

博士論文

論文題目 Total Synthesis of 4-Hydroxyzinowol and Synthetic
Study of Talatisamine
(4-ヒドロキシジノウォールの全合成とタラチサミ
ンの合成研究)

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Total Synthesis of 4-Hydroxyzinowol and Synthetic Study of Talatisamine

(4-ヒドロキシジノウォールの全合成とタラチサミンの合成研究)

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To my family and friends

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Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
cat.	catalyst
cod	cyclooctadiene
COSY	correlation spectroscopy
CSA	(1 <i>S</i>)-(+)-10-camphorsulfonic acid
Δ	heat
DIBAL	diisobutylaluminum hydride
DMAP	<i>N,N'</i> -dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	<i>N, N'</i> -dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
eq.	equivalent
ESI	electrospray ionization
g	gram
<i>gem</i>	geminal
h	hour(s)
h ν	Irradiation with light
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectra
<i>i</i>	iso
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
M	metal or molar
<i>m</i>	meta
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid

MDR	multidrug resistance
Me	methyl
min	minute(s)
MOM	methoxymethyl
m.p.	melting point
MS	molecular sieves
<i>n</i>	<i>normal</i>
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
<i>p</i>	para
PG	protecting group
pH	power of hydrogen
ph	phenyl
Piv	pivaloyl
Pr	propyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
rt	room temperature
<i>sec</i>	secondary
SOMO	singly occupied molecular orbital
<i>t</i>	tertiary
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
Temp.	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N, N, N', N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Ts	<i>p</i> -toluenesulfonyl
UV	ultraviolet
V-40	1,1'-azobiscyclohexanecarbonitrile
°C	degrees Celsius

Chapter 1:
Total Synthesis of 4-Hydroxyzinowol

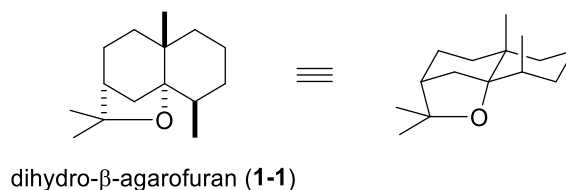
1.1 Introduction

1.1.1 Dihydro- β -agarofuran sesquiterpenoids

1.1.1.1 The Celastraceae family

Folk medicine is a continuous source of natural products with interesting biological activity.¹ Among a myriad of families of plants, the Celastraceae is one of the privileged family used in folk medicines around the world, especially in North Africa, South America, and East Asia.² The family has roughly 90 genera and 1300 species, from which various biologically-active secondary metabolites have been isolated³: maytansinoids,⁴ spermidine macrocyclic alkaloids,⁵ cardenolides,⁶ flavonoids,⁷ and so on. The most prevalent metabolite of the family is, however, a kind of sesquiterpenoid based on a unique tricyclic skeleton called dihydro- β -agarofuran (**1-1**) (Figure 1.1).⁸

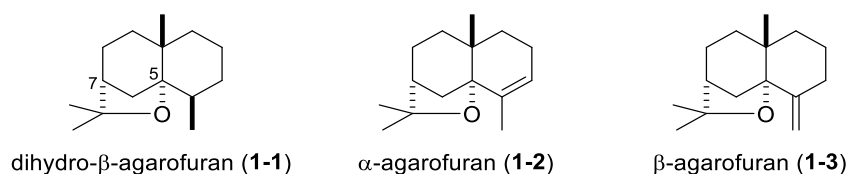
Figure 1.1 Dihydro- β -agarofuran skeleton



