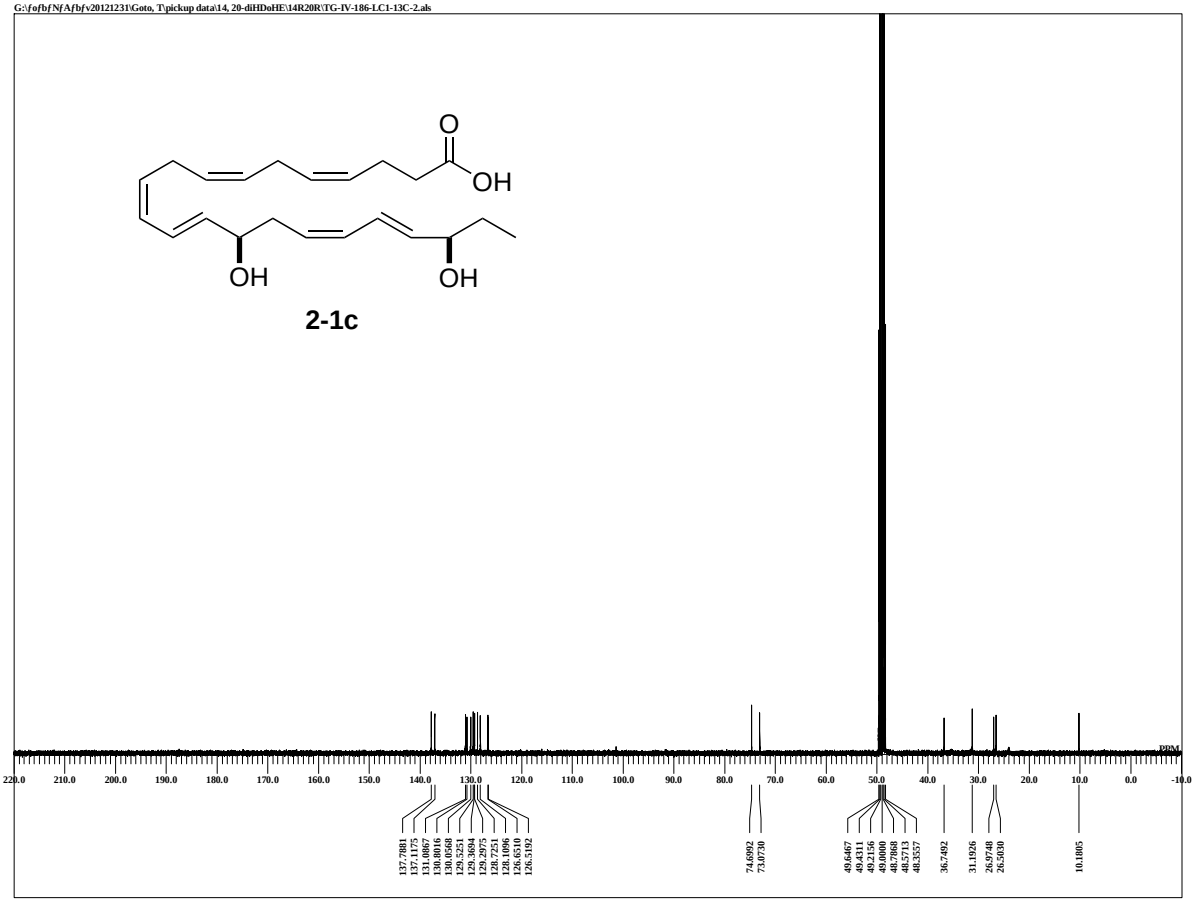
G:\fofbf\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-186-LC1-1H-2.als



DFILE	TG-IV-186-LC1-1H-2.als
COMNT	TG-IV-186-LC1-1H
DATIM	12-05-2012 09:43:48
MENUF	
OBNUC	1H
OFR	490.15 MHz
OBFRQ	490.15 MHz
OBSET	9.16 KHz
OBFIN	7.60 Hz
PW1	8.55 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	32
DUMMY	1
FREQU	7352.83 Hz
FLT	37000 Hz
DELAY	13.52 usec
ACQTM	1.7826 sec
PD	2.0000 sec
SCANS	32
ADBIT	16
RGAIN	40
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	490.15 MHz
IRSET	9.16 KHz
IRFIN	7.60 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-IV-186-LC1-1H-2.als
SF	
LKSET	70.00 KHz
LKFIN	36.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.7 c
SLVNT	CD3OD
EXREF	3.31 ppm

TG-IV-186-LC1-13C

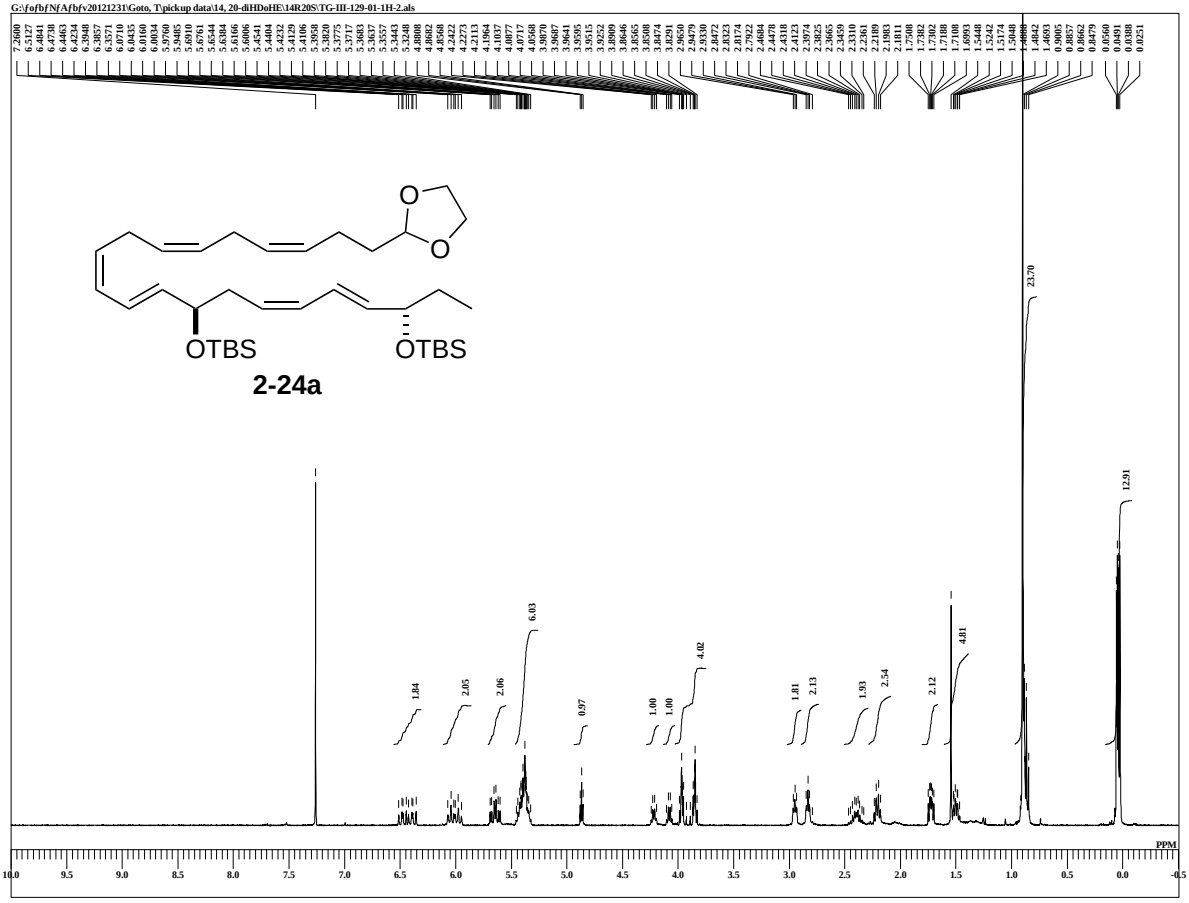
G:\fofbf\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20R\TG-IV-186-LC1-13C-2.als



DFILE	TG-IV-186-LC1-13C-2.als
COMNT	TG-IV-186-LC1-13C
DATIM	12-05-2012 08:45:45
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.67 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	4335
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	4335
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-IV-186-LC1-13C-2.als
SF	
LKSET	13.00 KHz
LKFIN	35.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.8 c
SLVNT	CD3OD
EXREF	49.00 ppm

TG-III-129-01-1H

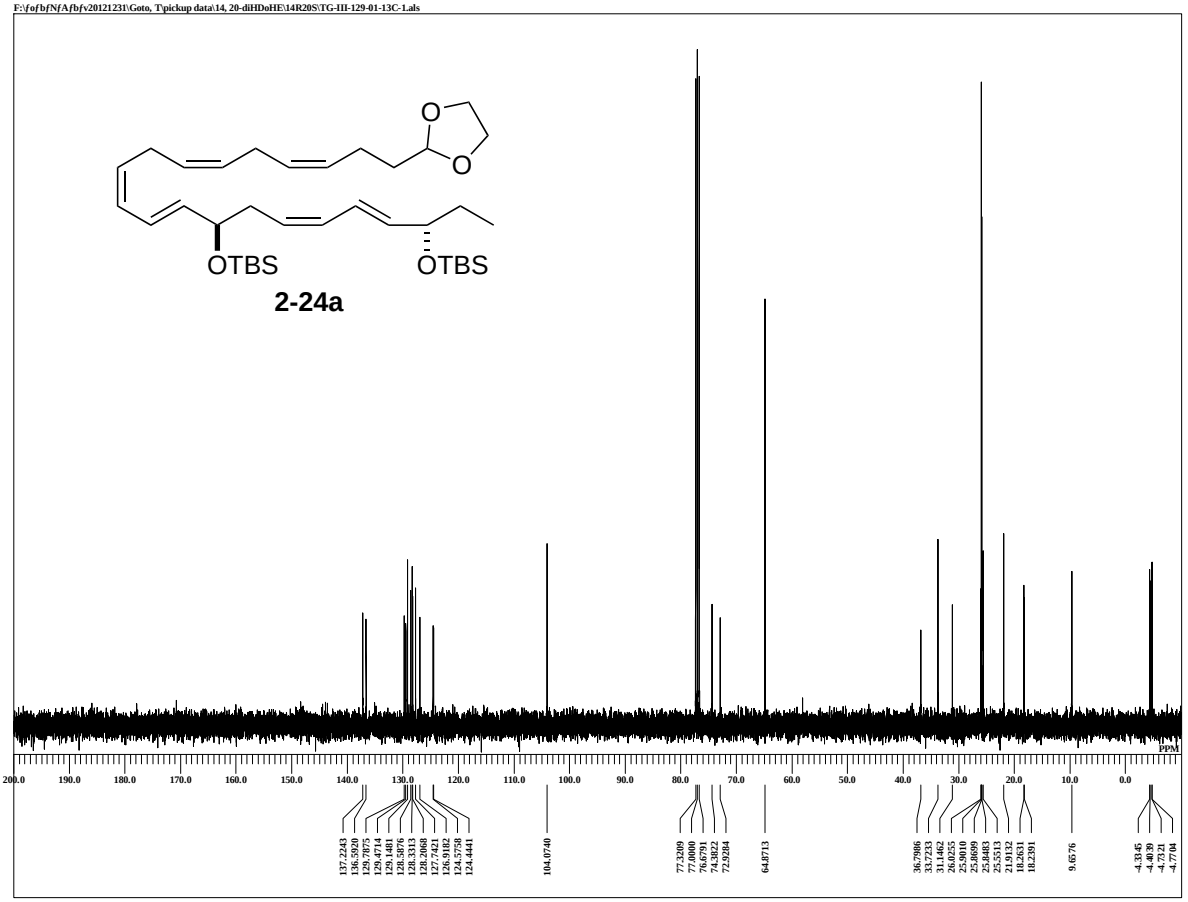
G:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20S\TG-III-129-01-1H-2.als




```
DFILE    TG-III-129-01-1H-2.als
COMNT    TG-III-129-01-1H
DATIM    29-11-2011 21:18:21
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.62 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    8
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    46
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-III-129-01-1H-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    23.6 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-III-129-01-13C

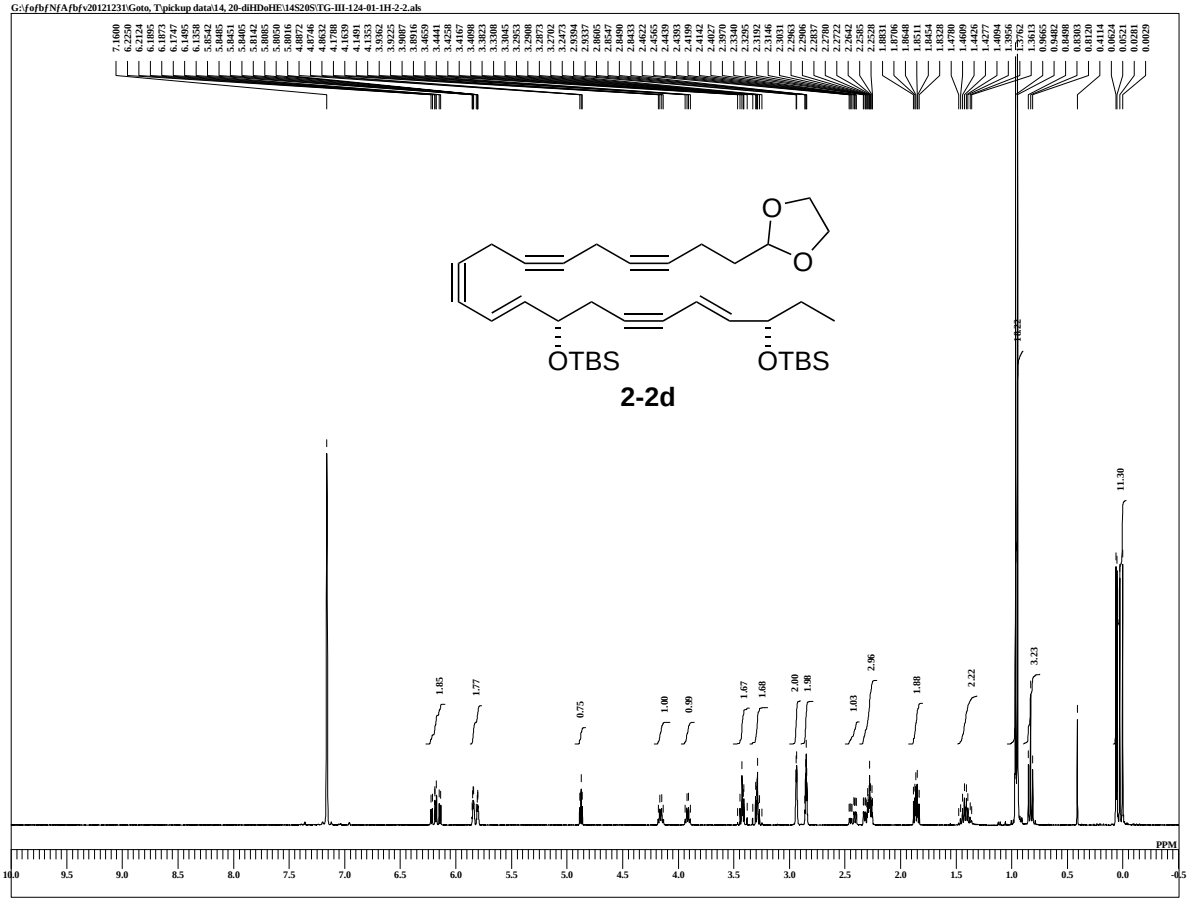
F:\fofbfNfAfbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14R20S\TG-III-129-01-13C-1.als




```
DFILE    TG-III-129-01-13C-1.als
COMNT    TG-III-129-01-13C
DATIM    29-11-2011 21:28:43
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      2.92 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    104856
SPO      104856
TIMES    97
DUMMY    4
FREQU    24999.62 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       2.0000 sec
SCANS    97
ADBIT    16
RGAIN    60
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-III-129-01-13C-1.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    23.4 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-III-124-01-1H-2

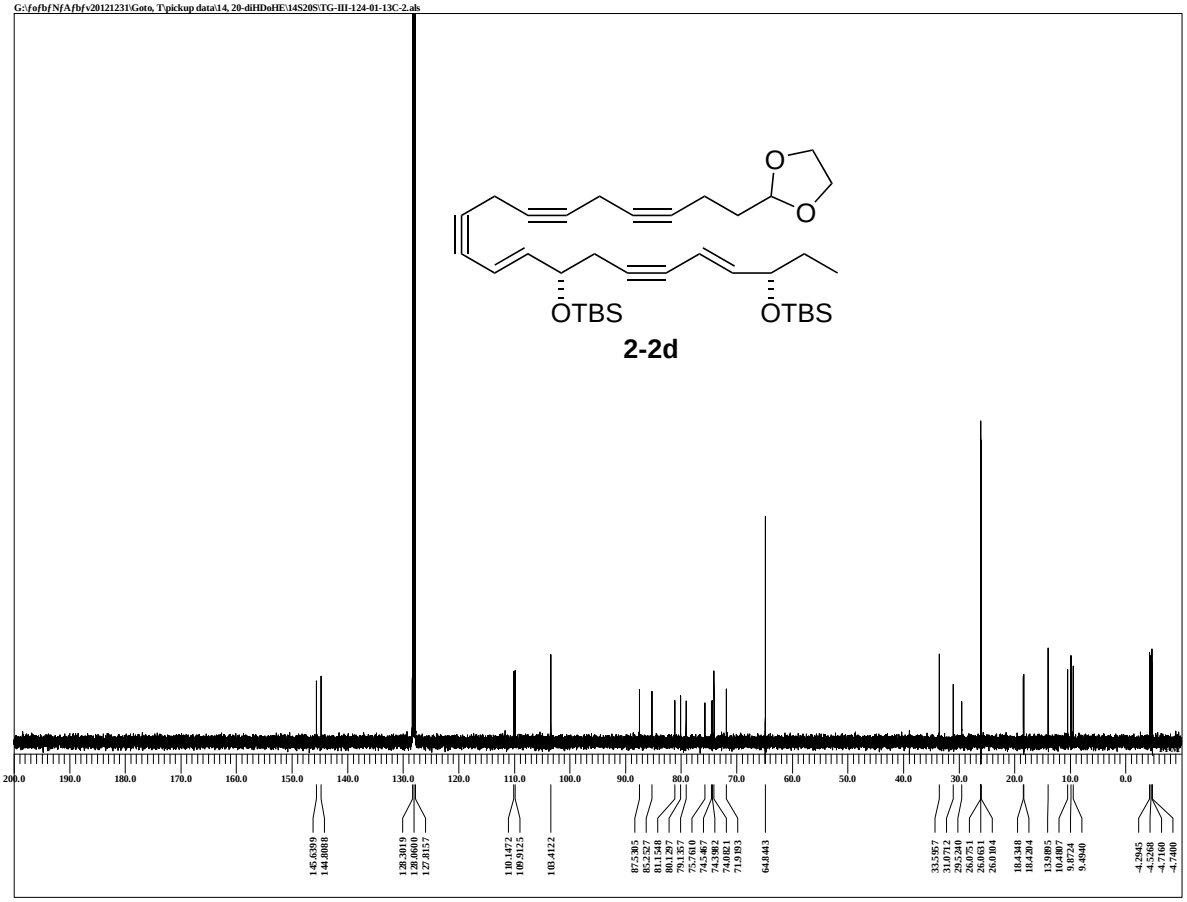
G:\fofbf\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20S\TG-III-124-01-1H-2-2.als



DFILE	TG-III-124-01-1H-2-2.als
COMNT	TG-III-124-01-1H-2
DATIM	25-11-2011 16:11:44
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.62 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	44
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRPPW	115 usec
IRATN	79
DFILE	TG-III-124-01-1H-2-2.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.6 c
SLVNT	C6D6
EXREF	7.16 ppm

TG-III-124-01-13C

G:\fofbf\NfA\fbfv20121231\Goto, T\pickup data\14, 20-diHDoHE\14S20S\TG-III-124-01-13C-2.als



DFILE	TG-III-124-01-13C-2.als
COMNT	TG-III-124-01-13C
DATIM	25-11-2011 16:25:50
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	2.92 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	174
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	2.0000 sec
SCANS	174
ADBIT	16
RGAIN	58
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRPPW	115 usec
IRATN	79
DFILE	TG-III-124-01-13C-2.als
SF	
LKSET	13.20 KHz
LKFIN	69.6 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.0 c
SLVNT	C6D6
EXREF	128.06 ppm

TG-VI-126-01-1H

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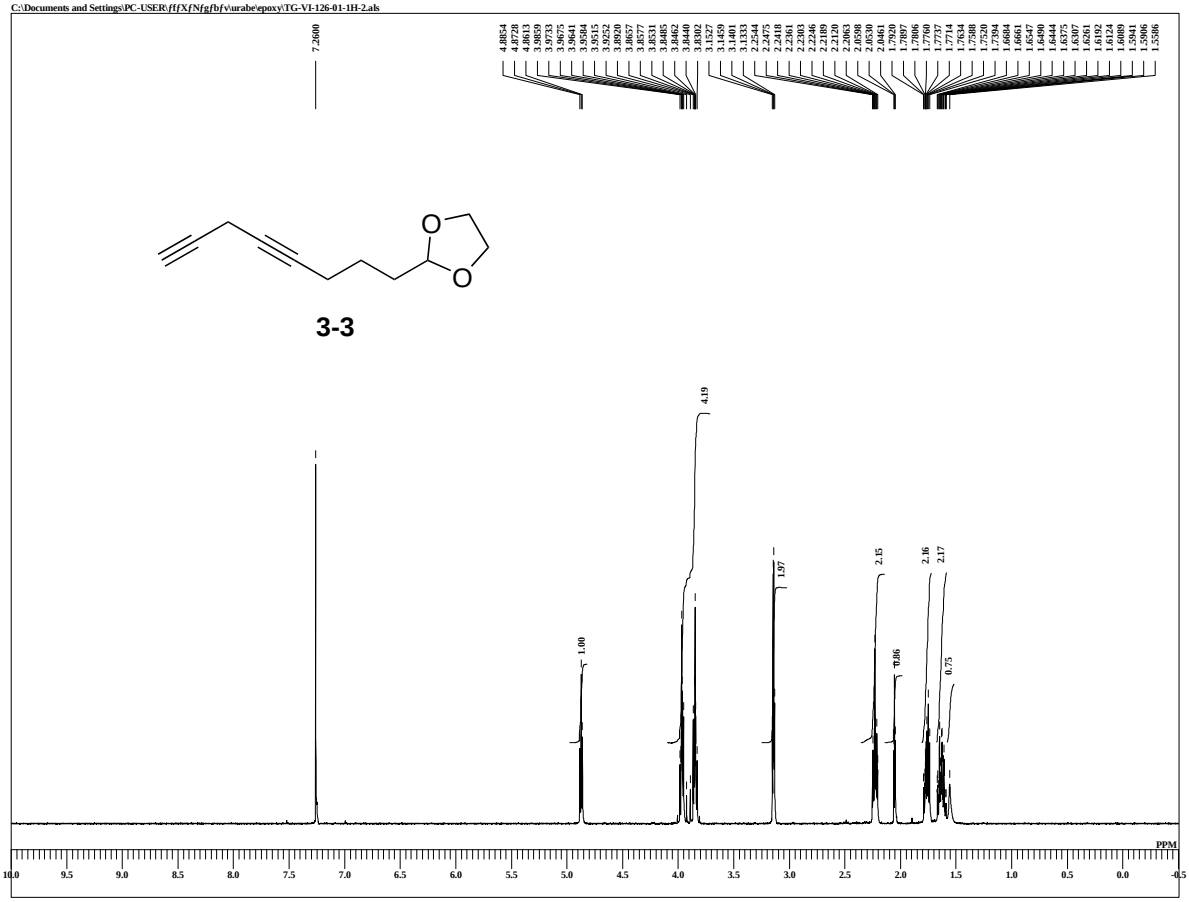

DFILE TG-VI-126-01-1H-2.als
COMNT TG-VI-126-01-1H
DATIM 03-12-2012 14:17:30
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.38 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 48
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-VI-126-01-1H-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 20.4 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-VI-126-01-13C

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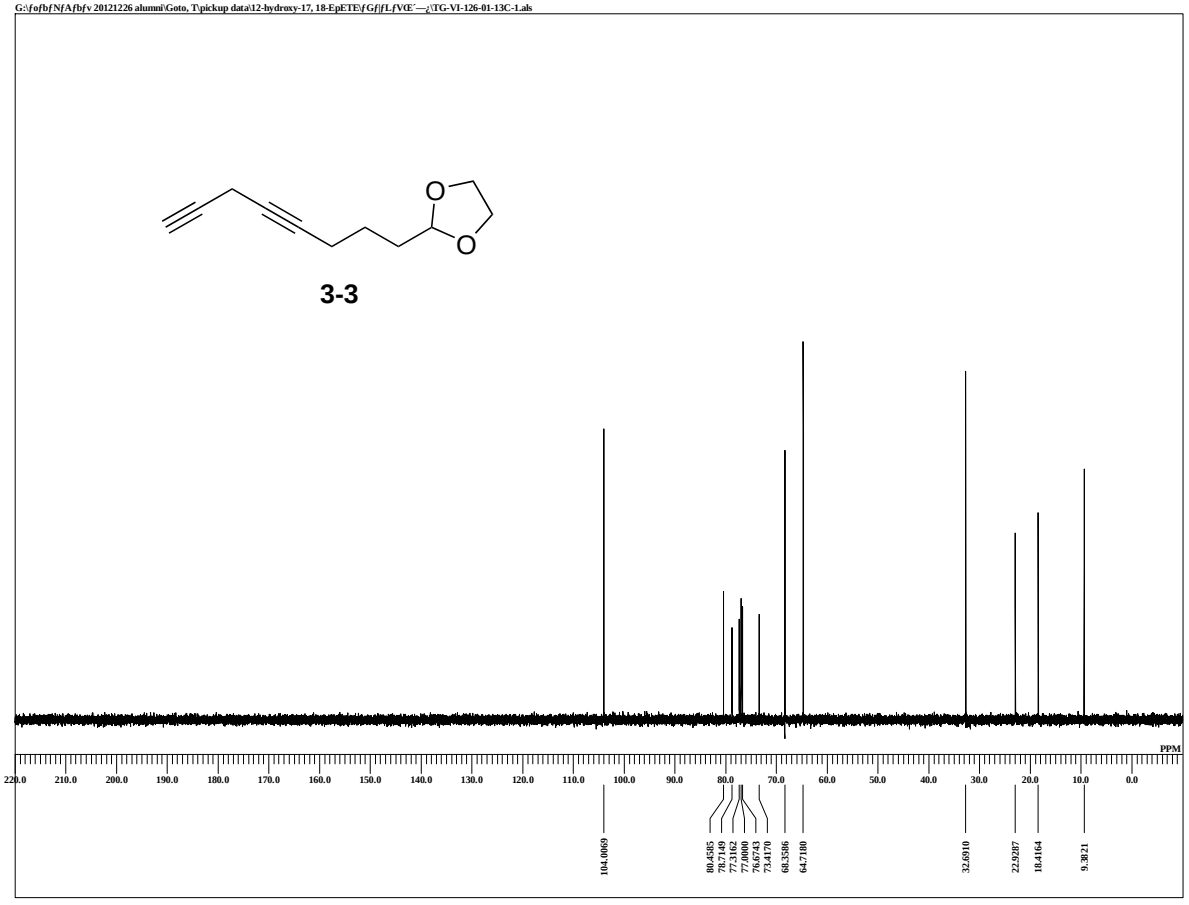
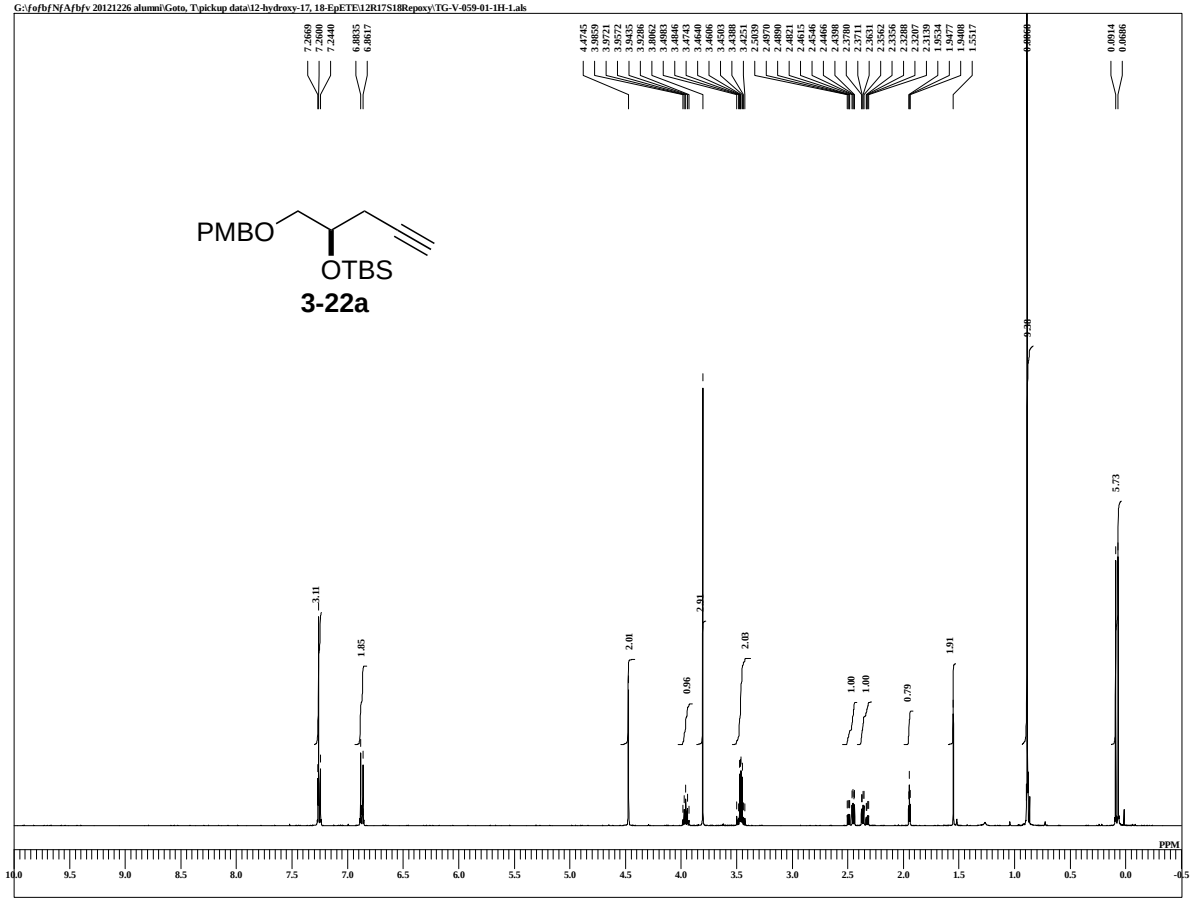


DFILE TG-VI-126-01-13C-1.als
COMNT TG-VI-126-01-13C
DATIM 03-12-2012 14:24:01
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 3.25 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 15
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 8.0000 sec
SCANS 15
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-VI-126-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 20.8 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-V-059-01-1H

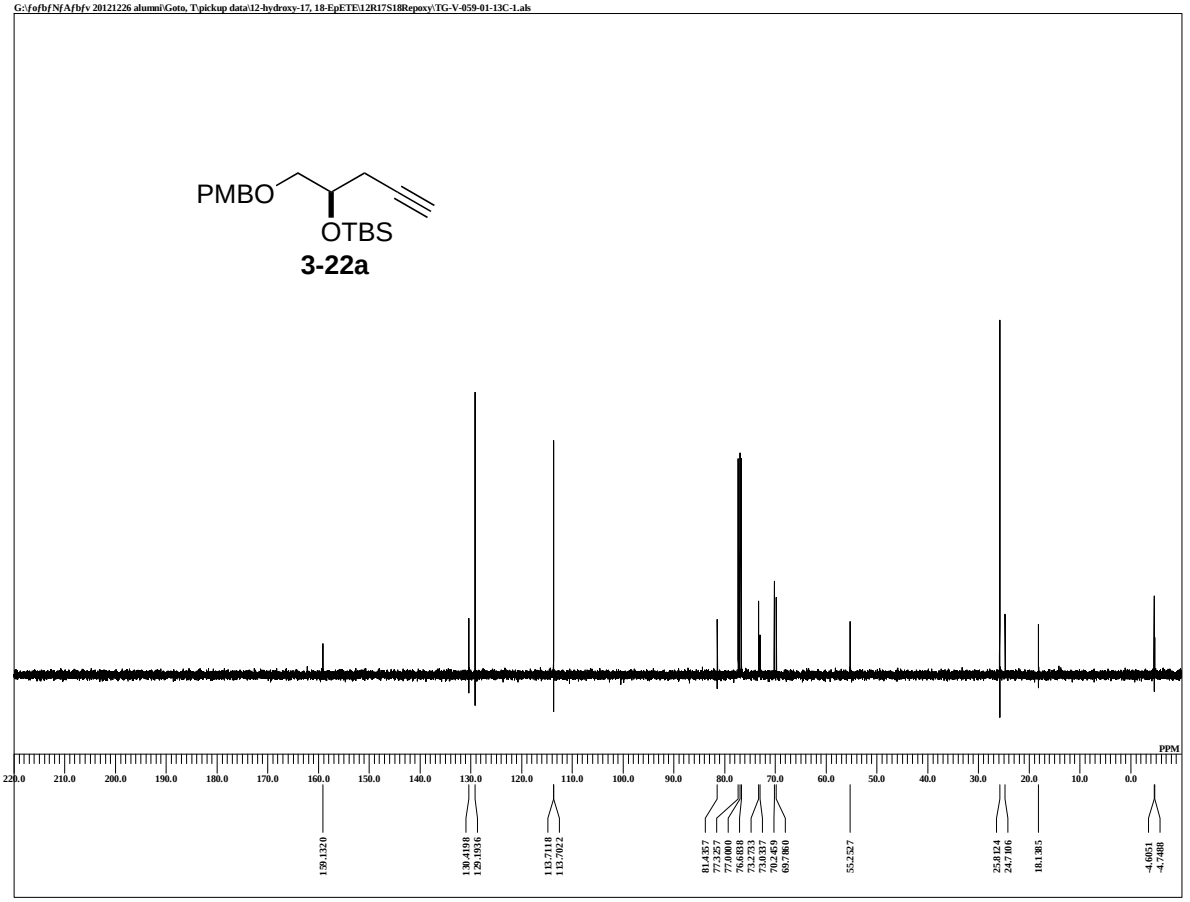
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-059-01-1H-1.als



DFILE	TG-V-059-01-1H-1.als
COMNT	TG-V-059-01-1H
DATIM	08-06-2012 10:39:04
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	16
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	16
ADBIT	16
RGAIN	46
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	147 usec
IRATN	79
DFILE	TG-V-059-01-1H-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.7 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-059-01-13C

G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-059-01-13C-1.als



DFILE	TG-V-059-01-13C-1.als
COMNT	TG-V-059-01-13C
DATIM	08-06-2012 10:53:21
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	127
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	2.0000 sec
SCANS	127
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-059-01-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.0 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-172-02

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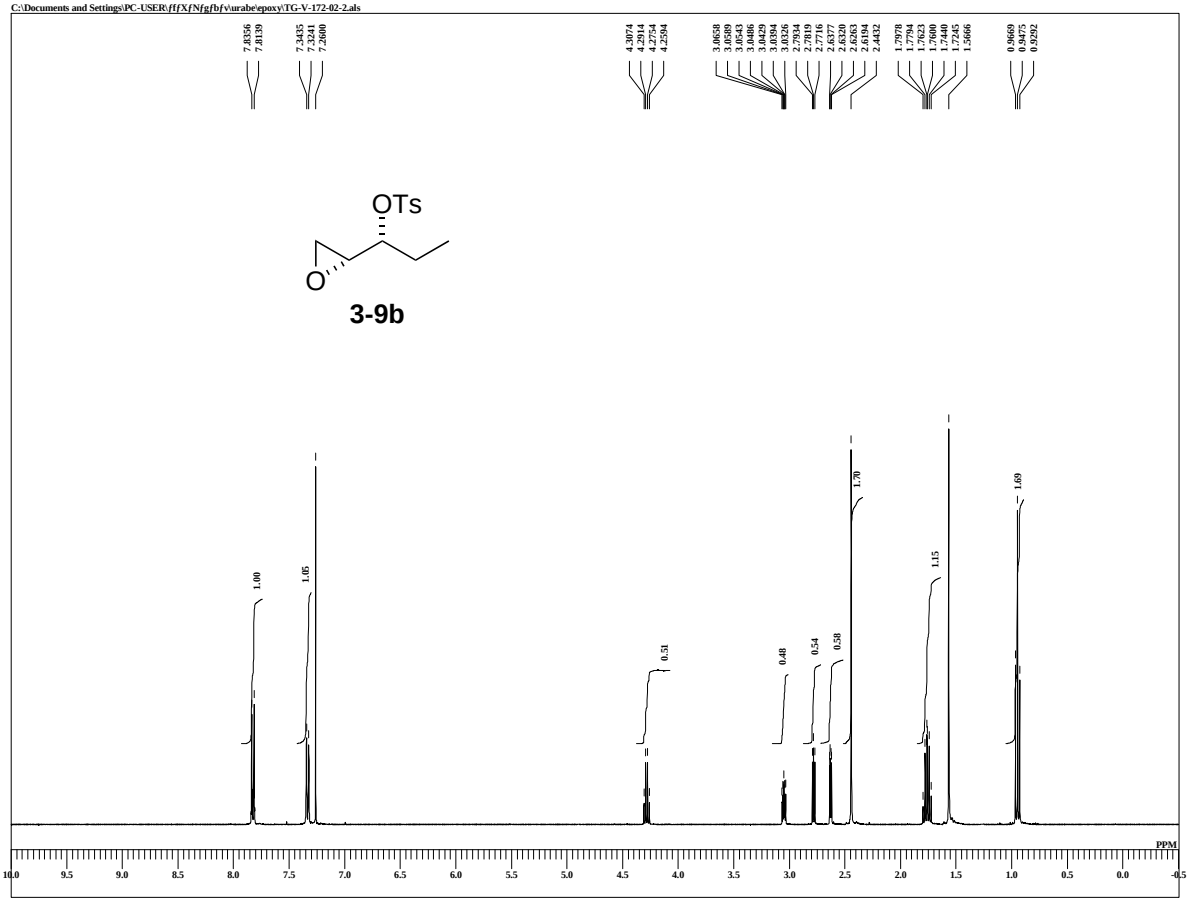

DFILE	TG-V-172-02-2.als
COMNT	TG-V-172-02
DATIM	17-08-2012 14:03:38
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	50
BF	0.01 Hz
T1	0.00
T2	0.00
T3	100.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-172-02-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.5 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-172-02-13C

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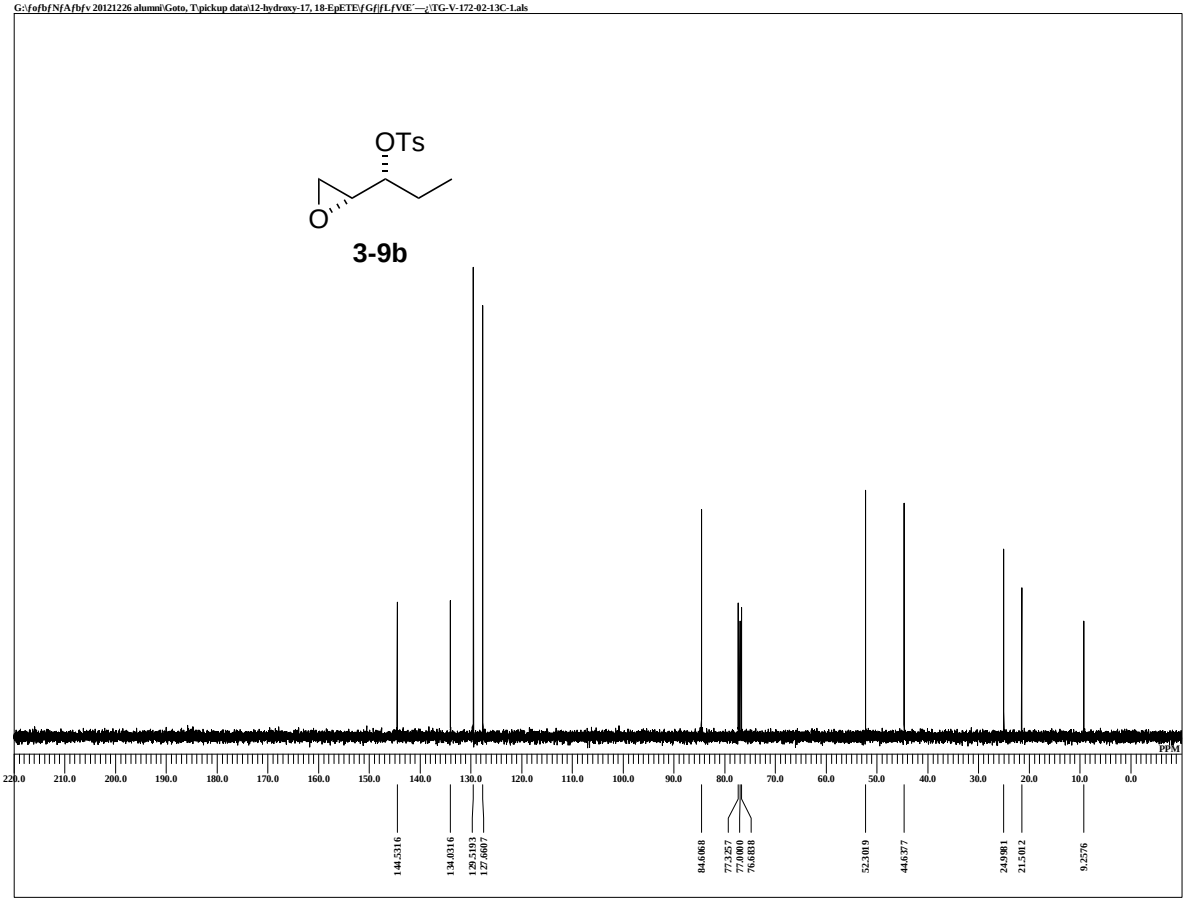

DFILE	TG-V-172-02-13C-1.als
COMNT	TG-V-172-02-13C
DATIM	03-12-2012 20:19:13
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	7
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	7
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	100.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-172-02-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	20.7 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-132-01-1H

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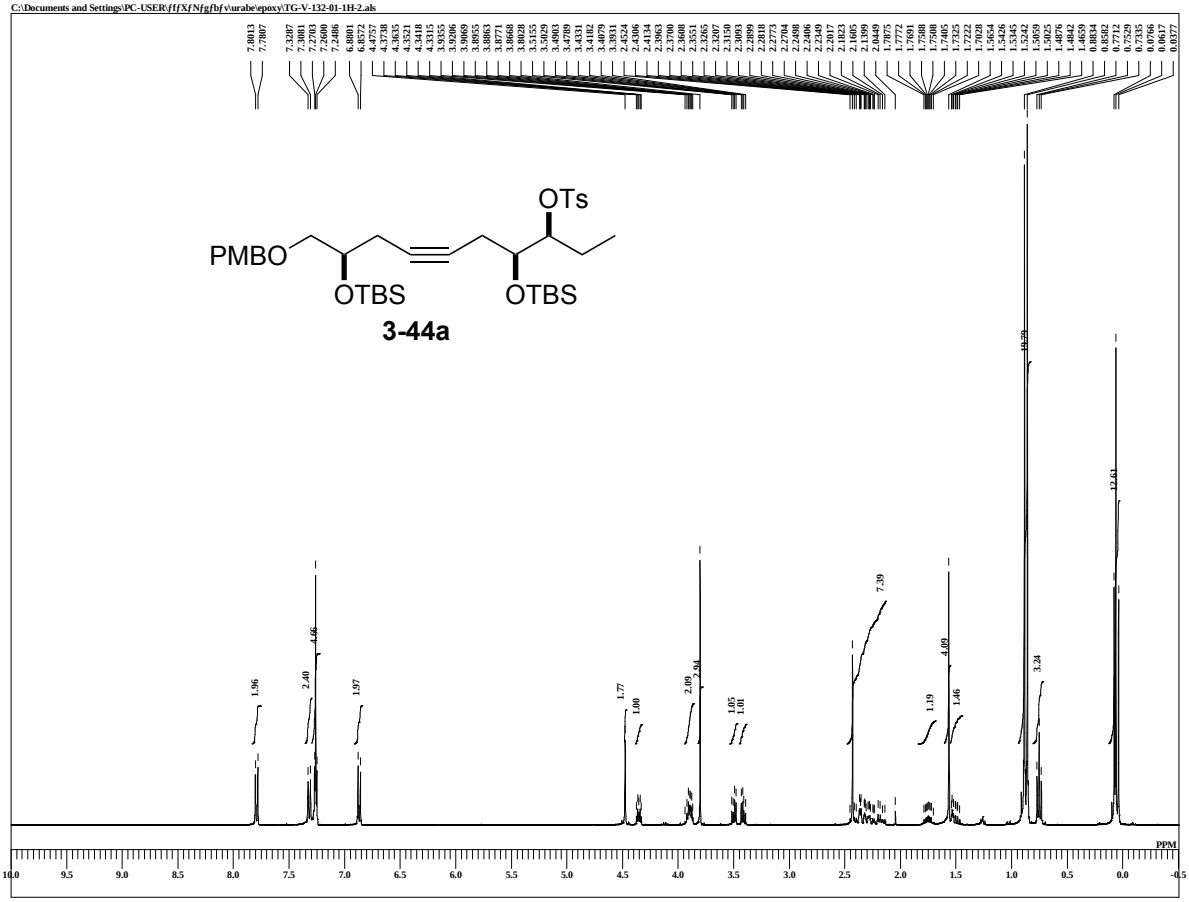

DFILE	TG-V-132-01-1H-2.als
COMNT	TG-V-132-01-1H
DATIM	23-07-2012 08:52:51
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	44
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-132-01-1H-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.2 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-132-01-13C

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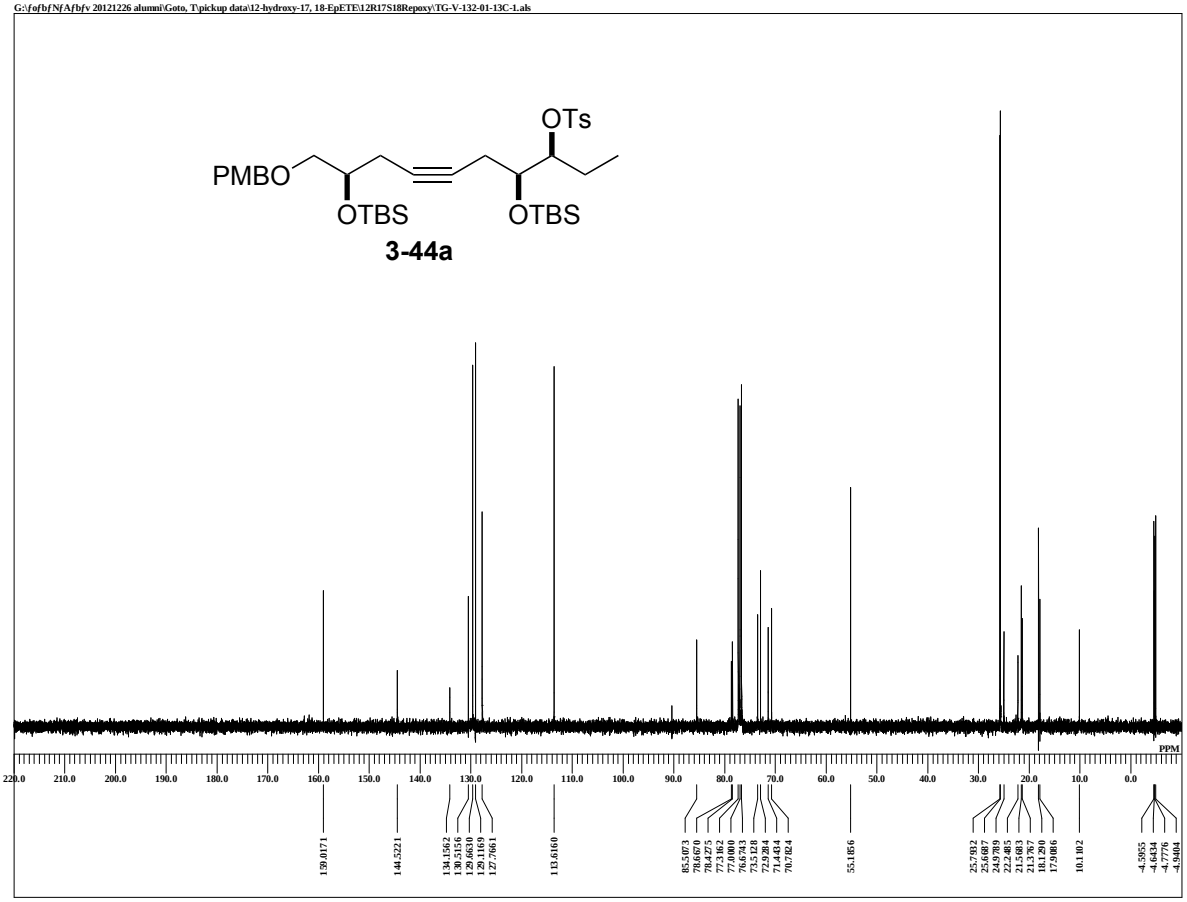