1.1.1.2 Structure determination of agarofuran sesquiterpenoids

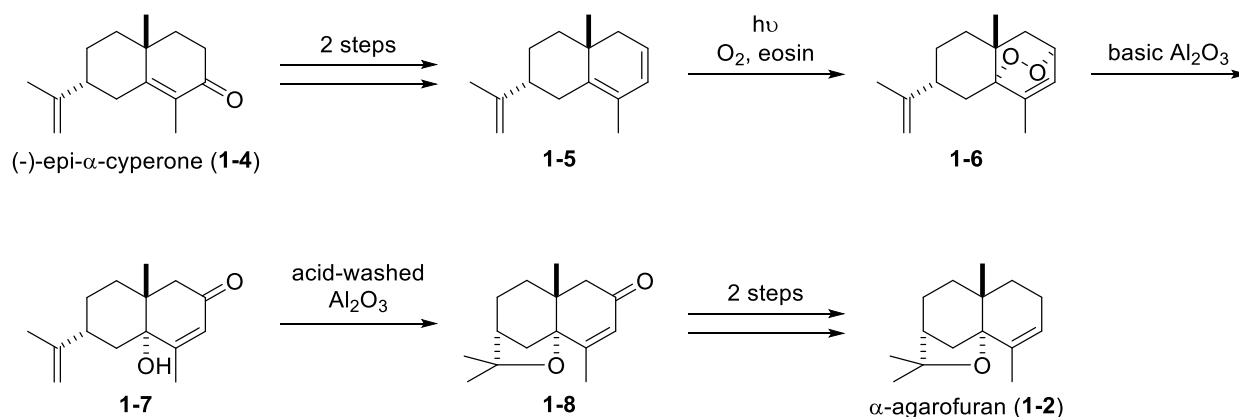
A discovery and elucidation of the intriguing tricyclic skeleton of dihydro- β -agarofuran dates back to 1960s. Bhattacharyya and co-workers isolated dihydro- β -agarofuran (**1-1**), α -agarofuran (**1-2**), and β -agarofuran (**1-3**) from the oil of the fungus infected agarwood (*Aquillaria agallocha* Roxb.) in 1963 (Figure 1.2).⁹

Figure 1.2 Structures of agarofurans isolated in the first time



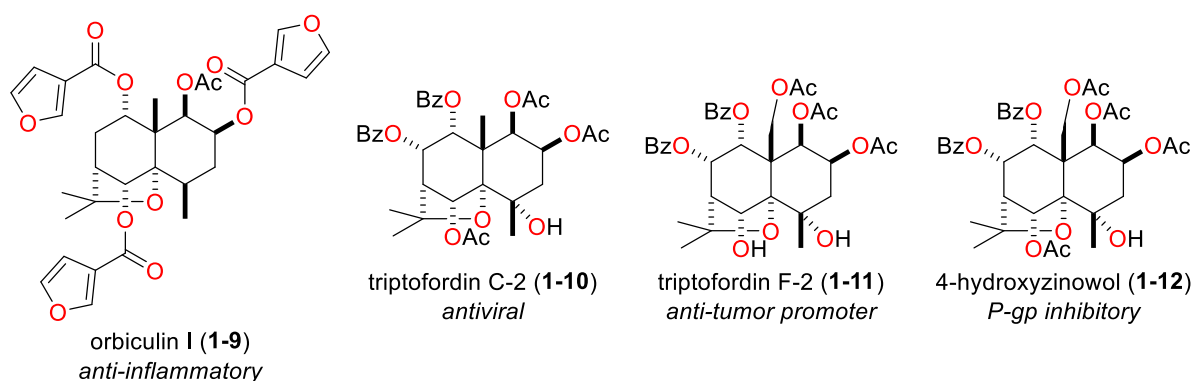
Although the planar structure of these natural products were correctly elucidated, the initially proposed stereochemistries at C5- and C7-position were found to be wrong (only the correct structure is shown in Figure 1.2), which was later corrected by Büchi *et al.* through the groundbreaking total synthesis of α -agarofuran (Scheme 1.1).¹⁰ Specifically, starting from (-)-epi- α -cyperone (**1-4**), whose absolute configuration had already been established at the time, diene **1-5** was synthesized in two steps. Stereoselective oxidation of **1-5** by photo-irradiated molecular oxygen in the presence of the eosin as a photosensitizer afforded the endoperoxide **1-6**. Conversion of **1-6** to the tertiary alcohol **1-7** followed by etherification under the acidic conditions led to the tricyclic skeleton **1-8**. Two-step deoxygenation of **1-8** afforded α -agarofuran (**1-2**), which unambiguously established the correct stereochemistry of the natural product.