DFILE	TG-V-132-01-13C-1.als
COMNT	TG-V-132-01-13C
DATIM	23-07-2012 09:11:59
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	67
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	67
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-132-01-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.6 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-135-01-1H

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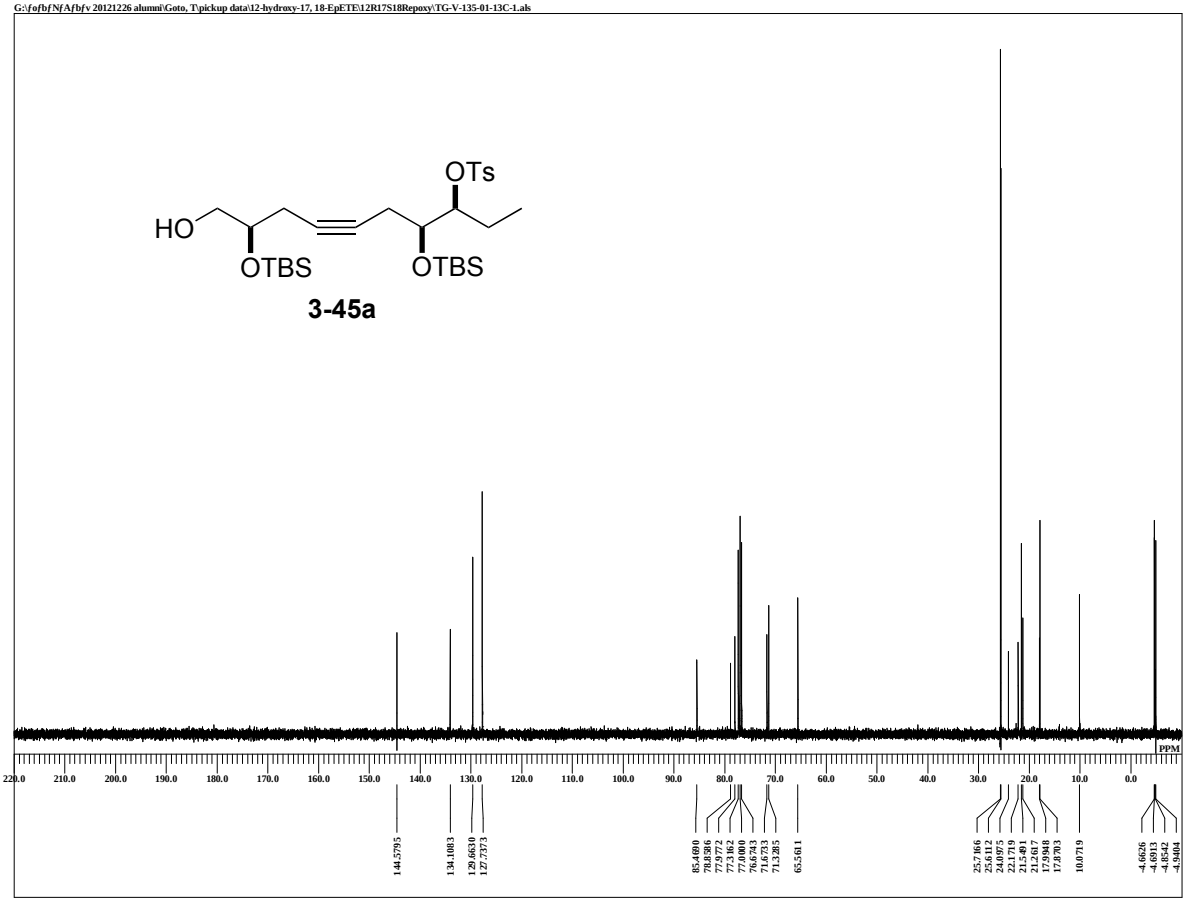
```
DFILE    TG-V-135-01-1H-2.als
COMNT    TG-V-135-01-1H
DATIM    23-07-2012 19:58:55
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.38 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    8
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    38
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-V-135-01-1H-2.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    22.7 c
SLVNT    CDCL3
EXREF    7.26 ppm
```

TG-V-135-01-13C

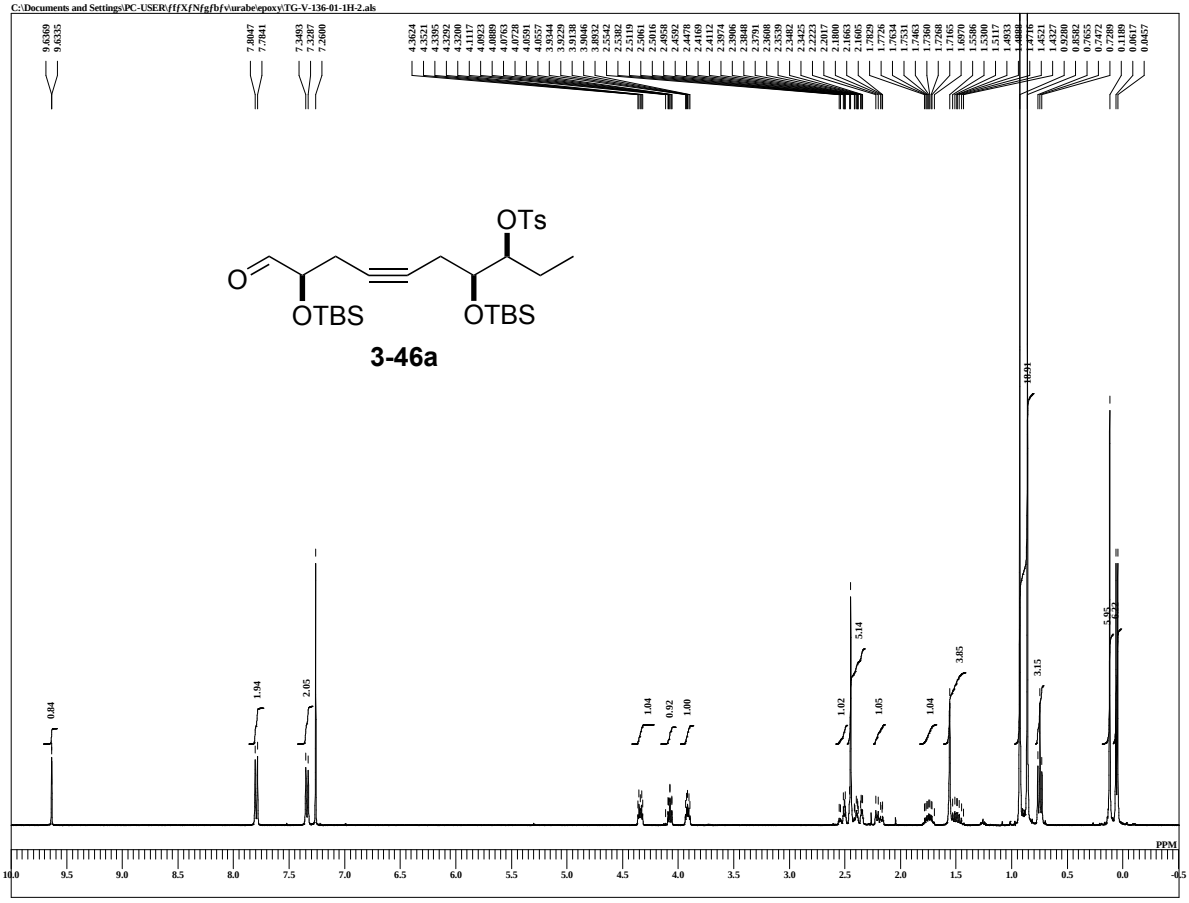
G:\fo\bf\Nf\Af\bf\v 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-135-01-13C-1.als




```
DFILE    TG-V-135-01-13C-1.als
COMNT    TG-V-135-01-13C
DATIM    23-07-2012 20:09:14
MENUF
OBNUC    13C
OFR      99.55 MHz
OBFRQ    99.55 MHz
OBSET    5.13 KHz
OBFIN    0.98 Hz
PW1      3.25 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    26214
SPO      26214
TIMES    42
DUMMY    4
FREQU    24999.62 Hz
FLT      125000 Hz
DELAY    20.50 usec
ACQTM    1.0486 sec
PD       8.0000 sec
SCANS    42
ADBIT    16
RGAIN    60
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse_dec
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    115 usec
IRATN    79
DFILE    TG-V-135-01-13C-1.als
SF
LKSET    13.20 KHz
LKFIN    75.7 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    22.9 c
SLVNT    CDCL3
EXREF    77.00 ppm
```

TG-V-136-01-1H

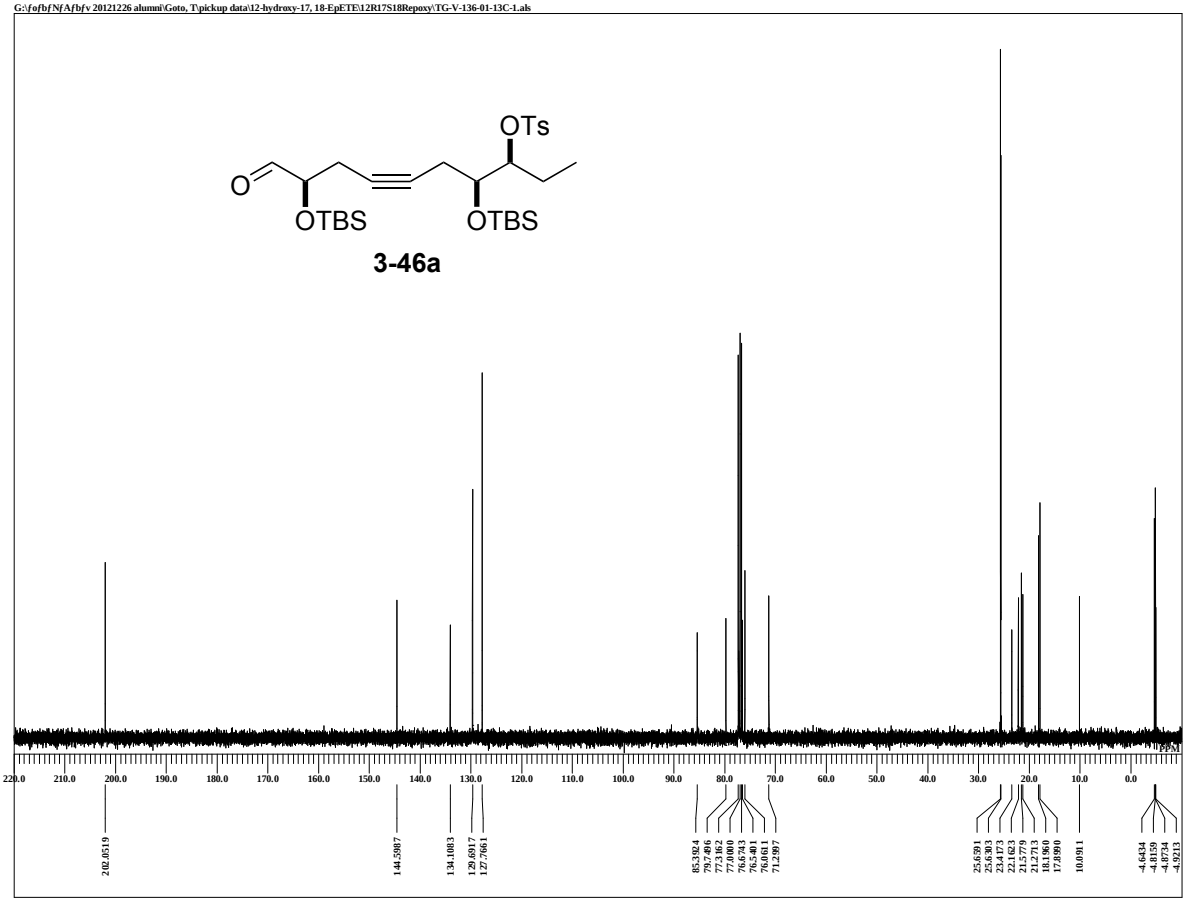
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-136-01-1H-2.als




```
DFILE   TG-V-136-01-1H-2.als
COMNT   TG-V-136-01-1H
DATIM   24-07-2012 13:25:36
MENUF
OBNUC   1H
OFR       395.88 MHz
OBFRQ     395.88 MHz
OBSET       6.28 KHz
OBFIN       0.87 Hz
PW1         6.38 usec
DEADT       0.00 usec
PREDL       0.00000 msec
IWT         1.0000 sec
POINT      13107
SPO        13107
TIMES          8
DUMMY          1
FREQU       5938.15 Hz
FLT        30000 Hz
DELAY      16.68 usec
ACQTM       2.2073 sec
PD          2.0000 sec
SCANS          8
ADBIT         16
RGAIN         42
BF          0.01 Hz
T1          0.00
T2          0.00
T3         90.00
T4        100.00
EXMOD   single_pulse.ex2
EXPCM
IRNUC   1H
IFR       395.88 MHz
IRSET       6.28 KHz
IRFIN       0.87 Hz
IRRPW       115 usec
IRATN          79
DFILE   TG-V-136-01-1H-2.als
SF
LKSET      13.20 KHz
LKFIN       75.7 Hz
LKLEV          0
LGAIN          0
LKPHS          0
LKSIG          0
CSPED        0 Hz
FILDC
FILDF
CTEMP       22.6 c
SLVNT   CDCL3
EXREF       7.26 ppm
```

TG-V-136-01-13C

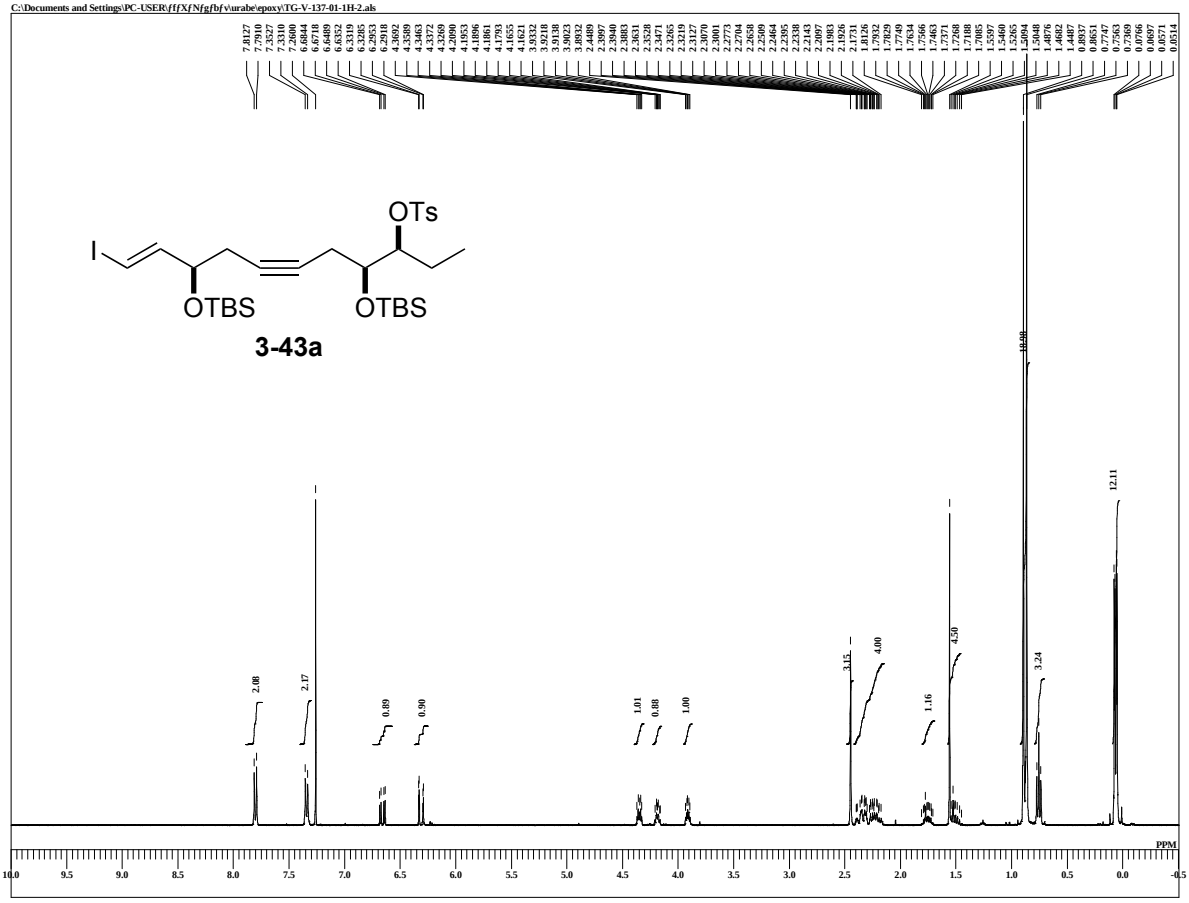
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-136-01-13C-1.als




```
DFILE   TG-V-136-01-13C-1.als
COMNT   TG-V-136-01-13C
DATIM   24-07-2012 13:42:27
MENUF
OBNUC   13C
OFR        99.55 MHz
OBFRQ      99.55 MHz
OBSET       5.13 KHz
OBFIN       0.98 Hz
PW1         3.25 usec
DEADT       0.00 usec
PREDL       0.00000 msec
IWT         1.0000 sec
POINT      26214
SPO        26214
TIMES         56
DUMMY          4
FREQU      24999.62 Hz
FLT       125000 Hz
DELAY      20.50 usec
ACQTM       1.0486 sec
PD          8.0000 sec
SCANS         56
ADBIT         16
RGAIN         60
BF          0.01 Hz
T1          0.00
T2          0.00
T3         90.00
T4        100.00
EXMOD   single_pulse_dec
EXPCM
IRNUC   1H
IFR       395.88 MHz
IRSET       6.28 KHz
IRFIN       0.87 Hz
IRRPW       115 usec
IRATN          79
DFILE   TG-V-136-01-13C-1.als
SF
LKSET      13.20 KHz
LKFIN       75.7 Hz
LKLEV          0
LGAIN          0
LKPHS          0
LKSIG          0
CSPED        0 Hz
FILDC
FILDF
CTEMP       22.7 c
SLVNT   CDCL3
EXREF       77.00 ppm
```

TG-V-137-01-1H

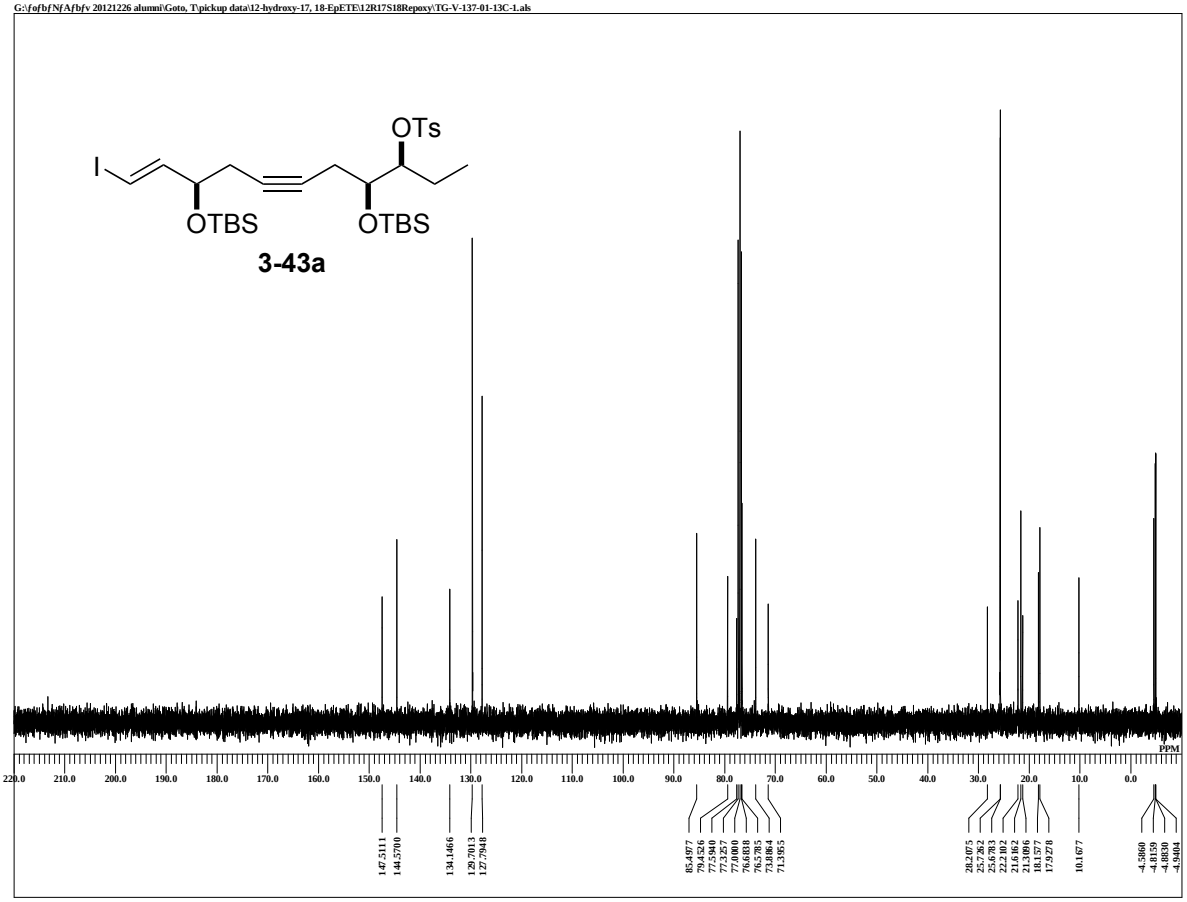
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-137-01-1H-2.als



DFILE	TG-V-137-01-1H-2.als
COMNT	TG-V-137-01-1H
DATIM	25-07-2012 10:37:59
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	5.0000 sec
SCANS	8
ADBIT	16
RGAIN	50
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	147 usec
IRATN	79
DFILE	TG-V-137-01-1H-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.2 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-137-01-13C

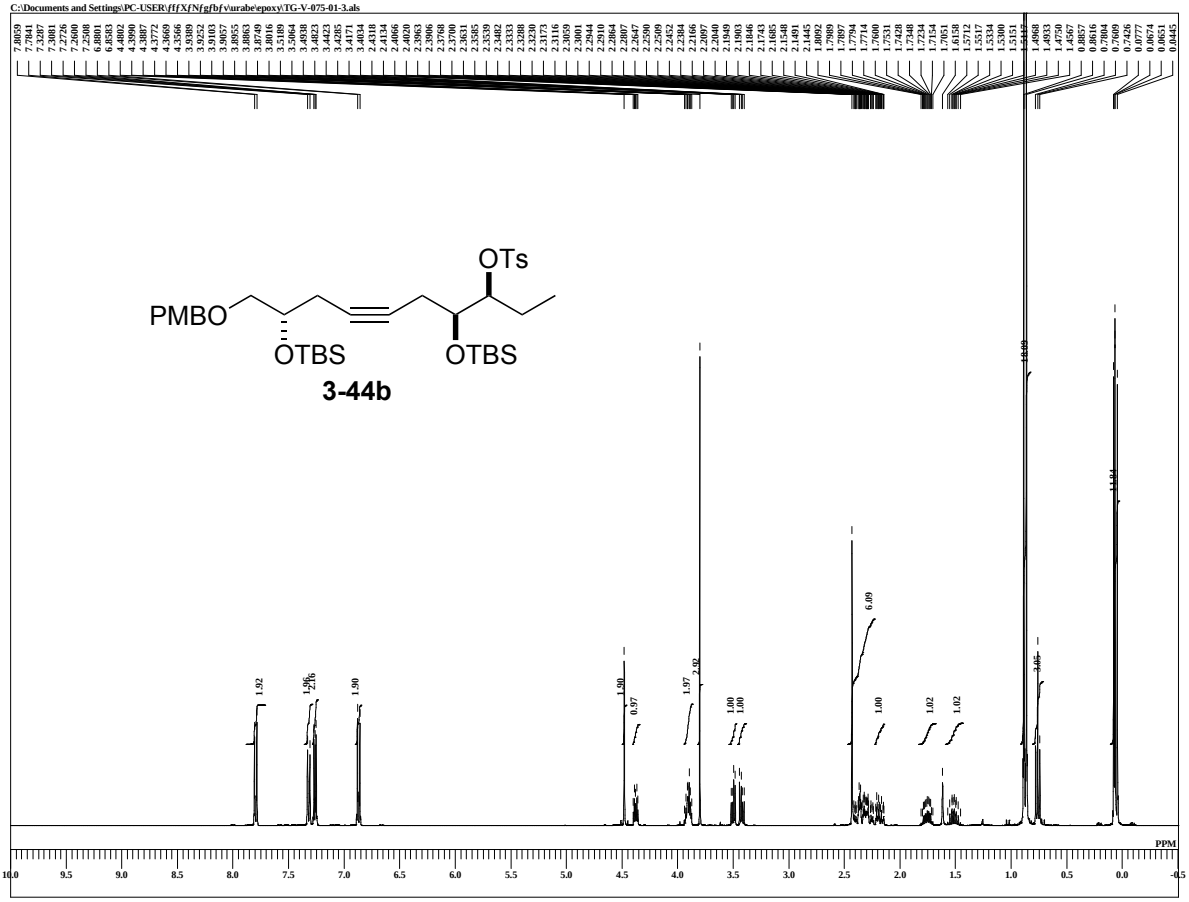
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-137-01-13C-1.als



DFILE	TG-V-137-01-13C-1.als
COMNT	TG-V-137-01-13C
DATIM	25-07-2012 10:46:52
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	31
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	31
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-137-01-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.6 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-075-01

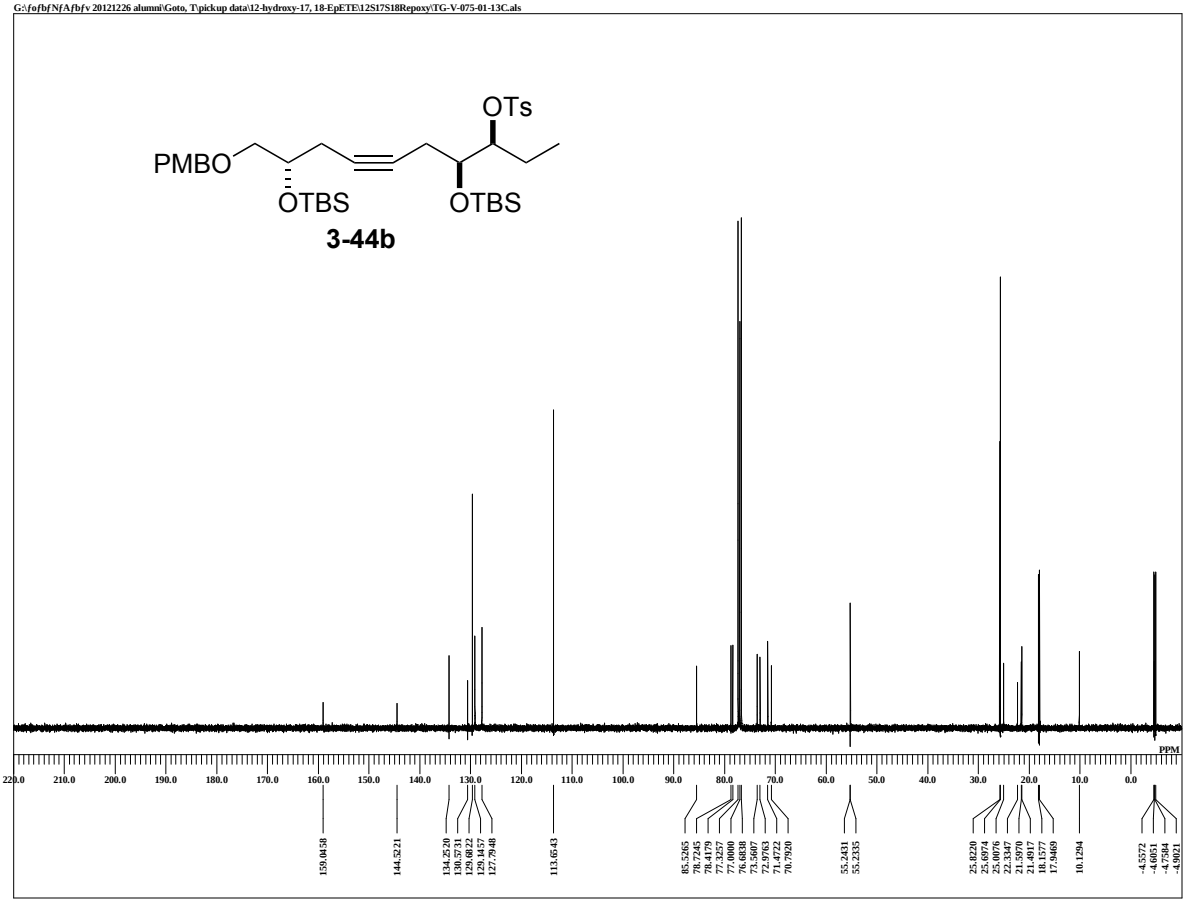
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-075-01-3.als



DFILE	TG-V-075-01-3.als
COMNT	TG-V-075-01
DATIM	18-06-2012 08:12:33
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	28
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-075-01-3.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.8 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-075-02

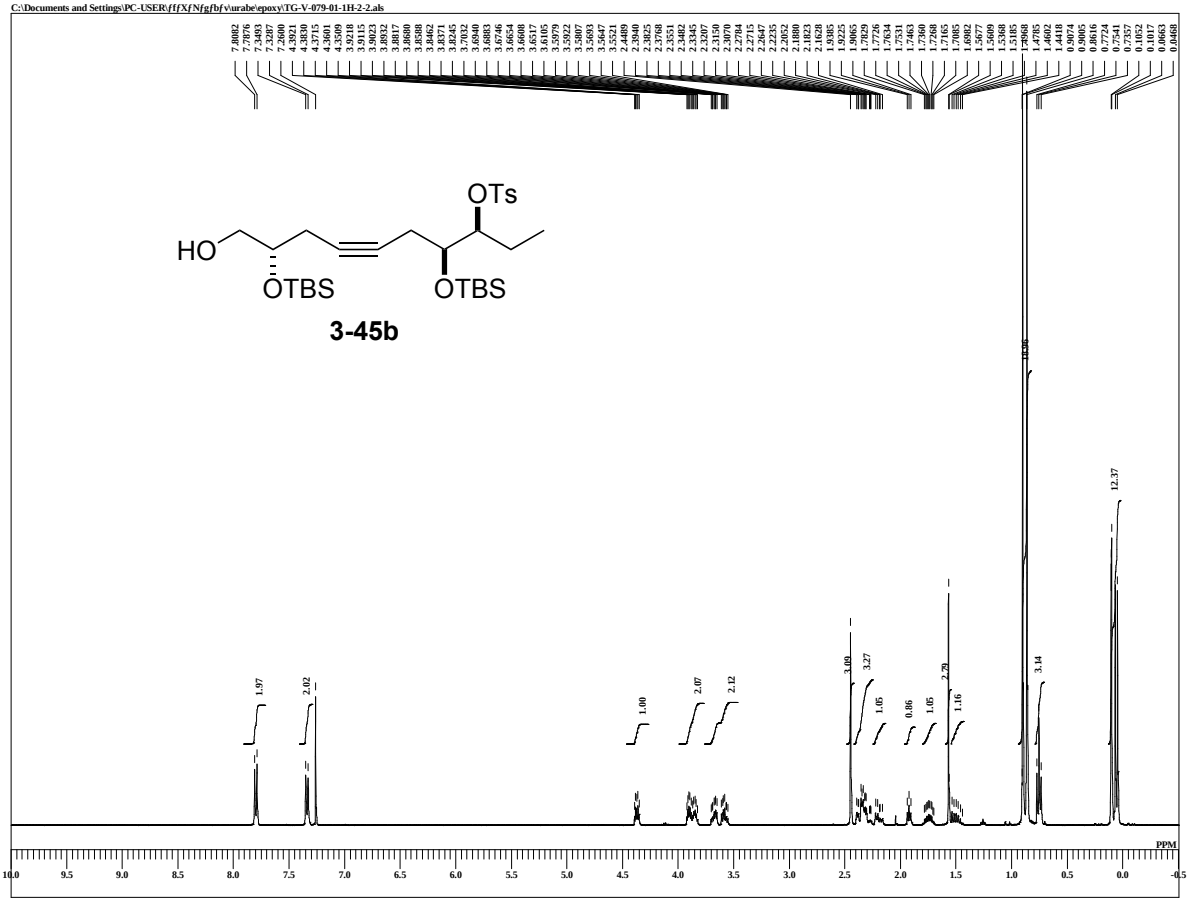
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-075-01-13C.als



DFILE	TG-V-075-01-13C.als
COMNT	TG-V-075-02
DATIM	18-06-2012 09:03:05
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	320
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	320
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-075-01-13C.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.0 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-079-01-1H-2

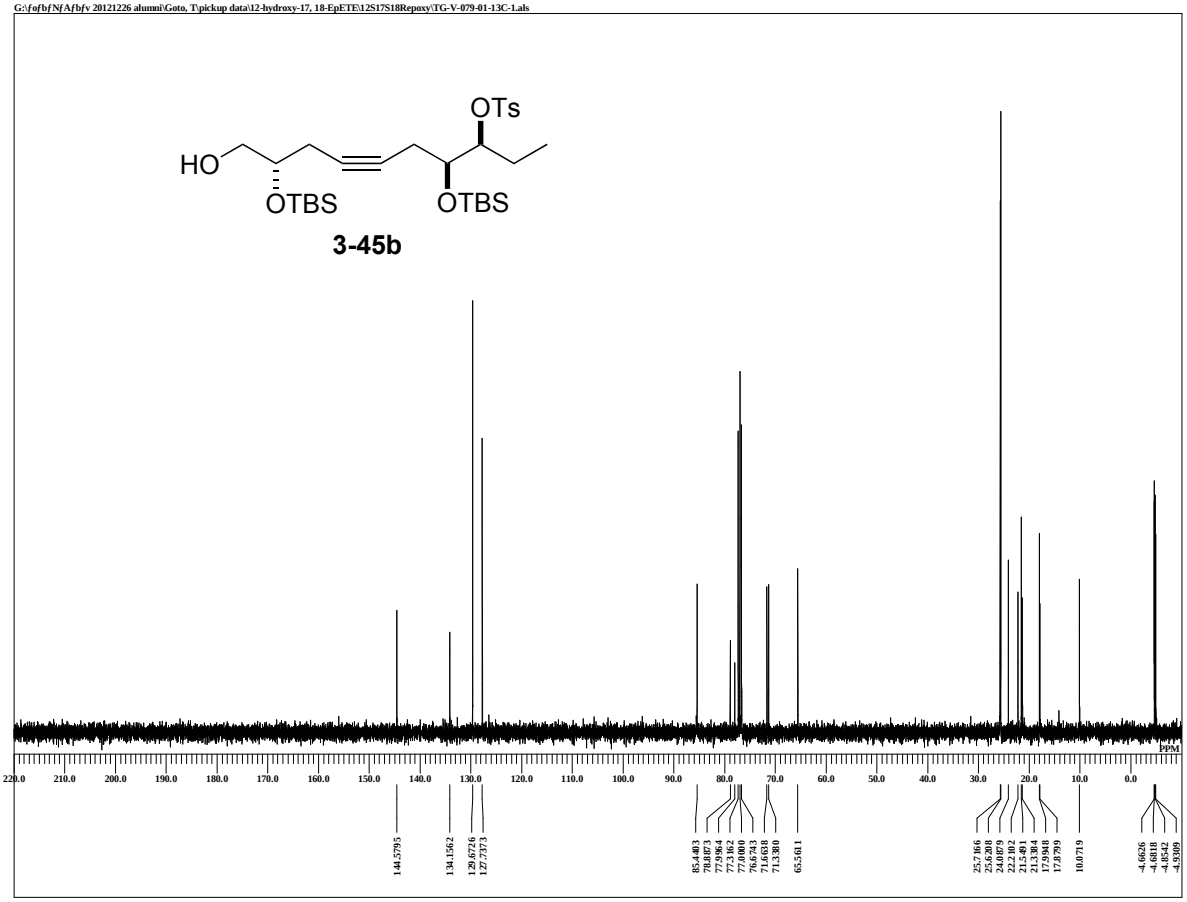
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-079-01-1H-2-2.als



DFILE TG-V-079-01-1H-2-2.als
COMNT TG-V-079-01-1H-2
DATIM 19-06-2012 17:37:40
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFRQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.38 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 8
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 2.0000 sec
SCANS 8
ADBIT 16
RGAIN 40
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-V-079-01-1H-2-2.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.7 c
SLVNT CDCL3
EXREF 7.26 ppm

TG-V-079-01-13C

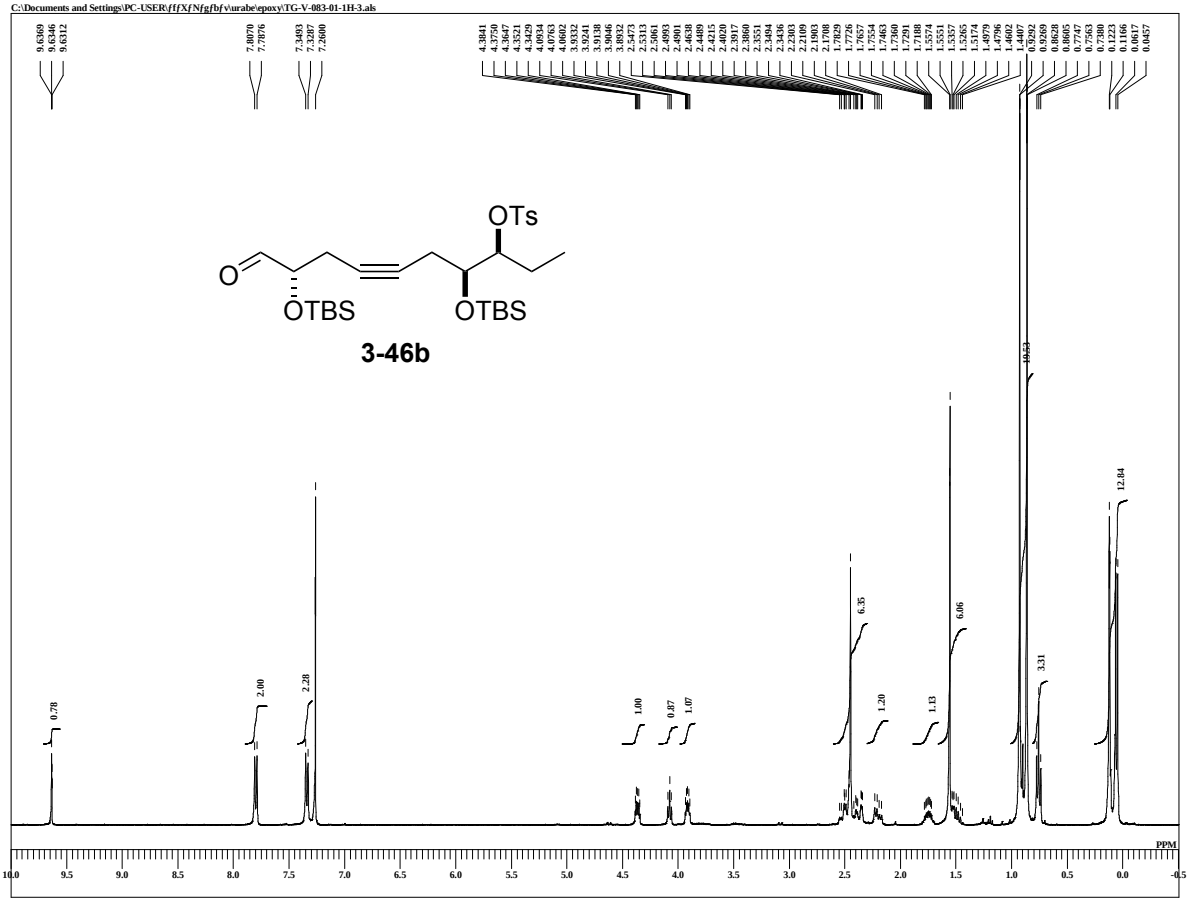
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-079-01-13C-1.als



DFILE TG-V-079-01-13C-1.als
COMNT TG-V-079-01-13C
DATIM 18-06-2012 16:57:43
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFRQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PW1 3.25 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 26214
SPO 26214
TIMES 36
DUMMY 4
FREQU 24999.62 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 8.0000 sec
SCANS 36
ADBIT 16
RGAIN 60
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE TG-V-079-01-13C-1.als
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.3 c
SLVNT CDCL3
EXREF 77.00 ppm

TG-V-083-01-1H

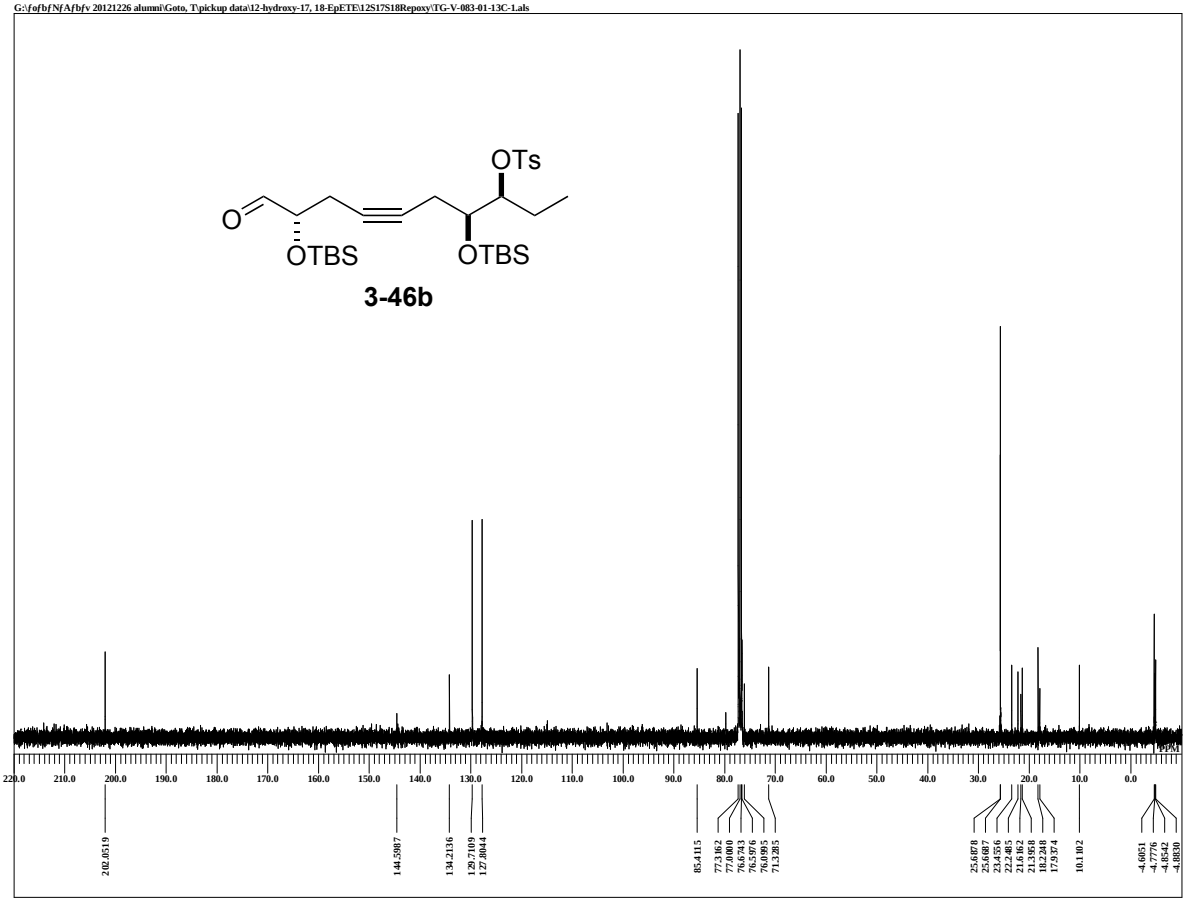
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-083-01-1H-3.als



DFILE	TG-V-083-01-1H-3.als
COMNT	TG-V-083-01-1H
DATIM	19-06-2012 18:40:25
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	32
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	32
ADBIT	16
RGAIN	46
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-083-01-1H-3.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.6 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-083-01-13C

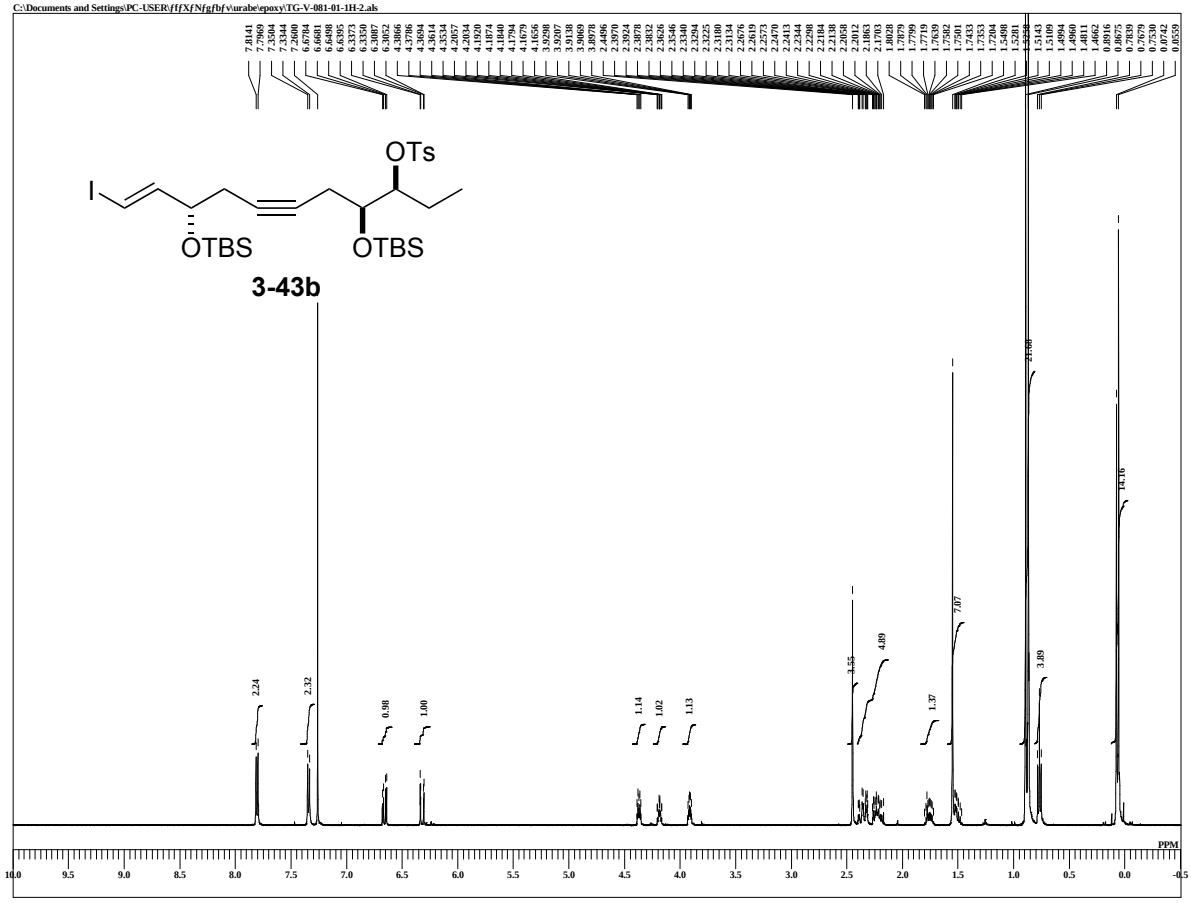
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-083-01-13C-1.als



DFILE	TG-V-083-01-13C-1.als
COMNT	TG-V-083-01-13C
DATIM	19-06-2012 19:18:26
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	26214
SPO	26214
TIMES	223
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	223
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-083-01-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.7 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-081-01-1H

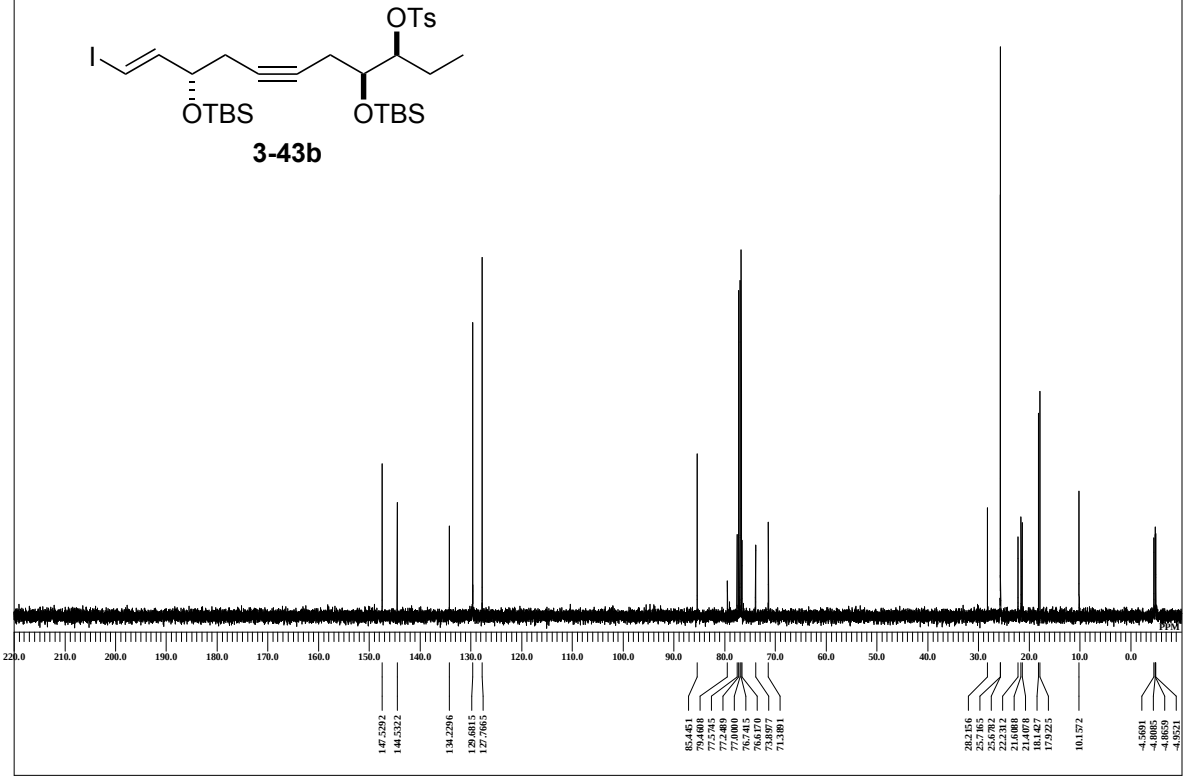
C:\Documents and Settings\PC-USER\ƒfƒXƒNƒgƒbƒv\urabe\epoxy\TG-V-081-01-1H-2.als




```
DFILE     TG-V-081-01-1H-2.als
COMNT     TG-V-081-01-1H
DATIM     19-06-2012 19:57:22
MENUF
OBNUC     1H
OFR       495.13 MHz
OBFRQ     495.13 MHz
OBSET     4.38 KHz
OBFIN     9.64 Hz
PW1       6.00 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     13107
SPO       13107
TIMES     16
DUMMY     1
FREQU     7429.31 Hz
FLT       38000 Hz
DELAY     13.16 usec
ACQTM     1.7642 sec
PD        2.0000 sec
SCANS     16
ADBIT     16
RGAIN     54
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse.ex2
EXPCM
IRNUC     1H
IFR       495.13 MHz
IRSET     4.38 KHz
IRFIN     9.64 Hz
IRRPW     92 usec
IRATN     79
DFILE     TG-V-081-01-1H-2.als
SF
LKSET     748.40 KHz
LKFIN     98.2 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     24.9 c
SLVNT     CDCL3
EXREF     7.26 ppm
```

TG-V-081-01-13C

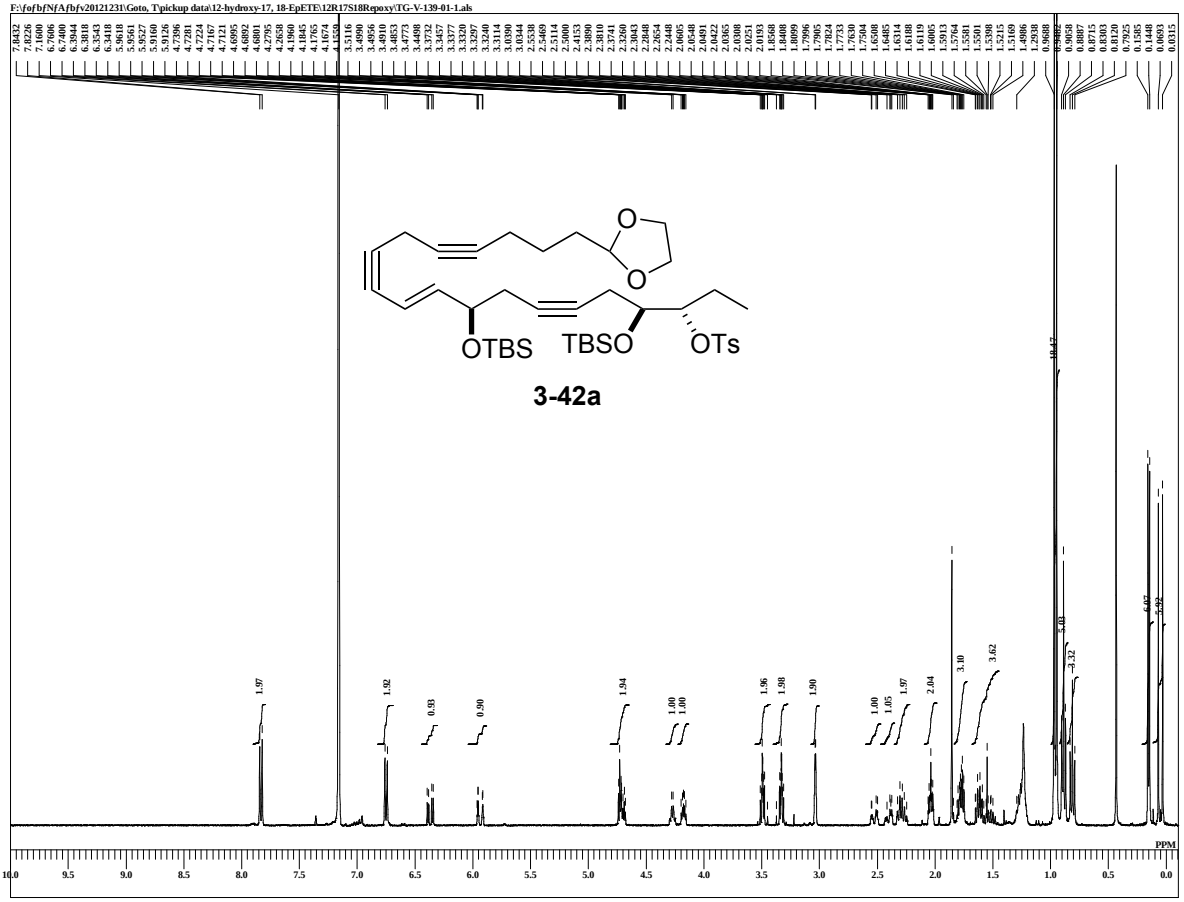
G:\ƒofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-081-01-13C.als




```
DFILE     TG-V-081-01-13C.als
COMNT     TG-V-081-01-13C
DATIM     19-06-2012 20:08:37
MENUF
OBNUC     13C
OFR       124.51 MHz
OBFRQ     124.51 MHz
OBSET     3.45 KHz
OBFIN     6.00 Hz
PW1       3.70 usec
DEADT     0.00 usec
PREDL     0.00000 msec
IWT       1.0000 sec
POINT     26214
SPO       26214
TIMES     54
DUMMY     4
FREQU     31249.52 Hz
FLT       157000 Hz
DELAY     20.80 usec
ACQTM     0.8389 sec
PD        8.0000 sec
SCANS     54
ADBIT     16
RGAIN     50
BF        0.01 Hz
T1        0.00
T2        0.00
T3        90.00
T4        100.00
EXMOD     single_pulse_dec
EXPCM
IRNUC     1H
IFR       495.13 MHz
IRSET     4.38 KHz
IRFIN     9.64 Hz
IRRPW     92 usec
IRATN     79
DFILE     TG-V-081-01-13C.als
SF
LKSET     748.40 KHz
LKFIN     98.2 Hz
LKLEV     0
LGAIN     0
LKPHS     0
LKSIG     0
CSPED     0 Hz
FILDC
FILDF
CTEMP     25.6 c
SLVNT     CDCL3
EXREF     77.00 ppm
```

TG-V-139-01

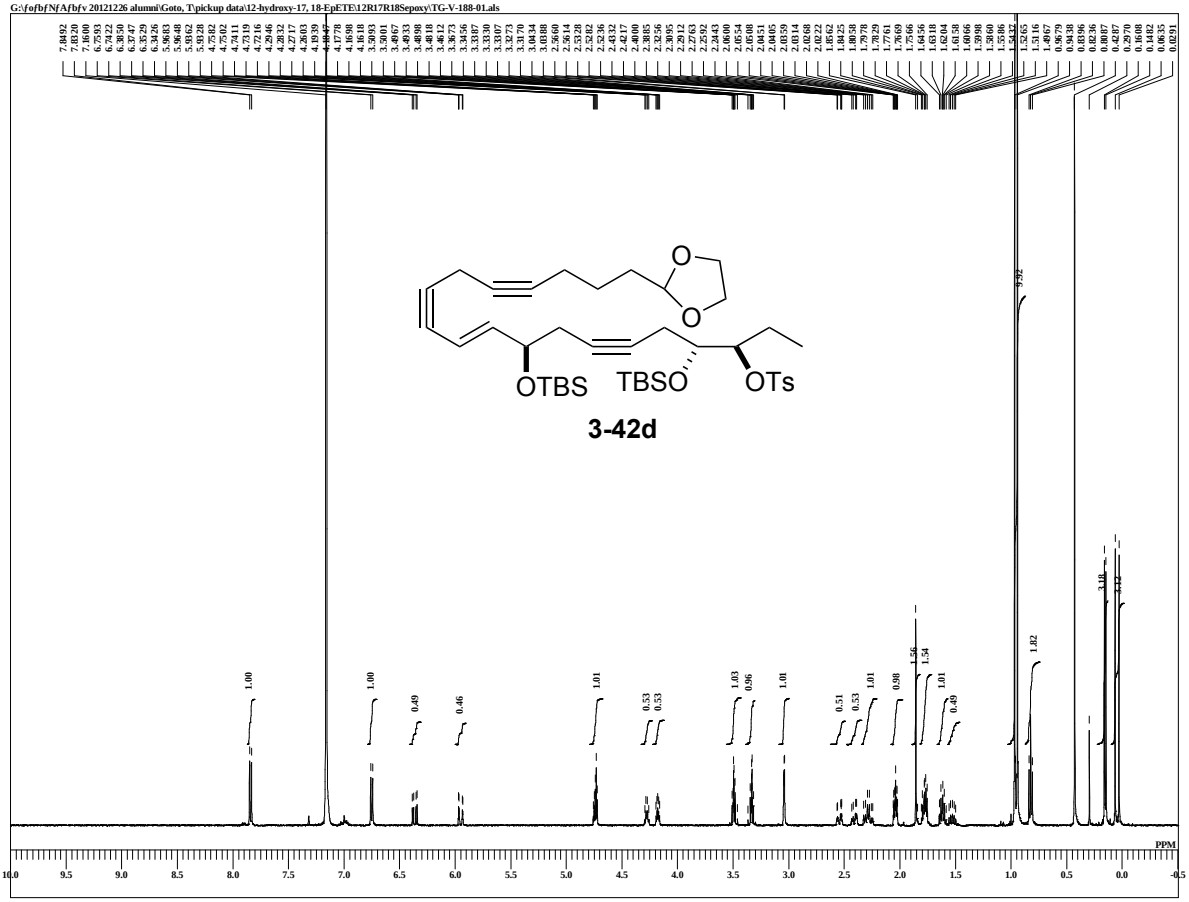
F:\fofbfNfAfbfv20121231\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-139-01-1.als




```
DFILE    TG-V-139-01-1.als
COMNT    TG-V-139-01
DATIM    26-07-2012 11:31:14
MENUF
OBNUC    1H
OFR      395.88 MHz
OBFRQ    395.88 MHz
OBSET    6.28 KHz
OBFIN    0.87 Hz
PW1      6.38 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    10
DUMMY    1
FREQU    5938.15 Hz
FLT      30000 Hz
DELAY    16.68 usec
ACQTM    2.2073 sec
PD       2.0000 sec
SCANS    10
ADBIT    16
RGAIN    42
BF       0.01 Hz
T1       0.00
T2       0.00
T3       90.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      395.88 MHz
IRSET    6.28 KHz
IRFIN    0.87 Hz
IRRPW    147 usec
IRATN    79
DFILE    TG-V-139-01-1.als
SF
LKSET    13.20 KHz
LKFIN    69.6 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    22.8 c
SLVNT    C6D6
EXREF    7.16 ppm
```

TG-V-188-01

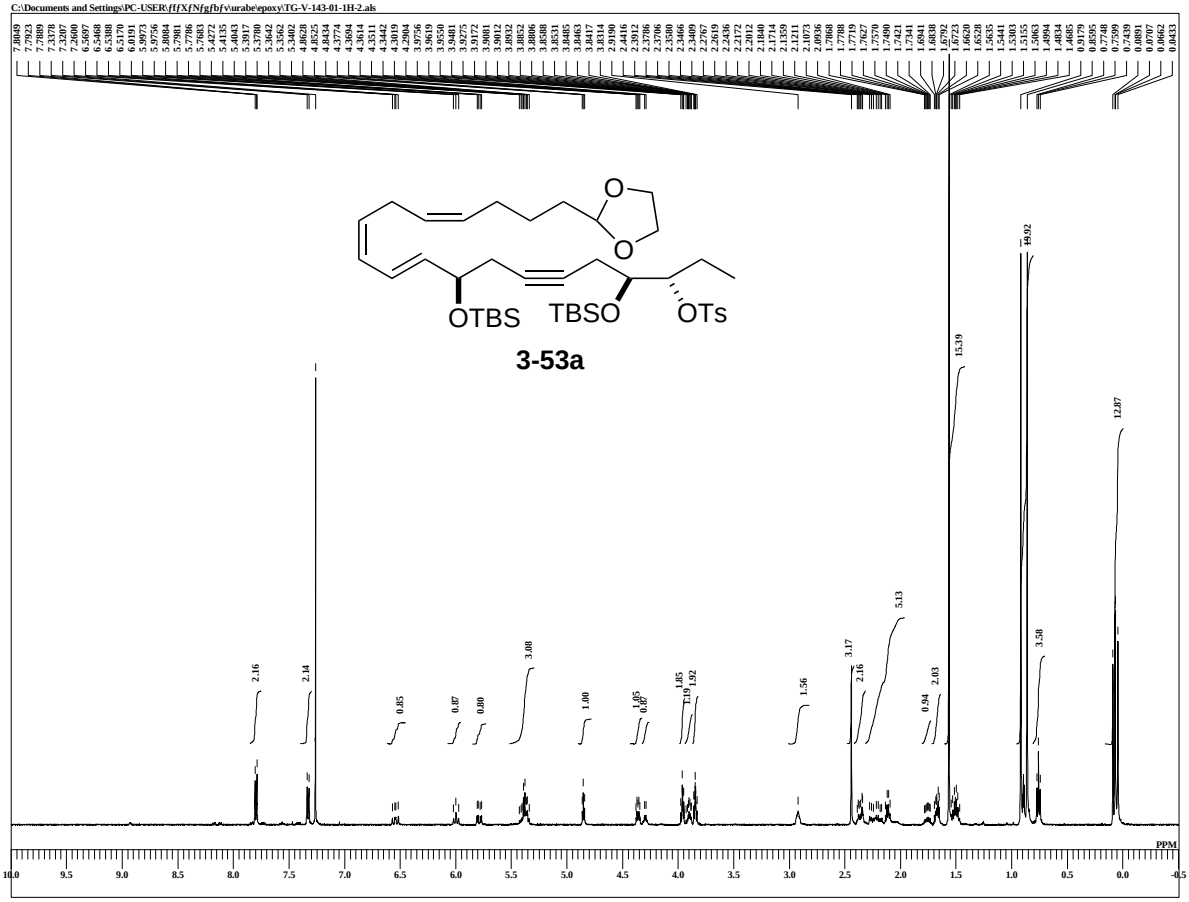
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17R18Sepoxy\TG-V-188-01.als




```
DFILE    TG-V-188-01.als
COMNT    TG-V-188-01
DATIM    04-09-2012 11:11:20
MENUF
OBNUC    1H
OFR      495.13 MHz
OBFRQ    495.13 MHz
OBSET    4.38 KHz
OBFIN    9.64 Hz
PW1      6.00 usec
DEADT    0.00 usec
PREDL    0.00000 msec
IWT      1.0000 sec
POINT    13107
SPO      13107
TIMES    8
DUMMY    1
FREQU    7429.31 Hz
FLT      38000 Hz
DELAY    13.16 usec
ACQTM    1.7642 sec
PD       2.0000 sec
SCANS    8
ADBIT    16
RGAIN    50
BF       0.01 Hz
T1       0.00
T2       0.00
T3       100.00
T4       100.00
EXMOD    single_pulse.ex2
EXPCM
IRNUC    1H
IFR      495.13 MHz
IRSET    4.38 KHz
IRFIN    9.64 Hz
IRRPW    92 usec
IRATN    79
DFILE    TG-V-188-01.als
SF
LKSET    748.40 KHz
LKFIN    90.6 Hz
LKLEV    0
LGAIN    0
LKPHS    0
LKSIG    0
CSPED    0 Hz
FILDC
FILDF
CTEMP    23.5 c
SLVNT    C6D6
EXREF    7.16 ppm
```

TG-V-143-01-1H

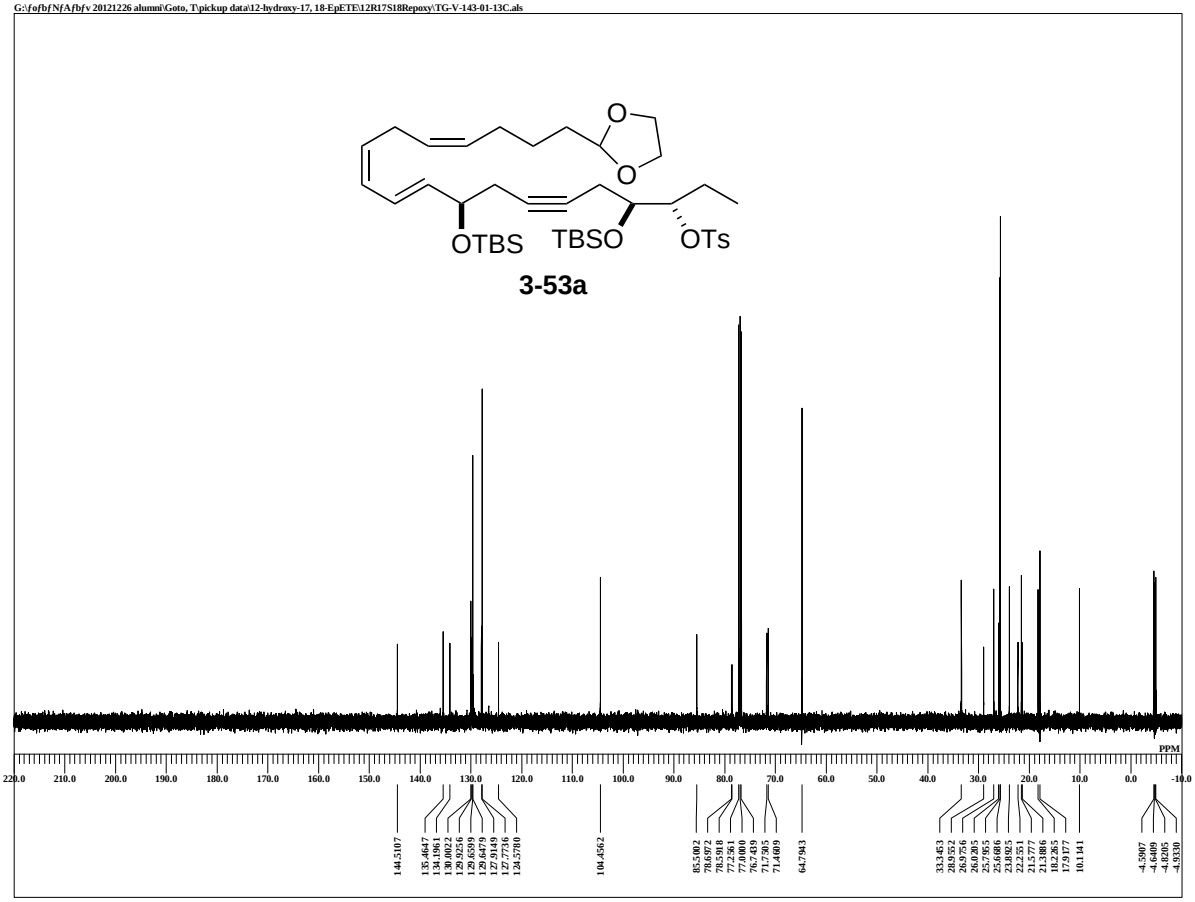
C:\Documents and Settings\PC-USER\ff{XfNfgfbfv\urabe\epoxy\TG-V-143-01-1H-2.als



DFILE	TG-V-143-01-1H-2.als
COMNT	TG-V-143-01-1H
DATIM	26-07-2012 19:51:28
MENUF	
OBNUC	1H
OFR	495.13 MHz
OBFRQ	495.13 MHz
OBSET	4.38 KHz
OBFIN	9.64 Hz
PW1	6.00 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	7429.31 Hz
FLT	38000 Hz
DELAY	13.16 usec
ACQTM	1.7642 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	54
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	70 usec
IRATN	79
DFILE	TG-V-143-01-1H-2.als
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.0 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-143-01-13C

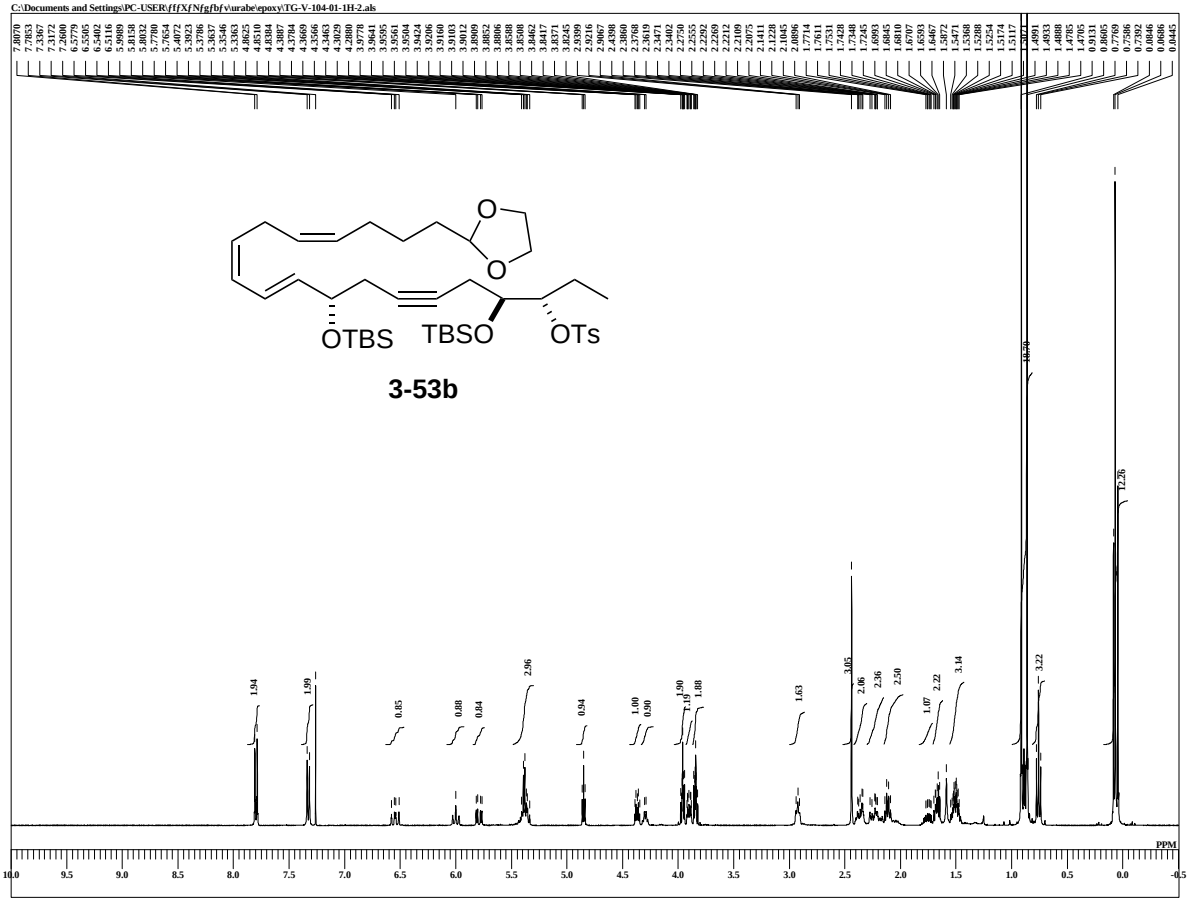
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-143-01-13C.als



DFILE	TG-V-143-01-13C.als
COMNT	TG-V-143-01-13C
DATIM	26-07-2012 20:02:26
MENUF	
OBNUC	13C
OFR	124.51 MHz
OBFRQ	124.51 MHz
OBSET	3.45 KHz
OBFIN	6.00 Hz
PW1	3.70 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	42
DUMMY	4
FREQU	31249.52 Hz
FLT	157000 Hz
DELAY	20.80 usec
ACQTM	0.8389 sec
PD	8.0000 sec
SCANS	42
ADBIT	16
RGAIN	50
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-V-143-01-13C.als
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.5 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-104-01-1H

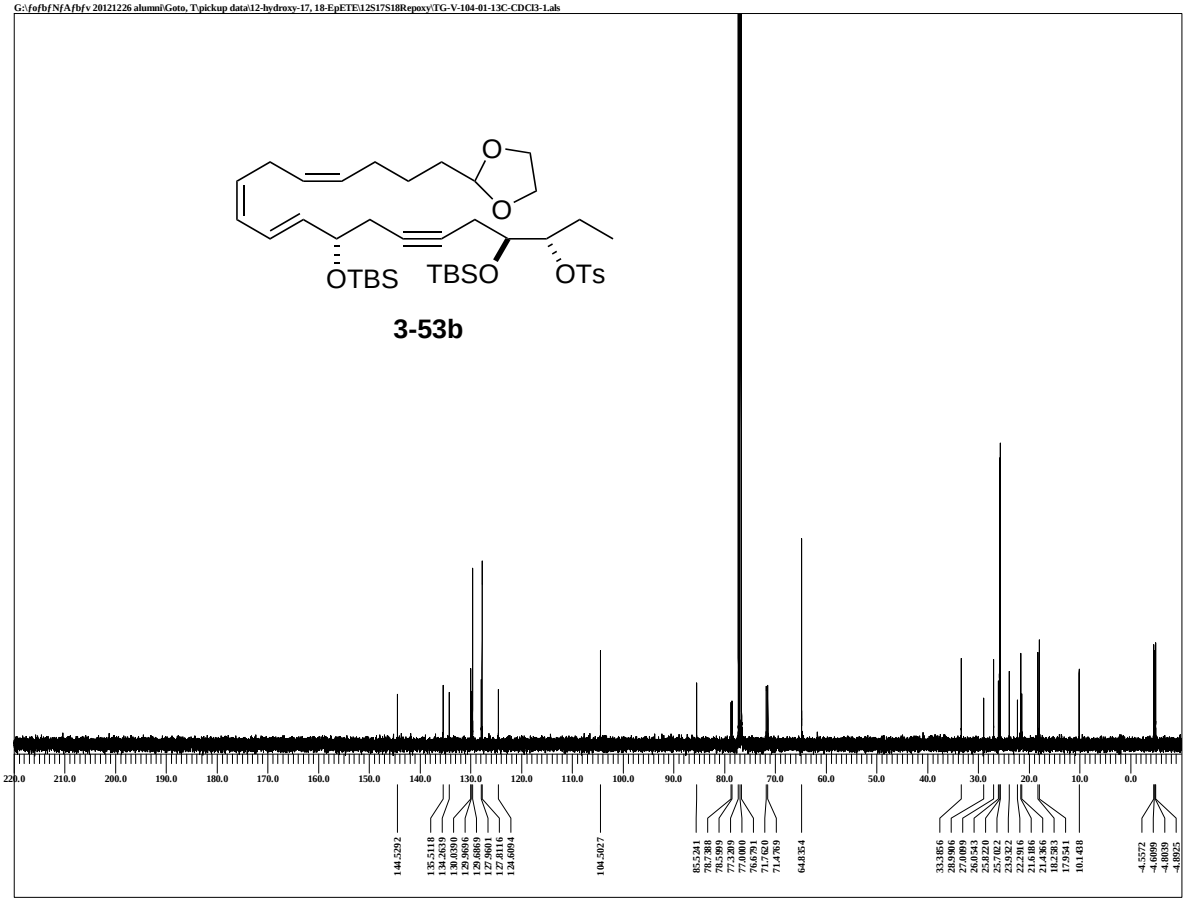
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-104-01-1H-2.als



DFILE	TG-V-104-01-1H-2.als
COMNT	TG-V-104-01-1H
DATIM	06-07-2012 08:34:47
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	30
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	147 usec
IRATN	79
DFILE	TG-V-104-01-1H-2.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.7 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-104-01-13C

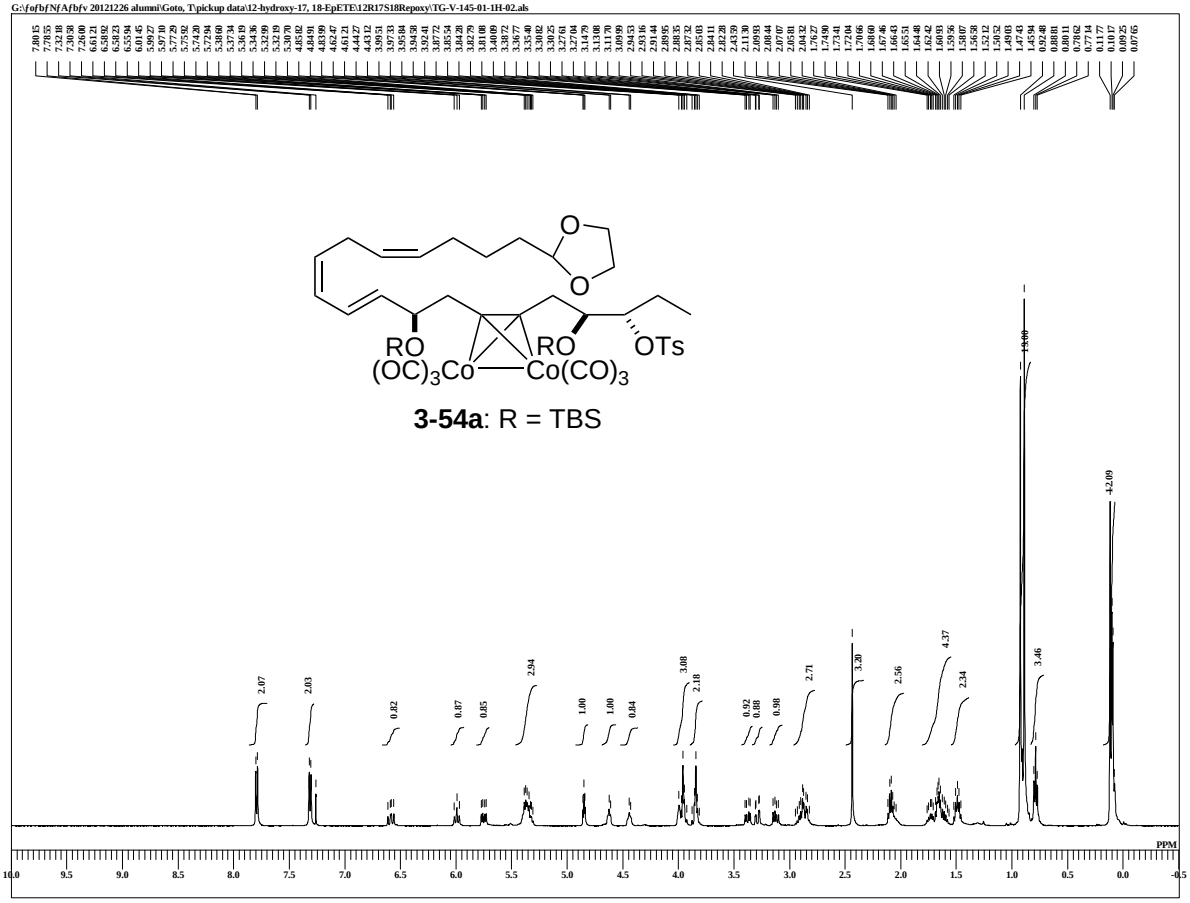
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-104-01-13C-CDCl3-1.als



DFILE	TG-V-104-01-13C-CDCl3
COMNT	TG-V-104-01-13C
DATIM	06-07-2012 09:30:34
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	360
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	360
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-104-01-13C-CDCl3
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.4 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-145-01-1H-02

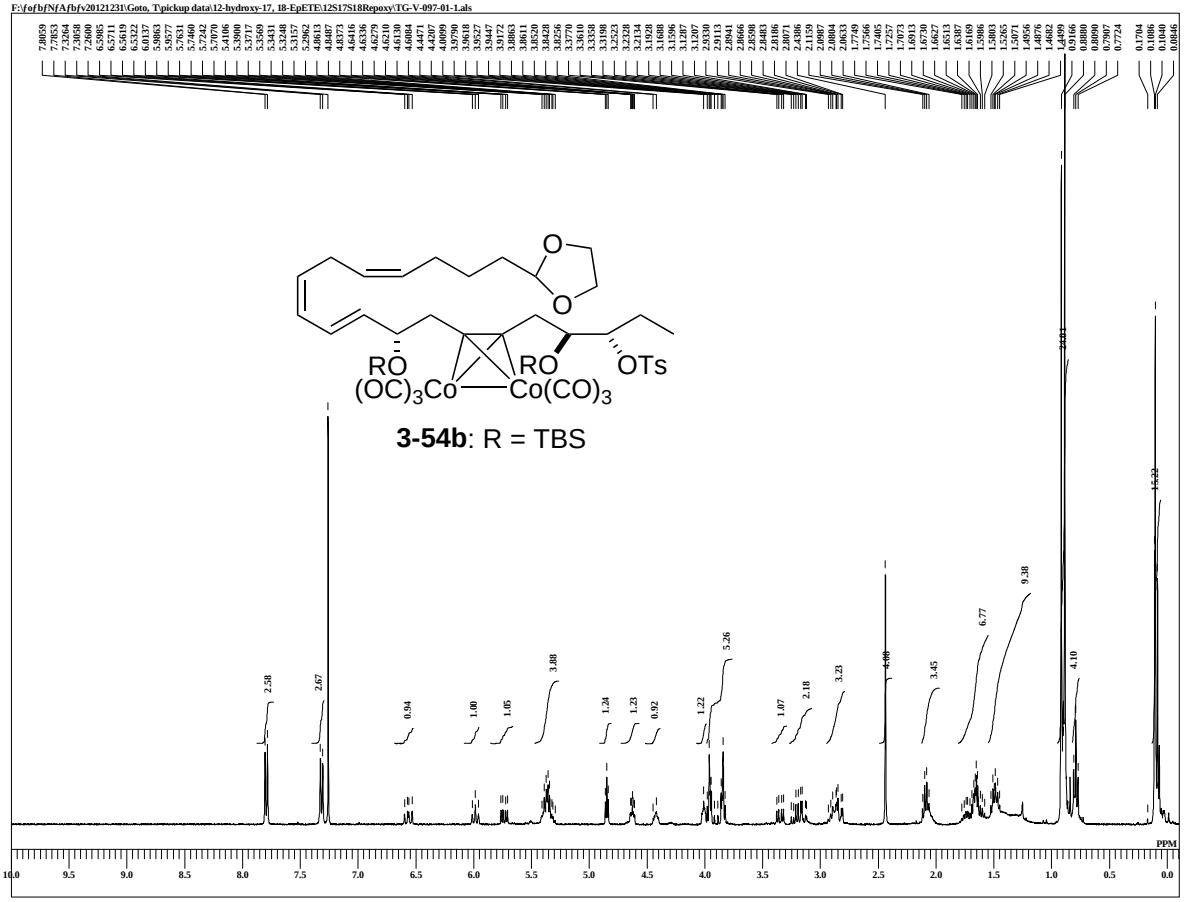
G:*fofbfNfAfbfv* 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-145-01-1H-02.als



DFILE	TG-V-145-01-1H-02.als
COMNT	TG-V-145-01-1H-02
DATIM	28-07-2012 17:04:25
MENUF	
OBNUC	1H
OFR	495.13 MHz
OBFRQ	495.13 MHz
OBSET	4.38 KHz
OBFIN	9.64 Hz
PW1	6.00 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	7429.31 Hz
FLT	38000 Hz
DELAY	13.16 usec
ACQTM	1.7642 sec
PD	5.0000 sec
SCANS	8
ADBIT	16
RGAIN	36
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	118 usec
IRATN	79
DFILE	TG-V-145-01-1H-02.als
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.0 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-097-01

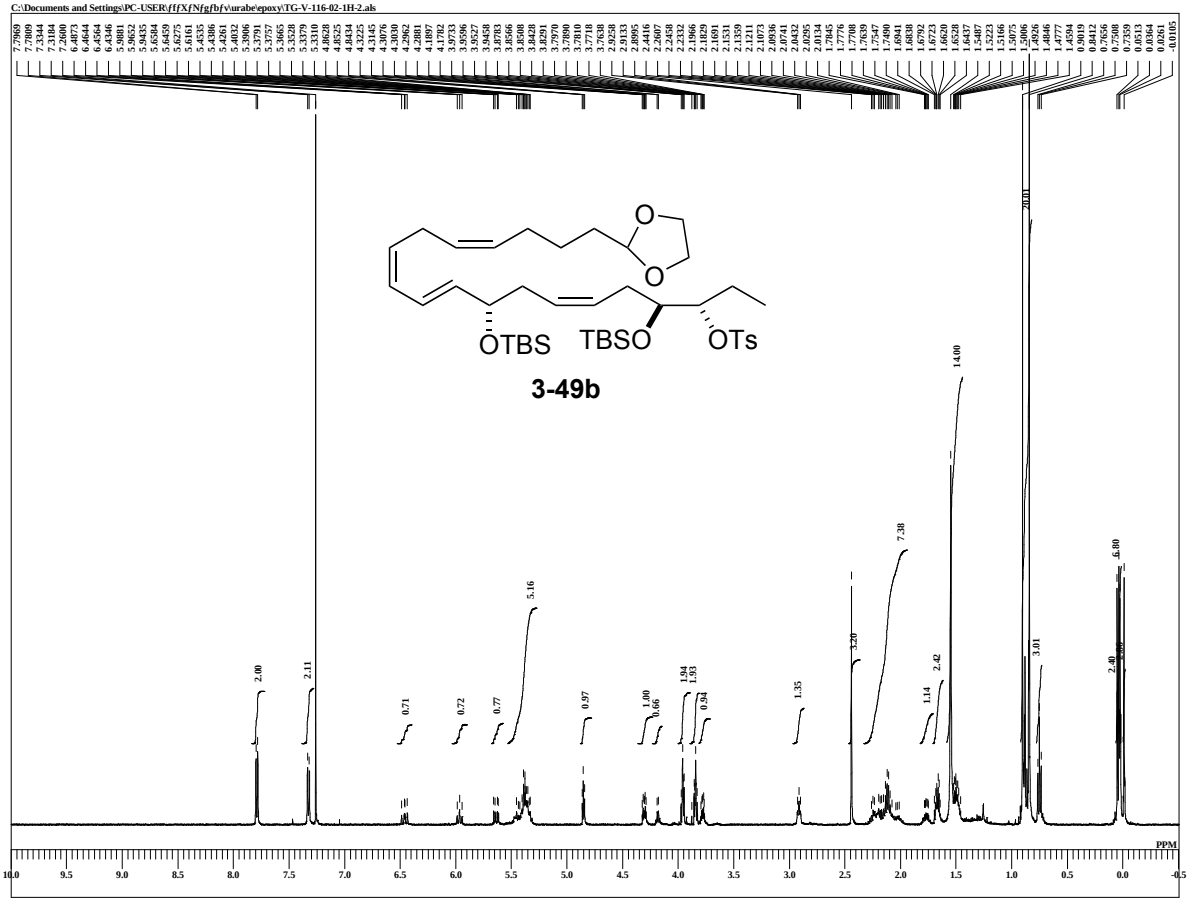
F:*fofbfNfAfbfv*20121231\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-097-01-1.als



DFILE	TG-V-097-01-1.als
COMNT	TG-V-097-01
DATIM	28-06-2012 08:06:41
MENUF	
OBNUC	1H
OFR	395.88 MHz
OBFRQ	395.88 MHz
OBSET	6.28 KHz
OBFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	16
DUMMY	1
FREQU	5938.15 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	2.0000 sec
SCANS	16
ADBIT	16
RGAIN	44
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-097-01-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	23.4 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-116-02-1H

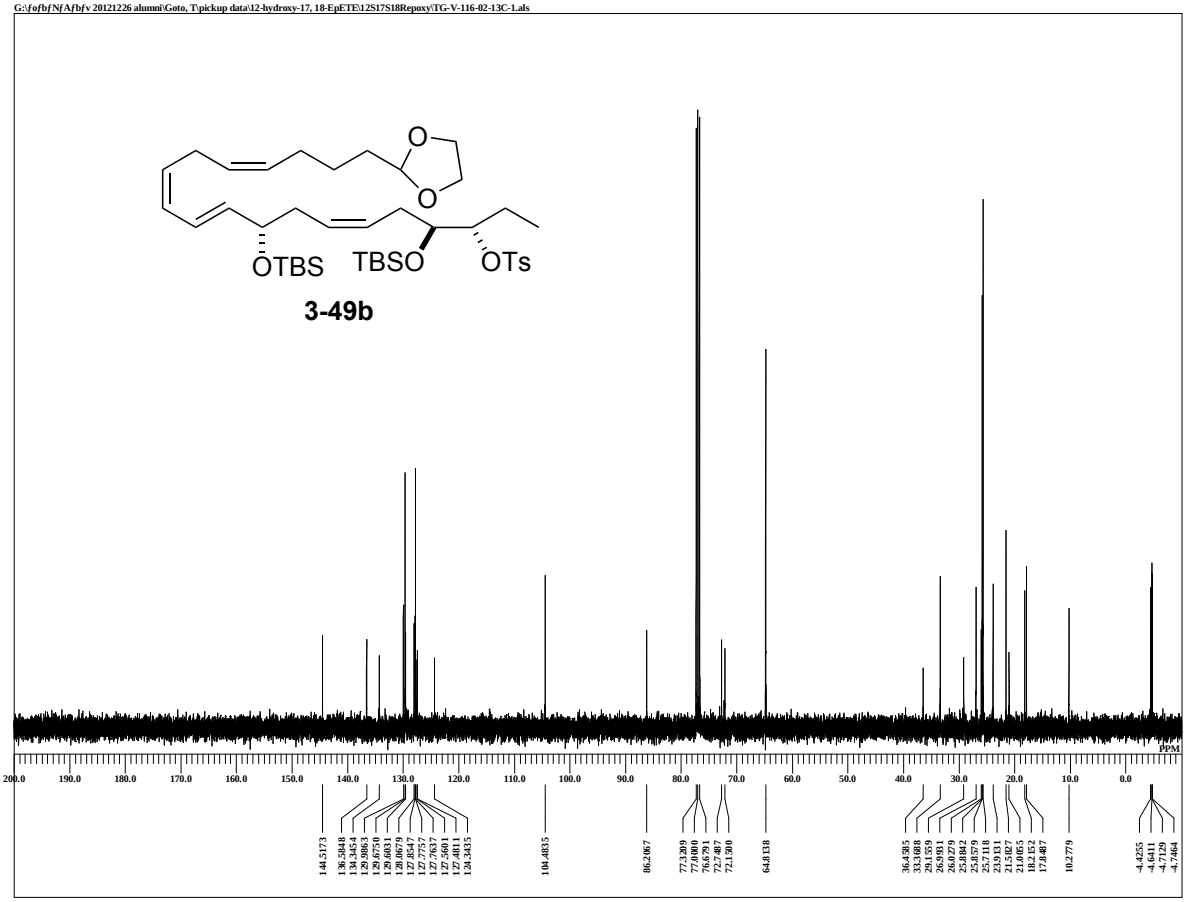
C:\Documents and Settings\PC-USER\ff{XfNfgfbfv\urabe\epoxy\TG-V-116-02-1H-2.als



DFILE	TG-V-116-02-1H-2.als
COMNT	TG-V-116-02-1H
DATIM	12-07-2012 21:27:33
MENUF	
OBNUC	1H
OFR	495.13 MHz
OBFRQ	495.13 MHz
OBSET	4.38 KHz
OBFIN	9.64 Hz
PW1	6.00 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	16
DUMMY	1
FREQU	7429.31 Hz
FLT	38000 Hz
DELAY	13.16 usec
ACQTM	1.7642 sec
PD	2.0000 sec
SCANS	16
ADBIT	16
RGAIN	54
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-V-116-02-1H-2.als
SF	
LKSET	748.40 KHz
LKFIN	98.2 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.8 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-116-02-13C

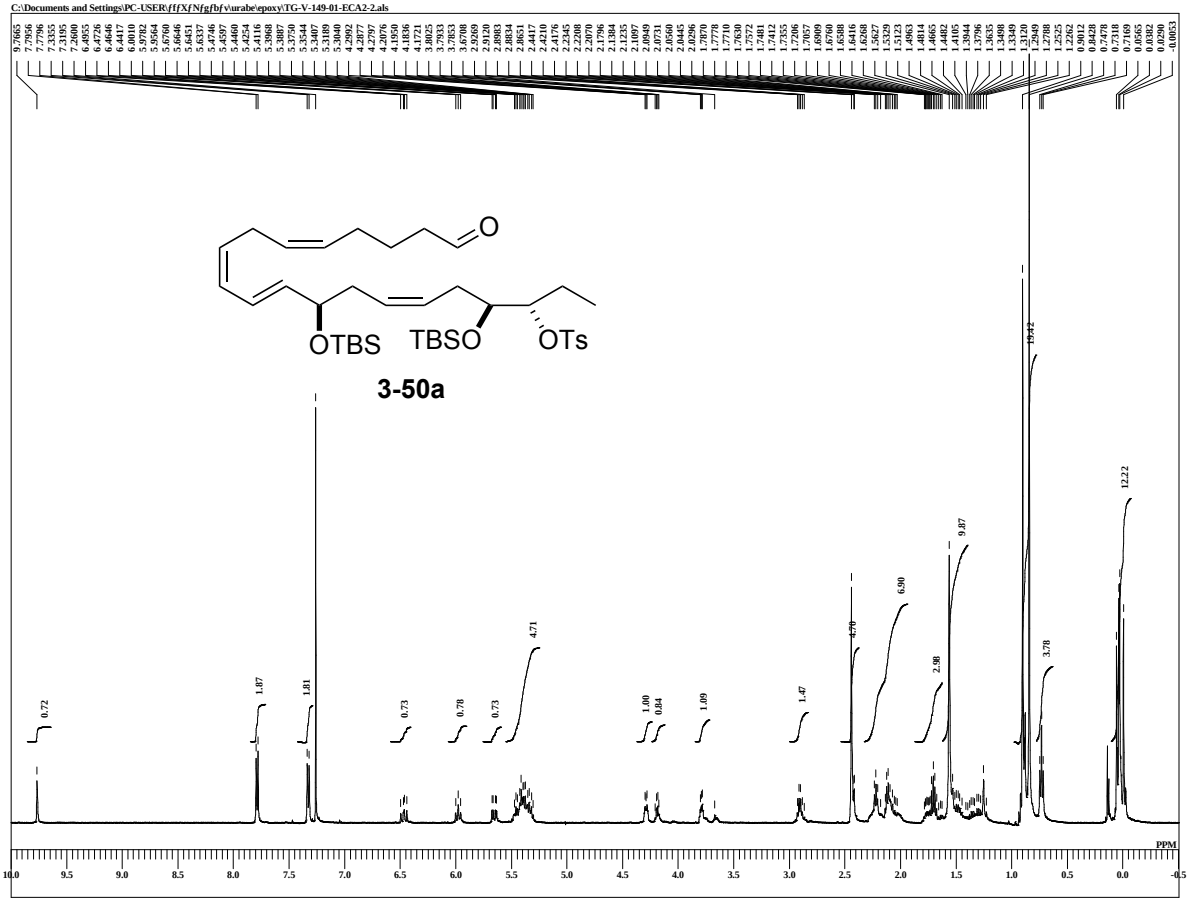
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-116-02-13C-1.als



DFILE	TG-V-116-02-13C-1.als
COMNT	TG-V-116-02-13C
DATIM	12-07-2012 20:44:33
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	40
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	40
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-116-02-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.2 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-149-01-ECA2