Scheme 1.1 Total synthesis of α -agarofuran by Büchi *et al.*



1.1.1.3 Biological activities and structural features of dihydro- β -agarofurans

Since then, nearly 500 dihydro- β -agarofurans have been identified to date. A great deal of attention has been paid to this class of natural products because of their complex architectures and wide range of biological activities. A couple of examples are shown in Figure 1.3: anti-inflammatory orbiculin I (**1-9**),¹¹ antiviral triptofordin C-2 (**1-10**),¹² anti-tumor promoting triptofordin F-2 (**1-11**),¹³ and P-gp inhibitory 4-hydroxyzinowol (**1-12**).^{14, 15} Other biological activities of this class of compounds include immunosuppressive, cytotoxic, insecticidal, and antifeedant activities.

Figure 1.3 Examples of highly oxygenated dihydro- β -agarofurans and their biological activities

As shown by these examples, the tricyclic skeleton of dihydro- β -agarofurans is generally highly oxygenated and thus bears many stereocenters, among which the contiguous tetrasubstituted carbons at the angular positions are common to all the congeners. For example, 4-hydroxyzinowol has the eight oxygen functionalities modified by the six acyl groups, and its nine contiguous stereocenters includes the three contiguous tetrasubstituted carbons.

From the viewpoint of the structure-activity relationship, these diverse biological activities are known to be affected not only by the disposition of the oxygen functionalities on the skeleton but also by the diverse pattern of acyl groups attached to the oxygen atoms.^{14b}

1.1.1.4 P-gp inhibitory activity

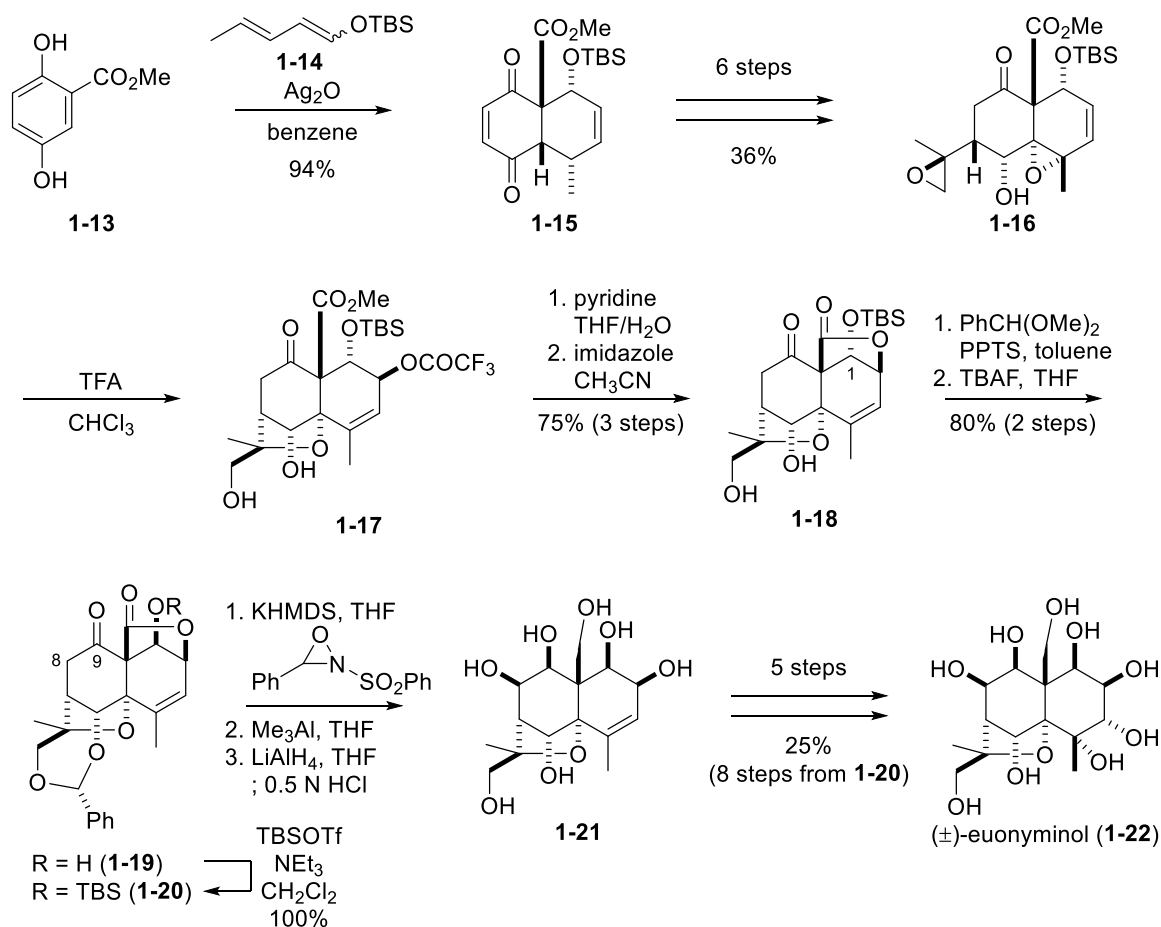
Among the diverse biological activities listed above, P-glycoprotein (P-gp) inhibitory activity seemed quite interesting. P-gp is a kind of molecular pumps that transport various xenobiotic small molecules out of cells.¹⁶ Diverse drug molecules are known to be substrates of P-gp. Hence, when P-gp is overexpressed on tumor cells, they acquire multi-drug resistance (MDR), which results in low sensitivity to current chemotherapies.¹⁷

In order to improve the efficiency of chemotherapies, selective inhibitors for P-gp is of high clinical relevance. Actually, some *in vitro* P-gp inhibitors, which had structurally no relationships with dihydro- β -agarofurans, were in the clinical trials in recent years. But they failed to show the expected effect.¹⁸ Thus the development of another class of selective P-gp inhibitors has been highly required. Therefore, motivated by its complex structure and promising biological activity, 4-hydroxyzinowol (**1-12**) was chosen as a synthetic target out of various highly oxygenated congeners.

1.1.2 Total synthesis of euonyminol by White and co-workers

The intriguing structures and fascinating biological activities have involved many researchers in the synthetic study of dihydro- β -agarofuran sesquiterpenoids. Although the construction of the simple tricyclic skeleton was achieved by many research groups,¹⁹ introduction of multiple oxygen functionalities onto the skeleton poses a tremendous challenge. To date, only one total synthesis of highly oxygenated dihydro- β -agarofuran has been reported. In 1995, White and co-workers reported the total synthesis of euonyminol, which is a core structure of various polyacylated agarofurans (Scheme 1.2).²⁰

Starting from *p*-quinol **1-13**, Diels-Alder reaction of *in situ*-generated *p*-quinone and diene **1-14** afforded diketone **1-15** bearing the quaternary carbon at the angular position. Six-step transformations from **1-15** led to bis-epoxide **1-16**. Treatment of **1-16** with TFA resulted in the cascade epoxide opening reaction to yield the dihydro- β -agarofuran skeleton **1-17**. After the lactonization, benzylidene protection of **1-18** followed by removal of the TBS group furnished ketone **1-19** with inversion of the stereochemistry at C1 position. Secondary alcohol of **1-19** was re-protected as the TBS ether, and the C8- and C9-stereocenters were introduced in 3 steps from **1-20**. Finally, heptaol **1-21** was converted to (\pm)-euonyminol (**1-22**) in 5 steps, accomplishing the total synthesis in 21 steps with a respectable 5.2% overall yield from **1-13**.