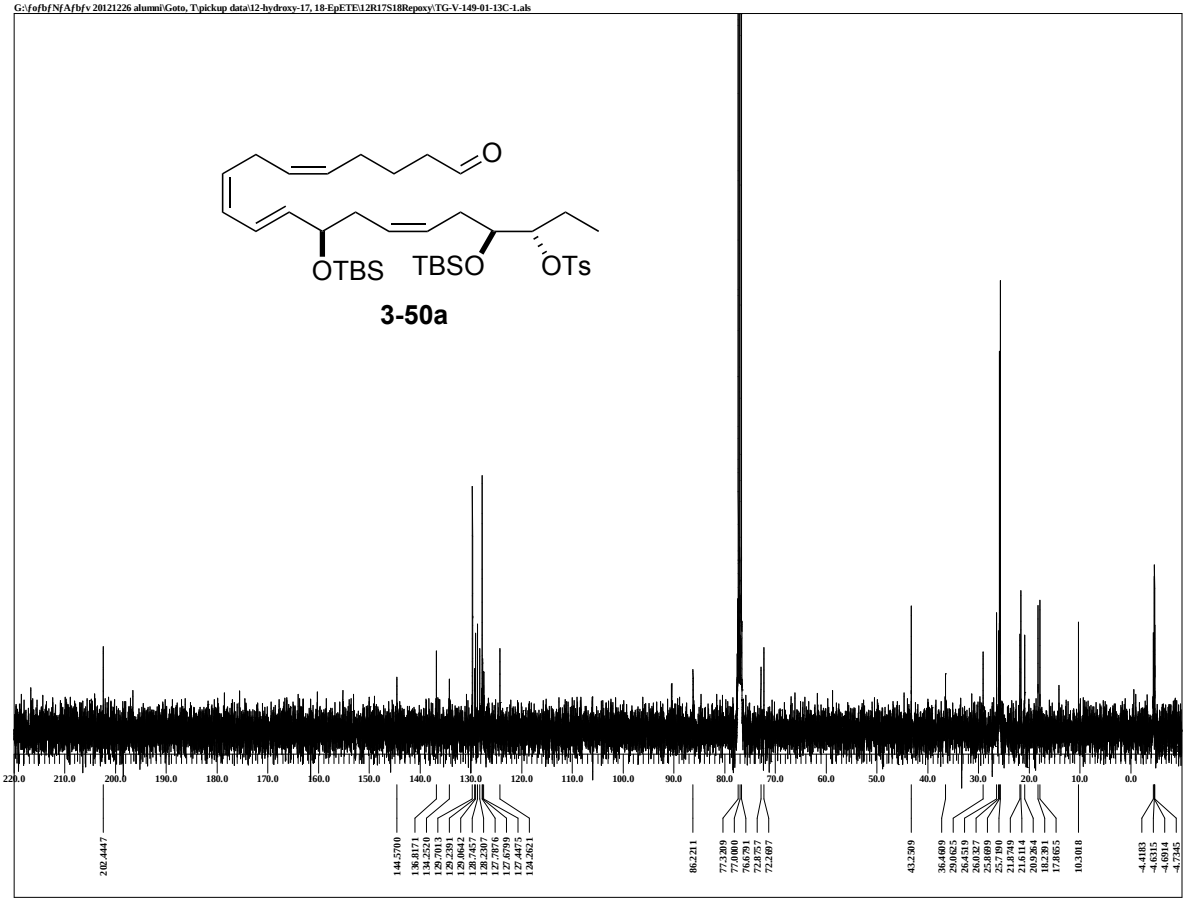
C:\Documents and Settings\PC-USER\ffXfNfgfbfv\urabe\epoxy\TG-V-149-01-ECA2-2.als



DFILE	TG-V-149-01-ECA2-2.als
COMNT	TG-V-149-01-ECA2
DATIM	31-07-2012 04:54:28
MENUF	
OBNUC	1H
OFR	490.15 MHz
OBFRQ	490.15 MHz
OBSET	9.16 KHz
OBFIN	7.60 Hz
PW1	6.50 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	32
DUMMY	1
FREQU	7352.83 Hz
FLT	37000 Hz
DELAY	13.52 usec
ACQTM	1.7826 sec
PD	2.0000 sec
SCANS	32
ADBIT	16
RGAIN	34
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	490.15 MHz
IRSET	9.16 KHz
IRFIN	7.60 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-V-149-01-ECA2-2.als
SF	
LKSET	70.30 KHz
LKFIN	32.5 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.6 c
SLVNT	CDCL3
EXREF	7.26 ppm

TG-V-149-01-13C

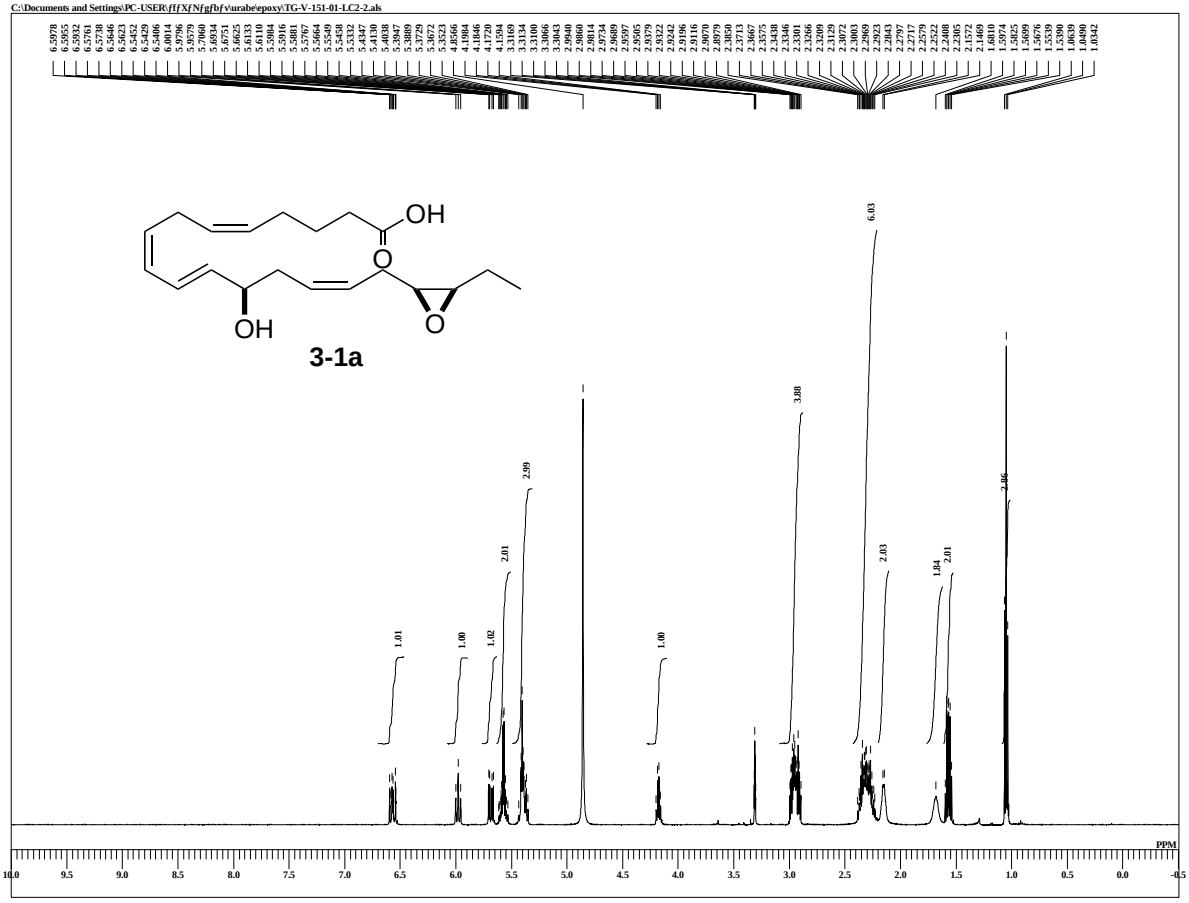
G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-149-01-13C-1.als



DFILE	TG-V-149-01-13C-1.als
COMNT	TG-V-149-01-13C
DATIM	31-07-2012 12:01:47
MENUF	
OBNUC	13C
OFR	99.55 MHz
OBFRQ	99.55 MHz
OBSET	5.13 KHz
OBFIN	0.98 Hz
PW1	3.25 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	104856
SPO	104856
TIMES	202
DUMMY	4
FREQU	24999.62 Hz
FLT	125000 Hz
DELAY	20.50 usec
ACQTM	1.0486 sec
PD	8.0000 sec
SCANS	202
ADBIT	16
RGAIN	60
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
IRNUC	1H
IFR	395.88 MHz
IRSET	6.28 KHz
IRFIN	0.87 Hz
IRRPW	115 usec
IRATN	79
DFILE	TG-V-149-01-13C-1.als
SF	
LKSET	13.20 KHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.7 c
SLVNT	CDCL3
EXREF	77.00 ppm

TG-V-151-01-LC2

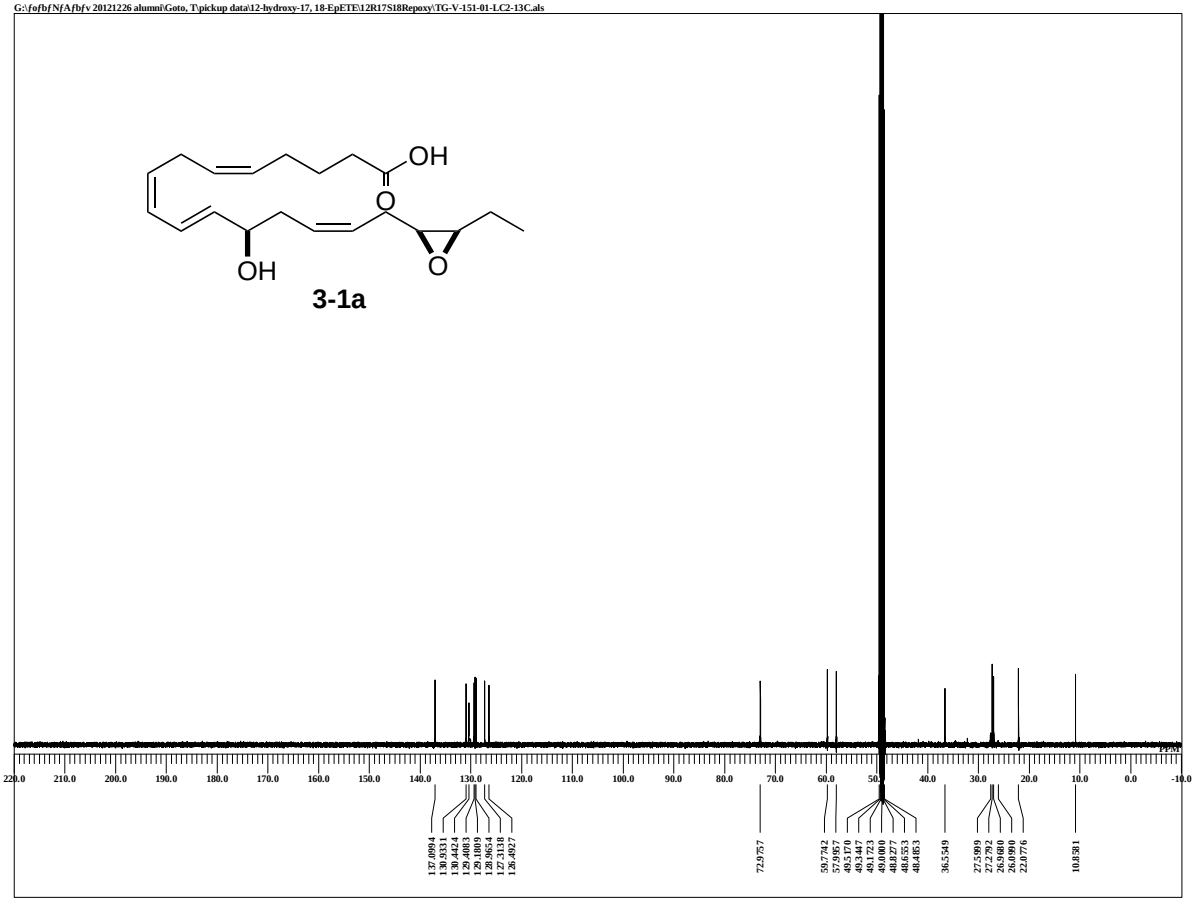
C:\Documents and Settings\PC-USER\ff XfNfgfbfv\urabe\epoxy\TG-V-151-01-LC2-2.als



DFILE	TG-V-151-01-LC2-2.als
COMNT	TG-V-151-01-LC2
DATIM	07-08-2012 16:58:41
MENUF	
OBNUC	1H
OFR	495.13 MHz
OBFRQ	495.13 MHz
OBSET	4.38 KHz
OBFIN	9.64 Hz
PW1	6.00 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	13107
SPO	13107
TIMES	8
DUMMY	1
FREQU	7429.31 Hz
FLT	38000 Hz
DELAY	13.16 usec
ACQTM	1.7642 sec
PD	2.0000 sec
SCANS	8
ADBIT	16
RGAIN	48
BF	0.01 Hz
T1	0.00
T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse.ex2
EXPCM	
IRNUC	1H
IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
DFILE	TG-V-151-01-LC2-2.als
SF	
LKSET	748.10 KHz
LKFIN	98.0 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.0 c
SLVNT	CD3OD
EXREF	3.31 ppm

TG-V-151-01-LC2-13C

G:\fofbfNfAfbfv 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12R17S18Repoxy\TG-V-151-01-LC2-13C.als



DFILE	TG-V-151-01-LC2-13C.al
COMNT	TG-V-151-01-LC2-13C
DATIM	09-08-2012 05:40:24
MENUF	
OBNUC	13C
OFR	124.51 MHz
OBFRQ	124.51 MHz
OBSET	3.45 KHz
OBFIN	6.00 Hz
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PD	8.0000 sec
SCANS	3000
ADBIT	16
RGAIN	50
BF	0.01 Hz
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T2	0.00
T3	90.00
T4	100.00
EXMOD	single_pulse_dec
EXPCM	
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IFR	495.13 MHz
IRSET	4.38 KHz
IRFIN	9.64 Hz
IRRPW	92 usec
IRATN	79
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LKLEV	0
LGAIN	0
LKPHS	0
LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	22.1 c
SLVNT	CD3OD
EXREF	49.00 ppm

TG-V-117-01-1H

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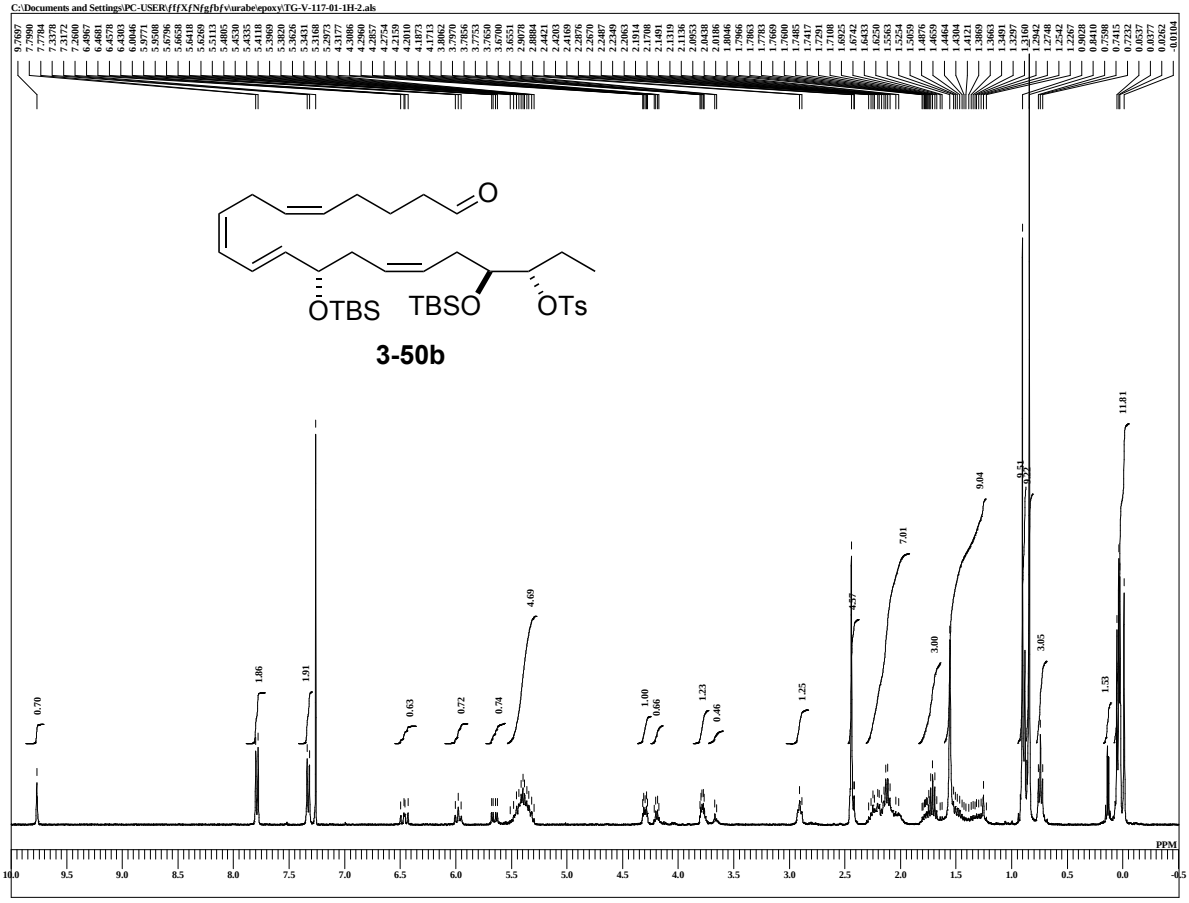


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T3        90.00
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EXPCM
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IFR       395.88 MHz
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LKPHS     0
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CSPED     0 Hz
FILDC
FILDF
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SLVNT     CDCL3
EXREF     7.26 ppm
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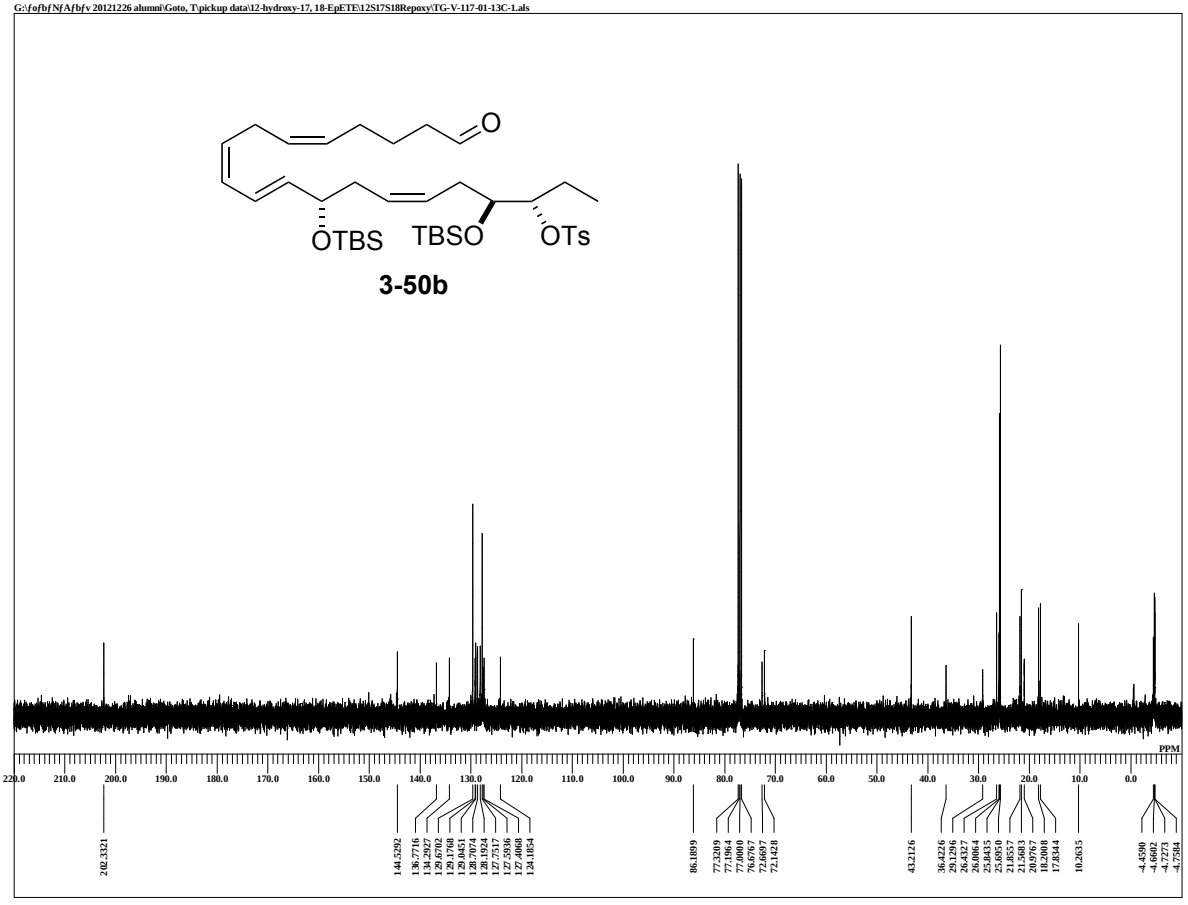
TG-V-117-01-13C

G:\fo\bf\Nf\A\bf\v 20121226 alumni\Goto, T\pickup data\12-hydroxy-17, 18-EpETE\12S17S18Repoxy\TG-V-117-01-13C-1.als

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RGAIN     60
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EXMOD     single_pulse_dec
EXPCM
IRNUC     1H
IFR       395.88 MHz
IRSET     6.28 KHz
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FILDC
FILDF
CTEMP     25.0 c
SLVNT     CDCL3
EXREF     77.00 ppm
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TG-V-119-02-LC2-1H

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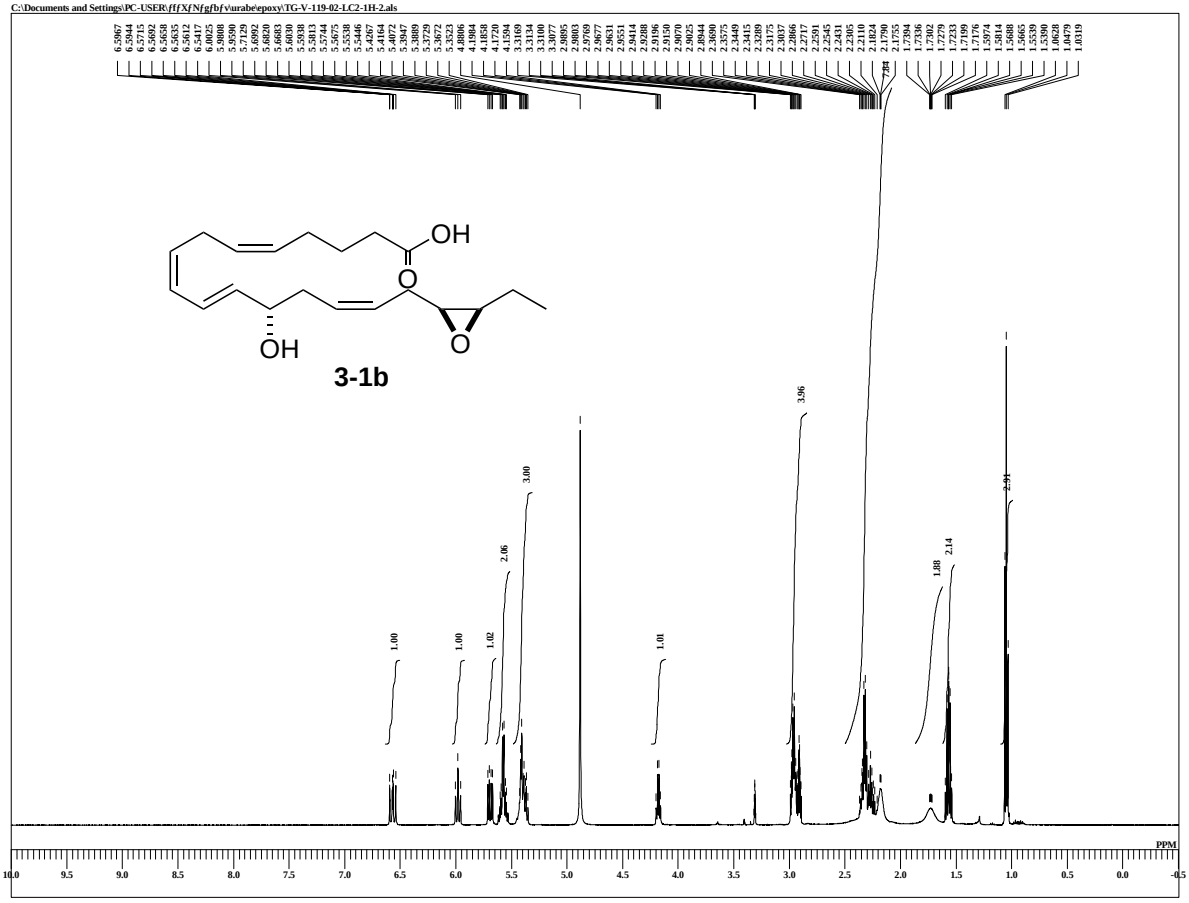

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SPO 13107
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DUMMY 1
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PD 2.0000 sec
SCANS 8
ADBIT 16
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T4 100.00
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EXPCM
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IRSET 4.38 KHz
IRFIN 9.64 Hz
IRRPW 92 usec
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DFILE TG-V-119-02-LC2-1H-2.a
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LKSET 748.10 KHz
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LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 22.8 c
SLVNT CD3OD
EXREF 3.31 ppm

TG-V-119-02-LC2-13C

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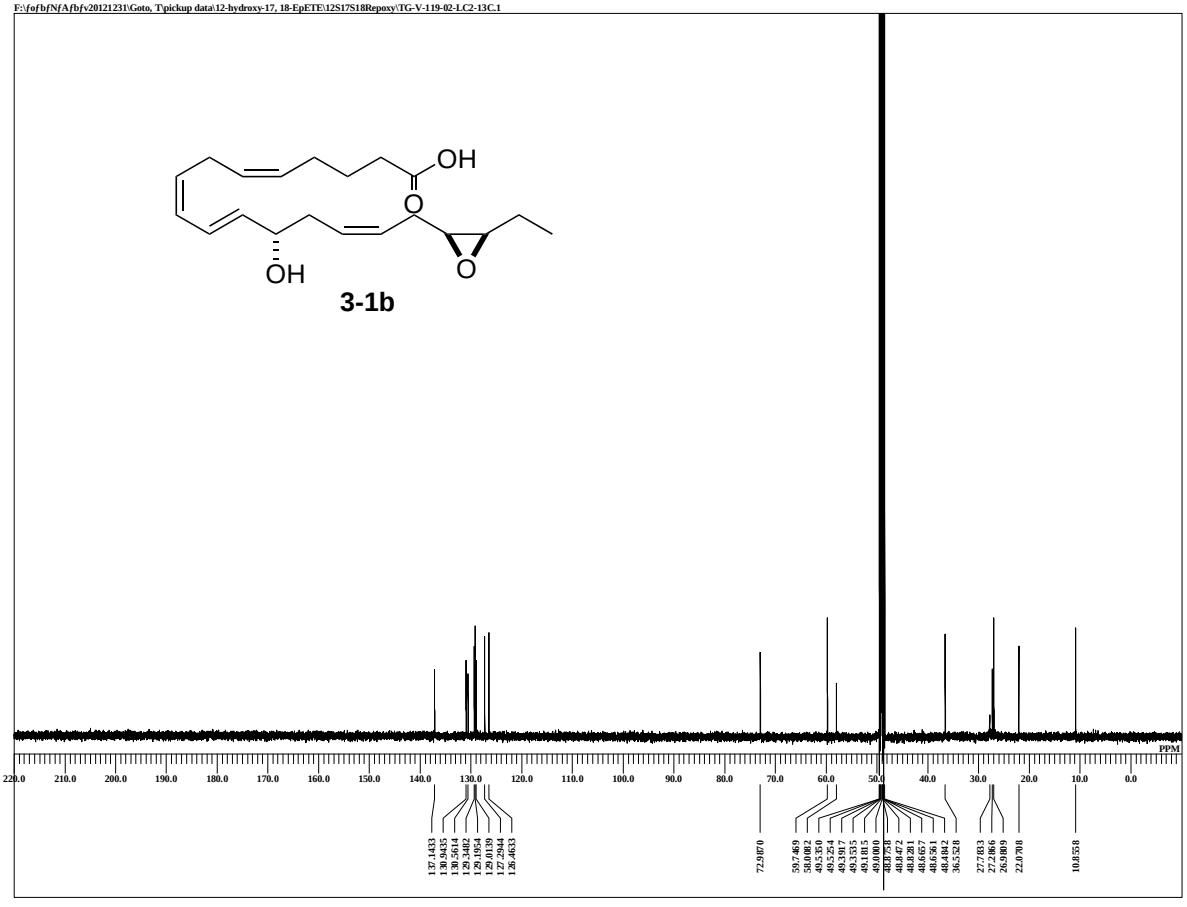

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OBFRQ 123.26 MHz
OBSET 2.31 KHz
OBFIN 6.71 Hz
PW1 3.23 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
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FREQU 38580.25 Hz
FLT 155000 Hz
DELAY 21.06 usec
ACQTM 0.8493 sec
PD 8.0000 sec
SCANS 3000
ADBIT 16
RGAIN 60
BF 0.01 Hz
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T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
EXPCM
IRNUC 1H
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IRFIN 7.60 Hz
IRRPW 92 usec
IRATN 79
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SF
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CSPED 0 Hz
FILDC
FILDF
CTEMP 23.0 c
SLVNT CD3OD
EXREF 49.00 ppm

TG-VI-012-01

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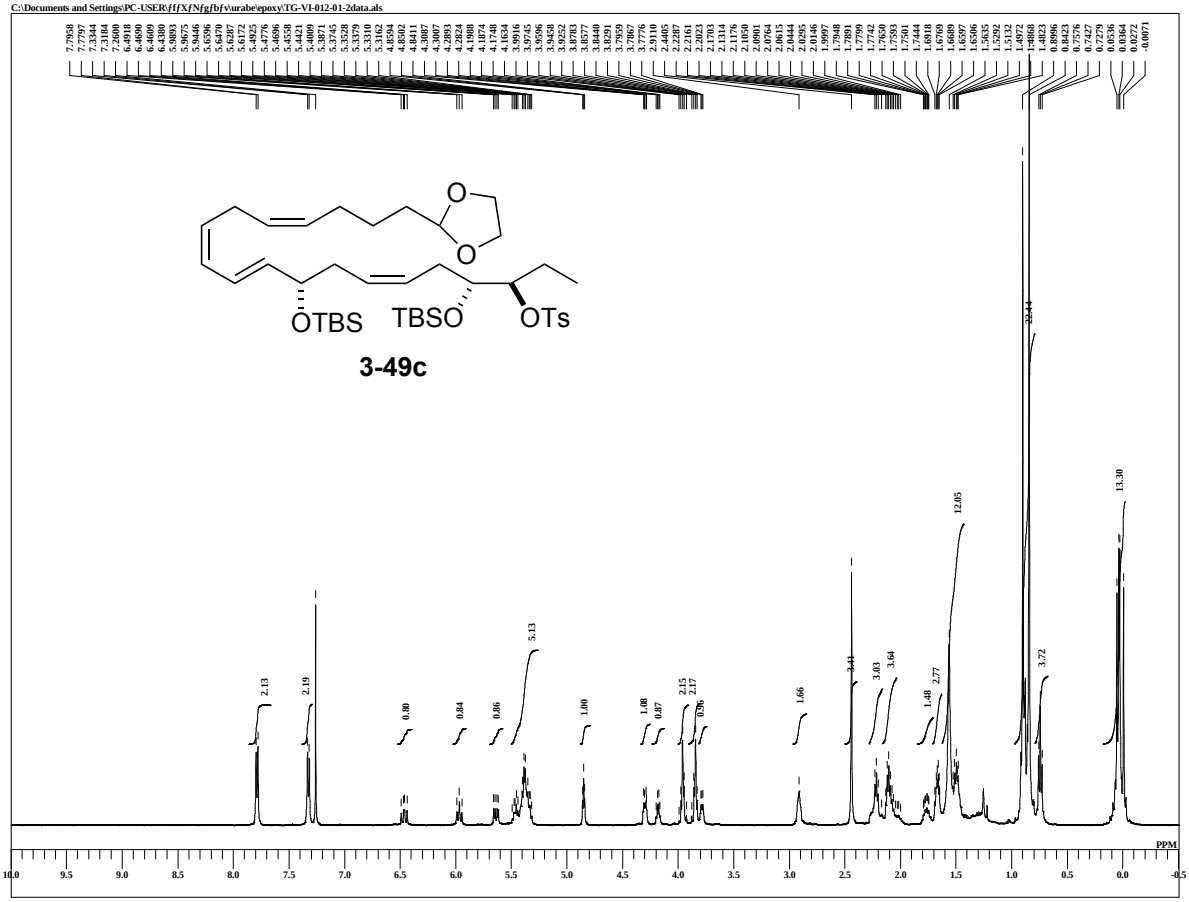

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PREDL	0.00000 msec
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EXREF	7.26 ppm

TG-VI-012-01-13C

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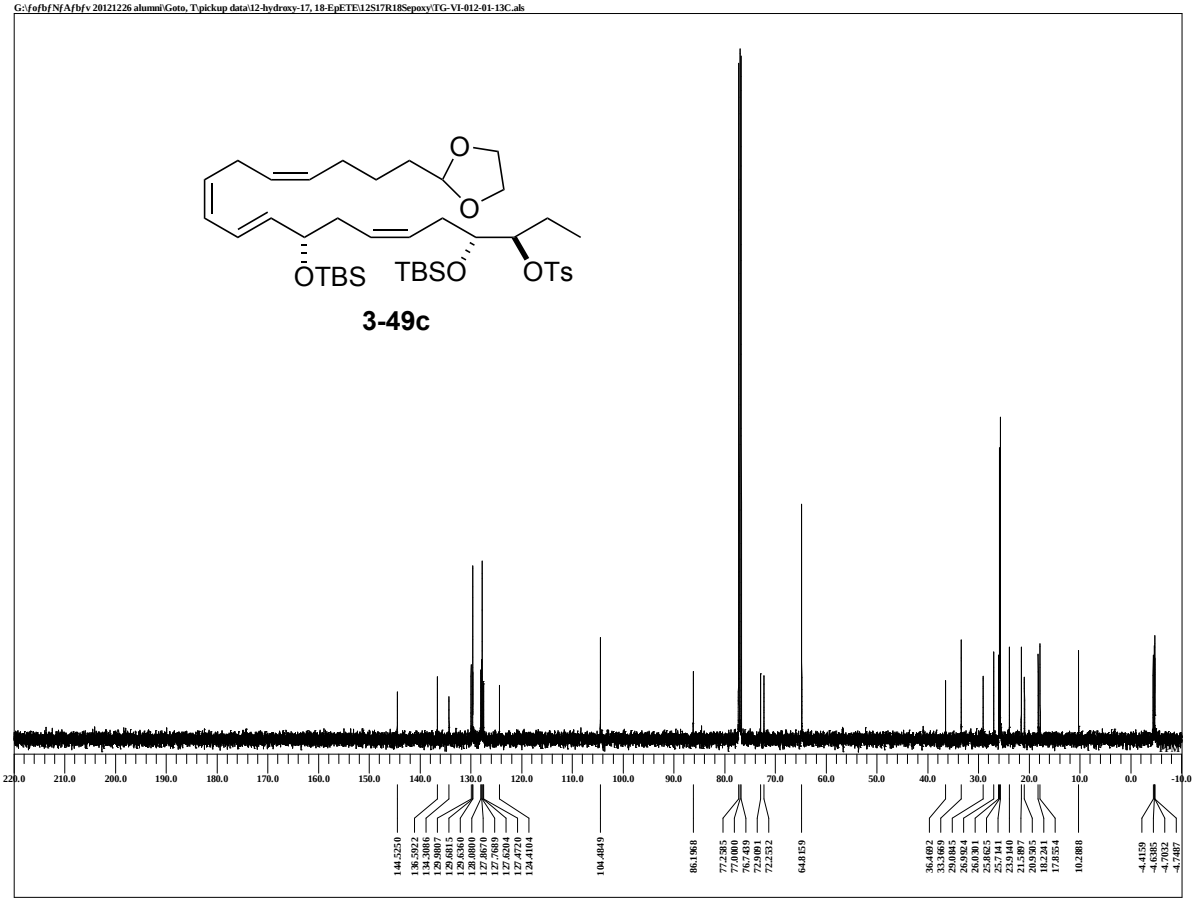

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EXPCM	
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IFR	495.13 MHz
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IRRPW	92 usec
IRATN	79
DFILE	TG-VI-012-01-13C.als
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LKSIG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.3 c
SLVNT	CDCL3
EXREF	77.00 ppm

謝辞

本研究を遂行するにあたり、懇切丁寧かつ的確にご指導くださり、また豊富な知識と経験に基づくご鞭撻を賜りました東京大学大学院薬学系研究科　井上　将行　教授に心より感謝致します。

本研究に関して、東京大学での貴重な学びの機会を与えてくださいました塩野義製薬株式会社　花崎　浩二　経理財務部長に深く感謝致します。

本研究の遂行にあたり、実験の手技や進め方をご指導いただき、また研究の本質、面白さ、研究に向き合う姿勢など本研究内容に留まらず、研究者として成長を促してくださいました東京大学大学院薬学系研究科　占部　大介　講師に感謝致します。

本研究の遂行にあたり、有益なご指導、ご助言を賜りました大阪大学大学院理学研究科　松岡　茂　特任准教授、山口大学大学院理工学研究科　上條　真　准教授、北海道大学大学院薬学研究院　倉永　健史　講師、東京大学大学院薬学系研究科　長友　優典　助教に深謝致します。

本研究の遂行にあたり、共同研究者として多くのご助言を賜り、また合成化合物を用いて天然物の立体化学を決定していただき、抗炎症活性試験を行っていただきました東京大学大学院薬学系研究科　新井　洋由　教授、理化学研究所　統合生命医科学研究センター　有田　誠　チームチームリーダー、磯部　洋輔　基礎科学特別研究員に感謝致します。

本研究の遂行にあたり、産学共同研究の推進にご尽力いただき、格別なご指導、ご助言を賜りました塩野義製薬株式会社　医薬研究本部　吉岡　健　博士、増田　功嗣　氏、藤原　拓司　氏に心より感謝致します。

本研究の遂行にあたり、温かく受け入れてくださり、常に快く助けてくださいました有機反応化学教室の皆様に感謝致します。

研究者になる志をご教授くださり、博士号取得に関しても常に応援し続けてくださいました東北大学大学院生命科学研究科　佐々木　誠　教授、不破　春彦　准教授に深謝致します。

最後に、私のやりたいことを尊重し、常に励まし、温かく見守ってくれている家族と友人に心から感謝します。

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Total Synthesis of Four Stereoisomers of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-Dihydroxy-4,7,10,12,16,18-docosahexaenoic Acid and Their Anti-inflammatory Activities

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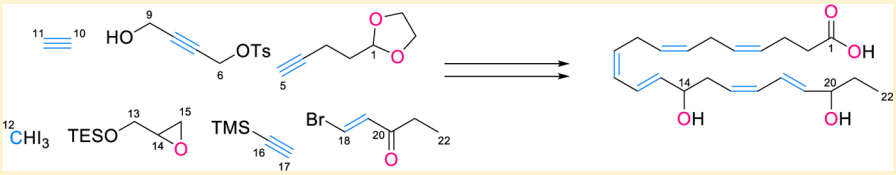
Supporting Information



ABSTRACT: A novel anti-inflammatory lipid mediator, (4*Z*,7*Z*,10*Z*,12*E*,14*S*,16*Z*,18*E*,20*R*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid (**1aa**), and its three C14,C20 stereoisomers (**1ab,ba,bb**) were synthesized in a convergent fashion. The carbon backbone of the target compounds was assembled from seven simple fragments by employing two Sonogashira coupling and three S_N2 alkynylation reactions. The thus constructed four internal alkynes were chemoselectively reduced to the corresponding (*Z*)-alkenes by applying a newly developed stepwise protocol: (i) hydrogenation of the three alkynes using Lindlar catalyst and (ii) formation of the dicobalt hexacarbonyl complex from the remaining alkyne and subsequent reductive decomplexation. The synthetic preparation of the stereochemically defined four isomers **1aa,ab,ba,bb** permitted determination of the absolute structure of the isolated natural product to be **1aa**. Biological testing of the four synthetic 14,20-dihydroxydocosahexaenoic acids disclosed similar anti-inflammatory activities of the non-natural isomers (**1ab,ba,bb**) and the natural form (**1aa**).

INTRODUCTION

Endogenous lipid mediators control acute or innate inflammatory response toward microorganisms or tissue injury and play an important role in the active resolution phase of inflammation for protecting organs from collateral damage.[1] Metabolites of omega-3 polyunsaturated fatty acids (e.g., docosahexaenoic acid (DHA)) have attracted significant attention as lipid mediators, as they exhibit in vivo anti-inflammatory activities (Figure 1).[2,3] Maresin 1[4] is a representative lipid mediator, and its intriguing structural features, such as a (*E*,*E*,*Z*)-triene and two allylic hydroxy groups, are biosynthetically constructed from DHA.

The structure determination of these biologically important lipid mediators has been highly challenging. Whereas UV spectroscopic and LC-MS/MS analyses are effective in deducing planar structures of lipid mediators, stereochemical assignments of the double bonds and hydroxy groups by detailed NMR analyses have been hampered due to the scarce availability of lipid mediators from natural sources. Accordingly, practical preparation of all the stereoisomers by stereoselective total synthesis is necessary in order to establish the absolute structure of the lipid mediators.[5,6]

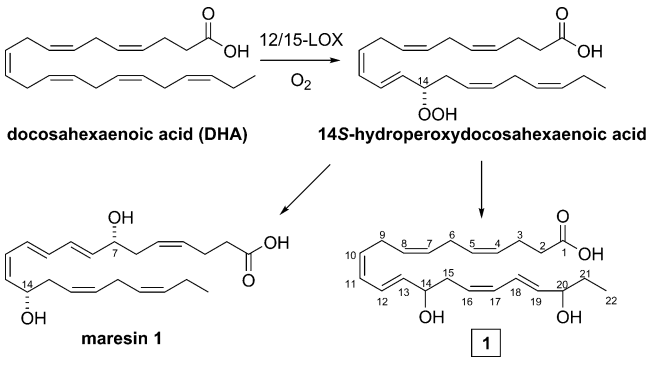


Figure 1. Structures of DHA and anti-inflammatory active lipid mediators and the possible biosynthetic pathway of maresin 1 and **1** from DHA.

Recently, we identified a novel anti-inflammatory metabolite of DHA (**1**; Figure 1), produced by eosinophils during the resolution phase of a mouse acute inflammation model.[7]

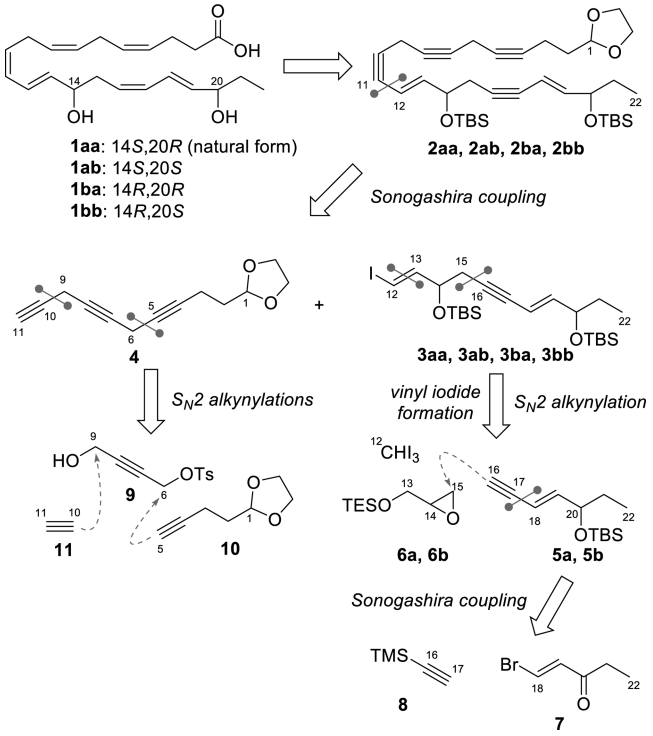
Received: June 27, 2015
Published: July 14, 2015

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

Biological tests revealed that nanomolar concentrations of **1** inhibited infiltration of polymorphonuclear (PMN) leukocytes in a zymosan-induced mouse peritonitis model. The planar structure of **1** was tentatively assigned as (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid from UV and LS-MS/MS analysis of the minute amount of sample available. *E* regiochemistries at C12 and C18 were also suggested from the biogenetic oxidation pathway of **1**. Additionally, the C14 configuration of **1** was speculated to be *S*, because biosynthetic production of both **1** and maresin 1 was shown to involve 12/15-lipoxygenase (LOX)-promoted oxidation of DHA to 14*S*-hydroperoxydocosahexaenoic acid.[4a,7]

We set about unambiguously establishing the absolute structure of naturally occurring **1** by synthesizing the four possible stereoisomers at the C14- and C20-hydroxy groups. Here we report the detailed stereoselective total synthesis of the four stereoisomers of **1**, (14*S*,20*R*)-, (14*S*,20*S*)-, (14*R*,20*R*)-, and (14*R*,20*S*)-14,20-dihydroxydocosahexaenoic acids (**1aa**,**ab**,**ba**,**bb**; Scheme 1). HPLC analysis of the natural

Scheme 1. Synthetic Plan of the Four Stereoisomers of 1



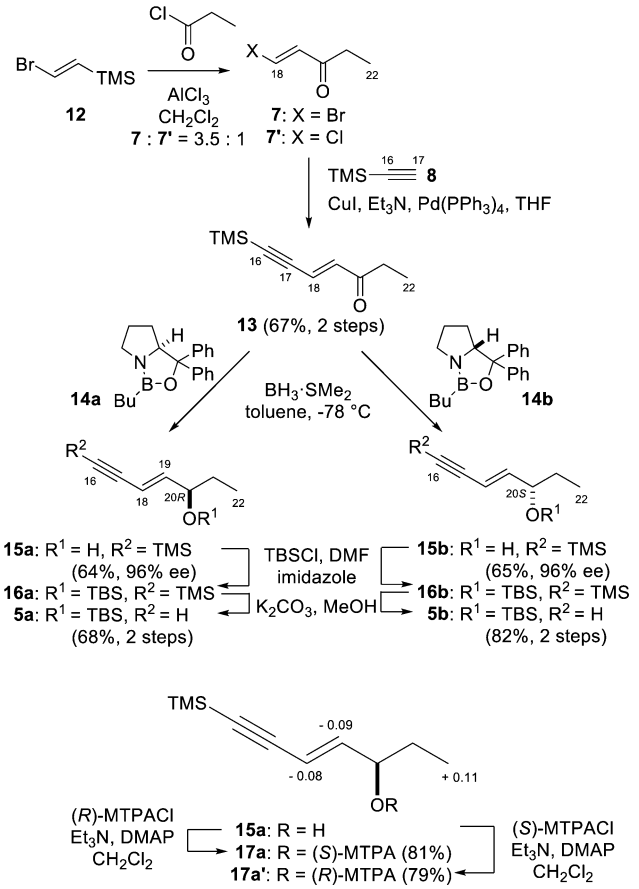
and synthetic compounds established the absolute structure of natural **1** to be **1aa** with the 14*S*,20*R* configuration. Furthermore, a structure–activity relationship (SAR) study of the four isomers disclosed similar anti-inflammatory activities of the synthesized natural (**1aa**) and non-natural compounds (**1ab**,**ba**,**bb**).

RESULTS AND DISCUSSION

To establish a unified synthetic route to the four stereoisomers of 14,20-dihydroxydocosahexaenoic acid (**1aa**,**ab**,**ba**,**bb**), we designed a convergent strategy using two chiral fragments (**5a**/**5b**, **6a**/**6b**), three achiral fragments (**9**–**11**), and iodoform (Scheme 1). 14,20-Dihydroxydocosahexaenoic acid (**1**) was first retrosynthetically converted to tetrayne **2**, which possesses the four internal alkynes as surrogates of the requisite (*Z*)-alkenes of **1**. Compound **2** was dissected into the halves **3** and **4**. In the synthetic direction, Sonogashira coupling between C12–C22 vinyl iodide **3** and the copper alkynide of triyne **4** was envisioned to furnish the carboskeleton of **2**. C12–C22 vinyl iodide **3** could be synthesized by S_N2 alkynylation of the lithium alkynide of **5** and TES-protected glycidol **6** and subsequent vinyl iodide formation with iodoform. The four stereoisomers **3aa**,**ab**,**ba**,**bb** of **3** could be synthesized in enantiopure form by combining the enantiomeric pairs **5a**/**5b** and **6a**/**6b**. Chiral **5a**/**5b** was to be prepared through two-carbon elongation by Sonogashira coupling between **7** and **8** and subsequent asymmetric reduction of the C20-ketone. On the other hand, achiral triyne **4** could be synthesized from **9** by sequential S_N2 alkynylation of the copper acetylides generated from **10** and **11**.

The synthesis began with preparation of enantiomers **5a**,**b** from **7** (Scheme 2). Compound **7** was obtained as an inseparable mixture with **7′** (**7**:**7′** = 3.5:1) by $AlCl_3$-promoted acylation of **12** with propionyl chloride.[8] The mixture was subjected to Sonogashira coupling using TMS-acetylene **8**, CuI, and $Pd(PPh_3)_4$ to produce the C16–C22 carbon chain **13**.[9] The chiral complex of $BH_3{\cdot}SMe_2$ and (*S*)-2-butyl-CBS-oxazaborolidine **14a** in turn induced the asymmetric reduction

Scheme 2. Synthesis of C16–C22 Fragments 5a,b through Asymmetric Reduction and Determination of the Absolute Stereochemistry of the C20 Position[a]



[a]The values on the lowermost structure are the differences ($\Delta\delta$) in ^{1}H chemical shifts between **17a** and **17a′** ($\Delta\delta = \delta(\mathbf{17a}) - \delta(\mathbf{17a'})$) in $CDCl_3$.

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713–7726

of the C20-ketone of **13** to produce the optically active **15a** in 96% ee.[10,11] Protection of the C20-hydroxy group of **15a** as its TBS ether, followed by removal of the C16-TMS group under basic conditions, afforded the requisite C16−C22 fragment (20*R*)-**5a**. Alternative use of (*R*)-2-butyl-CBS-oxazaborolidine **14b** in the reduction of **13** led to **15b** (96% ee), which was converted to the C16−C22 fragment (20*S*)-**5b** using the above two-step protocol. The C20 absolute configurations of **5a,b** were established by application of the modified Mosher method to **15a**.[12] Namely, **15a** was transformed to (*S*)-MTPA ester **17a** and (*R*)-MTPA ester **17a′**. The difference in the ^{1}H NMR chemical shifts between **17a** and **17a′** confirmed the 20*R*-configuration of **15a**.

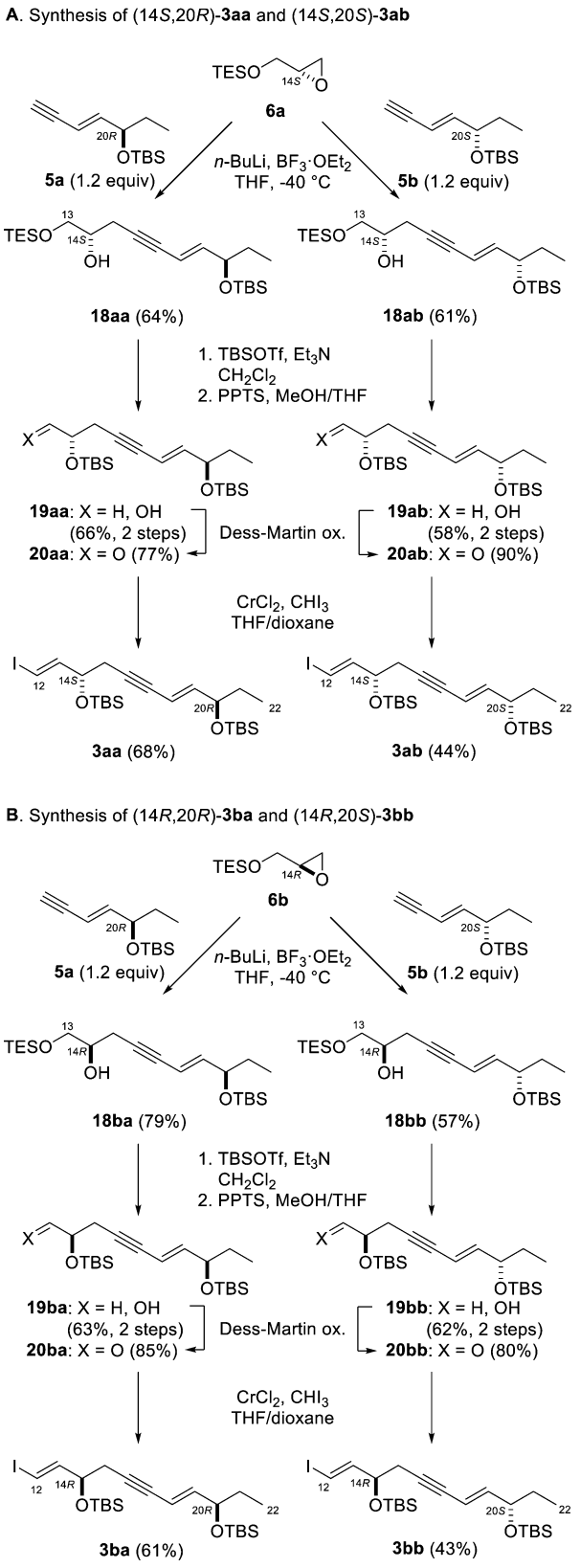
Parts A and B of Scheme 3 show the synthesis of the four C12−C22 fragments **3aa,ab,ba,bb**. The lithium alkynides, which were prepared from (20*R*)-**5a** and (20*S*)-**5b** using *n*-BuLi, reacted with TES-protected glycidol (14*S*)-**6a**[13] in the presence of $BF_3{\cdot}OEt_2$, resulting in formation of (14*S*,20*R*)-**18aa** and (14*S*,20*S*)-**18ab**, respectively.[14] The obtained **18aa,ab** were transformed to aldehydes **20aa,ab**, respectively, by the following three steps: (i) TBS protection of the C14-hydroxy group, (ii) chemoselective removal of the TES group, and (iii) Dess−Martin oxidation[15] of the resulting C13-primary alcohol. Next, treatment of aldehydes **20aa,ab** with CHI_3 and $CrCl_2$[16] in THF and 1,4-dioxane[17] resulted in formation of the (*E*)-vinyl iodide of C12−C22 fragments (14*S*,20*R*)-**3aa** and (14*S*,20*S*)-**3ab**, respectively.[18] The stereoisomers (14*R*,20*R*)-**3ba** and (14*R*,20*S*)-**3bb** were synthesized by following the same five-step transformation from TES-protected glycidol (14*R*)-**6b**.

C1−C11 fragment **4** was synthesized from the known **9**[19] and **10**[20] through two Cu-mediated S_N2 alkynylations (Scheme 4). The copper alkynide was formed from C1−C5 alkyne **10** by the action of CuI and Cs_2CO_3[21] and attached on C6 of propargyl tosylate **9** to produce C1−C9 diyne **21**. The C9-hydroxy group of **21** was then converted to the corresponding bromide by treatment with CBr_4 and $(PPh_2CH_2)_2$.[22] The second S_N2 alkynylation between **22** and ethynylcopper, derived from ethynylmagnesium bromide **11′** and CuCl, furnished C1−C11 triyne **4**.

Next, the entire carbon backbone of **1** was assembled by Sonogashira coupling between the four stereoisomeric C12−C22 fragments and the C1−C11 fragment (Scheme 5). Compounds **3aa,ab,ba,bb** were separately subjected to C1−C11 fragment **4** (1.2−1.5 equiv) and CuI in the presence of catalytic $Pd(PPh_3)_4$, delivering tetraynes **2aa,ba,ab,bb**, respectively. Hence, a series of C−C bond formations using metal alkynides successfully transformed the simple fragments into the functionalized carbon structure of **1** bearing the four triple bonds.

The most challenging task in the synthesis of **1** was reduction of the four alkynes to the corresponding *Z*-alkenes, because the chemoselective reductions should be realized without over-reduction of the C12−C13 and C18−C19 (*E*)-alkenes and the generating (*Z*)-alkenes (Scheme 6). To achieve the requisite conversion, reagents and conditions were tuned using **2aa** as the substrate. Lindlar reduction[23] of **2aa** in the presence of quinoline in hexane at room temperature resulted in generation of a mixture of desired hexaene **23aa** (30% yield) and over-reduced products.[24] Contamination of **23aa** with the over-reduced byproducts at this stage was found to be problematic. Purification of the final product **1aa** was not possible using various chromatographic methods when the contaminated **23aa** was subjected to the last three steps.[25] Thus, further efforts to produce pure **23aa** were pursued. Optimization of the amount of Lindlar catalyst (300 wt %), quinoline (12 equiv), reaction time (100 min), and temperature (0 °C) allowed selective reduction of three (C4−C5, C7−C8, and C10−C11) of the

Scheme 3. Synthesis of Four C12−C22 Fragments 3aa,ab,ba,bb



DOI: 10.1021/acs.joc.5b01461
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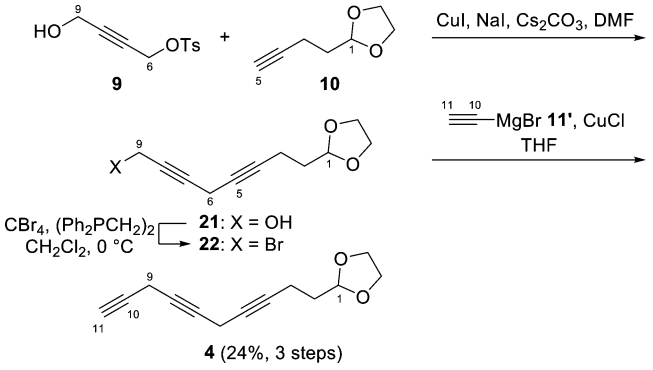
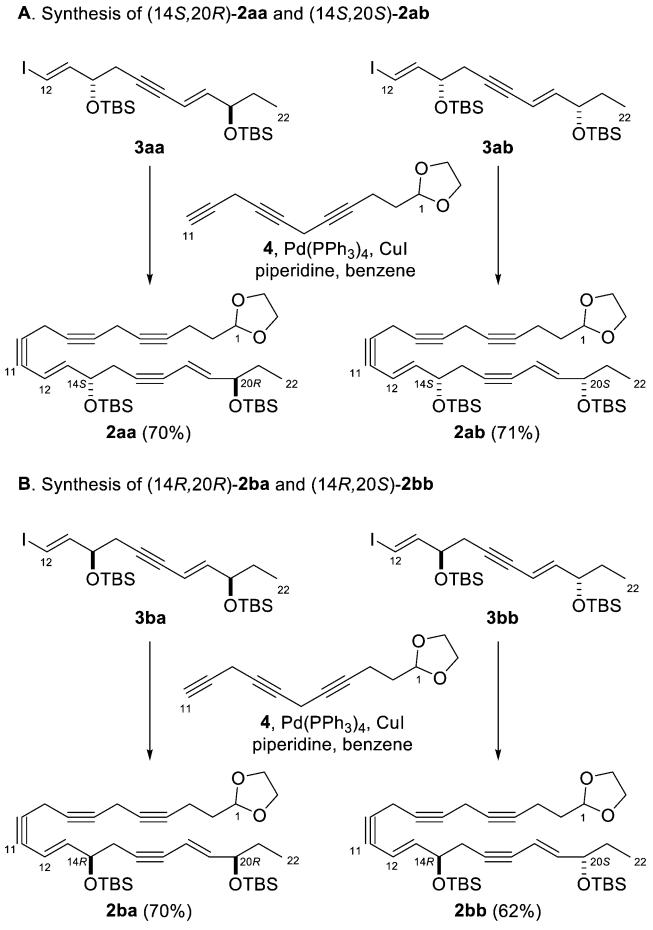
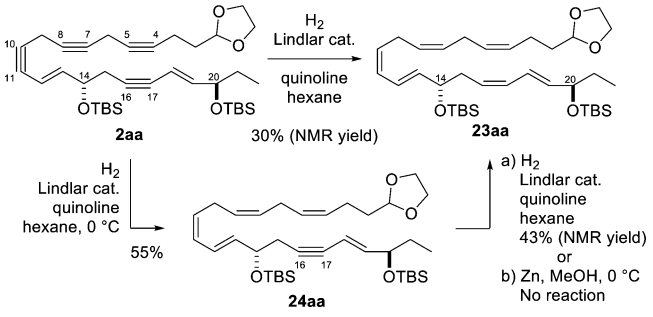
Scheme 4. Synthesis of C1−C11 Triyne 4



Scheme 5. Assembly of the Carbon Backbone of 1



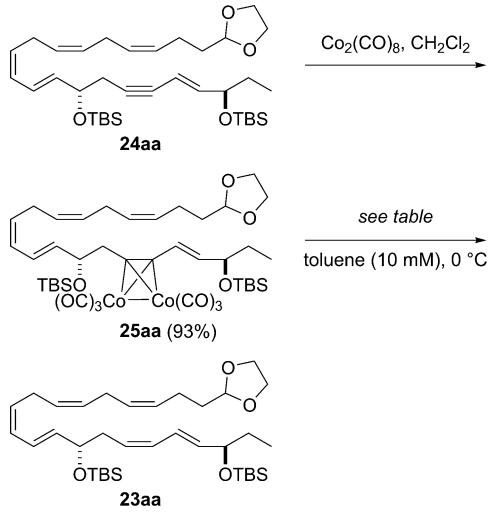
Scheme 6. Chemoselective Reduction of Tetrayne 2aa to Monoyne 24aa



four alkynes to generate pure **24aa**. Consequently, the C16−C17 alkyne, sterically protected by the neighboring bulky C14-TBS ether, was more resistant to hydrogenation than the other three triple bonds. Indeed, reduction of the remaining C16−C17 alkyne of **24aa** with Lindlar catalyst under more forceful conditions only produced a mixture of **23aa** and over-reduced products, while the alternative use of Cu/Ag-activated Zn in MeOH[26] with **24aa** did not induce the requisite reduction.

A more powerful yet chemoselective method was required to obtain pure **23aa** from **24aa**. Numerous unsuccessful attempts to hydrogenate **24aa** led us to note the mechanistically distinct reductive protocol reported by Isobe and co-workers.[27,28] They demonstrated that treatment of alkyne dicobalt hexacarbonyl complexes with *n*-Bu_3SnH at elevated temperature afforded the corresponding (*Z*)-alkenes. This protocol was indeed applicable to transformation of **24aa** to **23aa** (Table 1). The alkyne

Table 1. Synthesis of Hexaene 23aa by Isobe Reduction[a]



entry	reductant	additive	temp, °C	yield, %
1	*n*-Bu_3SnH	none	65	41[b]
2	*n*-Bu_3SnH	*N*-methylmorpholine oxide	0	86
3	Ph_3SnH	*N*-methylmorpholine oxide	0	94
4	$(TMS)_3SiH$	*N*-methylmorpholine oxide	0	18[c]
5[d]	$NaH_2PO_2·H_2O$	*N*-methylmorpholine oxide	0	48[b]

[a]Conditions: **25aa** (1 equiv), reductant (15 equiv), additive (10 equiv), toluene (10 mM), 0 °C. [b]Yield was calculated by ^1H NMR analysis of a mixture of **23aa**, **24aa**, and over-reduced compounds. [c]Yield was calculated by ^1H NMR analysis of a mixture of **23aa**, **24aa**, and hydrosilylated products. [d]Methoxyethanol was used as a solvent.

dicobalt hexacarbonyl complex **25aa** was first prepared by treatment of **24aa** with $Co_2(CO)_8$ and then was submitted to the original conditions (*n*-Bu_3SnH (10 equiv), 65 °C, toluene, entry 1),[27] leading to hexaene **23aa** in 41% yield. Despite generation of **23aa**, the reaction suffered from decomposition and over-reduction. Thus, milder reaction conditions needed to be realized by accelerating the reductive decomplexation step.

N-Methylmorpholine oxide is known to increase the rate of the Pauson−Khand reaction of an alkyne dicobalt hexacarbonyl complex.[29] It is widely accepted that reaction between an amine oxide and cobalt-coordinating carbon monoxide generates a coordinately unsaturated cobalt species, which triggers the Pauson−Khand reaction at low temperature.[30] Accordingly, we speculated that *N*-methylmorpholine oxide would strongly promote the reductive decomplexation of **25aa** through

DOI: 10.1021/acs.joc.5b01461
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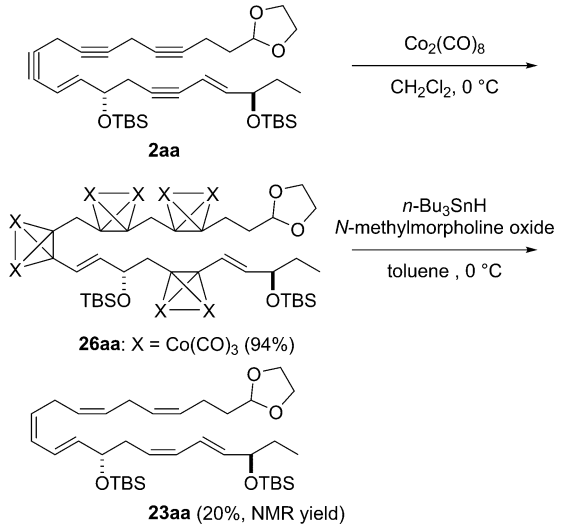
decarbonylation of the complex.[31] When *N*-methylmorpholine oxide (10 equiv) was added to the reaction mixture (Table 1, entry 2), the reaction of **25aa** proceeded at 0 °C to afford pure **23aa** in 86% yield. Importantly, no decomposition of **23aa**/**24aa** or over-reduction was observed under these conditions. Screening of the reductants clarified that *n*-Bu_3SnH and Ph_3SnH (entries 2 and 3) were superior to $(TMS)_3SiH$ and $NaH_2PO_2{\cdot}H_2O$[32] (entries 4 and 5). Because residual Ph_3SnH could not be separated from **23aa**, entry 2 was chosen as the optimized conditions for synthesis of pure hexaene **23aa**.

Thus, a combination of the Lindlar reduction and modified Isobe reaction successfully converted tetrayne **2aa** to pure hexaene **23aa** by the intermediacy of monoyne **24aa**. It is noteworthy that direct application of tetrayne **2aa** to the Co-complexation/decomplexation protocol was much less effective (Scheme 7). Although complex **26aa** was smoothly formed

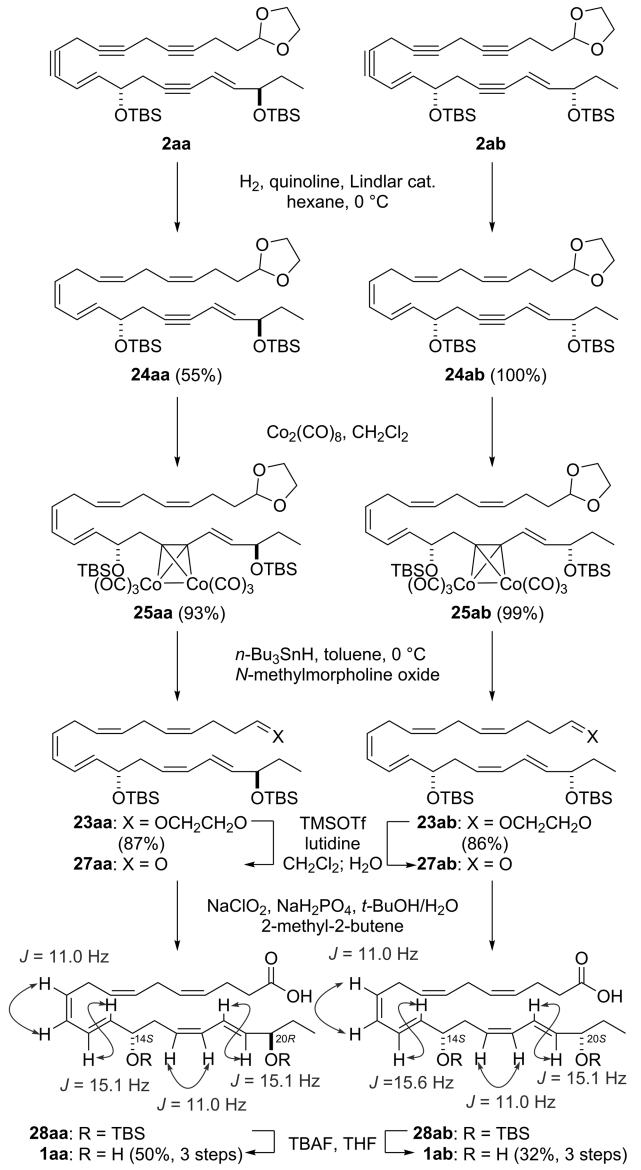
Scheme 7. Attempted Isobe Reduction of 2aa



from **2aa** and $Co_2(CO)_8$, reductive decomplexation of **26aa** using *n*-Bu_3SnH and *N*-methylmorpholine oxide produced **23aa** in only poor yield along with the over-reduced products. The observed byproducts were attributable to reduction of the less sterically shielded olefins by in situ generated cobalt hydride species.[33]

As with **2aa**, the optimized Lindlar and Isobe reductions were applied to stereoisomer tetrayne **2ab** (Scheme 8). Hydrogenation of tetrayne **2ab** produced monoyne **24ab**, which was then converted to the alkyne dicobalt hexacarbonyl complex and treated with *n*-Bu_3SnH and *N*-methylmorpholine oxide to provide **23ab**. Total synthesis of **1aa**/**1ab** was completed from the obtained hexaene **23aa**/**23ab** in three steps.[5] Specifically, the cyclic acetal of hexaene **23aa** and **23ab** was selectively removed in the presence of acid-sensitive TBS ethers under Kita−Fujioka conditions (TMSOTf and 2,6-lutidine; aqueous workup), leading to **27aa,ab**, respectively.[34] After oxidation of aldehydes **27aa,ab** to the carboxylic acids **28aa,ab** with $NaClO_2$, removal of the two TBS groups with TBAF delivered (14*S*,20*R*)-**1aa** and (14*S*,20*S*)-**1ab**, respectively. The $^1H-^1H$ coupling constants confirmed no geometric isomerization from the (*E*,*Z*)-diene to the more stable (*E*,*E*)-diene under this series of reaction conditions. As shown in Scheme 9, two other stereoisomers of **1aa**, (14*R*,20*R*)-**1ba** and (14*R*,20*S*)-**1bb**, were also synthesized by application of the same 6-step sequence to

Scheme 8. Total Synthesis of (14*S*,20*R*)-1aa and (14*S*,20*S*)-1ab



2ba and **2bb**. Hence, the total synthesis of all the stereoisomers of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-4,7,10,12,16,18-docosahexaenoic acid was accomplished. HPLC analysis of DHA-derived natural **1** and the synthetic **1aa,ab,ba,bb** established the absolute structure of natural **1** to be (14*S*,20*R*)-**1aa**.[7,35]

We evaluated the anti-inflammatory activity of synthetic (14*S*,20*R*)-**1aa**, (14*S*,20*S*)-**1ab**, (14*R*,20*R*)-**1ba**, and (14*R*,20*S*)-**1bb** using an in vivo inflammation model (Figure 2).[36] Zymosan A, a glucan from the yeast cell wall, was used to induce acute peritonitis in mice. Intravenous administration of the four compounds at a concentration as low as 1 ng significantly blocked the infiltration of PMN leucocytes at 2 h in the inflamed peritoneal cavity. Importantly, all of the artificial isomers **1ab,ba,bb** displayed the same level of anti-inflammatory activity as the natural form (**1aa**), indicating the inconsequential nature of the stereochemistries of the two hydroxy groups of (4*Z*,7*Z*,10*Z*,12*E*,16*Z*,18*E*)-14,20-dihydroxy-

DOI: 10.1021/acs.joc.5b01461
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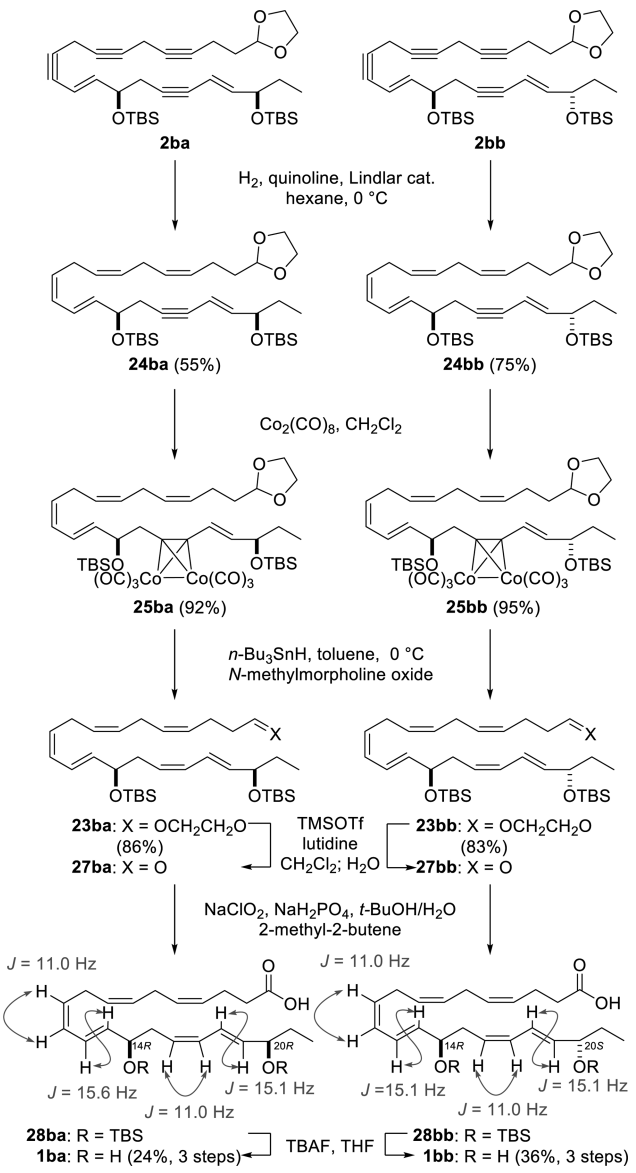
Scheme 9. Total Synthesis of (14*R*,20*R*)-1ba and (14*R*,20*S*)-1bb



4,7,10,12,16,18-docosahexaenoic acid for potent anti-inflammatory activity.

CONCLUSION

We established a unified route to the four stereoisomers of the new lipid mediator **1**, (14*S*,20*R*)-**1aa**, (14*S*,20*S*)-**1ab**, (14*R*,20*R*)-**1ba**, and (14*R*,20*S*)-**1bb**, from the six simple fragments **6**−**11** and iodoform in 16 longest linear steps and 19 overall steps. These total syntheses allowed the absolute structure of the naturally occurring **1** to be determined as **1aa**, and the anti-inflammatory activities of all four stereoisomers were shown to be equipotent for the first time. The key features of the synthesis route include (i) enantioselective reduction of the C20-ketone with chiral 2-butyl-CBS-oxazaborolidines for the synthesis of C16−C22 fragments **5a**,**b**, (ii) construction of the carbon backbone of **1** by employing two Sonogashira couplings and three S_N2 alkynylations, and (iii) chemoselective formation of the four (*Z*)-alkenes by stepwise reduction using Lindlar reduction of the three alkynes (C4−C5, C7−C8, and

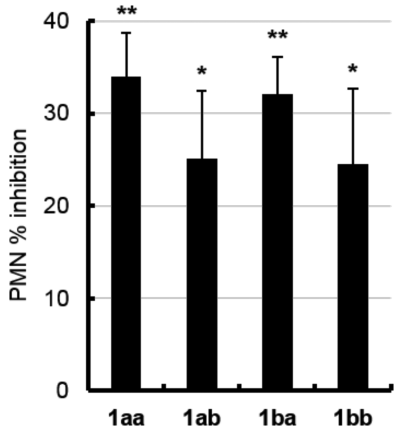


Figure 2. Bioassay of synthetic **1aa**,**ab**,**ba**,**bb**. The compounds (1 ng) were injected intravenously through the tail vein, followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected and the number of PMN leucocytes was counted. Values represent mean ± SE, $n \geq 3$ (*P < 0.05, **P < 0.01), versus vehicle control.

C10−C11) and modified Isobe reduction of the remaining C16−C17 alkyne. Construction of the (*Z*)-alkene from the sterically shielded alkyne by combining Co-complexation and reductive decomplexation should have wider application for the chemoselective preparation of various (*Z*)-alkenes beyond this target. Further studies toward functional analysis of **1aa** and the non-natural isomers are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out under an argon atmosphere in dry solvents, unless otherwise noted. THF, CH_2Cl_2, and toluene were purified by a Glass Contour solvent dispensing system. Et_3N and piperidine were purified by distillation over CaH_2. $BF_3{\cdot}OEt_2$ was purified by distillation over P_2O_5. All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel (spherical, neutral, 40−50 μm; granular, neutral, 32−53 μm; spherical, carboxylic acid supported (Chromatorex-ACD COOH), 45−75 μm). Medium-pressure liquid chromatography was carried out by using a system equipped with prepacked silica gel 40 μm (45 g (26 × 150 mm) or 120 g (46 × 130 mm)). Optical rotations were measured using the sodium D line. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using an FT/IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 or 500 MHz and 100 or 150 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ for ^1H NMR (δ 7.26), $CDCl_3$ for ^{13}C NMR (δ 77.0), C_6HD_5 for ^1H NMR (δ 7.16), C_6D_6 for ^{13}C NMR (δ 128.06), CD_2HOD for ^1H NMR (δ 3.31), and CD_3OD for ^{13}C NMR (δ 49.0) as internal references. Signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. High-resolution mass spectra were measured on ESI-TOF and DART-TOF mass spectrometers.

(*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-one (13). A solution of propionyl chloride (1.86 g, 20.1 mmol) in CH_2Cl_2 (30 mL) and a solution of **12** (3.00 g, 16.8 mmol) in CH_2Cl_2 (30 mL) were successively added to a solution of $AlCl_3$ (2.69 g, 20.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h, and then saturated aqueous NH_4Cl (70 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (50 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium-pressure liquid chromatography on silica gel (45 g, pentane to pentane/Et_2O 16/1) to afford a 3.5/1 mixture of bromide **7** and

DOI: 10.1021/acs.joc.5b01461
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chloride 7′ along with pentane and Et_2O (3.05 g), which was used in the next reaction without further purification due to the volatility of 7.

$Pd(PPh_3)_4$ (528 mg, 0.457 mmol), CuI (174 mg, 0.916 mmol), Et_3N (5.3 mL, 38 mmol), and (trimethylsilyl)acetylene **8** (4.3 mL, 30 mmol) were successively added to a solution of the above 3.5/1 mixture of 7 and 7′ at room temperature. The reaction mixture was stirred at room temperature for 2.5 h. After the reaction mixture was cooled to 0 °C, saturated aqueous NH_4Cl (50 mL) was added. The resultant mixture was extracted with Et_2O (50 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (120 g, pentane to pentane/Et_2O 16/1) to afford **13** (2.74 g, 11.2 mmol, a 5/1.5/1 mixture of ketone **13**, Et_2O, and pentane). The yield of **13** was determined to be 67% over two steps by the ^1H NMR analysis of the mixture. For characterization of **13**, the residual solvents of the above mixture were completely removed: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 2.56 (q, J = 7.3 Hz, 2H), 1.10 (t, J = 7.3 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 137.7, 122.4, 105.5, 101.9, 34.3, 7.8, −0.5 (×3); IR (neat) ν 2962, 2940, 2902, 1692, 1677, 1596, 1252, 1081, 1020 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}OSiNa$ 203.0863 $[M + Na]^+$, found 203.0864.

(*R*,*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol (15a). $BH_3{\cdot}Me_2S$ (1.5 mL, 16 mmol) was added to a solution of (*S*)-2-butyl-CBS-oxazaborolidine **14a** (1.0 M solution in toluene, 14 mL, 14 mmol) in toluene (46 mL) at room temperature. The mixture was stirred at room temperature for 30 min. After the mixture was cooled to −78 °C, a solution of **13** (2.42 g, 7.41 mmol, a 27/53/1 mixture of **13**, pentane and Et_2O) in toluene (23 mL) was added over 35 min. The reaction mixture was stirred at −78 °C for 1 h, and then 0.4 M aqueous HCl (60 mL) was added. The mixture was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (100 and 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium-pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 5/1) to afford **15a** (868 mg, 4.77 mmol) in 64% yield. The enantiopurity of **15a** was determined to be 96% ee by the ^1H NMR analysis of the corresponding MTPA ester: colorless oil; $[\alpha]_D^{28}$ −4.2 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (dd, J = 16.0, 6.0 Hz, 1H), 5.73 (dd, J = 16.0, 1.4 Hz, 1H), 4.09 (m, 1H), 1.57 (qd, J = 7.3, 6.0 Hz, 2H), 1.46 (d, J = 4.6 Hz, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 110.0, 103.1, 95.1, 73.5, 29.8, 9.5, −0.12 (×3); IR (neat) ν 3357, 2962, 2935, 2877, 2155, 2130, 1457, 1250 cm^{-1}; HRMS (DART) calcd for $C_{10}H_{19}OSi$ 183.1200 $[M + H]^+$, found 183.1208.

(*S*,*E*)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol (15b). According to the synthetic procedure of **15a**, **15b** (965 mg, 5.30 mmol) was synthesized from **13** (2.82 g, 8.65 mmol, a 27/53/1 mixture of **13**, pentane, and Et_2O) in 65% yield by using (*R*)-2-butyl-CBS-oxazaborolidine **14b** (1.0 M solution in toluene, 16.3 mL, 16.3 mmol) and $BH_3{\cdot}Me_2S$ (1.8 mL, 18 mmol) in toluene (83 mL). Purification was performed twice by medium-pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 6/1; 45 g, hexane to hexane/EtOAc 6/1). The enantiopurity of **15b** was determined to be 96% ee by the ^1H NMR analysis of the corresponding MTPA ester: colorless oil; $[\alpha]_D^{30}$ +4.3 (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}OSi$: C, 65.87; H, 9.95. Found: C, 66.04; H, 9.71. The other analytical data of **15b** were identical with those of **15a**.

C16−C22 Fragment 5a. TBSCl (1.43 g, 9.49 mmol) was added to a solution of alcohol **15a** (864 mg, 4.75 mmol) and imidazole (1.29 g, 20.0 mmol) in DMF (47 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h, and then H_2O (100 mL) was added. The resultant solution was extracted with Et_2O (60 and 40 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude TBS ether **16a**, which was used in the next reaction without further purification.

K_2CO_3 (980 mg, 7.10 mmol) was added to a solution of the above crude TBS ether **16a** in MeOH (45 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h. After the reaction mixture was cooled to 0 °C, Et_2O (50 mL) and saturated aqueous NH_4Cl (60 mL) were successively added. The resultant mixture was extracted with Et_2O (100 and 50 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified three times by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 25/1; 30 g, hexane/EtOAc 100/1 to 50/1; 30 g, hexane to hexane/EtOAc 100/1) to afford C16−C22 fragment **5a** (718 mg, 3.21 mmol) in 68% over two steps: colorless oil; $[\alpha]_D^{24}$ +19 (*c* 0.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, J = 16.0, 6.0 Hz, 1H), 5.65 (ddd, J = 16.0, 2.3, 1.8 Hz, 1H), 4.12 (dtd, J = 6.0, 6.0, 1.8 Hz, 1H), 2.86 (d, J = 2.3 Hz, 1H), 1.52 (m, 2H), 0.90 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 107.6, 82.2, 77.2, 73.3, 30.5, 25.8 (×3), 18.2, 9.2, −4.6, −4.9; IR (neat) ν 3427, 2956, 2930, 2858, 2221, 1471, 1463, 1362, 1255 cm^{-1}. Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.42; H, 10.48.

C16−C22 Fragment 5b. According to the synthetic procedure of **5a**, **5b** (1.73 g, 7.72 mmol) was synthesized from **15b** (1.71 g, 9.40 mmol) in 82% yield over two steps by using TBSCl (2.84 g, 18.8 mmol) and imidazole (2.55 g, 37.5 mmol) in DMF (100 mL) for the first step and K_2CO_3 (1.94 g, 14.1 mmol) in MeOH (100 mL) for the second. Purification was performed twice by medium-pressure liquid chromatography on silica gel (120 g, hexane to hexane/EtOAc 30/1 to 20/1; 45 g, hexane to hexane/EtOAc 30/1 to 20/1): colorless oil; $[\alpha]_D^{24}$ −18 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.39; H, 10.48. The other analytical data of **5b** were identical with those of **5a**.

(*S*)-MTPA Ester 17a. (*R*)-MTPACl (12 μL, 64 μmol) was added to a solution of **15a** (3.0 mg, 16 μmol), Et_3N (16 μL, 0.12 mmol), and DMAP (10 mg, 82 μmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min, and then H_2O (5 mL) was added. The resultant mixture was extracted with EtOAc (5 mL × 3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 20/1) to afford (*S*)-MTPA ester **17a** (4.9 mg, 13 μmol) in 81% yield: colorless oil; ^1H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.42−7.36 (m, 3H), 6.02 (dd, J = 16.0, 7.3 Hz, 1H), 5.70 (d, J = 16.0 Hz, 1H), 5.40 (dt, J = 7.3, 6.4 Hz, 1H), 3.55 (s, 3H), 1.80−1.67 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.19 (s, 9H).

(*R*)-MTPA Ester 17a′. According to the synthetic procedure of **17a**, (*R*)-MTPA ester **17a**′ (4.1 mg, 11 μmol) was synthesized from **15a** (2.6 mg, 14 μmol) in 79% yield by using (*S*)-MTPACl (5.5 μL, 29 μmol), Et_3N (10 μL, 0.12 mmol), and DMAP (4.4 mg, 36 μmol) in CH_2Cl_2 (0.7 mL). The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 20/1): colorless oil; ^1H NMR ($CDCl_3$) δ 7.51−7.48 (m, 2H), 7.42−7.38 (m, 3H), 6.10 (dd, J = 16.0, 6.8 Hz, 1H), 5.79 (d, J = 16.0 Hz, 1H), 5.42 (td, J = 6.8, 6.8 Hz, 1H), 3.54 (s, 3H), 1.75−1.55 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H), 0.19 (9H, s).

Alcohol 18aa. *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) was added to a solution of C16−C22 fragment **5a** (714 mg, 3.19 mmol) in THF (25 mL) at −78 °C over 10 min. The mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for 30 min. After the mixture was cooled to −78 °C, $BF_3{\cdot}OEt_2$ (0.36 mL, 2.9 mmol) and a solution of glycidol derivative **6a** (503 mg, 2.68 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at −78 °C for 1 h and warmed to −40 °C over 3 h, and then saturated aqueous NH_4Cl (30 mL) was added. The resultant mixture was extracted with Et_2O (30 mL × 3), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1) and flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford alcohol **18aa** (707 mg,

DOI: 10.1021/acs.joc.5b01461
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1.71 mmol) in 64% yield: colorless oil; $[\alpha]_D^{28}$ +31 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.61 (dtd, *J* = 16.0, 1.8, 1.8 Hz, 1H), 4.08 (dtd, *J* = 6.0, 6.0, 1.8 Hz, 1H), 3.81 (m, 1H), 3.72 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.62 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.60−2.50 (m, 2H), 1.50 (qd, *J* = 7.8, 6.0 Hz, 2H), 0.97 (t, *J* = 8.2 Hz, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.8 Hz, 3H), 0.63 (q, *J* = 8.2 H, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 108.7, 85.8, 80.8, 73.6, 70.4, 65.4, 30.7, 25.8 (×3), 24.1, 18.2, 9.3, 6.7 (×3), 4.3 (×3), −4.6, −4.9; IR (neat) ν 3566, 2956, 2926, 2852, 1956, 1478, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2726.

Alcohol 18ab. According to the synthetic procedure of **18aa**, **18ab** (791 mg, 1.92 mmol) was synthesized from C16−C22 fragment **5b** (833 mg, 3.72 mmol) and glycidol derivative **6a** (596 mg, 3.17 mmol) in 61% yield by using *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol) and $BF_3{\cdot}OEt_2$ (0.41 mL, 3.3 mmol) in THF (31 mL). Purification was performed by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ −5.9 (*c* 0.98, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2716. The other analytical data of **18ab** were identical with those of **18ba**.

Alcohol 18ba. According to the synthetic procedure of **18aa**, **18ba** (760 mg, 1.84 mmol) was synthesized from C16−C22 fragment **5a** (610 mg, 2.72 mmol) and glycidol derivative **6b** (436 mg, 2.32 mmol) in 79% yield by using *n*-BuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.4 mmol) in THF (26 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{30}$ +6.2 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.61 (dtd, *J* = 16.0, 2.3, 1.4 Hz, 1H), 4.08 (dtd, *J* = 6.0, 5.5, 1.4 Hz, 1H), 3.81 (m, 1H), 3.72 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.60−2.50 (m, 2H), 1.50 (qd, *J* = 7.3, 5.5 Hz, 2H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 108.7, 85.8, 80.8, 73.6, 70.4, 65.3, 30.7, 25.8 (×3), 24.1, 18.2, 9.3, 6.7 (×3), 4.3 (×3), −4.5, −4.9; IR (neat) ν 3429, 2956, 2931, 2877, 1463, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2744.

Alcohol 18bb. According to the synthetic procedure of **18aa**, **18bb** (777 mg, 1.88 mmol) was synthesized from C16−C22 fragment **5b** (867 mg, 3.87 mmol) and glycidol derivative **6b** (624 mg, 3.32 mmol) in 57% yield by using *n*-BuLi (1.6 M in hexane, 2.6 mL, 4.2 mmol) and $BF_3{\cdot}OEt_2$ (0.43 mL, 3.5 mmol) in THF (37 mL). Purification was performed by medium-pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{24}$ −32 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2713. The other analytical data of **18bb** were identical with those of **18aa**.

Alcohol 19aa. TBSOTf (0.43 mL, 1.9 mmol) was added to a solution of alcohol **18aa** (704 mg, 1.70 mmol) and Et_3N (0.60 mL, 4.3 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 and 20 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) to afford the crude TBS ether, which was used in the next reaction without further purification.

PPTS (37 mg, 0.15 mmol) was added to a solution of the above crude TBS ether in a mixture of MeOH (15 mL) and THF (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min. After the reaction mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with Et_2O (50 and 20 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified three times by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 9/1; 20 g, hexane to hexane/EtOAc 20/1) to afford TBS ether **19aa** (463 mg, 1.12 mmol) in 66% over two steps: colorless oil; $[\alpha]_D^{21}$ +21 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.60 (dtd, *J* = 16.0, 1.8, 1.4 Hz, 1H), 4.07 (tdd, *J* = 6.4, 6.0, 1.4 Hz, 1H), 3.91 (m, 1H), 3.68 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.58 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.53 (ddd, *J* = 17.0, 6.9, 1.8 Hz, 1H), 2.42 (ddd, *J* = 17.0, 6.4, 1.8 Hz, 1H), 1.50 (qd, *J* = 7.3, 6.4 Hz, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 109.1, 86.7, 81.0, 74.0, 72.0, 66.2, 31.0, 26.2 (×3), 26.1 (×3), 25.1, 18.5, 18.4, 9.6, −4.21, −4.24, −4.5, −4.6; IR (neat) ν 3449, 2955, 2929, 2857, 1471, 1461, 1362, 1255, 1113 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2709.

Alcohol 19ab. According to the synthetic procedure of **19aa**, **19ab** (453 mg, 1.10 mmol) was synthesized from alcohol **18ab** (780 mg, 1.89 mmol) in 58% yield over two steps by using Et_3N (0.66 mL, 4.7 mmol) and TBSOTf (0.48 mL, 2.1 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (40 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 20/1) for the first step, and on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{25}$ −17 (*c* 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2721. The other analytical data of **19ab** were identical with those of **19ba**.

Alcohol 19ba. According to the synthetic procedure of **19aa**, **19ba** (427 mg, 1.04 mmol) was synthesized from alcohol **18ba** (676 mg, 1.64 mmol) in 63% yield over two steps by using Et_3N (0.58 mL, 4.2 mmol) and TBSOTf (0.42 mL, 1.8 mmol) in CH_2Cl_2 (16 mL) for the first step, and PPTS (37 mg, 0.15 mmol) in a mixture of MeOH (15 mL) and THF (2.5 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step, and twice on silica gel (30 g, hexane to hexane/EtOAc 9/1; 30 g, hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{31}$ +17 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.60 (ddt, *J* = 16.0, 2.3, 1.4 Hz, 1H), 4.07 (tdd, *J* = 6.0, 6.0, 1.4 Hz, 1H), 3.91 (m, 1H), 3.68 (ddd, *J* = 11.4, 6.0, 3.7 Hz, 1H), 3.58 (ddd, *J* = 11.4, 6.0, 5.0 Hz, 1H), 2.53 (ddd, *J* = 16.9, 7.3, 2.3 Hz, 1H), 2.47 (ddd, *J* = 16.9, 6.0, 2.3 Hz, 1H), 1.87 (t, *J* = 6.0 Hz, 1H), 1.50 (qd, *J* = 7.8, 6.0 Hz, 2H), 0.904 (s, 9H), 0.895 (s, 9H), 0.86 (t, *J* = 7.8 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.6, −4.5, 9.3, 18.1, 18.2, 24.8, 25.77 (×3), 25.84 (×3), 30.7, 65.9, 71.7, 73.6, 80.7, 86.4, 108.8, 145.5; IR (neat) ν 3434, 2956, 2929, 2857, 2221, 1634, 1472, 1464, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2744.

Alcohol 19bb. According to the synthetic procedure of **19aa**, **19bb** (480 mg, 1.16 mmol) was synthesized from alcohol **18bb** (766 mg, 1.86 mmol) in 62% yield over two steps by using Et_3N (0.65 mL, 4.7 mmol) and TBSOTf (0.47 mL, 2.0 mmol) in CH_2Cl_2 (19 mL) for the first step, and PPTS (41 mg, 0.16 mmol) in a mixture of MeOH (16 mL) and THF (2.6 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 9/1) for the first step and twice on silica gel (30 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{23}$ −20 (*c* 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{44}O_3Si_2Na$ 435.2721 $[M + Na]^+$, found 435.2738. The other analytical data of **19bb** were identical with those of **19aa**.

Aldehyde 20aa. Dess−Martin periodinane (693 mg, 1.63 mmol) was added to a suspension mixture of alcohol **19aa** (449 mg, 1.09 mmol) and $NaHCO_3$ (887 mg, 10.6 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 5 h, and then H_2O (50 mL) was added. The resultant mixture was extracted with Et_2O (50 and 30 mL × 2), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1) to afford aldehyde **20aa** (343 mg, 0.835 mmol) in 77% yield: colorless oil; $[\alpha]_D^{29}$ −3.4 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.4 Hz, 1H), 6.04 (dd, *J* = 16.0, 5.5 Hz, 1H), 5.60 (br d, *J* = 16.0 Hz, 1H), 4.13 (ddd, *J* = 7.8, 5.0, 1.4 Hz, 1H), 4.07

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

(td, J = 6.0, 5.5 Hz, 1H), 2.71 (ddd, J = 16.9, 5.0, 1.8 Hz, 1H), 2.57 (ddd, J = 16.9, 7.8, 1.8 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.93 (s, 9H), 0.89 (s, 9H), 0.86 (t, J = 7.3 Hz, 3H), 0.13 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 145.9, 108.6, 85.0, 81.2, 76.2, 73.6, 30.7, 25.8 (×3), 25.7 (×3), 24.1, 18.23, 18.22, 9.3, −4.6, −4.78, −4.82, −4.9; IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2819.

Aldehyde 20ab. According to the synthetic procedure of **20aa**, **20ab** (393 mg, 0.956 mmol) was synthesized from alcohol **19ab** (437 mg, 1.06 mmol) in 90% yield by using $NaHCO_3$ (861 mg, 10.3 mmol) and Dess−Martin periodinane (677 mg, 1.60 mmol) in CH_2Cl_2 (22 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{25}$ −52 (c 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2832. The other analytical data of **20ab** were identical with those of **20ba.**

Aldehyde 20ba. According to the synthetic procedure of **20aa**, **20ba** (352 mg, 0.856 mmol) was synthesized from alcohol **19ba** (418 mg, 1.01 mmol) in 85% yield by using $NaHCO_3$ (818 mg, 10.8 mmol) and Dess−Martin periodinane (645 mg, 1.52 mmol) in CH_2Cl_2 (21 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ +47 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 1.0 Hz, 1H), 6.04 (dd, J = 16.0, 6.0 Hz, 1H), 5.60 (dd, J = 16.0, 1.8 Hz, 1H), 4.13 (ddd, J = 7.8, 5.0, 1.0 Hz, 1H), 4.08 (td, J = 6.0, 6.0 Hz, 1H), 2.71 (ddd, J = 17.0, 5.0, 1.8 Hz, 1H), 2.57 (ddd, J = 17.0, 7.8, 1.8 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.86 (t, J = 7.3 Hz, 3H), 0.136 (s, 3H), 0.132 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 146.0, 108.6, 85.0, 81.2, 76.2, 73.6, 30.7, 25.8 (×3), 25.7 (×3), 24.1, 18.2 (×2), 9.3, −4.6, −4.78, −4.82, −4.9; IR (neat) ν 2956, 2930, 2858, 1741, 1472, 1464, 1362, 1255 1117 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2851.

Aldehyde 20bb. According to the synthetic procedure of **20aa**, **20bb** (378 mg, 0.920 mmol) was synthesized from alcohol **19bb** (472 mg, 1.15 mmol) in 80% yield by using $NaHCO_3$ (904 mg, 10.8 mmol) and Dess-Martin periodinane (1.20 g, 2.83 mmol) in CH_2Cl_2 (24 mL). Purification was performed twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 9/1; 30 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{22}$ +12 (c 1.2, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{46}O_4Si_2Na$ 465.2827 [M + MeOH + Na]$^+$, found 465.2825. The other analytical data of **20bb** were identical with those of **20aa**.

C12−C22 Fragment 3aa. Iodoform (644 mg, 1.63 mmol) and a solution of aldehyde **20aa** (334 mg, 0.813 mmol) in 1,4-dioxane (13.5 mL) were successively added to a suspension of $CrCl_2$ (600 mg, 4.88 mmol) in THF (0.98 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (40 mL) and H_2O (20 mL) were successively added. The resultant mixture was extracted with Et_2O (50 and 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified twice by flash column chromatography on silica gel (40 g, hexane to hexane/EtOAc 20/1; 40 g, hexane/EtOAc 20/1) to afford **3aa** (297 mg, 0.555 mmol) in 68% yield: colorless oil; $[\alpha]_D^{31}$ +47 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dd, J = 14.8, 5.5 Hz, 1H), 6.33 (dd, J = 14.8, 1.4 Hz, 1H), 6.03 (dd, J = 16.0, 6.0 Hz, 1H), 5.61 (ddt, J = 16.0, 2.3, 1.8 Hz, 1H), 4.24 (td, J = 6.9, 5.5, 1.4 Hz, 1H), 4.08 (td, J = 6.0, 6.0 Hz, 1H), 2.49 (ddd, J = 16.9, 6.9, 2.3 Hz, 1H), 2.42 (ddd, J = 16.9, 6.9, 2.3 Hz, 1H), 1.50 (qd, J = 7.3, 6.0 Hz, 2H), 0.899 (s, 9H), 0.896 (s, 9H), 0.87 (t, J = 7.8 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.7, 108.8, 86.1, 81.1, 76.7, 74.0, 73.6, 30.7, 28.8, 25.9 (×3), 25.7 (×3), 18.22, 18.19, 9.3, −4.5, −4.7, −4.86, −4.89; IR (neat) ν 2956, 2929, 2857, 1607, 1471, 1463, 1362, 1255, 1092 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1733.