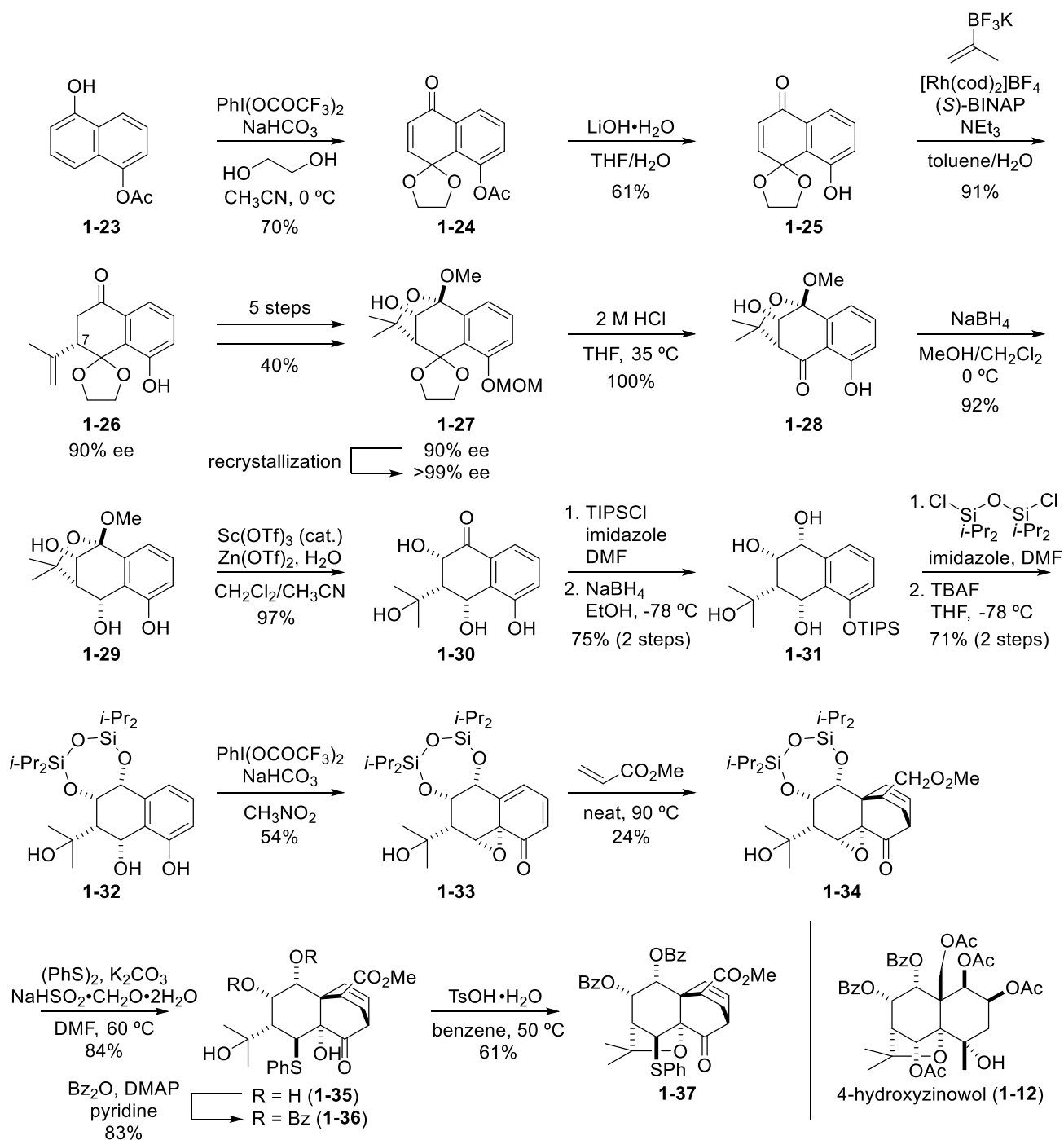
Scheme 1.2 Total synthesis of (±)-euonyminol by White group

Although the synthesis by White group is highly efficient, it seems difficult to regioselectively introduce different acyl groups on the oxygen atoms from nonaol **1-22**. As mentioned earlier, the acyl groups are reported to have important roles for the biological activities. However, despite a pile of synthetic works, there are virtually no reports addressing the problem of regioselective introduction of acyl groups. Thus, the synthetic route that enables both the construction of highly oxygenated skeleton and the introduction of various acyl groups would be of great value.