C12−C22 Fragment 3ab. According to the synthetic procedure of **3aa**, **3ab** (218 mg, 0.407 mmol) was synthesized from aldehyde **20ab** (384 mg, 0.934 mmol) in 44% yield by using iodoform (739 mg, 1.88 mmol) and $CrCl_2$ (687 mg, 5.58 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15.5 mL). Purification was performed three times by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1; 30 g, hexane to hexane/EtOAc 20/1; 30 g, hexane/CH_2Cl_2 100/1 to 20/1): colorless oil; $[\alpha]_D^{23}$ +25 (c 1.1, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1728. The other analytical data of **3ab** were identical with those of **3ba.**

C12−C22 Fragment 3ba. According to the synthetic procedure of **3aa**, **3ba** (270 mg, 0.505 mmol) was synthesized from aldehyde **20ba** (342 mg, 0.832 mmol) in 61% yield by using iodoform (657 mg, 1.67 mmol) and $CrCl_2$ (615 mg, 5.00 mmol) in a mixture of THF (1.0 mL) and 1,4-dioxane (14 mL). Purification was performed three times by flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1; 30 g, hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{31}$ −16 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (ddd, J = 14.6, 5.5 Hz, 1H), 6.33 (dd, J = 14.6, 1.4 Hz, 1H), 6.03 (dd, J = 16.0, 6.0 Hz, 1H), 5.61 (dd, J = 16.0, 1.4 Hz, 1H), 4.24 (td, J = 6.9, 5.5 Hz, 1H), 4.08 (dt, J = 6.0, 6.0 Hz, 1H), 2.49 (ddd, J = 16.9, 6.9, 1.8 Hz, 1H), 2.42 (ddd, J = 16.9, 6.9, 1.8 Hz, 1H), 1.50 (qd, J = 7.8, 6.0 Hz, 2H), 0.899 (s, 9H), 0.896 (s, 9H), 0.87 (t, J = 7.8 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.7, 108.8, 86.1, 81.0, 76.7, 74.0, 73.7, 30.7, 28.8, 25.9 (×3), 25.7 (×3), 18.23, 18.19, 9.3, −4.5, −4.7, −4.86, −4.89; IR (neat) ν 2956, 2929, 2857, 1607, 1463, 1362, 1255, 1090 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1754.

C12−C22 Fragment 3bb. According to the synthetic procedure of **3aa**, **3bb** (213 mg, 0.391 mmol) was synthesized from aldehyde **20bb** (370 mg, 0.900 mmol) in 43% yield by using iodoform (571 mg, 1.45 mmol) and $CrCl_2$ (657 mg, 5.34 mmol) in a mixture of THF (1.1 mL) and 1,4-dioxane (15 mL). Purification was performed by flash column chromatography on silica gel (40 g, hexane to hexane/CH_2Cl_2 20/1 to 12/1): colorless oil; $[\alpha]_D^{22}$ −50 (c 0.77, $CHCl_3$); HRMS (ESI) calcd for $C_{23}H_{43}IO_2Si_2Na$ 557.1738 [M + Na]$^+$, found 557.1719. The other analytical data of **3bb** were identical with those of **3aa.**

Triyne 4. A mixture of CuI (833 mg, 4.37 mmol), NaI (650 mg, 4.34 mmol), and Cs_2CO_3 (1.41 g, 4.32 mmol) was dried at 95 °C in vacuo. After the mixture was cooled to 0 °C, a solution of alcohol **9** (548 mg, 4.35 mmol) in DMF (4.0 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **10** (1.18 g, 4.91 mmol) in DMF (4.8 mL) was added. The reaction mixture was warmed to room temperature and stirred for 16 h, and then saturated aqueous NH_4Cl (20 mL) was added. The resultant solution was filtered through a pad of Celite with Et_2O, and the filtrate was extracted with Et_2O (30 and 20 mL × 2). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium-pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/2) to afford the crude diyne **21**, which was used in the next reaction without further purification.

DIPHOS (1.48 g, 3.72 mmol) and CBr_4 (827 mg, 2.49 mmol) were successively added to a solution of the above crude **21** in CH_2Cl_2 (12 mL) to 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then was directly subjected to medium-pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 8/1) to afford bromide **22**, which was immediately used in the next reaction.

CuCl (181 mg, 1.83 mmol) was dried at 90 °C in vacuo, and then THF (25 mL) was added. Ethynylmagnesium bromide (**11′**; 0.5 M in THF, 27 mL, 14 mmol) was added to the suspension at room temperature. The mixture was stirred for 10 min at room temperature, and then a solution of the above bromide **22** in THF (30 mL) was added. The reaction mixture was stirred at room temperature for 14 h, and then saturated aqueous NH_4Cl (50 mL) was added. The resultant solution was filtered through a pad of Celite, and the filtrate was extracted with EtOAc (50 and 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 20/1 to 9/1) to afford triyne **4** (228 mg, 1.04 mmol) in 24% yield over three steps. Triyne **4** was immediately used in the next reaction due to its

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

instability in air: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (t, J = 4.6 Hz, 1H), 4.00−3.91 (m, 2H), 3.91−3.82 (m, 2H), 3.17 (dt, J = 2.7, 2.3 Hz, 2H), 3.13 (tt, J = 2.3, 2.3 Hz, 2H), 2.30 (tt, J = 7.2, 2.3 Hz, 2H), 2.06 (t, J = 2.7 Hz, 1H), 1.85 (td, J = 7.3, 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.2, 79.7, 78.1, 75.5, 73.9, 73.4, 68.7, 64.9 (×2), 32.9, 13.6, 9.7, 9.6; IR (neat) ν 3287, 2887, 1413, 1317, 1138, 1038 cm^{-1}.

Tetrayne 2aa. $Pd(PPh_3)_4$ (92 mg, 80 μmol), CuI (32 mg, 0.17 mmol), a solution of C12−C22 fragment **3aa** (278 mg, 0.520 mmol) in benzene (4.5 mL), and piperidine (0.16 mL, 1.6 mmol) were successively added to a solution of **4** (157 mg, 0.777 mmol) in benzene (14 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h, and then Et_2O (10 mL) and saturated aqueous NH_4Cl (40 mL) were successively added. The resultant mixture was extracted with Et_2O (30 and 10 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 15/1) to afford tetrayne **2aa** (223 mg, 0.366 mmol) in 70% yield. Tetrayne **2aa** was immediately used in the next reaction due to its instability in air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 6.20 (dd, J = 15.6, 5.5 Hz, 1H), 6.16 (dd, J = 15.6, 5.5 Hz, 1H), 5.87−5.78 (m, 2H), 4.87 (t, J = 5.0 Hz, 1H), 4.16 (td, J = 6.0, 5.5 Hz, 1H), 3.91 (td, J = 6.0, 5.5 Hz, 1H), 3.47−3.38 (m, 2H), 3.33−3.25 (m, 2H), 2.94 (s, 2H), 2.85 (br s, 2H), 2.41 (dd, J = 16.0, 6.9 Hz, 1H), 2.30 (dd, J = 16.0, 6.4 Hz, 1H), 2.28 (br t, J = 7.8 Hz, 2H), 1.86 (td, J = 7.8, 5.0 Hz, 2H), 1.42 (qd, J = 7.3, 6.0 Hz, 2H), 0.97 (s, 9H), 0.95 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.6, 144.8, 110.1, 109.9, 103.4, 87.5, 85.2, 81.2, 80.1, 79.1, 75.8, 74.5, 74.4, 74.1, 71.9, 64.8 (×2), 33.6, 31.1, 29.5, 26.1 (×3), 26.0 (×3), 18.43, 18.41, 14.0, 10.5, 9.9, 9.5, −4.3, −4.5, −4.71, −4.73; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 [M + Na]$^+$, found 631.3587.

Tetrayne 2ab. According to the synthetic procedure of **2aa**, **2ab** (175 mg, 0.287 mmol) was synthesized from **3ab** (218 mg, 0.407 mmol) and **4** (98 mg, 0.49 mmol) in 71% yield by using $Pd(PPh_3)_4$ (69 mg, 60 μmol), CuI (23 mg, 0.12 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 6.20 (dd, J = 15.1, 5.0 Hz, 1H), 6.16 (dd, J = 15.6, 5.5 Hz, 1H), 5.88−5.78 (m, 2H), 4.87 (t, J = 5.0 Hz, 1H), 4.16 (dt, J = 6.0, 6.0 Hz, 1H), 3.92 (dt, J = 6.0, 6.0 Hz, 1H), 3.47−3.38 (m, 2H), 3.33−3.27 (m, 2H), 2.94 (d, J = 2.3 Hz, 2H), 2.85 (tt, J = 2.3, 2.3 Hz, 2H), 2.42 (ddd, J = 16.5, 6.9, 1.8 Hz, 1H), 2.30 (ddd, J = 16.5, 6.0, 1.8 Hz, 1H), 2.28 (tt, J = 7.3, 2.3 Hz, 2H), 1.86 (td, J = 7.3, 5.0 Hz, 2H), 1.41 (qd, J = 7.3, 6.0 Hz, 2H), 0.97 (s, 9H), 0.95 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H) 0.00 (3H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 145.6, 144.8, 110.1, 109.9, 103.4, 87.5, 85.2, 81.2, 80.1, 79.1, 75.8, 74.5, 74.4, 74.1, 71.9, 64.8 (×2), 33.6, 31.1, 29.5, 26.1 (×3), 26.0 (×3), 18.43, 18.42, 14.0, 10.5, 9.9, 9.5, −4.3, −4.5, −4.72, −4.74.

Tetrayne 2ba. According to the synthetic procedure of **2aa**, **2ba** (174 mg, 0.286 mmol) was synthesized from **3ba** (218 mg, 0.407 mmol) and **4** (127 mg, 0.629 mmol) in 70% yield by using $Pd(PPh_3)_4$ (74 mg, 64 μmol), CuI (23 mg, 0.12 mmol), and piperidine (0.12 mL, 1.6 mmol) in benzene (14.5 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 15/1): pale yellow oil; HRMS (ESI) calcd for $C_{36}H_{56}O_4Si_2Na$ 631.3609 [M + Na]$^+$, found 631.3613. The ^{1}H NMR spectrum of **2ba** was identical with that of **2ab**.

Tetrayne 2bb. According to the synthetic procedure of **2aa**, **2bb** (144 mg, 0.236 mmol) was synthesized from **3bb** (203 mg, 0.380 mmol) and **4** (93 mg, 0.460 mmol) in 62% yield by using $Pd(PPh_3)_4$ (65 mg, 56 μmol), CuI (22 mg, 0.12 mmol), and piperidine (0.12 mL, 1.20 mmol) in benzene (13 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 15/1): pale yellow oil. The ^{1}H NMR spectrum of **2bb** was identical with that of **2aa**.

Alkyne 24aa. A suspension of tetrayne **2aa** (32.4 mg, 53.2 μmol), quinoline (75 μL, 0.64 mmol), and Lindlar catalyst (65 mg) in hexane (3.0 mL) was stirred 0 °C for 1 h under an H_2 atmosphere (1 atm). Then Lindlar catalyst (39 mg) was added. The reaction mixture was stirred at 0 °C for a further 40 min under an H_2 atmosphere and was filtered through a pad of Celite with hexane. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1) and twice on Chromatorex-ACD (10 g, hexane/EtOAc 500/1 to 300/1; 8 g, hexane/EtOAc 500/1 to 200/1) to afford alkyne **24aa** (18.1 mg, 29.4 μmol) in 55% yield: colorless oil; $[\alpha]_D^{27}$ +41 (c 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.74 (dd, J = 15.6, 11.4 Hz, 1H), 6.19 (dd, J = 15.6, 6.0 Hz, 1H), 6.02 (dd, J = 11.4, 11.4 Hz, 1H), 5.86 (ddt, J = 15.6, 1.4, 1.4 Hz, 1H), 5.77 (dd, J = 15.6, 6.0 Hz, 1H), 5.50−5.47 (m, 5H), 4.84 (t, J = 4.6 Hz, 1H), 4.38 (dt, J = 6.4, 6.0 Hz, 1H), 3.93 (dt, J = 6.0, 6.0 Hz, 1H), 3.60−3.52 (m, 2H), 3.42−3.35 (m, 2H), 2.99 (t, J = 6.4 Hz, 2H), 2.87 (m, 2H), 2.59 (ddd, J = 16.9, 7.3, 2.3 Hz, 1H), 2.45 (ddd, J = 16.9, 5.9, 2.3 Hz, 1H), 2.31 (m, 2H), 1.81 (m, 2H), 1.43 (m, 2H), 1.04 (s, 9H), 0.97 (s, 9H), 0.83 (t, J = 7.3 Hz, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.6, 129.9, 129.2, 128.6, 128.3, 128.0, 127.6, 124.7, 109.0, 104.1, 87.3, 80.4, 73.7, 72.0, 64.9 (×2), 33.7, 30.7, 29.6, 26.0, 25.83 (×3), 25.80 (×3), 25.5, 21.9, 18.3, 18.2, 9.3, −4.5, −4.6, −4.8, −4.9; IR (neat) ν 2961, 2926, 2855, 1733, 1457, 1260, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4094.

Alkyne 24ab. According to the synthetic procedure of **24aa**, **24ab** (87.8 mg, 0.143 mmol) was synthesized from **2ab** (86.9 mg, 0.143 mmol) in 100% yield by using Lindlar catalyst (180 mg) and quinoline (0.20 mL, 1.4 mmol) in hexane (8.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 30/1): colorless oil; $[\alpha]_D^{19}$ +16 (c 1.4, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4083. The other analytical data of **24ab** were identical with those of **24ba**.

Alkyne 24ba. According to the synthetic procedure of **24aa**, **24ba** (34.0 mg, 55.3 μmol) was synthesized from **2ba** (61.7 mg, 0.101 mmol) in 55% yield by using Lindlar catalyst (500 mg) and quinoline (0.14 mL, 1.2 mmol) in hexane (6.2 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 30/1 to 20/1) and three times on Chromatorex-ACD (20 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{24}$ −20 (c 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.75 (dd, J = 15.6, 11.4 Hz, 1H), 6.19 (dd, J = 15.6, 6.0 Hz, 1H), 6.02 (dd, J = 11.4, 11.4 Hz, 1H), 5.86 (ddt, J = 15.6, 1.4, 1.4 Hz, 1H), 5.77 (dd, J = 15.6, 6.0 Hz, 1H), 5.50−5.47 (m, 5H), 4.84 (t, J = 4.6 Hz, 1H), 4.38 (dt, J = 6.4, 6.0 Hz, 1H), 3.93 (dt, J = 6.0, 6.0 Hz, 1H), 3.60−3.52 (m, 2H), 3.42−3.35 (m, 2H), 3.00 (t, J = 6.4 Hz, 2H), 2.87 (m, 2H), 2.59 (ddd, J = 16.9, 7.3, 2.3 Hz, 1H), 2.45 (ddd, J = 16.9, 5.9, 2.3 Hz, 1H), 2.31 (m, 2H), 1.81 (m, 2H), 1.43 (m, 2H), 1.04 (s, 9H), 0.97 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H), 0.17 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.6, 129.9, 129.2, 128.6, 128.3, 128.0, 127.7, 124.7, 109.0, 104.1, 87.3, 80.4, 73.7, 72.0, 64.9 (×2), 33.7, 30.7, 29.6, 26.0, 25.84 (×3), 25.81 (×3), 25.6, 21.9, 18.3, 18.2, 9.3, −4.5, −4.6, −4.8, −4.9; IR (neat) ν 2956, 2928, 2856, 1472, 1255, 1136 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{62}O_4Si_2Na$ 637.4079 [M + Na]$^+$, found 637.4080.

Allkyne 24bb. According to the synthetic procedure of **24aa**, **24bb** (51.7 mg, 84.1 μmol) was synthesized from **2bb** (68.4 mg, 0.112 mmol) in 75% yield by using Lindlar catalyst (173 mg) and quinoline (0.16 mL, 1.4 mmol) in hexane (7.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1) and twice on Chromatorex-ACD (20 g, hexane/EtOAc 500/1 to 100/1; 15 g, hexane/EtOAc 300/1 to 100/1): colorless oil; $[\alpha]_D^{21}$ −43 (c 0.69, $CHCl_3$).. The other analytical data of **24bb** were identical with those of **24aa**.

Complex 25aa. $Co_2(CO)_8$ (69 mg, 0.20 mmol) was added to a solution of **24aa** (31.1 mg, 50.5 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1) to afford **25aa** (42.2 mg, 46.8 mol) in 93% yield: brown oil; ^{1}H

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 15.6 Hz, 1H), 6.58 (dd, J = 15.6, 11.5 Hz, 1H), 6.00 (dd, J = 11.5, 11.5 Hz, 1H), 5.99 (dd, J = 15.6, 6.0 Hz, 1H), 5.74 (dd, J = 15.6, 6.0 Hz, 1H), 5.47−5.30 (m, 5H), 4.87 (t, J = 4.6 Hz, 1H), 4.44 (td, J = 6.0, 5.0 Hz, 1H), 4.13 (td, J = 6.4, 6.0 Hz, 1H), 4.01−3.91 (m, 2H), 3.90−3.80 (m, 2H), 3.26−3.15 (m, 2H), 3.00−2.89 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.20 (td, J = 7.3, 7.3 Hz, 2H), 1.72 (m, 2H), 1.54 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.89 (t, J = 7.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.3, 130.5, 129.2, 128.7, 128.3, 128.0, 127.6, 126.4, 125.9, 104.1, 93.8, 74.4, 73.6, 64.9 (×2), 44.0, 33.7, 31.0, 26.0, 25.9 (×3), 25.8 (×3), 25.5, 21.9, 18.34, 18.26, 9.6, −4.46, 4.54, −4.8, some of the ^{13}C peaks were missing due to broadening of the spectrum; IR (neat) ν 2956, 2930, 2858, 2088, 2048, 2018, 1255, 1061 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2457.

Complex 25ab. According to the synthetic procedure of **25aa**, **25ab** (80.2 mg, 89.1 μmol) was synthesized from **24ab** (54.2 mg, 88.1 μmol) in 99% yield by using $Co_2(CO)_8$ (119 mg, 0.348 mmol) in CH_2Cl_2 (6.0 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2507. The ^{1}H NMR spectrum of **25ab** was identical with that of cobalt complex **25ba**.

Complex 25ba. According to the synthetic procedure of **25aa**, **25ba** (41.3 mg, 45.9 μmol) was synthesized from **24ba** (30.5 mg, 49.6 μmol) in 92% yield by using $Co_2(CO)_8$ (69 mg, 0.20 mmol) in CH_2Cl_2 (4.4 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 20/1): brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 15.6 Hz, 1H), 6.59 (dd, J = 15.6, 11.5 Hz, 1H), 6.00 (dd, J = 11.5, 11.5 Hz, 1H), 5.99 (dd, J = 15.6, 6.0 Hz, 1H), 5.75 (dd, J = 15.6, 6.0 Hz, 1H), 5.47−5.30 (m, 5H), 4.87 (t, J = 4.6 Hz, 1H), 4.44 (td, J = 6.0, 5.0 Hz, 1H), 4.13 (td, J = 6.4, 6.0 Hz, 1H), 4.01−3.91 (m, 2H), 3.90−3.80 (m, 2H), 3.26−3.15 (m, 2H), 3.00−2.89 (m, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.20 (td, J = 7.3, 7.3 Hz, 2H), 1.72 (m, 2H), 1.54 (m, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.88 (t, J = 7.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 140.5, 135.3, 130.4, 129.2, 128.7, 128.3, 128.0, 127.6, 126.4, 125.8, 104.1, 93.7, 91.8, 74.3, 73.5, 64.9 (×2), 44.0, 33.7, 31.0, 26.0, 25.9 (×3), 25.8 (×3), 25.5, 21.9, 18.33, 18.26, 9.6, −4.5, −4.6, −4.78, −4.80, some of the ^{13}C peaks were missing due to broadening of the spectrum; IR (neat) ν 2955, 2929, 2857, 2088, 2048, 2018, 1472, 1255, 1062 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2425.

Complex 25bb. According to the synthetic procedure of **25aa**, **25bb** (92.0 mg, 0.102 mmol) was synthesized from **24bb** (66.0 mg, 0.107 mmol) in 95% yield by using $Co_2(CO)_8$ (149 mg, 0.436 mmol) in CH_2Cl_2 (10 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1): brown oil; HRMS (ESI) calcd for $C_{42}H_{62}Co_2O_{10}Si_2Na$ 923.2438 [M + Na]$^+$, found 923.2449. The ^{1}H NMR spectrum of **25bb** was identical with that of complex **25aa**.

Complex 26aa. $Co_2(CO)_8$ (213 mg, 0.623 mmol) was added to a solution of **2aa** (38.3 mg, 62.8 μmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 4 h, and then concentrated. The residue was directly subjected to flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1) to afford **26aa** (104 mg, 59.4 μmol) in 94% yield: brown oil. Because signals in the ^{1}H NMR spectrum of **26aa** were broad, the formation was confirmed by the MS analysis: LRMS (ESI) calcd for $C_{60}H_{56}Co_8O_{28}Si_2Na$ 1774.7 [M + Na]$^+$, found 1774.7.

Hexaene 23aa. n-Bu_3SnH (0.19 mL, 0.71 mmol) and N-methylmorpholine oxide (55 mg, 0.47 mmol) were successively added to a solution of **25aa** (42.2 mg, 46.9 μmol) in toluene (45 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h under air and was directly subjected to flash column chromatography (a column consecutively packed with silica gel 4 g and 10% (w/w) KF in silica gel 4 g, hexane to hexane/EtOAc 20/1) to afford **23aa** (25.2 mg, 40.8 mmol) in 87% yield: colorless oil; $[\alpha]_D^{27}$ +10 (c 0.93, $CHCl_3$); IR (neat) ν 2955, 2928, 2856, 1471, 1463, 1361, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4233. The ^{1}H NMR spectrum of **23aa** was identical with that of **23bb**.

Hexaene 23ab. According to the synthetic procedure of **23aa**, **23ab** (47.2 mg, 76.6 μmol) was synthesized from **25ab** (80.2 mg, 89.1 μmol) in 86% yield by using n-Bu_3SnH (0.34 mL, 1.3 mmol) and N-methylmorpholine oxide (101 mg, 0.86 mmol) in toluene (45 mL). Purification was performed twice by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 20/1; 8 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{22}$ +21 (c 0.96, $CHCl_3$); HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4246. The other analytical data of **23ab** were identical with those of **23ba**.

Hexaene 23ba. According to the synthetic procedure of **23aa**, **23ba** (24.5 mg, 39.7 μmol) was synthesized from **25ba** (41.3 mg, 45.9 μmol) in 86% yield by using n-Bu_3SnH (0.19 mL, 0.71 mmol) and N-methylmorpholine oxide (54 mg, 0.46 mmol) in toluene (40 mL). Purification was performed by flash column chromatography (a column consecutively packed with silica gel 3 g and 10% (w/w) KF in silica gel 1 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{23}$ −24 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 15.6, 11.4 Hz, 1H), 6.38 (dd, J = 15.6, 11.0 Hz, 1H), 6.04 (dd, J = 11.4, 11.0 Hz, 1H), 5.98 (dd, J = 11.0, 11.0 Hz, 1H), 5.66 (dd, J = 15.6, 6.0 Hz, 1H), 5.62 (dd, J = 15.6, 6.0 Hz, 1H), 5.48−5.32 (m, 6H), 4.87 (t, J = 5.0 Hz, 1H), 4.22 (td, J = 6.0, 6.0 Hz, 1H), 4.07 (dt, J = 6.4, 6.0 Hz, 1H), 4.02−3.91 (m, 2H), 3.90−3.80 (m, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.40 (m, 2H), 2.21 (td, J = 8.2, 6.9 Hz, 2H), 1.72 (m, 2H), 1.52 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.1, 128.6, 128.3, 128.2, 127.7, 127.0, 124.7, 124.5, 104.1, 74.5, 72.9, 64.8 (×2), 36.8, 33.7, 31.1, 26.0, 25.90 (×3), 25.86 (×3), 25.6, 21.9, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8; IR (neat) ν 2956, 2927, 2856, 1471, 1462, 1362, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4247.

Hexaene 23bb. According to the synthetic procedure of **23aa**, **23bb** (52.4 mg, 84.9 μmol) was synthesized from **25bb** (92.0 mg, 0.102 mmol) in 83% yield by using n-Bu_3SnH (0.40 mL, 1.50 mmol) and N-methylmorpholine oxide (119 mg, 1.02 mmol) in toluene (50 mL). Purification was performed twice by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 20/1; 10 g, hexane to hexane/EtOAc 20/1): colorless oil; $[\alpha]_D^{21}$ −10 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 15.6, 11.4 Hz, 1H), 6.38 (dd, J = 15.6, 11.0 Hz, 1H), 6.04 (dd, J = 11.4, 11.0 Hz, 1H), 5.98 (dd, J = 11.0, 11.0 Hz, 1H), 5.66 (dd, J = 15.6, 6.0 Hz, 1H), 5.62 (dd, J = 15.6, 6.0 Hz, 1H), 5.48−5.32 (m, 6H), 4.87 (t, J = 5.0 Hz, 1H), 4.22 (td, J = 6.0, 6.0 Hz, 1H), 4.07 (dt, J = 6.4, 6.0 Hz, 1H), 4.02−3.91 (m, 2H), 3.90−3.80 (m, 2H), 2.94 (t, J = 6.4 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.40 (m, 2H), 2.21 (td, J = 8.2, 6.9 Hz, 2H), 1.72 (m, 2H), 1.52 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.2, 128.6, 128.3, 128.2, 127.7, 126.9, 124.6, 124.5, 104.1, 74.4, 72.9, 64.9 (×2), 36.8, 33.7, 31.1, 26.0, 25.90 (×3), 25.87 (×3), 25.6, 21.9, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8; HRMS (ESI) calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 [M + Na]$^+$, found 639.4240.

(14*S*,20*R*)-1aa. TMSOTf (0.15 mL, 0.83 mmol) was added to a solution of **23aa** (34.1 mg, 55.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (3.5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 45 min, and then H_2O (1.0 mL) was added. The resultant mixture was warmed to room temperature and stirred for 30 min. Then the mixture was extracted with EtOAc (8 mL × 2), and the combined organic layers were washed with aqueous 0.1 M HCl (4 mL), H_2O (4 mL), and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 20/1) to afford the crude aldehyde **27aa**, which was used in the next reaction without further purification. Aldehyde **27aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.47 (dd, J = 15.1, 11.0 Hz, 1H), 6.38 (dd, J = 15.1, 11.0 Hz, 1H), 6.04 (dd, J = 11.0, 11.0 Hz, 1H), 5.91 (dd, J = 11.0, 11.0 Hz, 1H), 5.67 (dd, J = 15.1, 6.0 Hz, 1H), 5.62 (dd, J = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (q, J = 6.0 Hz, 2H), 4.07 (dt, J = 6.4, 6.0 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.84 (t, J = 5.9 Hz, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.40 (m, 4H), 1.50 (m, 2H), 0.90 (s, 18H), 0.87 (t, J = 7.3

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 137.2, 136.7, 129.8, 129.3, 129.2, 128.3, 128.2, 128.0, 127.7, 126.9, 124.5, 124.3, 74.4, 72.9, 43.7, 36.8, 31.1, 26.1, 25.90 (×3), 25.87 (×3), 25.6, 20.1, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8.

A solution of $NaClO_2$ (80% purity, 55 mg, 0.49 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (80 mg, 0.52 mmol) in H_2O (1.5 mL) was added to a solution of the above crude aldehyde **27aa** in a mixture of *t*-BuOH (1.5 mL) and 2-methyl-2-butene (1.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Then the mixture was extracted with EtOAc (8 mL × 2), and the combined organic layers were washed with H_2O (4 mL) and brine (4 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) to afford the crude carboxylic acid **28aa**, which was used in the next reaction without further purification. Carboxylic acid **28aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (dt, *J* = 6.0, 6.0 Hz, 2H), 4.07 (dt, *J* = 6.4, 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.42−2.35 (m, 6H), 1.55−1.44 (m, 2H), 0.90 (s, 18H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.3, 128.3 (×2), 128.0, 127.6, 126.9, 124.6, 124.4, 74.4, 72.9, 36.8, 33.9, 31.1, 26.0, 25.91 (×3), 25.87 (×3), 25.6, 22.5, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M - H]^-$, found 587.3951.

TBAF (1.0 M in THF, 0.55 mL, 0.55 mmol) was added to a solution of the above crude carboxylic acid **28aa** in THF (3.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, and then saturated aqueous NH_4Cl (4 mL) and 0.1 M HCl (10 mL) were successively added. The resultant mixture was extracted with EtOAc (10 and 5 mL), and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) to afford the crude (14*S*,20*R*)-**1aa**. Then the crude **1aa** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 40 min) to afford **1aa** (10.0 mg, 27.8 μmol) in 50% over three steps. **(14*S*,20*R*)-1aa**: pale yellow oil; $[\alpha]_D^{18}$ −28 (*c* 0.42, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.57 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.08 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.69 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.65 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50−5.32 (m, 6H), 4.18 (dt, *J* = 6.4, 6.4 Hz, 1H), 4.01 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.87 (m, 2H), 2.52−2.27 (m, 6H), 1.53 (m, 2H), 0.91 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.8, 137.2, 131.1, 130.8, 130.2, 129.7, 129.5, 129.3, 128.7, 128.1, 126.7, 126.5, 74.8, 73.1, 36.8, 31.2, 27.0, 26.6, 10.2, the C1, C2, and C3 peaks were missing due to broadening of the spectrum; IR (neat) ν 3348, 3010, 2956, 2923, 2851, 1726, 1451, 1389, 1274 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2222; UV (MeOH) λ_{max} 237 nm (ε 2.82 × 10^4).

(14*S*,20*S*)-1ab. According to the synthetic procedure of **1aa**, **1ab** (8.64 mg, 24.1 μmol) was synthesized from **23ab** (47.2 mg, 76.4 μmol) in 32% yield over three steps by using TMSOTf (0.21 mL, 1.2 mmol) and 2,6-lutidine (0.20 mL, 1.7 mmol) in CH_2Cl_2 (4.7 mL) for the first step, $NaClO_2$ (80% purity, 76 mg, 0.67 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (113 mg, 0.73 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (6.0 mL) for the second, and TBAF (1.0 M in THF, 0.76 mL, 0.76 mmol) in THF (5.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (8 g, hexane/EtOAc 4/1 to 3/1 to 3/2) for the second step and by flash column chromatography on silica gel (6 g, hexane/EtOAc/AcOH 40/60/0.05 to 30/70/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 36 min) for the third: pale yellow oil; $[\alpha]_D^{19}$ +13 (*c* 0.41, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 [M-H]$^-$, found 359.2223; UV (MeOH) λ_{max} 236 nm (ε 2.60 × 10^4). The other analytical data of **1ab** were identical with those of **1ba**.

(14*R*,20*R*)-1ba. According to the synthetic procedure of **1aa**, **1ba** (5.60 mg, 15.6 μmol) was synthesized from **23ba** (40.7 mg, 66.0 μmol) in 24% yield over three steps by using TMSOTf (0.18 mL, 0.99 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) in CH_2Cl_2 (4.2 mL) for the first step, $NaClO_2$ (80% purity, 68 mg, 0.60 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (99 mg, 0.64 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (4.5 mL) for the second, and TBAF (1.0 M in THF, 0.66 mL, 0.66 mmol) in THF (4.2 mL) for the third. Purification was performed by flash column chromatography on silica gel (4 g, hexane/EtOAc 4/1 to 3/1) for the second step and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 40/60/0.05 to 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 33 min) for the third. Aldehyde **27ba**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.91 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (m, 2H), 4.07 (dt, *J* = 6.4, 6.0 Hz, 2H), 2.95 (t, *J* = 6.4 Hz. 2H), 2.84 (t, *J* = 5.9 Hz, 2H), 2.50 (t, *J* = 6.8 Hz, 2H), 2.40 (m, 4H), 1.50 (m, 2H), 0.90 (s, 18H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 137.2, 136.7, 129.8, 129.3, 129.2, 128.3, 128.2, 128.0, 127.4, 127.0, 124.6, 124.4, 74.5, 72.8, 43.7, 36.8, 31.1, 26.0, 25.91 (×3), 25.86 (×3), 25.6, 20.1, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8. Carboxylic acid **28ba**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.38 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.04 (d, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.62 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.46−5.30 (m, 6H), 4.23 (dt, *J* = 6.0, 6.0 Hz, 2H), 4.07 (dt, *J* = 6.4, 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.42−2.35 (m, 6H), 1.55−1.44 (m, 2H), 0.90 (s, 18H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.6, 129.8, 129.5, 129.3, 128.3, 128.2, 128.0, 127.6, 127.0, 124.7, 124.4, 74.5, 72.9, 36.8, 33.9, 31.1, 26.0, 25.91 (×3), 25.87 (×3), 25.6, 22.5, 18.3, 18.2, 9.7, −4.3, −4.4, −4.7, −4.8, the C1 peak was missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{34}H_{59}O_4Si_2$ 587.3957 $[M - H]^-$, found 587.3974. **(14*R*,20*R*)-1ba**: pale yellow oil; $[\alpha]_D^{27}$ −16 (*c* 0.28, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.58 (dd, *J* = 15.6, 11.0 Hz, 1H), 6.51 (ddt, *J* = 15.1, 11.0. 1.4 Hz, 1H), 6.08 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.69 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.66 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.50−5.32 (m, 6H), 4.18 (dt, *J* = 6.4, 6.4 Hz, 1H), 4.01 (dt, *J* = 6.4, 6.4 Hz, 1H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 5.5 Hz, 2H), 2.52−2.27 (m, 6H), 1.53 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.8, 137.1, 131.1, 130.8, 130.1, 129.6, 129.4, 129.3, 128.7, 128.1, 126.6, 126.5, 74.7, 73.1, 36.7, 31.2, 27.0, 26.5, 10.2, the C1, C2, and C3 peaks were missing due to broadening of the spectrum; IR (neat) ν 3380, 3011, 2958, 2925, 2855, 1713, 1556, 1415, 1260 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2243.

(14*R*,20*S*)-1bb. According to the synthetic procedure of **1aa**, **1bb** (4.59 mg, 12.8 μmol) was synthesized from **23bb** (22.0 mg, 35.6 μmol) in 36% yield over three steps by using TMSOTf (95 μL, 0.52 mmol) and 2,6-lutidine (95 μL, 0.82 mmol) in CH_2Cl_2 (2.2 mL) for the first step, $NaClO_2$ (80% purity, 35 mg, 0.31 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (54 mg, 0.35 mmol) in a 1/1/1 mixture of *t*-BuOH, 2-methyl-2-butene, and H_2O (3.0 mL) for the second, and TBAF (1.0 M in THF, 0.36 mL, 0.36 mmol) in THF (2.3 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 3/1) for the second step and by flash column chromatography on silica gel (4 g, hexane/EtOAc/AcOH 50/50/0.05 to 40/60/0.05) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 3 mL/min, t_R = 42 min) for the third: pale yellow oil; $[\alpha]_D^{17}$ +22 (*c* 0.21, MeOH); HRMS (ESI) calcd for $C_{22}H_{31}O_4$ 359.2228 $[M - H]^-$, found 359.2224. The other analytical data of **1bb** were identical with those of **1aa**.

Bioassay. Peritonitis was induced as described in ref 36. Synthetic **1aa**,**ab**,**ba**,**bb** (each 1 ng) were injected intravenously through the tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

2 h, peritoneal lavages were collected, PMN leucocyte numbers were counted, cell viability was determined using Trypan blue exclusion, and differential cell counts were monitored by Wright−Giemsa staining.

Statistical Analysis. Results are expressed as means ± SE. Differences between two groups were tested by the Student *t* test. Multiple comparisons were analyzed using ANOVA followed by the Tukey test. Significance levels of $P < 0.05$ and $P < 0.01$ were used.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra for all isolated compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01461.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by the Funding Program for a Grant-in-Aid for Scientific Research (A) (JSPS) to M.I. and for Scientific Research (C) (JSPS) and on Innovative Areas (MEXT) to D.U. We are grateful to Prof. Minoru Isobe (National Tsing Hua University) and Dr. Akinari Hamajima (Chiba University) for the crucial suggestion to use amine oxides in the reductive decomplexation of alkyne dicobalt hexacarbonyl complexes.

■ REFERENCES

(1) For reviews, see: (a) Serhan, C. N.; Chiang, N.; Van Dyke, T. E. *Nat. Rev. Immunol.* **2008**, *8*, 349. (b) Serhan, C. N.; Chiang, N. *Br. J. Pharmacol.* **2008**, *153*, S200. (c) Serhan, C. N.; Petasis, N. A. *Chem. Rev.* **2011**, *111*, 5922.

(2) Schwab, J. M.; Chiang, N.; Arita, M.; Serhan, C. N. *Nature* **2007**, *447*, 869.

(3) Simopoulos, A. P. *J. Am. Coll. Nutr.* **2002**, *21*, 495.

(4) (a) Serhan, C. N.; Yang, R.; Martinod, K.; Kasuga, K.; Pillai, P. S.; Porter, T. F.; Oh, S. F.; Spite, M. *J. Exp. Med.* **2009**, *206*, 15. (b) Serhan, C. N.; Dalli, J.; Karamnov, S.; Choi, A.; Park, C.-K.; Xu, Z.-Z.; Ji, R.-R.; Zhu, M.; Petasis, N. A. *FASEB J.* **2012**, *26*, 1755.

(5) Total syntheses of lipid mediators from our laboratory. Resolvin E2: (a) Ogawa, S.; Urabe, D.; Yokokura, Y.; Arai, H.; Arita, M.; Inoue, M. *Org. Lett.* **2009**, *11*, 3602. Maresin 1: (b) Sasaki, K.; Urabe, D.; Arai, H.; Arita, M.; Inoue, M. *Chem. - Asian J.* **2011**, *6*, 534. Resolvin E3: (c) Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Tetrahedron* **2012**, *68*, 3210.

(6) Total syntheses of lipid mediators derived from DHA from other laboratories. Protectin D1: (a) Petasis, N. A.; Yang, R.; Winkler, J. W.; Zhu, M.; Uddin, J.; Bazan, N. G.; Serhan, C. N. *Tetrahedron Lett.* **2012**, *53*, 1695. (b) Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2011**, *52*, 3001. (c) Aursnes, M.; Tungen, J. E.; Vik, A.; Dalli, J.; Hansen, T. V. *Org. Biomol. Chem.* **2014**, *12*, 432. (d) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2014**, *55*, 6011. Maresin 1: (e) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 4169. (f) Ogawa, N.; Tojo, T.; Kobayashi, Y. *Tetrahedron Lett.* **2014**, *55*, 2738. (g) Tungen, J. E.; Aursnes, M.; Hansen, T. V. *Tetrahedron Lett.* **2015**, *56*, 1843. Maresin 2: (h) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2015**, *56*, 256. Resolvin D1: (i) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 6990. Resolvin D2: (j) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2004**, *45*, 8717. (k) Li, J.; Leong, M. M.; Stewart, A.; Rizzacasa, M. A. *Beilstein J. Org. Chem.* **2013**, *9*, 2762. Resolvin D3: (l) Winkler, J. W.; Uddin, J.; Serhan, C. N.; Petasis, N. A. *Org. Lett.* **2013**, *15*, 1424. Resolvin D5: (m) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2005**, *46*, 3623. Resolvin D6: (n) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 86. For a review on syntheses of eicosanoids, see: (o) Nicolaou, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1100.

(7) Yokokura, Y.; Isobe, Y.; Matsueda, S.; Iwamoto, R.; Goto, T.; Yoshioka, T.; Urabe, D.; Inoue, M.; Arai, H.; Arita, M. *J. Biochem.* **2014**, *156*, 315.

(8) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **2000**, *56*, 327.

(9) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. For a review on Sonogashira coupling reactions, see: (b) Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Ed.; Wiley-VCH, Weinheim, Germany, 2004; Vol. *1*, pp 317.

(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(11) The enantiopurity of **15a**,**b** was determined by ^{1}H NMR analyses of the corresponding MTPA esters.

(12) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(13) Glycidol derivatives **6a**/**6b** were synthesized from the commercially available (*R*)-/(*S*)-glycidols (98% ee), respectively, according to the literature. See: Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299.

(14) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(16) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(17) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(18) Epimerization of the C14-hydroxy group was not observed during the vinyl iodide formation. The configurational stability of the similar α-siloxy aldehydes was reported previously. See: (a) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548. (b) Taffer, I. M.; Zipkin, R. E. *Tetrahedron Lett.* **1987**, *28*, 6543.

(19) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, *2001*, 2577.

(20) Abdel Ghani, S. B.; Chapman, J. M.; Figadère, B.; Herniman, J. M.; Langley, G. J.; Niemann, S.; Brown, R. C. D. *J. Org. Chem.* **2009**, *74*, 6924.

(21) Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59*, 7787.

(22) (a) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789. (b) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.

(23) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. (b) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313.

(24) Hydrogenation using Pd/$BaSO_4$ or Pd/polyethyleneimine of **2aa** provided a mixture of **23aa**, **24aa**, and the over-reduced compounds. (a) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518. (b) Sajiki, H.; Mori, S.; Ohkubo, T.; Ikawa, T.; Kume, A.; Maegawa, T.; Monguchi, Y. *Chem. - Eur. J.* **2008**, *14*, 5109.

(25) The position of the hydrogenated double bond of the over-reduced compounds could not be determined because they were inseparable from **23aa**. The generation of the over-reduced product was confirmed by the ^{1}H NMR and MS analyses of the mixture.

(26) (a) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025. (b) Avignon-Tropis, M.; Pougny, J. R. *Tetrahedron Lett.* **1989**, *30*, 4951. (c) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4725. For a report on the reduction of the conjugated tetrayne to the corresponding tetraene by employing Rieke zinc, see: (d) Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 4221.

(27) (a) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609. (b) Isobe, M.; Nishizawa, R.; Hoshokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665.

(28) For reports on the other reductive decomplexations of the alkyne dicobalt hexacarbonyl complexes to yield the corresponding

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

alkenes, see: (a) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032. (b) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, *1994*, 916. (c) Iwasawa, N.; Inaba, K.; Nakayama, S.; Aoki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7447.

(29) (a) Shambayani, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, *1991*, 204.

(30) Cambeiro, X. C.; Pericàs, M. A. In *The Pauson-Khand Reaction: Scope, Variations and Applications*; Torres, R. R., Ed.; Wiley: New York, 2012; p 23.

(31) Isobe and a co-worker reported the alternative conditions of the reductive Co-decomplexation (n-Bu_3SnH and NBS in 1,4-cyclohexadiene at 39 °C): Shibuya, S.; Isobe, M. *Tetrahedron* **1998**, *54*, 6677.

(32) Takai, S.; Ploypradith, P.; Hamajima, A.; Kira, K.; Isobe, M. *Synlett* **2002**, *2002*, 588.

(33) Generation of $(Bu_3P)(CO)_3CoH$ from $Co_2(CO)_6(PBu_3)_2$ and n-Bu_3SnH was proposed by Brown and co-worker. See: (a) Wegman, R. W.; Brown, T. L. *Organometallics* **1982**, *1*, 47. In addition, Isobe and co-workers proposed the generation of $(CO)_3CoH$ upon hydrosilylations of alkyne dicobalt hexacarbonyl complexes with trialkylsilane: (b) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485.

(34) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.

(35) The four isomers were separated by reverse-phase chiral HPLC (column CHIRALPAK AD-3R, 4.6 mm × 150 mm, eluent 50% CH_3CN/MeOH (4/1) in 0.1% aqueous AcOH for 5 min, 50−95% CH_3CN /MeOH (4/1) in 0.1% aqueous AcOH over 22.5 min, and then 95% CH_3CN /MeOH (4/1) in 0.1% aqueous AcOH for 8 min at 0.5 mL/min). Retention times of the synthetic **1**: t_R = 17.3 min for **1aa**, 14.6 min for **1ab**,**ba**, 14.0 min for **1bb**. Retention time of the natural **1aa**: t_R = 17.2 min.

(36) Yamada, T.; Tani, Y.; Nakanishi, H.; Taguchi, R.; Arita, M.; Arai, H. *FASEB J.* **2011**, *25*, 561.

DOI: 10.1021/acs.joc.5b01461
J. Org. Chem. 2015, 80, 7713−7726

Tetrahedron 71 (2015) 8320–8332

Contents lists available at ScienceDirect

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Total synthesis of four stereoisomers of (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid and their *anti*-inflammatory activities

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ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form 18 August 2015
Accepted 20 August 2015
Available online 22 August 2015

Keywords:
Lipid mediators
Eicosapentaenoic acid
Total synthesis
Convergent strategy
Reduction

ABSTRACT

The four stereoisomers of novel lipid mediator **1**, (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid, were synthesized from six simple fragments. Triyne **2** was convergently assembled through three S_N2 alkynylation reactions and one Sonogashira coupling reaction. Two of the three alkynes of **2** were hydrogenated using Lindlar catalyst, while the third alkyne was reduced through formation of the alkyne-dicobalt hexacarbonyl complex and subsequent reductive decomplexation, producing the requisite tetraene structure in a stereoselective manner. Next, a two-step functional group manipulation at C1, followed by simultaneous deprotection and epoxide formation, gave rise to the four isomers, (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**. The present work allowed determination of the absolute structure of naturally occurring **1** to be **1aa** and **1ab**, as well as biological evaluation of the two natural (**1aa**, **1ab**) and two unnatural (**1ba**, **1bb**) isomers. Intriguingly, natural **1aa** and unnatural **1ba** were found to exhibit more potent *anti*-inflammatory activities than **1ab** and **1bb**, indicating the greater importance of the stereochemistry of the C17,18-epoxide compared to that of the C12-hydroxy group.

1. Introduction

Omega-3 polyunsaturated fatty acids exhibit therapeutic effects towards various human inflammatory disorders.[1] Recently, many oxidized metabolites of eicosapentaenoic acid (EPA, Fig. 1), an omega-3 polyunsaturated fatty acid comprising 20 carbons and five *Z*-olefins, have been identified from inflamed biogenetic sources. Resolvins E1,[2] E2,[3] and E3[4] are metabolites of EPA produced by human polymorphonuclear leukocytes or eosinophils.[5] Biosynthetically, aspirin-acetylated COX (cyclooxygenase)-2 or cytochrome P450 monooxygenase first oxidize EPA into 18-hydroxy-eicosapentaenoic acid, which further undergoes oxidation to produce resolvins by the action of 5-LOX (lipoxygenase) or 12/15-LOX. Resolvins possess potent *anti*-inflammatory activity at nanomolar concentrations, suggesting that these endogenous compounds play an active role in resolving acute inflammations.[6]

Determination of the absolute structures of lipid mediators has been highly challenging due to their extremely low availability from biogenetic sources. Although the planar structures were deduced from UV spectroscopic and LC-MS/MS analyses using small amounts of material, full NMR assignments of the stereochemistries of the hydroxy groups have not generally been realized. Consequently, the extensive effort has been devoted to the total chemical construction of lipid mediators,[7,8] and the synthesis of all possible stereoisomers of these lipid mediators has enabled the NMR and HPLC analyses that led to elucidation of their absolute configurations. Accordingly, we previously reported the total synthesis of the four stereoisomers of resolvin E3[7c] and showed that two isomers are naturally occurring.

More recently, it was reported that peritoneal fluid of an EPA-supplemented murine model of acute inflammation contained the structurally distinct metabolite **1** of EPA (Fig. 1).[9] The potent *anti*-inflammatory activity of **1** was demonstrated by its inhibition of infiltration of polymorphonuclear (PMN) leukocytes in murine zymosan-induced peritonitis, and against leukotriene B_4-induced neutrophil chemotaxis and polarization. While the biosynthesis of all resolvins of the E-class involves the formation of 18-hydroxy-eicosapentaenoic acid, **1** appears to be derivatized through an alternative key intermediate produced from EPA. Specifically, the intermediacy of 17,18-epoxy-5,8,11,14-eicosatetraenoic acid was indicated by its detection in the above murine peritoneal fluid and by a separate in vitro experiment, where porcine 12-LOX transformed 17,18-epoxy-5,8,11,14-eicosatetraenoic acid into **1**. Thus,

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http://dx.doi.org/10.1016/j.tet.2015.08.047
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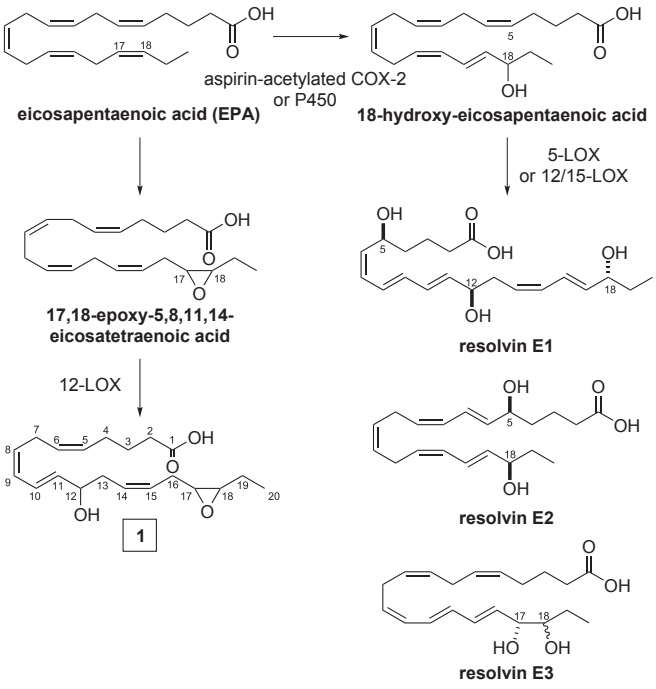


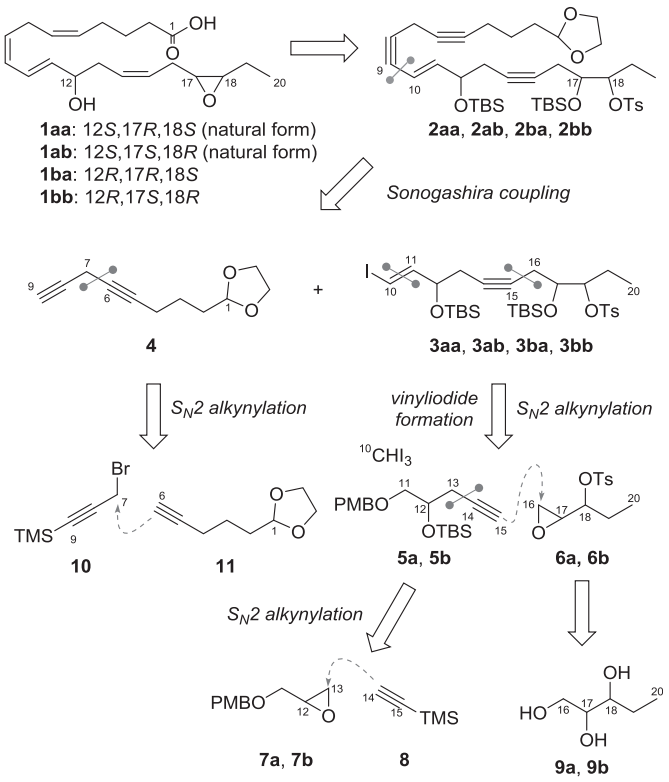
Fig. 1. Structures of EPA and its metabolites, and possible biosynthetic pathways of the metabolites.

a new endogenous *anti*-inflammatory cascade was proposed by the isolation of **1**.