1.1.3 Previous synthetic study in our laboratory

In our laboratory, the study towards the synthesis of highly oxygenated dihydro- β -agarofuran skeleton had been conducted by Dr. Iwatsu (Scheme 1.3).²¹⁻²³ The synthesis commenced from the known naphthalene derivative **1-23**.²⁴ After the oxidative dearomatization to quinone monoketal **1-24**, acetyl group was removed to give phenol **1-25**. Then, the rhodium-catalyzed asymmetric 1,4-addition of the isopropenyl group^{25, 26} established the C7-stereocenter, yielding the adduct **1-26** in 90% ee. Five-step sequence from **1-26** to **1-27**, followed by recrystallization improved the enantiomeric purity to >99%. After the removal of the ethylene glycol ketal and MOM group, C6-ketone of **1-28** was stereoselectively reduced from the *convex* face to give **1-29**. Sc(OTf)₃-catalyzed hydrolysis of the cyclic ketal, protection of phenolic hydroxy group with TIPS group, and stereoselective reduction gave rise to tetraol **1-31**. 1,2-diol of **1-31** was protected as cyclic siloxane, and the TIPS group was removed to yield phenol **1-32**. Then, oxidative dearomatization of **1-32** in nitromethane afforded epoxide **1-33** in moderate yield. Following construction of the angular quaternary carbon by Diels-Alder reaction was low yielding, giving the adduct **1-34** in only 24% yield. Finally, epoxide was opened by thiophenolate²⁷ to **1-35**, benzoylated derivative of which was treated with acid to afford 5-membered ether **1-37**.

Scheme 1.3 Synthetic study by Dr. Iwatsu



Although the two consecutive tetrasubstituted carbons at the angular positions and the BC-ring system of the agarofuran skeleton were successfully constructed by the sequence, the yield of oxidative dearomatization and Diels-Alder reaction was not satisfactory. In addition, future functionalization of the right ring toward 4-hydroxyzinowol seemed to be problematic.

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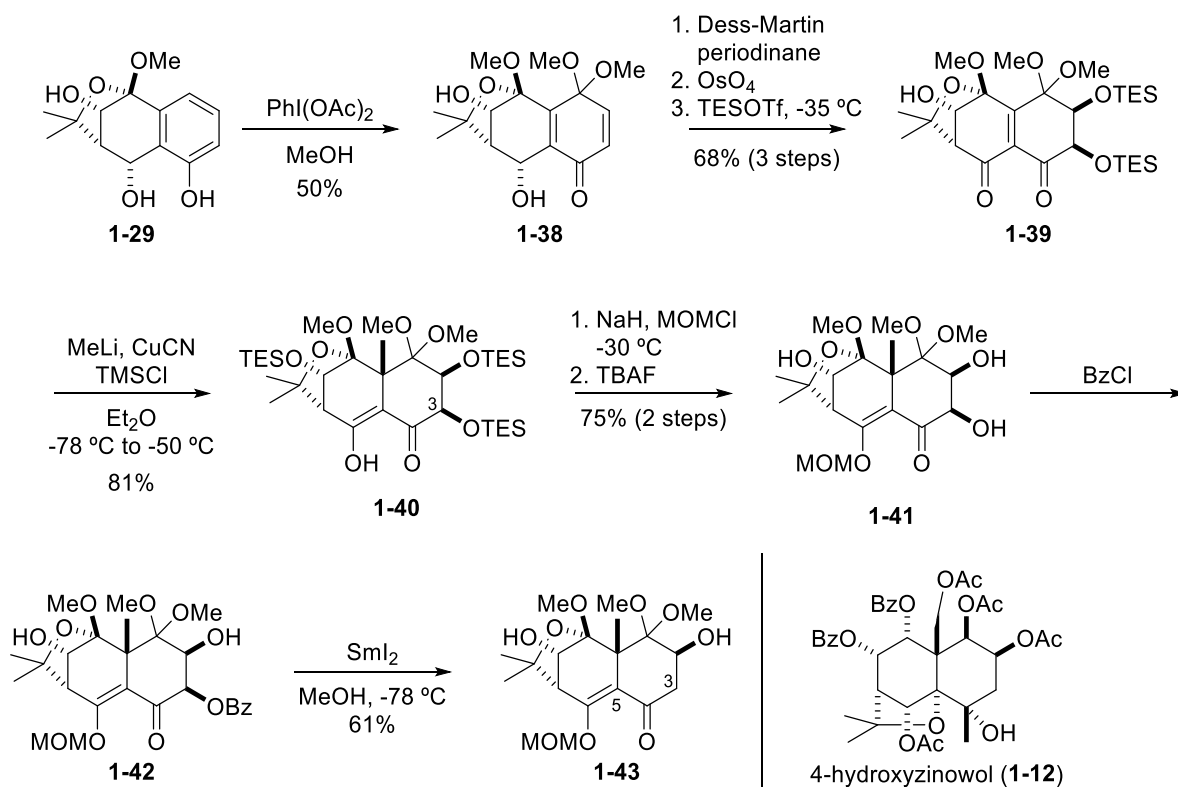
²⁷ Guo, W.; Chen, J.; Wu, D.; Ding, J.; Chen, F.; Wu, H. *Tetrahedron* **2009**, 65, 5240.