UV and LC-MS/MS spectra were the only available data for natural **1** and allowed tentative assignment of its planar structure to be (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid, leaving the stereochemistry of the C12-hydroxy and C17,18-epoxide groups unassigned. We therefore embarked on establishing the absolute configuration of **1** by full synthetic construction of the four stereoisomers of **1**. Here we report details of the stereoselective total synthesis of (12*S*,17*R*,18*S*)-, (12*S*,17*S*,18*R*)-, (12*R*,17*R*,18*S*)- and (12*R*,17*S*,18*R*)-(5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa**, **1ab**, **1ba** and **1bb**). HPLC comparison analyses revealed that the EPA-derived natural **1** is **1aa** and **1ab**. Furthermore, evaluation of the *anti*-inflammatory activities of synthetic **1aa**, **1ab**, **1ba** and **1bb** demonstrated that the stereochemistry of the C17,18-epoxide has greater biological importance than that of the C12-hydroxy group.

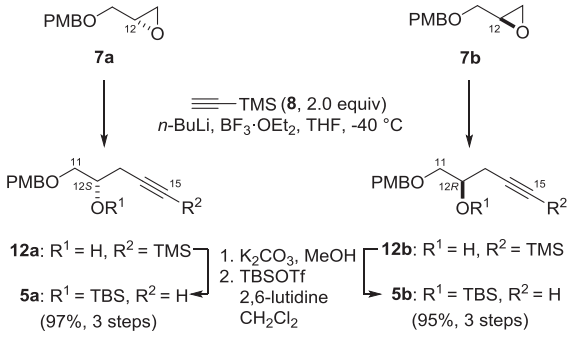
2. Results and discussion

We mapped out a convergent route to the four stereoisomers of (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa**, **1ab**, **1ba** and **1bb**, Scheme 1), and designed two chiral fragments (**7a**/**7b**, **9a**/**9b**), three achiral fragments (**8**, **10**, **11**) and iodoform for the assembly. The chemically unstable C17,18-epoxide of **1** would be constructed in the very last step of the synthesis, and the *Z*-alkenes would be generated from the corresponding internal alkynes. These retrosynthetic considerations led to intermediate **2**, which possesses a C17-hydroxy group and a C18-tosylate for epoxide formation, and three internal alkynes (C5–6, C8–9, and C14–15) as surrogates of the *Z*-alkenes. The carbon backbone of **2** would be assembled by Sonogashira coupling of C10–20 fragments **3** and the copper alkynide of C1–9 fragment **4**. Achiral **4** would be readily synthesized from **10** and **11** by applying copper-mediated S_N2-alkynylation. On the other hand, the four stereoisomers of chiral **3** (**3aa**, **3ab**, **3ba**, **3bb**) would be synthesized through S_N2-alkynylative coupling of the enantiomeric pairs of C11–15 fragment **5a**/**5b** and C16–20 fragment **6a**/**6b**, followed by vinyl iodide formation using iodoform. Compounds **5a**/**5b** would be further dissected into glycidol derivative **7a**/**7b** and TMS-acetylene **8**, while **6a**/**6b** would be simplified into triol **9a**/**9b**.



Scheme 1. Synthetic plan of the four stereoisomers of **1**.

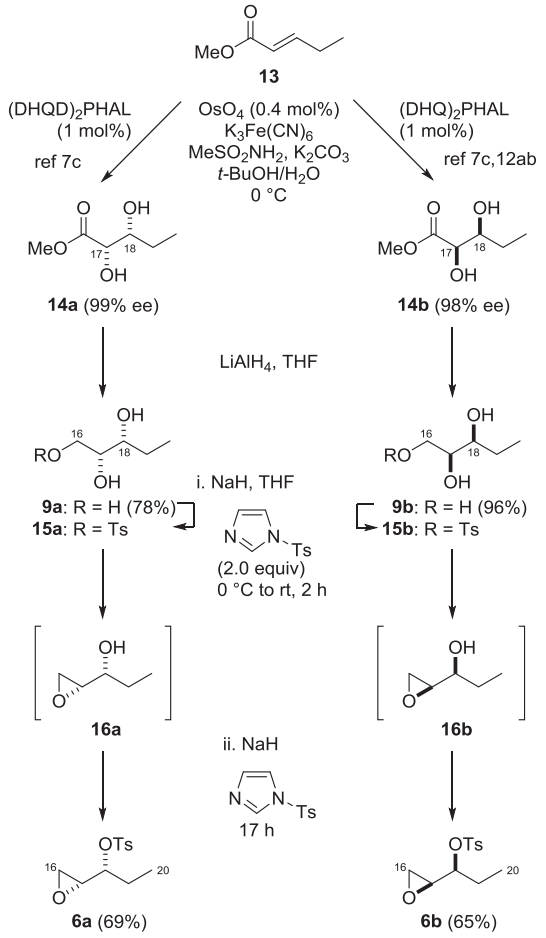
The synthesis commenced with preparation of two C11–15 fragments, **5a** and **5b** (Scheme 2). The lithium acetylide of TMS-acetylene **8** reacted with PMB-protected glycidol **7a**[10] in the presence of $BF_3 \cdot OEt_2$, leading to **12a**.[11] Removal of the C15-TMS group of the resultant **12a** was followed by TBS-protection of the C12-hydroxy group to afford (12*S*)-**5a**. The enantiomer (12*R*)-**5b** was synthesized from **7b** by employing the same three-step sequence.



Scheme 2. Synthesis of C11–15 fragments **5a** and **5b**.

C16–20 fragments **6a** and **6b**, the coupling partners of C11–15 fragments **5a** and **5b**, were synthesized from **13** (Scheme 3). Enantiomeric *syn*-diols **14a** (99% ee) and **14b** (98% ee)[7c,12] were prepared from olefin **13** by Sharpless asymmetric dihydroxylation[13] using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$, respectively, as the chiral ligand. Ester **14a** was reduced with $LiAlH_4$ to provide triol **9a**,[12b] which was then converted to C16–20 fragment **6a** by treatment with NaH and tosyl imidazole.[14] Remarkably, this one-pot reaction

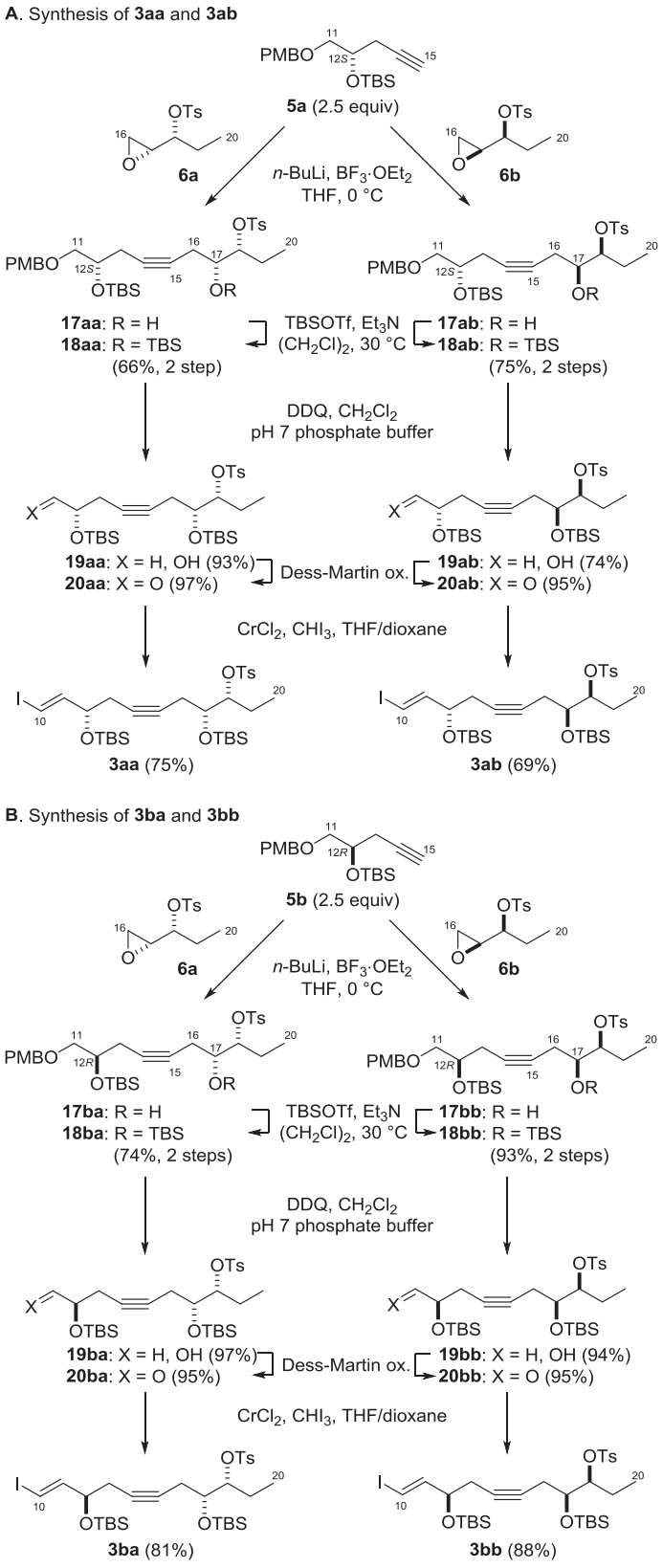
involved three transformations: i) chemoselective C16-tosylation (**9a**→**15a**), ii) nucleophilic epoxide formation (**15a**→**16a**), and iii) C18-tosylation (**16a**→**6a**). The same two steps transformed the enantiomeric diol **14b** into **6b**.[15]



Scheme 3. Synthesis of C16–20 fragments **6a** and **6b**.

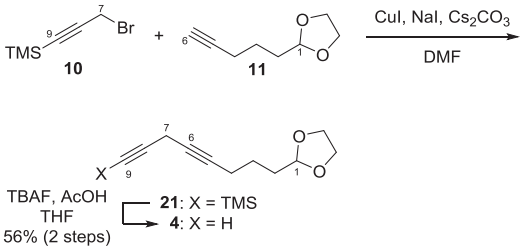
Scheme 4 illustrates the synthesis of the four C10–20 fragments **3aa**, **3ab**, **3ba** and **3bb** from the synthesized enantiomeric pairs **5a**/**5b** and **6a**/**6b**. $BF_3{\cdot}OEt_2$-activated S_N2 reaction of the lithiated species of C11-15 fragment (12*S*)-**5a** with C16-20 epoxides **6a** and **6b** at 0 °C produced **17aa** and **17ab**, respectively. In this reaction, in situ generated C17-lithium alkoxides did not participate in formation of the C17,18-epoxide, and the free C17-hydroxy group of **17aa**/**17ab** was generated after aqueous work-up. TBS-protection of C17-secondary alcohol **17aa**/**17ab** and subsequent removal of the PMB group gave rise to C11-primary alcohol **19aa**/**19ab**. After Dess-Martin oxidation of alcohol **19aa**/**19ab** to aldehyde **20aa**/**20ab**,[16] Takai's vinyl iodination[17] of **20aa**/**20ab** with iodoform and $CrCl_2$ in THF and dioxane[18] yielded *E*-vinyl iodide **3aa**/**3ab**.[19] This five-step reaction sequence also converted **6a** and **6b** into the two C10–20 fragments **3ba** and **3bb**, respectively, upon alternative use of **5b**.

Achiral C1–9 fragment **4** was prepared in two steps from propargyl bromide **10** and alkyne **11**[20] (Scheme 5). Propargyl bromide **10** was treated with the copper alkynide of C1–6 alkyne **11**,[21] giving rise to diyne **21**. The C9-TMS group of thus obtained **21** was removed using TBAF in the presence of AcOH to provide **4**. Of note, buffering with AcOH effectively suppressed deprotonation of the acidic double propargylic protons at C7, thereby preventing decomposition of the product **4**.



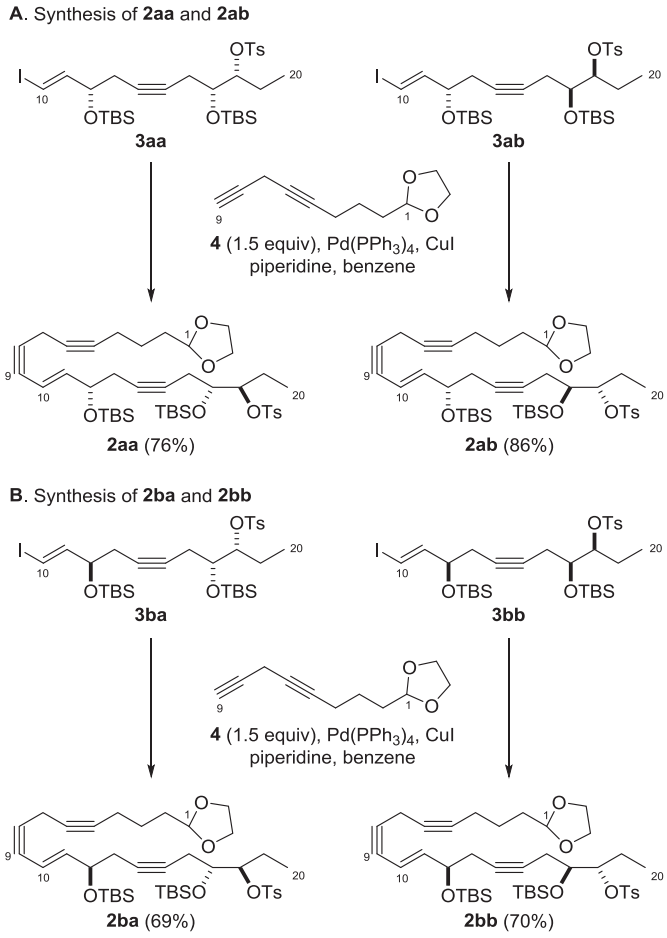
Scheme 4. Synthesis of the four C10–20 fragments **3aa**, **3ab**, **3ba**, and **3bb**.

The carbon backbone of **1** was then assembled by Sonogashira coupling between C10–20 fragments **3** and C1–9 fragment **4** (Scheme 6).[22] Separate treatment of the four stereoisomers **3aa**,



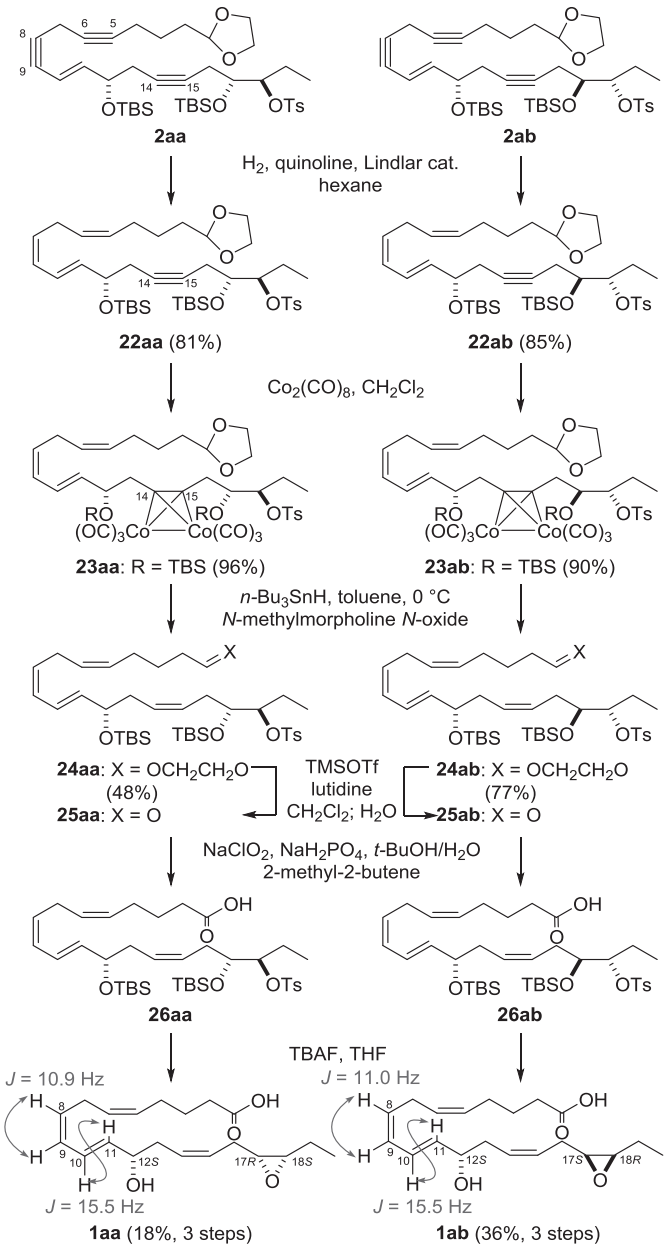
Scheme 5. Synthesis of the C1–9 fragment **4**.

3ab, **3ba** and **3bb** with **4** in the presence of catalytic $Pd(PPh_3)_4$ and CuI induced C–C bond formation to yield triynes **2aa**, **2ab**, **2ba** and **2bb**, respectively. Thus, the three S_N2-alkynylation reactions and one Sonogashira coupling reactions efficiently built the appropriately functionalized carbon skeleton of **1** from six simple units.



Scheme 6. Assembly of the carbon backbone of **1**.

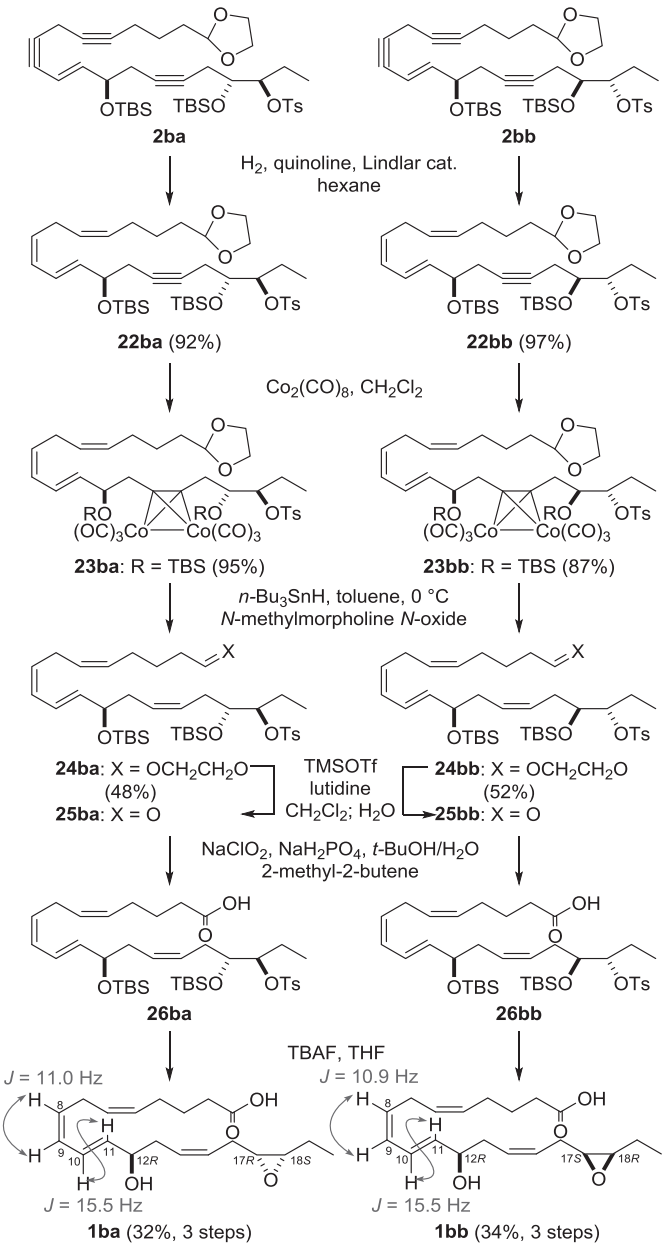
Next, we focused on reduction of the three internal alkynes (C5–6, C8–9, and C14–15) of **2aa** to the corresponding *Z*-alkenes of **24aa** without touching the preexisting *E*-alkene and generating *Z*-alkenes (Scheme 7). This transformation turned out to be challenging. Lindlar reduction[23] of triyne **2aa** in the presence of quinoline in hexane smoothly effected reduction of two of the three alkynes, leading to monoyne **22aa** with the two *Z*-alkenes. However, the most hindered C14–15 alkyne, surrounded by two proximal TBSO groups, was resistant to hydrogenation conditions. For instance, application of an excess amount of Lindlar catalyst or increasing the reaction time induced over-reduction of the less hindered alkenes prior to reduction of the remaining C14–15 alkyne of **22aa**. Hence, an alternative approach was required to realize high chemoselective reduction of the alkyne in the presence of multiple alkenes.



Scheme 7. Total synthesis of (12*S*,17*R*,18*S*)-**1aa** and (12*S*,17*S*,18*R*)-**1ab**.

Recently, we have modified the Isobe reduction[24] and developed a robust Co-complexation/decomplexation protocol for formation of the *Z*-alkene from the hindered alkyne.[25] This highly chemoselective method was applied to **22aa** (Scheme 7). The C14–15 alkyne of **22aa** was first converted to the alkyne-dicobalt hexacarbonyl complex with $Co_2(CO)_8$ to afford **23aa**. The Co-complex moiety of **23aa** was smoothly reduced to the *Z*-alkene by the action of *n*-Bu_3SnH (15 equiv) and *N*-methylmorpholine *N*-oxide (10 equiv) at 0 °C, delivering **24aa** with negligible formation of over-reduced compounds.[26] Moreover, the combination of the Lindlar and modified Isobe reductions was reliably applied to the stereoisomeric triyne **2ab**. Partial reduction of **2ab** with Lindlar catalyst produced **22ab**, which was then subjected to alkyne-dicobalt hexacarbonyl complex formation to furnish **23ab**. The subsequent reductive decomplexation under the above conditions gave rise to tetraene **24ab**.

The total synthesis of **1aa**/**1ab** was completed from the obtained tetraenes **24aa**/**24ab** (Scheme 7). The cyclic acetal of **24aa**/**24ab** was chemoselectively hydrolyzed in the presence of the two acid labile TBS ethers under Kita-Fujioka's conditions, leading to **25aa**/**25ab**.[27] Aldehyde **25aa**/**25ab** was then oxidized to carboxylic acid **26aa**/**26ab**. Finally, removal of the two TBS groups and formation of the C17,18-epoxide were simultaneously attained by treating with TBAF, transforming **26aa** and **26ab** into (12*S*,17*R*,18*S*)-**1aa** and (12*S*,17*S*,18*R*)-**1ab**, respectively. Hence, the chemically labile epoxide of **1aa**/**1ab** was constructed at the final step of the total synthesis via nucleophilic displacement of the C18-tosylate by the in situ formed C17-alkoxide. As illustrated in Scheme 8, the two diastereomeric triynes **2ba** and **2bb** were submitted to the same six-steps to produce (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**, respectively. The geometry of the conjugated *E*,*Z*-diene of **1aa**/**1ab**/**1ba**/**1bb** was confirmed from the H8–H9 and H10–H11 coupling constants, indicating its non-isomerization throughout the series of transformations from **22aa**/**22ab**/**22ba**/**22bb**. The total synthesis of the four isomers **1aa**, **1ab**, **1ba** and **1bb** allowed us to compare their retention times with that of the naturally occurring **1** using HPLC. As a result, the absolute structures of the EPA-derived natural lipids were established to be (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*R*,18*S*)-, and (5*Z*,8*Z*,10*E*,12*S*,14*Z*,17*S*,18*R*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acids (**1aa** and **1ab**).[9,28] Therefore, the natural forms were disclosed to be diastereomers at the C17,18-epoxide.



Scheme 8. Total synthesis of (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**.

A preliminary structure-activity relationship (SAR) study was performed using synthetic (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb** (Fig. 2). Specifically, the *anti*-inflammatory activities of these four compounds were evaluated using an in vivo inflammation model.[29] Zymosan A, a glucan from the yeast cell wall, was used to induce acute peritonitis in mice. Intravenous administration of as little as 1 ng of the 4 compounds blocked the infiltration of PMN leucocytes at 2 h in the inflamed peritoneal cavity, showing that all of the synthesized lipids possessed *anti*-inflammatory activity. Intriguingly, one of the natural forms, **1aa**, displayed more potent *anti*-inflammatory activity than the other natural form, **1ab**, and the activity of the unnatural compound **1ba** was stronger than those of natural **1ab** and unnatural **1bb**. These results together clarified the importance of the presence of the (17*R*,18*S*)-epoxide and the relative indifference of activity to the stereochemistry of the C12-hydroxy group.

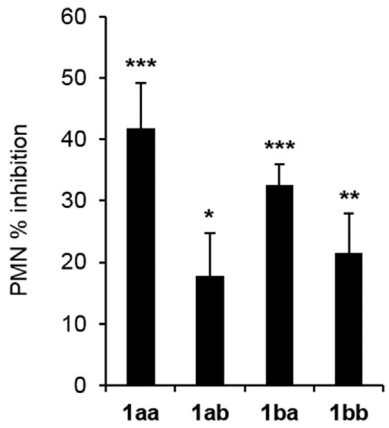


Fig. 2. Bioassay of synthetic **1aa**, **1ab**, **1ba** and **1bb**. The compounds (1 ng) were injected intravenously through the tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected, and the number of PMN leucocytes was counted. Values represent mean ± SE, n≥3, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ versus vehicle control.

3. Conclusion

We achieved the convergent total synthesis of the four stereoisomers of a new lipid mediator, (5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxy-17,18-epoxy-5,8,10,14-eicosatetraenoic acid (**1**). The stereoisomers, (12*S*,17*R*,18*S*)-**1aa**, (12*S*,17*S*,18*R*)-**1ab**, (12*R*,17*R*,18*S*)-**1ba** and (12*R*,17*S*,18*R*)-**1bb**, were synthesized from **7a**/**7b**, **8**, **9a**/**9b**, **10**, **11** and iodoform in 15 longest linear steps and 18 overall steps. The key features of the synthesis route include: i) construction of the carbon backbone of **1** through three S_N2 alkynylation reactions and one Sonogashira coupling reaction and ii) chemoselective formation of three *Z*-alkenes by stepwise reduction using Lindlar reduction of the two alkynes (C5–6 and C8–9) and modified Isobe reduction of the remaining C14–15 alkyne. The fully synthetic construction of the four isomers allowed both determination of the EPA-derived natural lipid mediators to be **1aa** and **1ab** and evaluation of their *anti*-inflammatory activities. The biological data revealed the importance of the stereochemistry of the epoxide: the isomers with the (17*R*,18*S*)-epoxide (**1aa**, **1ba**) were more potent than the isomers (**1ab**, **1bb**)

with the (17*S*,18*R*)-epoxide. More detailed functional and biological analyses of the synthesized compounds will be our next focus.

4. Experimental section

4.1. General methods

All reactions sensitive to air or moisture were carried out in dry solvents under argon atmosphere, unless otherwise noted. THF, CH_2Cl_2 and toluene were purified by Glass Contour solvent dispensing system. Et_3N and piperidine were purified by distillation over CaH_2. $BF_3\cdot OEt_2$ was purified by distillation over P_2O_5. All other reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel [granular, neutral, 32–53 μm; spherical, carboxylic acid supported (Chromatorex-ACD COOH), 45–75 μm]. Medium pressure liquid chromatography was carried out by using a system equipped with a pre-packed silica gel 40 μm (14 g, 20×75 mm; 45 g, 26×150 mm). Melting points are reported uncorrected. Optical rotations were measured using the sodium D line. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using an FT/IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 or 500 MHz, and 100 or 150 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ for ^1H NMR (δ=7.26), $CDCl_3$ for ^{13}C NMR (δ=77.0), C_6HD_5 for ^1H NMR (δ=7.16), CD_2HOD for ^1H NMR (δ=3.31), and CD_3OD for ^{13}C NMR (δ=49.0) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. The carbon numbering of the synthetic compounds corresponds to that of **1**. High resolution mass spectra were measured on ESI-TOF or DART-TOF mass spectrometers.

*4.1.1. C11–15 fragment **5a**.* *n*-BuLi (1.35 M in hexane, 12.5 mL, 16.9 mmol) was added to a solution of trimethylsilyl acetylene **8** (2.3 mL, 16 mmol) in THF (34 mL) at −78 °C. The solution was stirred at −78 °C for 10 min, warmed to 0 °C and stirred for 50 min. After the mixture was cooled to −78 °C, $BF_3\cdot OEt_2$ (2.0 mL, 16 mmol) and a solution of **7a** (1.56 g, 8.04 mmol) in THF (6.0 mL) were successively added. The reaction mixture was stirred at −78 °C for 30 min and warmed to −40 °C over 1 h, and then saturated aqueous NH_4Cl solution (30 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 4/1) to afford the crude alcohol **12a**, which was used in the next reaction without further purification.

K_2CO_3 (1.44 g, 10.4 mmol) was added to a solution of the above crude alcohol **12a** in MeOH (62 mL) at room temperature. The reaction mixture was stirred at room temperature for 11 h. After the mixture was cooled to 0 °C, saturated aqueous NH_4Cl solution (10 mL) was added. The resultant mixture was extracted with Et_2O (60 mL ×4), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 4/1 to 1/1) to afford the crude alcohol, which was used in the next reaction without further purification.

TBSOTf (0.28 mL, 1.2 mmol) was added to a solution of the above crude alcohol and 2,6-lutidine (0.32 mL, 2.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, warmed to room temperature and stirred for 1.5 h, and then TBSOTf (0.40 mL, 1.7 mmol) and 2,6-lutidine (0.68 mL, 5.8 mmol) were added. After 20 min, TBSOTf (1.4 mL, 5.9 mmol) and 2,6-lutidine (1.3 mL, 11 mmol) were added. After further 40 min, TBSOTf (1.0 mL, 4.4 mmol) and 2,6-lutidine (0.70 mL, 6.0 mmol) were added again. The mixture was stirred for 10 min and cooled to 0 °C, and then saturated aqueous $NaHCO_3$ solution (10 mL) was added. The resultant mixture was extracted with Et_2O (60 mL ×3), and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 7/1) to afford C11–15 fragment **5a** (2.61 g, 7.79 mmol) in 97% yield over three steps: colorless oil: $[\alpha]_D^{28}$ −0.60 (*c* 0.90, $CHCl_3$). The other analytical data of **5a** were identical to those of **5b**.

*4.1.2. C11–15 fragment **5b**.* According to the synthetic procedure of **5a**, C11–15 fragment **5b** (1.58 g, 4.73 mmol) was synthesized from **7b** (970 mg, 5.00 mmol) and trimethylsilyl acetylene **8** (1.4 mL, 9.9 mmol) in 95% yield over three steps by using *n*-BuLi (1.6 M in hexane, 6.6 mL, 11 mmol) and $BF_3\cdot OEt_2$ (1.2 mL, 9.7 mmol) in THF (25 mL) for the first reaction, K_2CO_3 (899 mg, 6.51 mmol) in MeOH (40 mL) for the second, and TBSOTf (1.3 mL, 5.7 mmol) and 2,6-lutidine (1.4 mL, 12 mmol) in CH_2Cl_2 (45 mL) for the third. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 6/1 to 5/1) for the first reaction, on silica gel (45 g, hexane/EtOAc 6/1 to 2/1) for the second and on silica gel (45 g, hexane to hexane/EtOAc 30/1) for the third: colorless oil; $[\alpha]_D^{27}$ +0.51 (*c* 1.1, $CHCl_3$); IR (neat) ν 3310, 2953, 2929, 2856, 2121, 1613, 1514, 1464, 1249, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.95 (1H, t, *J*=2.7 Hz, H15), 2.35 (1H, ddd, *J*=16.9, 6.0, 2.7 Hz, H13a), 2.47 (1H, ddd, *J*=16.9, 6.0, 2.7 Hz, H13b), 3.45 (1H, dd, *J*=14.2, 5.5 Hz, H11a), 3.47 (1H, dd, *J*=14.2, 5.5 Hz, H11b), 3.81 (3H, s, OMe), 3.96 (1H, tt, *J*=6.0, 5.5 Hz, H12), 4.47 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J*=8.7 Hz, aromatic), 7.26 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.6, 18.1, 24.7, 25.8 (×3), 55.3, 69.8, 70.2, 73.0, 73.3, 81.4, 113.7 (×2), 129.2 (×2), 130.4, 159.1; HRMS (ESI) calcd for $C_{19}H_{30}O_3SiNa$ 357.1856 $[M+Na]^+$, found 357.1862.

*4.1.3. Triol **9a**.* A solution of **14a** (3.71 g, 8.38 mmol, a 1.0:2.5:0.56:0.89 mixture of **14a**, *t*-BuOH, Et_2O and pentane) in THF (20 mL) was added to a suspension of $LiAlH_4$ (1.28 g, 33.7 mmol) in THF (65 mL) at 0 °C over 25 min. The reaction mixture was warmed to room temperature and stirred for 5 h. After the mixture was cooled to 0 °C, saturated aqueous potassium sodium tartrate solution (50 mL) and *n*-BuOH (100 mL) were added. The resultant mixture was warmed to room temperature and stirred for 19 h. After separation, the aqueous layer was extracted with *n*-BuOH (20 mL ×4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was performed by flash column chromatography on silica gel (30 g, $CHCl_3$/MeOH 9/1 to 5/1) to afford triol **9a** (783 mg, 6.51 mmol) in 78% yield: colorless oil. The analytical data of **9a** were identical to those reported previously.[12b]

*4.1.4. Triol **9b**.* According to the synthetic procedure of **9a**, triol **9b** (390 mg, 3.25 mmol) was synthesized from **14b** (1.00 g, 3.39 mmol, a 1.0:0.80:0.40:0.80 mixture of **14b**, *t*-BuOH, Et_2O and pentane) in 96% yield by using $LiAlH_4$ (520 mg, 13.7 mmol) in THF (36 mL). Purification was performed by flash column chromatography on silica gel (20 g, $CHCl_3$/MeOH 5/1): colorless oil. The other analytical data of **9b** were identical to those reported previously.[12b]

*4.1.5. C16–20 fragment **6a**.* NaH (60 wt % in mineral oil, 784 mg, 19.6 mmol) was added to a solution of **9a** (783 mg, 6.53 mmol) in THF (130 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at 0 °C for 50 min, warmed to room temperature, and stirred

for 40 min. After the mixture was cooled to 0 °C, NaH (60 wt % in mineral oil, 392 mg, 9.80 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1.5 h, and then tosyl imidazole (2.89 g, 13.0 mmol) was added. The reaction mixture was stirred at room temperature for 17 h. After the mixture was cooled to 0 °C, pH 7 phosphate buffer (20 mL) was added. The resultant mixture was extracted with EtOAc (150 mL and 100 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 20/1 to 9/1) to afford C16–20 fragment **6a** (1.16 g, 4.53 mmol) in 69% yield: white solid; mp 61 °C; $[\alpha]_D^{18}$−16 (*c* 1.0, $CHCl_3$); IR (neat) ν 2976, 2935, 2886, 1598, 1459, 1358, 1189, 1174, 1097, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J*=7.4 Hz, H20), 1.76 (2H, qd, *J*=7.4, 6.4 Hz, H19), 2.44 (3H, s, C*H*$_3$ of Ts), 2.63 (1H, dd, *J*=4.6, 2.3 Hz, H16a), 2.78 (1H, dd, *J*=4.6, 4.6 Hz, H16b), 3.05 (1H, ddd, *J*=6.4, 4.6, 2.3 Hz, H17), 4.28 (1H, dt, *J*=6.4, 6.4 Hz, H18), 7.33 (2H, d, *J*=7.8 Hz, aromatic), 7.82 (2H, d, *J*=7.8 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 21.5, 25.0, 44.6, 52.3, 84.6, 127.7 (×2), 129.5 (×2), 134.0, 144.5; HRMS (ESI) calcd for $C_{12}H_{16}O_4SNa$ 279.0662 $[M+Na]^+$, found 279.0661.

*4.1.6. C16–20 fragment **6b**.* According to the synthetic procedure of **6a**, C16–20 fragment **6b** (549 mg, 2.14 mmol) was synthesized from **9b** (393 mg, 3.28 mmol) in 65% yield by using NaH (60 wt % in mineral oil, 789 mg, 19.7 mmol) and tosyl imidazole (2.97 g, 13.4 mmol) in THF (65 mL). Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1): white solid; mp 61–62 °C; $[\alpha]_D^{18}$+16 (*c* 1.0, $CHCl_3$). The other analytical data of **6b** were identical to those of **6a** and the previously reported data.[15]

*4.1.7. TBS ether **18aa**.* *n*-BuLi (1.35 M in hexane, 1.7 mL, 2.3 mmol) was added to a solution of **5a** (722 mg, 2.16 mmol) in THF (3.0 mL) at −78 °C. The solution was stirred at −78 °C for 15 min, warmed to 0 °C and stirred for 30 min. After the mixture was cooled to −78 °C, $BF_3\cdot OEt_2$ (0.27 mL, 2.2 mmol) and a solution of **6a** (221 mg, 0.863 mmol) in THF (1.3 mL) were successively added. The reaction mixture was stirred at −78 °C for 30 min, warmed to 0 °C and stirred for 2 h, and then saturated aqueous NH_4Cl solution (10 mL) was added. The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 9/1 to 6/1 to 4/1 to 2/1) to afford the crude **17aa**, which was used in the next reaction without further purification.

TBSOTf (0.29 mL, 1.3 mmol) was added to a solution of the above crude **17aa** and Et_3N (0.44 mL, 3.1 mmol) in 1,2-dichloroethane (6.0 mL) at 0 °C. The reaction mixture was warmed to 30 °C and stirred for 1 h, and then TBSOTf (0.14 mL, 0.61 mmol) and Et_3N (0.13 mL, 0.93 mmol) were added. The reaction mixture was stirred for 20 min, and then was poured into saturated aqueous $NaHCO_3$ solution (15 mL). The resultant mixture was extracted with EtOAc (20 mL and 10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) to afford TBS ether **18aa** (401 mg, 0.570 mmol) in 66% over two steps: colorless oil; $[\alpha]_D^{24}$+17 (*c* 0.97, $CHCl_3$). The other analytical data of **18aa** were identical to those of **18bb**.

*4.1.8. TBS ether **18ab**.* According to the synthetic procedure of **18aa**, **18ab** (319 mg, 0.452 mmol) was synthesized from **5a** (504 mg, 1.50 mmol) and **6b** (155 mg, 0.605 mmol) in 75% yield over two steps by using *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.6 mmol) and $BF_3\cdot OEt_2$ (0.19 mL, 1.5 mmol) in THF (3.0 mL) for the first reaction, and TBSOTf (0.23 mL, 1.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in 1,2-dichloroethane (5.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{26}$−7.5 (*c* 1.1, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1614, 1514, 1463, 1363, 1250, 1177, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.065 (3H, s, C*H*$_3$ of TBS), 0.067 (3H, s, C*H*$_3$ of TBS), 0.09 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.76 (1H, m, H19b), 2.14–2.43 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.42 (1H, dd, *J*=10.0, 5.5 Hz, H11a), 3.50 (1H, dd, *J*=10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.87–3.94 (2H, m, H12 and 17), 4.38 (1H, ddd, *J*=8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.87 (2H, d, *J*=8.7 Hz, aromatic), 7.26 (2H, d, *J*=8.7 Hz, aromatic), 7.32 (2H, d, *J*=8.7 Hz, aromatic), 7.80 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.61, −4.56, 10.1, 17.9, 18.2, 21.5, 21.6, 22.3, 25.0, 25.7 (×3), 25.8 (×3), 55.2, 70.8, 71.5, 73.0, 73.6, 78.4, 78.7, 85.5, 113.7 (×2), 127.8 (×2), 129.1 (×2), 129.7 (×2), 130.6, 134.3, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3470.

*4.1.9. TBS ether **18ba**.* According to the synthetic procedure of **18aa**, **18ba** (444 mg, 0.629 mmol) was synthesized from **5b** (711 mg, 2.12 mmol) and **6a** (219 mg, 0.855 mmol) in 74% yield over two steps by using *n*-BuLi (1.6 M in hexane, 1.4 mL, 2.2 mmol) and $BF_3\cdot OEt_2$ (0.26 mL, 2.1 mmol) in THF (4.3 mL) for the first reaction, and TBSOTf (0.38 mL, 1.66 mmol) and Et_3N (0.51 mL, 3.7 mmol) in 1,2-dichloroethane (6.0 mL) for the second. Purification was performed by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 3/1) for the first reaction, and flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 9/1) for the second: colorless oil; $[\alpha]_D^{24}$+7.4 (*c* 1.0, $CHCl_3$). The other analytical data of **18ba** were identical to those of **18ab**.

*4.1.10. TBS ether **18bb**.* According to the synthetic procedure of **18aa**, **18bb** (781 mg, 1.11 mmol) was synthesized from **5b** (988 mg, 2.95 mmol) and **6b** (306 mg, 1.20 mmol) in 93% yield over two steps by using *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol) and $BF_3\cdot OEt_2$ (0.37 mL, 3.0 mmol) in THF (5.9 mL) for the first reaction, and TBSOTf (0.95 mL, 4.1 mmol) and Et_3N (1.4 mL, 10 mmol) in 1,2-dichloroethane (12 mL) for the second. Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 20/1 to 3/1) for the first reaction, and on silica gel (10 g, hexane to hexane/EtOAc 20/1) for the second: colorless oil; $[\alpha]_D^{26}$−15 (*c* 1.4, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1920, 1613, 1514, 1463, 1364, 1250, 1177, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (6H, s, C*H*$_3$ of TBS ×2), 0.08 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.88 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.76 (1H, m, H19b), 2.13–2.37 (4H, m, H13 and H16), 2.43 (3H, s, C*H*$_3$ of Ts), 3.41 (1H, dd, *J*=10.0, 6.0 Hz, H11a), 3.49 (1H, dd, *J*=10.0, 5.0 Hz, H11b), 3.80 (3H, s, OMe), 3.86–3.94 (2H, m, H12 and 17), 4.35 (1H, ddd, *J*=8.7, 4.1, 4.1 Hz, H18), 4.48 (2H, s, OC*H*$_2$Ar), 6.86 (2H, d, *J*=8.2 Hz, aromatic), 7.26 (2H, d, *J*=8.2 Hz, aromatic), 7.32 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.64, −4.59, 10.1, 17.9, 18.1, 21.4, 21.6, 22.2, 25.0, 25.7 (×3), 25.8 (×3), 55.2, 70.8, 71.5, 72.9, 73.5, 78.4, 78.7, 85.5, 113.6 (×2), 127.8 (×2), 129.1 (×2), 129.7 (×2), 130.5, 134.2, 144.5, 159.0; HRMS (ESI) calcd for $C_{37}H_{60}O_7SSi_2Na$ 727.3490 $[M+Na]^+$, found 727.3469.

*4.1.11. Alcohol **19aa**.* DDQ (284 mg, 1.28 mmol) was added to a solution of **18aa** (584 mg, 0.828 mmol) in a mixture of CH_2Cl_2 (8.0 mL) and pH 7 phosphate buffer (0.8 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. After the

mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ solution (10 mL) was added. The resultant mixture was extracted with EtOAc (50 mL and 40 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) to afford alcohol **19aa** (449 mg, 0.767 mmol) in 93% yield: colorless oil; $[\alpha]_D^{25}$+25 (*c* 1.2, $CHCl_3$). The other analytical data of **19aa** were identical to those of **19bb**.

*4.1.12. Alcohol **19ab**.* According to the synthetic procedure of alcohol **19aa**, **19ab** (452 mg, 0.773 mmol) was synthesized from **18ab** (736 mg, 1.04 mmol) in 74% yield by using DDQ (402 mg, 1.81 mmol) in a mixture of CH_2Cl_2 (80 mL) and pH 7 phosphate buffer (8 mL). The residue was purified twice by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1) and flash column chromatography on silica gel (15 g, hexane/EtOAc 20/1 to 6/1): colorless oil; $[\alpha]_D^{28}$−6.6 (*c* 2.0, $CHCl_3$); IR (neat) ν 3571, 2953, 2929, 2857, 1923, 1599, 1463, 1363, 1255, 1189, 1176, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 1.92 (1H, dd, *J*=6.4, 6.4 Hz, O*H*), 2.14–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.58 (1H, ddd, *J*=11.0, 7.3, 5.0 Hz, H11a), 3.67 (1H, ddd, *J*=11.0, 5.5, 3.6 Hz, H11b), 3.85 (1H, m, H12), 3.90 (1H, m, H17), 4.37 (1H, ddd, *J*=8.3, 8.3, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.80 (2H, d, *J*=8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.93, −4.85, −4.68, −4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (×3), 25.7 (×3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.4, 127.7 (×2), 129.7 (×2), 134.2, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2919.

*4.1.13. Alcohol **19ba**.* According to the synthetic procedure of alcohol **19aa**, **19ba** (420 mg, 0.718 mmol) was synthesized from **18ba** (523 mg, 0.742 mmol) in 97% yield by using DDQ (254 mg, 1.12 mmol) in a mixture of CH_2Cl_2 (7.0 mL) and pH 7 phosphate buffer (0.7 mL). The residue was purified by medium pressure liquid chromatography on silica gel (45 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$+8.9 (*c* 1.1, $CHCl_3$). The other analytical data of **19ba** were identical to those of **19ab**.

*4.1.14. Alcohol **19bb**.* According to the synthetic procedure of **19aa**, alcohol **19bb** (606 mg, 1.04 mmol) was synthesized from **18bb** (781 mg, 1.11 mmol) in 94% yield by using DDQ (279 mg, 1.23 mmol) in a mixture of CH_2Cl_2 (10 mL) and pH 7 phosphate buffer (1.0 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1), and three times by medium pressure liquid chromatography on silica gel (45 g, hexane to hexane/EtOAc 4/1; 45 g, hexane to hexane/EtOAc 4/1; 14 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{27}$−24 (*c* 0.91, $CHCl_3$); IR (neat) ν 3465, 2954, 2929, 2857, 1644, 1463, 1363, 1255, 1189, 1177, 1100, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.11 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J*=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 1.93 (1H, dd, *J*=7.3, 5.9 Hz, O*H*), 2.15–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.57 (1H, ddd, *J*=11.9, 7.3, 5.0 Hz, H11a), 3.68 (1H, ddd, *J*=11.9, 5.9, 3.6 Hz, H11b), 3.85 (1H, m, H17), 3.91 (1H, m, H12), 4.35 (1H, ddd, *J*=8.2, 8.2, 4.1 Hz, H18), 7.34 (2H, d, *J*=8.7 Hz, aromatic), 7.79 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.94, −4.86, −4.69, −4.66, 10.1, 17.9, 18.0, 21.3, 21.5, 22.2, 24.1, 25.6 (×3), 25.7 (×3), 65.6, 71.3, 71.7, 78.0, 78.9, 85.5, 127.7 (×2), 129.7 (×2), 134.1, 144.6; HRMS (ESI) calcd for $C_{29}H_{52}O_6SSi_2Na$ 607.2915 $[M+Na]^+$, found 607.2897.

*4.1.15. Aldehyde **20aa**.* Dess–Martin periodinane (493 mg, 1.16 mmol) was added to a suspension of alcohol **19aa** (445 mg, 0.761 mmol) and $NaHCO_3$ (625 mg, 7.44 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then H_2O (10 mL) was added. The resultant mixture was extracted with Et_2O (50 mL and 30 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 4/1) to afford aldehyde **20aa** (431 mg, 0.739 mmol) in 97% yield: colorless oil; $[\alpha]_D^{24}$+12 (*c* 1.0, $CHCl_3$). The other analytical data of **20aa** were identical to those of **20bb**.

*4.1.16. Aldehyde **20ab**.* According to the synthetic procedure of aldehyde **20aa**, **20ab** (303 mg, 0.520 mmol) was synthesized from **19ab** (320 mg, 0.547 mmol) in 95% yield by using Dess–Martin periodinane (471 mg, 1.11 mmol) and $NaHCO_3$ (449 mg, 5.35 mmol) in CH_2Cl_2 (32 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 10 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{27}$−22 (*c* 1.6, $CHCl_3$); IR (neat) ν 2953, 2929, 2857, 1741, 1600, 1471, 1463, 1363, 1255, 1177, 1120, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.117 (3H, s, C*H*$_3$ of TBS), 0.122 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.20 (1H, dd, *J*=16.0, 7.8 Hz, H16a), 2.37 (1H, m, H16b), 2.45–2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=7.8, 4.6 Hz, H17), 4.08 (1H, td, *J*=6.4, 1.4 Hz, H12), 4.36 (1H, dt, *J*=9.2, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.80 (2H, d, *J*=8.2 Hz, aromatic), 9.63 (1H, t, *J*=1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.85, −4.78, −4.6, 10.1, 17.9, 18.2, 21.4, 21.6, 22.2, 23.5, 25.67 (×3), 25.69 (×3), 71.3, 76.1, 76.6, 79.8, 85.4, 127.8 (×2), 129.7 (×2), 134.2, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3011.

*4.1.17. Aldehyde **20ba**.* According to the synthetic procedure of aldehyde **20aa**, **20ba** (395 mg, 0.679 mmol) was synthesized from **19ba** (420 mg, 0.718 mmol) in 95% yield by using Dess–Martin periodinane (461 mg, 1.09 mmol) and $NaHCO_3$ (593 mg, 7.06 mmol) in CH_2Cl_2 (7.2 mL). Purification was performed twice by flash column chromatography on silica gel (20 g, hexane/EtOAc 9/1 to 6/1; 20 g, hexane/EtOAc 9/1 to 6/1): colorless oil; $[\alpha]_D^{24}$+22 (*c* 1.7, $CHCl_3$). The other analytical data of **20ba** were identical to those of **20ab**.

*4.1.18. Aldehyde **20bb**.* According to the synthetic procedure of aldehyde **20aa**, **20bb** (577 mg, 0.990 mmol) was synthesized from **19bb** (606 mg, 1.04 mmol) in 95% yield by using Dess–Martin periodinane (887 mg, 2.09 mmol) and $NaHCO_3$ (832 mg, 9.90 mmol) in CH_2Cl_2 (10 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane/EtOAc 9/1 to 4/1): colorless oil; $[\alpha]_D^{23}$−13 (*c* 0.83, $CHCl_3$); IR (neat) ν 2953, 2930, 2857, 1741, 1463, 1365, 1254, 1177, 1119, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.12 (6H, s, C*H*$_3$ of TBS ×2), 0.75 (3H, t, *J*=7.3 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.49 (1H, m, H19a), 1.75 (1H, m, H19b), 2.19 (1H, ddt, *J*=16.5, 8.2, 2.3 Hz, H16a), 2.35 (1H, m, H16b), 2.45–2.55 (2H, m, H13), 2.45 (3H, s, C*H*$_3$ of Ts), 3.92 (1H, dt, *J*=7.3, 4.6 Hz, H17), 4.07 (1H, td, *J*=6.8, 1.4 Hz, H12), 4.34 (1H, dt, *J*=9.2, 3.7 Hz, H18), 7.34 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic), 9.63 (1H, t, *J*=1.4 Hz, H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.92, −4.87, −4.82, −4.6, 10.1, 17.9, 18.2, 21.3, 21.6, 22.2, 23.4, 25.6 (×3), 25.7 (×3), 71.3, 76.0, 76.5, 79.7, 85.4, 127.8 (×2), 129.7 (×2), 134.1, 144.6, 202.1; HRMS (ESI) calcd for $C_{30}H_{54}O_7SSi_2Na$ 637.3021 $[M+MeOH+Na]^+$, found 637.3020.

*4.1.19. C10–20 fragment **3aa**.* A solution of iodoform (676 mg, 1.72 mmol) and aldehyde **20aa** (431 mg, 0.739 mmol) in 1,4-dioxane (4.4 mL) was added to a suspension of $CrCl_2$ (629 mg,

5.11 mmol) in a mixture of THF (2.9 mL) and 1,4-dioxane (4.4 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then H_2O (5 mL) was added. The resultant mixture was extracted with Et_2O (15 mL ×3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified flash column chromatography on silica gel (25 g, hexane to hexane/CH_2Cl_2 1/1) to afford C10–20 fragment **3aa** (389 mg, 0.551 mmol) in 75% yield: colorless oil; $[\alpha]_D^{24}$+40 (*c* 1.3, $CHCl_3$). The other analytical data of **3aa** were identical to those of **3bb**.

*4.1.20. C10–20 fragment **3ab**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3ab** (244 mg, 0.346 mmol) was synthesized from aldehyde **20ab** (291 mg, 0.499 mmol) in 69% yield by using $CrCl_2$ (434 mg, 3.53 mmol) and iodoform (469 mg, 1.19 mmol) in a mixture of THF (2.0 mL) and 1,4-dioxane (6.2 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{27}$+12 (*c* 1.1, $CHCl_3$); IR (neat) ν 2954, 2929, 2857, 1600, 1463, 1363, 1255, 1189, 1177, 1098, 931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s, C*H*$_3$ of TBS ×2), 0.07 (6H, s, C*H*$_3$ of TBS ×2), 0.77 (3H, t, *J*=7.5 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.50 (1H, m, H19a), 1.76 (1H, m, H19b), 2.17–2.42 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=6.9, 4.5 Hz, H17), 4.18 (1H, m, H12), 4.37 (1H, dt, *J*=8.0, 4.0 Hz, H18), 6.32 (1H, dd, *J*=14.3, 1.8 Hz, H10), 6.66 (1H, dd, *J*=14.3, 5.2 Hz, H11), 7.34 (2H, d, *J*=8.6 Hz, aromatic), 7.80 (2H, d, *J*=8.6 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.95, −4.86, −4.81, −4.6, 10.2, 17.9, 18.1, 21.4, 21.6, 22.2, 25.68 (×3), 25.72 (×3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.4, 127.8 (×2), 129.7 (×2), 134.2, 144.5, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1952.

*4.1.21. C10–20 fragment **3ba**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3ba** (388 mg, 0.550 mmol) was synthesized from aldehyde **20ba** (395 mg, 0.677 mmol) in 81% yield by using $CrCl_2$ (591 mg, 4.84 mmol) and iodoform (636 mg, 1.61 mmol) in a mixture of THF (2.7 mL) and 1,4-dioxane (4.0 mL). Purification was performed by flash column chromatography on silica gel (20 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{26}$−7.9 (*c* 1.1, $CHCl_3$). The other analytical data of **3ba** were identical to those of **3ab**.

*4.1.22. C10–20 fragment **3bb**.* According to the synthetic procedure of C10–20 fragment **3aa**, **3bb** (613 mg, 0.868 mmol) was synthesized from aldehyde **20bb** (577 mg, 0.990 mmol) in 88% yield by using $CrCl_2$ (836 mg, 6.80 mmol) and iodoform (903 mg, 2.29 mmol) in a mixture of THF (4.0 mL) and 1,4-dioxane (12.4 mL). Purification was performed by flash column chromatography on silica gel (30 g, hexane to hexane/CH_2Cl_2 1/1): colorless oil; $[\alpha]_D^{24}$−41 (*c* 1.0, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1917, 1600, 1463, 1363, 1255, 1188, 1177, 1098, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.08 (3H, s, C*H*$_3$ of TBS), 0.76 (3H, t, *J*=7.4 Hz, H20), 0.87 (9H, s, *t*-Bu of TBS), 0.89 (9H, s, *t*-Bu of TBS), 1.51 (1H, m, H19a), 1.75 (1H, m, H19b), 2.16–2.40 (4H, m, H13 and H16), 2.45 (3H, s, C*H*$_3$ of Ts), 3.91 (1H, dt, *J*=8.7, 4.5 Hz, H17), 4.19 (1H, m, H12), 4.35 (1H, dt, *J*=8.7, 4.1 Hz, H18), 6.31 (1H, dd, *J*=14.6, 1.4 Hz, H10), 6.66 (1H, dd, *J*=14.6, 5.5 Hz, H11), 7.34 (2H, d, *J*=8.7 Hz, aromatic), 7.80 (2H, d, *J*=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.94, −4.88, −4.81, −4.6, 10.2, 17.9, 18.2, 21.3, 21.6, 22.2, 25.68 (×3), 25.73 (×3), 28.2, 71.4, 73.9, 76.6, 77.6, 79.5, 85.5, 127.8 (×2), 129.7 (×2), 134.1, 144.6, 147.5; HRMS (ESI) calcd for $C_{30}H_{51}IO_5SSi_2Na$ 729.1933 $[M+Na]^+$, found 729.1923.

*4.1.23. C1–9 fragment **4**.* A mixture of CuI (287 mg, 1.51 mmol), NaI (227 mg, 1.51 mmol) and Cs_2CO_3 (491 mg, 1.51 mmol) was dried in vacuo at room temperature. After the mixture was cooled to 0 °C, a solution of propargy bromide **10** (0.27 mL, 1.67 mmol) in DMF (2.6 mL) was added. The mixture was stirred at 0 °C for 5 min, and then a solution of alkyne **11** (332 mg, 1.80 mmol, a 1.0:0.27:0.30 mixture of **11**, Et_2O and pentane) in DMF (2.6 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. The resultant mixture was filtered through a pad of Celite with Et_2O. The filtrate was extracted with Et_2O (20 mL and 10 mL ×3), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 20/1) to afford the crude **21**, which was used in the next reaction without further purification.

AcOH (0.21 mL, 3.7 mmol) and TBAF (1.0 M in THF, 3.7 mL, 3.7 mmol) were successively added to a solution of the above crude **21** in THF (50 mL) at −5 °C. The reaction mixture was stirred at −5 °C for 1 h, warmed to room temperature, and stirred for 2 h. Then saturated aqueous NH_4Cl solution (15 mL) was added. The resultant mixture was extracted Et_2O (50 mL), and the organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 20/1) to afford C1–9 fragment **4** (165 mg, 0.927 mmol) in 56% over two steps: colorless oil; IR (neat) ν 3288, 2953, 2882, 2233, 2124, 1473, 1455, 1435, 1414, 1312, 1135, 1033, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59–1.67 (2H, m, H3), 1.73–1.80 (2H, m, H2), 2.05 (1H, t, *J*=2.7 Hz, H9), 2.23 (2H, tt, *J*=7.3, 2.7 Hz, H4), 3.14 (2H, dt, *J*=2.7, 2.7 Hz, H7), 3.81–4.01 (4H, m, acetal), 4.87 (1H, t, *J*=4.6 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 18.4, 22.9, 32.7, 64.7 (×2), 68.4, 73.4, 78.7, 80.5, 104.0; HRMS (DART) calcd for $C_{11}H_{15}O_2$ 179.1067 $[M+H]^+$, found 179.1073.

*4.1.24. Triyne **2aa**.* A mixture of $Pd(PPh_3)_4$ (58.5 mg, 50.6 μmol), CuI (19.3 mg, 0.101 mmol), piperidine (0.10 mL, 1.0 mmol), and C10–20 fragment **3aa** (237 mg, 0.336 mmol) in benzene (2.5 mL) was added to a solution of **4** (90.6 mg, 0.509 mmol) in benzene (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. The resultant mixture was extracted with Et_2O (10 mL ×2) and EtOAc (10 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1) to afford **2aa** (192 mg, 0.254 mmol) in 76% yield: pale yellow oil. Triyne **2aa** was immediately used in the next reaction due to its instability under air. The ^1H NMR spectrum of **2aa** was identical to that of **2bb**.

*4.1.25. Triyne **2ab**.* According to the synthetic procedure of triyne **2aa**, **2ab** (152 mg, 0.201 mmol) was synthesized from **3ab** (166 mg, 0.235 mmol) and **4** (63.4 mg, 0.356 mmol) in 86% yield by using $Pd(PPh_3)_4$ (41.0 mg, 35.5 μmol), CuI (13.5 mg, 70.9 mmol) and piperidine (70 μL, 0.71 mmol) in benzene (3.6 mL). Purification was performed by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 6/1). Triyne **2ab** was immediately used in the next reaction due to its instability under air: pale yellow oil; HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3828. The ^1H NMR spectrum of **2ab** was identical to that of **2ba**.

*4.1.26. Triyne **2ba**.* According to the synthetic procedure of triyne **2aa**, **2ba** (179 mg, 0.236 mmol) was synthesized from **3ba** (243 mg, 0.344 mmol) and **4** (92.2 mg, 0.518 mmol) in 69% yield by using $Pd(PPh_3)_4$ (60.0 mg, 51.9 μmol), CuI (20.3 mg, 0.106 mmol) and

piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 8 g, hexane to hexane/EtOAc 9/1). Triyne **2ba** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.03 (3H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.82 (3H, t, J=7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.53 (1H, m, H19a), 1.58–1.65 (2H, m, H3), 1.75–1.81 (3H, m, H2 and H19b), 1.86 (3H, s, CH_3 of Ts), 2.03 (2H, tt, J=6.9, 2.3 Hz, H4), 2.24–2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, J=1.8, 1.8 Hz, H7), 3.29–3.38 (2H, m, acetal), 3.45–3.54 (2H, m, acetal), 4.17 (1H, dt, J=6.8, 4.6 Hz, H17), 4.27 (1H, dt, J=5.5, 5.0 Hz, H12), 4.69 (1H, ddd, J=8.7, 4.6 Hz, H18), 4.73 (1H, t, J=5.0 Hz, H1), 5.94 (1H, ddt, J=16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, J=16.0, 5.0 Hz, H11), 6.75 (2H, d, J=8.2 Hz, aromatic), 7.83 (2H, d, J=8.2 Hz, aromatic).

*4.1.27. Triyne **2bb**.* According to the synthetic procedure of triyne **2aa**, **2bb** (181 mg, 0.240 mmol) was synthesized from **3bb** (242 mg, 0.342 mmol) and **4** (91.2 mg, 0.512 mmol) in 70% yield by using $Pd(PPh_3)_4$ (59.4 mg, 51.4 μmol), CuI (19.6 mg, 0.103 mmol) and piperidine (0.10 mL, 1.0 mmol) in benzene (5.1 mL). Purification was performed twice by flash column chromatography on silica gel (30 g, hexane to hexane/EtOAc 6/1; 30 g, hexane to hexane/EtOAc 9/1). Triyne **2bb** was immediately used in the next reaction due to its instability under air: pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 0.03 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.81 (3H, t, J=7.3 Hz, H20), 0.94 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.52 (1H, m, H19a), 1.58–1.65 (2H, m, H3), 1.75–1.81 (3H, m, H2 and H19b), 1.86 (3H, s, CH_3 of Ts), 2.03 (2H, tt, J=6.9, 2.3 Hz, H4), 2.24–2.33 (2H, m, H13a and H16a), 2.40 (1H, m, H13b or H16b), 2.53 (1H, m, H13b or H16b), 3.04 (2H, dt, J=1.8, 1.8 Hz, H7), 3.29–3.38 (2H, m, acetal), 3.45–3.54 (2H, m, acetal), 4.17 (1H, dt, J=6.8, 4.6 Hz, H17), 4.27 (1H, dt, J=5.5, 5.0 Hz, H12), 4.69 (1H, ddd, J=8.7, 4.6 Hz, H18), 4.73 (1H, t, J=5.0 Hz, H1), 5.93 (1H, ddt, J=16.0, 2.3, 1.8 Hz, H10), 6.37 (1H, dd, J=16.0, 5.0 Hz, H11), 6.75 (2H, d, J=8.2 Hz, aromatic), 7.83 (2H, d, J=8.2 Hz, aromatic); HRMS (ESI) calcd for $C_{41}H_{64}O_7SSi_2Na$ 779.3803 $[M+Na]^+$, found 779.3819.

*4.1.28. Alkyne **22aa**.* A suspension of triyne **2aa** (108 mg, 0.143 mmol), quinoline (0.20 mL, 1.7 mmol) and Lindlar catalyst (222 mg) in hexane (10 mL) was stirred at room temperature for 15 min under H_2 atmosphere (1 atm). Lindlar catalyst (50–100 wt %) was added in every 5–10 min until triyne **2aa** and the diyne intermediate were disappeared on TLC (540 mg of Lindlar catalyst was added in total). The reaction mixture was filtered through a pad of Celite with hexane, and the filtrate was concentrated. The residue was dissolved in EtOAc (15 mL). The resultant solution was washed with aqueous 0.2 M HCl solution (10 mL ×2), aqueous saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1) to afford alkyne **22aa** (88.2 mg, 0.116 mmol) in 81% yield: colorless oil; $[\alpha]_D^{25}$+38 (*c* 0.97, $CHCl_3$). The other analytical data of **22aa** were identical to those of **22bb**.

*4.1.29. Alkyne **22ab**.* According to the synthetic procedure of **22aa**, **22ab** (64.0 mg, 84.2 μmol) was synthesized from **2ab** (75.3 mg, 99.6 μmol) in 85% yield by using quinoline (0.14 mL, 1.2 mmol) and Lindlar catalyst (330 mg) in hexane (7.5 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$+15 (*c* 0.93, $CHCl_3$); IR (neat) ν 2953, 2928, 2856, 1599, 1471, 1462, 1364, 1257, 1177, 1099, 932 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s, CH_3 of TBS), 0.07 (6H, s, CH_3 of TBS ×2), 0.08 (3H, s, CH_3 of TBS), 0.76 (3H, t, J=7.8 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.63–1.70 (2H, m, H2), 1.76 (1H, m, H19b), 2.11 (2H, dt, J=7.3, 7.3 Hz, H4), 2.20–2.28 (2H, m, H13a and H16a), 2.33–2.41 (2H, m, H13b and H16b), 2.44 (3H, s, CH_3 of Ts), 2.92 (2H, m, H7), 3.82–3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.93–3.98 (2H, m, acetal), 4.30 (1H, dt, J=6.0, 6.0 Hz, H12), 4.37 (1H, ddd, J=8.7, 8.7, 3.6 Hz, H18), 4.85 (1H, t, J=5.0 Hz, H1), 5.33–5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, J=15.1, 5.0 Hz, H11), 6.00 (1H, dd, J=11.0, 11.0 Hz, H9), 6.45 (1H, dd, J=15.1, 11.0 Hz, H10), 7.33 (2H, d, J=8.7 Hz, aromatic), 7.80 (2H, d, J=8.7 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, -4.8, -4.61, -4.56, 10.1, 18.0, 18.3, 21.4, 21.6, 22.3, 23.9, 25.7 (×3), 25.8 (×3), 26.1, 27.0, 29.0, 33.4, 64.8 (×2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (×2), 128.0, 129.7 (×2), 129.9, 130.0, 134.3, 135.5, 144.5, one ^{13}C peak overlaps with other peaks; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4099.

*4.1.30. Alkyne **22ba**.* According to the synthetic procedure of **22aa**, **22ba** (84.3 mg, 0.111 mmol) was synthesized from **2ba** (91.1 mg, 0.120 mmol) in 92% yield by using quinoline (0.17 mL, 1.4 mmol) and Lindlar catalyst (462 mg) in hexane (9.0 mL). Purification was performed by flash column chromatography on silica gel (4 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{27}$−15 (*c* 1.4, $CHCl_3$). The other analytical data of **22ba** were identical to those of **22ab**.

*4.1.31. Alkyne **22bb**.* According to the synthetic procedure of **22aa**, **22bb** (96.0 mg, 0.126 mmol) was synthesized from **2bb** (98.1 mg, 0.130 mmol) in 97% yield by using quinoline (0.18 mL, 1.6 mmol) and Lindlar catalyst (800 mg) in hexane (10 mL). Purification was performed by flash column chromatography on silica gel (8 g, hexane to hexane/EtOAc 9/1): colorless oil; $[\alpha]_D^{24}$−37 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2929, 2856, 1461, 1364, 1254, 1177, 931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, CH_3 of TBS), 0.066 (3H, s, CH_3 of TBS), 0.071 (3H, s, CH_3 of TBS), 0.09 (3H, s, CH_3 of TBS), 0.76 (3H, t, J=7.5 Hz, H20), 0.86 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.64–1.70 (2H, m, H2), 1.75 (1H, m, H19b), 2.11 (2H, dt, J=7.4 Hz, H4), 2.15–2.29 (2H, m, H13a and H16a), 2.32–2.39 (2H, m, H13b and H16b), 2.44 (3H, s, CH_3 of Ts), 2.92 (2H, m, H7), 3.83–3.87 (2H, m, acetal), 3.90 (1H, m, H17), 3.94–3.98 (2H, m, acetal), 4.30 (1H, dt, J=6.0, 5.7 Hz, H12), 4.36 (1H, dt, J=9.0, 4.0 Hz, H18), 4.85 (1H, t, J=5.0 Hz, H1), 5.33–5.45 (3H, m, H5, H6 and H8), 5.79 (1H, dd, J=15.0, 5.5 Hz, H11), 6.00 (1H, dd, J=11.0, 11.0 Hz, H9), 6.54 (1H, dd, J=15.0, 11.0 Hz, H10), 7.33 (2H, d, J=8.5 Hz, aromatic), 7.80 (2H, d, J=8.5 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, −4.64, −4.59, 10.1, 17.9, 18.2, 21.4, 21.6, 22.3, 23.9, 25.7 (×3), 25.8 (×3), 26.0, 27.0, 29.0, 33.3, 64.8 (×2), 71.5, 71.8, 78.6, 78.7, 85.5, 104.5, 124.6, 127.8 (×2), 127.9, 129.7 (×2), 129.9, 130.0, 134.2, 135.5, 144.5, one ^{13}C peak overlaps with other peaks; HRMS (ESI) calcd for $C_{41}H_{68}O_7SSi_2Na$ 783.4116 $[M+Na]^+$, found 783.4117.

*4.1.32. Complex **23aa**.* $Co_2(CO)_8$ (175 mg, 0.512 mmol) was added to a solution of **22aa** (98.2 mg, 0.129 mmol) in CH_2Cl_2 (2.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1) to afford alkyne-dicobalt hexacarbonyl complex **23aa** (130 mg, 0.124 mmol) in 96% yield: brown oil. The ^{1}H NMR spectrum of **23aa** was identical of that of **23bb**.

*4.1.33. Complex **23ab**.* According to the synthetic procedure of complex **23aa**, **23ab** (146 mg, 0.139 mmol) was synthesized from **22ab** (117 mg, 0.154 mmol) in 90% yield by using $Co_2(CO)_8$ (342 mg, 1.00 mmol) in CH_2Cl_2 (3.0 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3

of TBS), 0.10 (6H, s, CH_3 of TBS ×2), 0.11 (3H, s, CH_3 of TBS), 0.79 (3H, t, *J*=7.3 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.45–1.55 (1H, m, H19a), 1.58–1.70 (4H, m, H2 and H3), 1.73 (1H, qd, *J*=7.4, 5.9 Hz, H19b), 2.09 (2H, dt, *J*=7.3, 6.8 Hz, H4), 2.44 (3H, s, CH_3 of Ts), 2.83 (1H, dd, *J*=16.5, 4.6 Hz, H16a), 2.88 (2H, m, H7), 3.14 (1H, dd, *J*=15.5, 3.2 Hz, H13a), 3.22 (1H, dd, *J*=15.5, 8.2 Hz, H13b), 3.35 (1H, dd, *J*=16.5, 6.4 Hz, H16b), 3.80–3.89 (2H, m, acetal), 3.92–3.99 (2H, m, acetal), 4.01 (1H, m, H17), 4.42 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J*=5.0 Hz, H1), 5.29–5.43 (3H, m, H5, H6 and H8), 5.73 (1H, dd, *J*=15.6, 6.9 Hz, H11), 5.99 (1H, dd, *J*=11.4, 11.4 Hz, H9), 6.56 (1H, dd, *J*=15.6, 11.4 Hz, H10), 7.31 (2H, d, *J*=8.3 Hz, aromatic), 7.79 (2H, d, *J*=8.3 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2482.

4.1.34. Complex ***23ba****.* According to the synthetic procedure of complex **23aa**, **23ba** (129 mg, 0.123 mmol) was synthesized from **22ba** (99 mg, 0.130 mmol) in 95% yield by using $Co_2(CO)_8$ (192 mg, 0.561 mmol) in CH_2Cl_2 (2.8 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 9/1): brown oil. The ^{1}H NMR spectrum of **23ba** was identical of that of **23ab**.

4.1.35. Complex ***23bb****.* According to the synthetic procedure of complex **23aa**, **23bb** (118 mg, 0.113 mmol) was synthesized from **22bb** (96 mg, 0.13 mmol) in 87% yield by using $Co_2(CO)_8$ (185 mg, 0.541 mmol) in CH_2Cl_2 (2.5 mL). Purification was performed by flash column chromatography on silica gel (10 g, hexane/EtOAc 20/1 to 9/1): brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3 of TBS), 0.09 (3H, s, CH_3 of TBS), 0.10 (6H, s, CH_3 of TBS ×2), 0.79 (3H, t, *J*=7.5 Hz, H20), 0.89 (9H, s, *t*-Bu of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.49 (2H, dq, *J*=7.5, 7.5 Hz, H19), 1.57–1.77 (4H, m, H2 and H3), 2.08 (2H, dt, *J*=7.4, 7.4 Hz, H4), 2.44 (3H, s, CH_3 of Ts), 2.80–2.92 (3H, m, H7 and H16a), 3.12 (1H, dd, *J*=16.0, 8.6 Hz, H13a), 3.28 (1H, dd, *J*=16.0, 2.9 Hz, H13b), 3.37 (1H, dd, *J*=16.6, 6.9 Hz, H16b), 3.80–3.86 (2H, m, acetal), 3.90–3.96 (2H, m, acetal), 3.97 (1H, m, H17), 4.44 (1H, m, H12), 4.62 (1H, m, H18), 4.85 (1H, t, *J*=4.6 Hz, H1), 5.30–5.42 (3H, m, H5, H6 and H8), 5.74 (1H, dd, *J*=15.5, 6.9 Hz, H11), 5.97 (1H, dd, *J*=11.5, 11.5 Hz, H9), 6.58 (1H, dd, *J*=15.5, 11.5 Hz, H10), 7.32 (2H, d, *J*=8.6 Hz, aromatic), 7.79 (2H, d, *J*=8.6 Hz, aromatic); HRMS (ESI) calcd for $C_{47}H_{68}Co_2O_{13}SSi_2Na$ 1069.2475 $[M+Na]^+$, found 1069.2445.

4.1.36. Tetraene ***24aa****.* *n*-Bu_3SnH (505 μL, 1.88 mmol) and *N*-methylmorpholine *N*-oxide (146 mg, 1.25 mmol) were successively added to a solution of alkyne dicobalt hexacarbonyl complex **23aa** (130 mg, 0.124 mmol) in toluene (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min under air, and then aqueous saturated KF (10 mL) was added. The resultant mixture was extracted with Et_2O (30 mL ×2), and the combined organic layers were washed with aqueous saturated KF (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography [a column consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 5 g, pentane to pentane/EtOAc 9/1] to afford tetraene **24aa** (45.4 mg, 0.0596 mmol) in 48% yield: colorless oil; $[\alpha]_D^{24}$+24 (*c* 1.3, $CHCl_3$); IR (neat) ν 2952, 2928, 2956, 1462, 1366, 1254, 1189, 1177, 1073 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.74 (3H, t, *J*=7.8 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45–1.56 (3H, m, H3 and H19a), 1.63–1.71 (2H, m, H2), 1.77 (1H, m, H19b), 1.98–2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, CH_3 of Ts), 2.91 (2H, m, H7), 3.79 (1H, ddd, *J*=9.2, 4.1, 4.1 Hz, H17), 3.82–3.89 (2H, m, acetal), 3.91–3.99 (2H, m, acetal), 4.18 (1H, dt, *J*=6.4, 6.4 Hz, H12), 4.30 (1H, dt, *J*=9.2, 4.1 Hz, H18), 4.85 (1H, t, *J*=4.6 Hz, H1), 5.30–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.64 (1H, dd, *J*=15.1, 6.4 Hz, H11), 5.97 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.47 (1H, dd, *J*=15.1, 11.0 Hz, H10), 7.33 (2H, d, *J*=8.3 Hz, aromatic), 7.79 (2H, d, *J*=8.3 Hz, aromatic). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.75, −4.71, −4.6, −4.4, 10.3, 17.9, 18.2, 21.0, 21.6, 23.9, 25.7 (×3), 25.9 (×3), 26.0, 27.0, 29.1, 33.4, 36.5, 64.8 (×2), 72.3, 72.9, 86.2, 104.5, 124.4, 127.5, 127.6, 127.8 (×2), 127.9, 128.1, 129.6, 129.7 (×2), 130.0, 134.3, 136.6, 144.5.

4.1.37. Tetraene ***24ab****.* According to the synthetic procedure of tetraene **24aa**, **24ab** (81.4 mg, 0.107 mmol) was synthesized from **23ab** (146 mg, 0.139 mmol) in 77% yield by using *n*-Bu_3SnH (0.56 mL, 2.1 mmol) and *N*-methylmorpholine *N*-oxide (164 mg, 1.40 mmol) in toluene (68 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g, hexane to hexane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{27}$−4.2 (*c* 0.85, $CHCl_3$); IR (neat) ν 2955, 2929, 2857, 1921, 1599, 1471, 1463, 1366, 1258, 1189, 1177, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.05 (3H, s, CH_3 of TBS), 0.75 (3H, t, *J*=7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.45–1.55 (3H, m, H3 and H19a), 1.63–1.70 (2H, m, H2), 1.77 (1H, m, H19b), 1.98–2.30 (6H, m, H4, H13 and H16), 2.44 (3H, s, CH_3 of Ts), 2.91 (2H, t, *J*=6.3 Hz, H7), 3.78 (1H, ddd, *J*=8.6, 4.0, 4.0 Hz, H17), 3.82–3.86 (2H, m, acetal), 3.92–3.99 (2H, m, acetal), 4.18 (1H, dt, *J*=6.9, 5.8 Hz, H12), 4.31 (1H, dt, *J*=8.6, 4.0 Hz, H18), 4.85 (1H, t, *J*=4.5 Hz, H1), 5.31–5.48 (5H, m, H5, H6, H8, H14 and H15), 5.64 (1H, dd, *J*=14.9, 5.8 Hz, H11), 5.97 (1H, dd, *J*=10.9, 10.9 Hz, H9), 6.46 (1H, dd, *J*=14.9, 10.9 Hz, H10), 7.33 (2H, d, *J*=8.0 Hz, aromatic), 7.79 (2H, d, *J*=8.0 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.75, −4.71, −4.6, −4.4, 10.3, 17.8, 18.2, 21.0, 21.6, 23.9, 25.7 (×3), 25.9 (×3), 26.0, 27.0, 29.2, 33.4, 36.5, 64.8 (×2), 72.2, 72.7, 86.2, 104.5, 124.3, 127.5, 127.6, 127.8 (×2), 127.9, 128.1, 129.6, 129.7 (×2), 130.0, 134.3, 136.6, 144.5; HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4254.

4.1.38. Tetraene ***24ba****.* According to the synthetic procedure of tetraene **24aa**, **24ba** (45.0 mg, 59.1 μmol) was synthesized from **23ba** (129 mg, 0.123 mmol) in 48% yield by using *n*-Bu_3SnH (0.49 mL, 1.8 mmol) and *N*-methylmorpholine *N*-oxide (141 mg, 1.21 mmol) in toluene (60 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 6 g and 10% (w/w) KF contained silica gel 2 g, pentane to pentane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{23}$+2.9 (*c* 1.2, $CHCl_3$). The other analytical data of **24ba** were identical to those of **24ab**.

4.1.39. Tetraene ***24bb****.* According to the synthetic procedure of tetraene **24aa**, **24bb** (45.1 mg, 59.2 μmol) was synthesized from **23bb** (118 mg, 0.113 mmol) in 52% yield by using *n*-Bu_3SnH (0.45 mL, 1.7 mmol) and *N*-methylmorpholine *N*-oxide (133 mg, 1.14 mmol) in toluene (55 mL). Purification was performed by flash chromatography [a column consecutively packed with silica gel 8 g and 10% (w/w) KF contained silica gel 2 g, pentane to pentane/EtOAc 9/1]: colorless oil; $[\alpha]_D^{25}$−26 (*c* 0.83, $CHCl_3$); HRMS (ESI) calcd for $C_{41}H_{70}O_7SSi_2Na$ 785.4273 $[M+Na]^+$, found 783.4259. The other analytical data of **24bb** were identical to those of **24aa**.

4.1.40. (12S,17R,18S)- ***1aa****.* TMSOTf (0.16 mL, 0.86 mmol) was added to a solution of **24aa** (42.9 mg, 56.3 μmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 15 min, and then H_2O (2.0 mL) and EtOAc (2.0 mL) were successively added. The resultant solution was warmed to room temperature and stirred for 30 min. After separation, the organic layer was washed with aqueous 0.1 M HCl solution (10 mL ×2), aqueous saturated $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude aldehyde **25aa**, which was used in the next reaction without further purification.

A solution of $NaClO_2$ (80 wt %, 56.3 mg, 0.498 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (82.5 mg, 0.529 mmol) in H_2O (0.6 mL) was added

to a solution of the above crude aldehyde **25aa** in a mixture of *t*-BuOH (0.6 mL) and 2-methyl-2-butene (0.6 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, and then diluted with H_2O (5 mL). The resultant solution was extracted with EtOAc (10 mL), and the organic layer was washed with H_2O (4 mL) and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) to afford the crude carboxylic acid **26aa**, which was used in the next reaction without further purification.

TBAF (1.0 M in THF, 0.56 mL, 0.56 mmol) was added to a solution of the above crude carboxylic acid **26aa** in THF (1.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then saturated aqueous NH_4Cl solution (5 mL) was added. After 0.1 M HCl solution (4 mL) was added, the mixture was extracted with EtOAc (10 mL and 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) to afford the crude **1aa**. The crude **1aa** was further purified by HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=36 min) to afford **1aa** (3.5 mg, 10 μmol) in 18% yield over three steps: colorless oil; $[\alpha]_D^{25}$+3.4 (*c* 0.18, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074. The other analytical data of **1aa** were identical to those of **1bb**.

*4.1.41. (12S,17S,18R)-**1ab**.* According to the synthetic procedure of **1aa**, **1ab** (12.3 mg, 36.8 μmol) was synthesized from **24ab** (78 mg, 0.102 mmol) in 36% yield over three steps by using TMSOTf (0.28 mL, 1.6 mmol) and 2,6-lutidine (0.27 mL, 2.3 mmol) in CH_2Cl_2 (2.0 mL) for the first reaction, $NaClO_2$ (80 wt %, 107 mg, 0.946 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (152 mg, 0.974 mmol) in a mixture of *t*-BuOH (1.0 mL), 2-methyl-2-butene (1.0 mL) and H_2O (1.0 mL) for the second, and TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) in THF (2.0 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=34 min) for the third. Aldehyde **25ab**: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.05 (3H, s, C*H*$_3$ of TBS), 0.74 (3H, t, *J*=7.3 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.43–1.82 (3H, m, H3 and H19a), 1.65–1.80 (3H, m, H2 and H19b), 2.00–2.24 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.91 (2H, t, *J*=7.8 Hz, H7), 3.78 (1H, m, H17), 4.19 (1H, dt, *J*=6.0, 5.5 Hz, H12), 4.30 (1H, dt, *J*=8.7, 4.1 Hz, H18), 5.29–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J*=15.1, 6.0 Hz, H11), 5.98 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.46 (1H, dd, *J*=15.1, 11.0 Hz, H10), 7.33 (2H, d, *J*=8.2 Hz, aromatic), 7.79 (2H, d, *J*=8.2 Hz, aromatic), 9.77 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.73, −4.66, −4.5, 10.3, 17.8, 18.2, 21.0, 21.6, 21.9, 25.7 (×3), 25.8 (×3), 26.0, 26.4, 29.1, 36.4, 43.2, 72.1, 72.7, 86.2, 124.2, 127.4, 127.6, 127.7 (×2), 128.2, 128.7, 129.0, 129.2, 129.7 (×2), 134.3, 136.8, 144.5, 202.3; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.4034. (12*S*,17*S*,18*R*)-**1ab**: colorless oil; $[\alpha]_D^{25}$−4.7 (*c* 0.18, $CHCl_3$); IR (neat) ν 3424, 3009, 2968, 2931, 2877, 2856, 1714, 1438, 1409, 1236, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J*=7.5 Hz, H20), 1.57 (2H, qd, *J*=7.5, 6.3 Hz, H19), 1.73 (2H, br s, H3), 2.18 (2H, br s, H4), 2.21–2.38 (6H, m, H2, H13 and H16), 2.91 (1H, td, *J*=6.3, 4.6 Hz, H18), 2.93–3.00 (2H, m, H7 and H17), 4.18 (1H, dt, *J*=6.3, 6.3 Hz, H12), 5.34–5.46 (3H, m, H5, H6 and H8), 5.53–5.62 (2H, m, H14 and H15), 5.69 (1H, dd, *J*=15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J*=11.0, 11.0 Hz, H9), 6.57 (1H, dd, *J*=15.5, 11.0 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 27.0, 27.3, 27.8, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.3, 130.5, 130.9, 137.1, the C1, C2 and C3 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2074; UV (MeOH) λ_{max} 236 nm (ε 2.17×10^4).

*4.1.42. (12R,17R,18S)-**1ba**.* According to the synthetic procedure of **1aa**, **1ba** (6.25 mg, 18.7 μmol) was synthesized from **24ba** (45.0 mg, 59.0 mmol) in 32% yield over three steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first reaction, $NaClO_2$ (80 wt %, 61.0 mg, 0.540 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (88.0 mg, 0.564 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=35 min) for the third: colorless oil; $[\alpha]_D^{24}$+7.6 (*c* 0.31, MeOH); HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$ found 333.2046. The other analytical data of **1ba** were identical to those of **1ab**.

*4.1.43. (12R,17S,18R)-**1bb**.* According to the synthetic procedure of **1aa**, **1bb** (6.64 mg, 19.9 μmol) was synthesized from **24bb** (45.1 mg, 59.2 mmol) in 34% yield over three steps by using TMSOTf (0.16 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.3 mmol) in CH_2Cl_2 (1.2 mL) for the first reaction, $NaClO_2$ (80 wt %, 60.9 mg, 0.539 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (85.7 mg, 0.549 mmol) in a mixture of *t*-BuOH (0.6 mL), 2-methyl-2-butene (0.6 mL) and H_2O (0.6 mL) for the second, and TBAF (1.0 M in THF, 0.59 mL, 0.59 mmol) in THF (1.2 mL) for the third. Purification was performed by flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 4/1 to 1/1) for the second reaction, and flash column chromatography on Chromatorex-ACD (4 g, hexane/EtOAc 1/1 to 1/4) and HPLC (Inertsil ODS-4, MeOH/H_2O/AcOH 7/3/0.1 2.5 mL/min, t_R=35 min) for the third. Aldehyde **25bb**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, C*H*$_3$ of TBS), 0.03 (3H, s, C*H*$_3$ of TBS), 0.04 (3H, s, C*H*$_3$ of TBS), 0.06 (3H, s, C*H*$_3$ of TBS), 0.73 (3H, t, *J*=7.5 Hz, H20), 0.84 (9H, s, *t*-Bu of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.44–1.60 (3H, m, H3 and H19a), 1.70–1.80 (3H, m, H2 and H19b), 2.00–2.28 (6H, m, H4, H13 and H16), 2.44 (3H, s, C*H*$_3$ of Ts), 2.90 (2H, m, H7), 3.79 (1H, m, H17), 4.19 (1H, dt, *J*=6.3, 5.8 Hz, H12), 4.29 (1H, m, H18), 5.29–5.51 (5H, m, H5, H6, H8, H14 and H15), 5.65 (1H, dd, *J*=15.5, 5.8 Hz, H11), 5.98 (1H, dd, *J*=11.5, 10.9 Hz, H9), 6.47 (1H, dd, *J*=15.5, 11.5 Hz, H10), 7.32 (2H, d, *J*=8.0 Hz, aromatic), 7.79 (2H, d, *J*=8.0 Hz, aromatic), 9.77 (1H, s, H1). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.73, -4.69, -4.63, -4.4, 10.3, 17.9, 18.2, 20.9, 21.6, 21.9, 25.7 (×3), 25.9 (×3), 26.0, 26.5, 29.1, 36.5, 43.3, 72.3, 72.9, 86.2, 124.3, 127.4, 127.7, 127.8 (×2), 128.2, 128.7, 129.1, 129.2, 129.7 (×2), 134.3, 136.8, 144.6, 202.4; HRMS (ESI) calcd for $C_{39}H_{66}O_6SSi_2Na$ 741.4011 $[M+Na]^+$, found 741.3996. (12*R*,17*S*,18*R*)-**1bb**: colorless oil; $[\alpha]_D^{24}$−4.1 (*c* 0.36, MeOH); IR (neat) ν 3416, 3010, 2966, 2927, 2875, 2854, 1714, 1565, 1437, 1409, 1260, 1169 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.05 (3H, t, *J*=7.5 Hz, H20), 1.57 (2H, qd, *J*=7.5, 6.3 Hz, H19), 1.68 (2H, br s, H3), 2.15 (2H, m, H4), 2.20–2.40 (6H, m, H2, H13 and H16), 2.90–3.00 (4H, m, H7, H17 and H18), 4.18 (1H, dt, *J*=6.3, 6.3 Hz, H12), 5.34–5.41 (3H, m, H5, H6 and H8), 5.53–5.61 (2H, m, H14 and H15), 5.69 (1H, dd, *J*=15.5, 6.3 Hz, H11), 5.98 (1H, dd, *J*=10.9, 10.9 Hz, H9), 6.57 (1H, ddt, *J*=15.5, 10.9, 1.2 Hz, H10); ^{13}C NMR (125 MHz, CD_3OD) δ 10.9, 22.1, 26.1, 27.0, 27.3, 27.6, 36.6, 58.0, 59.8, 73.0, 126.5, 127.3, 129.0, 129.2, 129.4, 130.4, 130.9, 137.1, the C1 and C2 peaks were missing due to broadening of the spectrum; HRMS (ESI) calcd for $C_{20}H_{29}O_4$ 333.2071 $[M-H]^-$, found 333.2059; UV (MeOH) λ_{max} 236 nm (ε 2.35×10^4).

4.2. Bioassay

Peritonitis was induced as described in Ref. 29. Synthetic **1aa**, **1ab**, **1ba** and **1bb** (each 1 ng) were injected intravenously through

tail vein followed by peritoneal injection of zymosan A (1 mg/mL). After 2 h, peritoneal lavages were collected, PMN leukocyte numbers were counted, cell viability was determined using Trypan blue exclusion, and differential cell counts were monitored by Wright-Giemsa staining.

4.3. Statistical analysis

Results are expressed as means±SE. Differences between two groups were tested by the Student's *t*-test. Multiple comparisons were analyzed using ANOVA followed by Tukey test. A significance level of $P<0.05$, $P<0.01$ and $P<0.001$ was used.

Associated content

NMR spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

This research was financially supported by the Funding Program for a Grant-in-Aid for Scientific Research (A) (JSPS Grant Number 26253003) to M.I., and for Scientific Research (C) (JSPS Grant Number 2546007) and on Innovative Areas (MEXT Grant Number 26102716) to D.U.

References and notes

1. Simopoulos, A. P. *J. Am. Coll. Nutr.* **2002**, *21*, 495.
2. (a) Serhan, C. N.; Clish, C. B.; Brannon, J.; Colgan, S. P.; Chiang, N.; Gronert, K. *J. Exp. Med.* **2000**, *192*, 1197; (b) Arita, M.; Bianchini, F.; Aliberti, J.; Sher, A.; Chiang, N.; Hong, S.; Yang, R.; Petasis, N. A.; Serhan, C. N. *J. Exp. Med.* **2005**, *201*, 713.
3. (a) Tjonahen, E.; Oh, S. F.; Siegelman, J.; Elangovan, S.; Percarpio, K. B.; Hong, S.; Arita, M.; Serhan, C. N. *Chem. Biol.* **2006**, *13*, 1193; (b) Oh, S. F.; Dona, M.; Fredman, G.; Krishnamoorthy, S.; Irimia, D.; Serhan, C. N. *J. Immunol.* **2012**, *188*, 4527.
4. (a) Isobe, Y.; Arita, M.; Matsueda, S.; Iwamoto, R.; Fujihara, T.; Nakanishi, H.; Taguchi, R.; Masuda, K.; Sasaki, K.; Urabe, D.; Inoue, M.; Arai, H. *J. Biol. Chem.* **2012**, *287*, 10525; (b) Isobe, Y.; Arita, M.; Iwamoto, R.; Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M.; Arai, H. *J. Biochem.* **2013**, *153*, 355.
5. Schwab, J. M.; Chiang, N.; Arita, M.; Serhan, C. N. *Nature* **2007**, *447*, 869.
6. For reviews, see: (a) Serhan, C. N.; Chiang, N.; Van Dyke, T. E. *Nat. Rev. Immunol.* **2008**, *8*, 349; (b) Serhan, C. N.; Chiang, N. *Br. J. Pharmacol.* **2008**, *153*, S200; (c) Serhan, C. N.; Petasis, N. A. *Chem. Rev.* **2011**, *111*, 5922.
7. Total syntheses of lipid mediators from our laboratory. Resolvin E2: (a) Ogawa, S.; Urabe, D.; Yokokura, Y.; Arai, H.; Arita, M.; Inoue, M. *Org. Lett.* **2009**, *11*, 3602. Maresin 1; (b) Sasaki, K.; Urabe, D.; Arai, H.; Arita, M.; Inoue, M. *Chem.—Asian J.* **2011**, *6*, 534. Resolvin E3; (c) Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Tetrahedron* **2012**, *68*, 3210.
8. Total syntheses of resolvin E series from other laboratories. Resolvin E1: (a) Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2009**, *50*, 6079; (b) Allard, M.; Barnes, K.; Chen, X.; Cheung, Y.-Y.; Duffy, B.; Heap, C.; Inthavongsay, J.; Johnson, M.; Krishnamoorthy, R.; Manley, C.; Steffke, S.; Varughese, D.; Wang, R.; Wang, Y.; Schwartz, C. E. *Tetrahedron Lett.* **2011**, *52*, 2623. Resolvin E2; (c) Kosaki, Y.; Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2010**, *51*, 1856; (d) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 1912. For a review on syntheses of eicosanoids, see; (e) Nicolaou, K. C.; Ramphal, J. Y.; Petasis, N. A.; Serhan, C. N. *Angew. Chem., Int. Ed.* **1991**, *30*, 1100.
9. Kubota, T.; Arita, M.; Isobe, Y.; Iwamoto, R.; Goto, T.; Yoshioka, T.; Urabe, D.; Inoue, M.; Arai, H. *FASEB J.* **2014**, *28*, 586.
10. Glycidol derivatives **7a** and **7b** were synthesized from the commercially available (*R*)- and (*S*)-glycidols (98% ee), respectively, according to the literature procedure, see: (a) Smith, A. B., III.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667; (b) Gaunt, M. J.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815; (c) White, J. D.; Lincoln, C. M.; Yang, J.; Martin, W. H. C.; Chan, D. B. *J. Org. Chem.* **2008**, *73*, 4139.
11. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
12. (a) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078; (b) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268; (c) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677 See also Ref. 7c.
13. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. For a review on asymmetric dihydroxylation, see; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
14. (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203; (b) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693; (c) Zhang, Z.-B.; Wang, Z.-M.; Wang, Y.-X.; Liu, H.-Q.; Lei, G.-X.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 837.
15. De Silva, E. C. A.; Silk, P. J.; Mayo, P.; Hillier, N. K.; Magee, D.; Cutler, G. C. *J. Chem. Ecol.* **2013**, *39*, 1169.
16. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
17. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
18. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
19. Epimerization of C12-hydroxy group was not observed during the vinyl iodide formation. The configurational stability of the similar α-siloxy aldehydes was reported previously, see: (a) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548; (b) Taffer, I. M.; Zipkin, R. E. *Tetrahedron Lett.* **1987**, *28*, 6543.
20. Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467.
21. Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59*, 7787.
22. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. For a review on the Sonogashira coupling, see; (b) Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 317.
23. (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446; (b) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313.
24. (a) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609; (b) Isobe, M.; Nishizawa, R.; Hoshokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665.
25. Goto, T.; Urabe, D.; Masuda, K.; Isobe, Y.; Arita, M.; Inoue, M. *J. Org. Chem.* **2015**, *80*, 7713.
26. The Isobe reduction of the tri-alkyne dicobalt hexacarbonyl complex prepared from **2aa** and $Co_2(CO)_8$ provided the inseparable mixture of **22aa**, **23aa** and the over-reduced compounds.
27. Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.
28. The four isomers were separated by the reverse-phase chiral HPLC (column: CHIRALPAK AD-3R, 4.6 mm×150 mm, eluent: 50% CH_3CN/MeOH (4/1) in 0.1 % aqueous AcOH for 5 min, 50–95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH over 22.5 min, and then 95% CH_3CN /MeOH (4/1) in 0.1 % aqueous AcOH for 8 min at 0.5 mL/min, retention times of the synthetic **1**: t_R=28.4 min for **1aa**, 23.9 min for **1ab**, 20.6 min for **1ba**, 20.1 min for **1bb**, retention times of the natural **1**: t_R=28.4 min for **1aa**, 24.0 min for **1ab**). For the comparison of the HPLC chart of the synthetic and natural **1**, see Ref. 9.
29. Yamada, T.; Tani, Y.; Nakanishi, H.; Taguchi, R.; Arita, M.; Arai, H. *FASEB J.* **2011**, *25*, 561.