1.2 Model study toward the construction of the C5-tetrasubstituted carbon

1.2.1 Previous model synthetic study by the author

The author previously established the efficient method for construction of the angular quaternary carbon using the model substrate (Scheme 1.4).¹ Specifically, the synthesis started from the oxidative dearomatization of Dr. Iwatsu's intermediate **1-29**. Obtained *p*-quinone monoketal **1-38** was functionalized over 3 steps to give diketone **1-39**. 1,4-Addition of methyl group to the *convex* face of the highly activated olefin of **1-39** furnished the adduct **1-40** in high yield. Following deoxygenation at the C3-position through the intermediates **1-41** and **1-42** afforded ketone **1-43**, which was used for construction of the C5-tetrasubstituted carbon.²

Scheme 1.4 The previous model study by the author

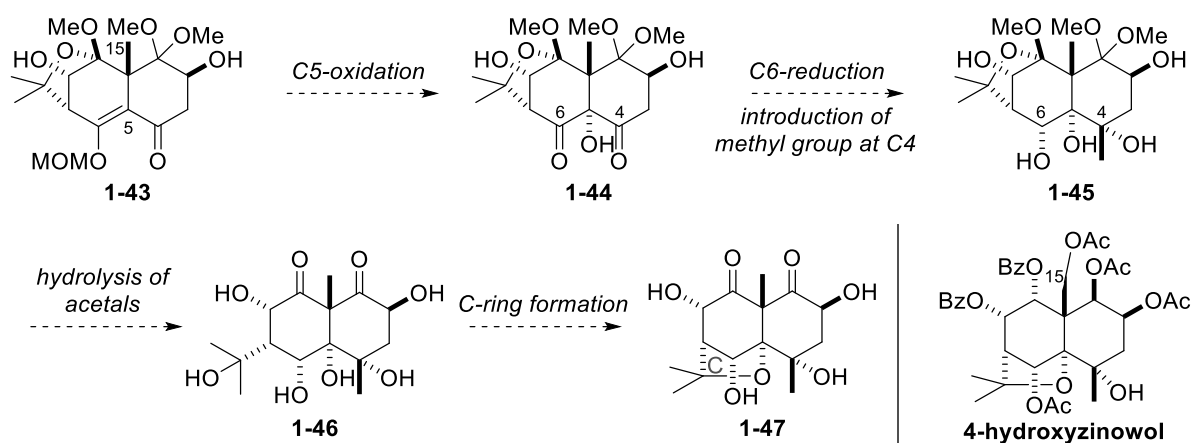


1.2.2 Initial synthetic study

1.2.2.1 Initial synthetic plan

Although the oxidation state at the C15-position of **1-43** was not the same as that of 4-hydroxyzinowol, the author determined to continue the model study toward the construction of the highly oxygenated agarofuran skeleton (Scheme 1.5). Construction of the C5-tetrasubstituted carbon would be achieved by oxidation of enol **1-43**. After manipulation of the C4- and C6-ketones of **1-44**, hydrolysis of the acetals in **1-45** would give diketone **1-46**, which could be a substrate for C-ring formation toward **1-47**.

Scheme 1.5 Plan for model study from **1-43**

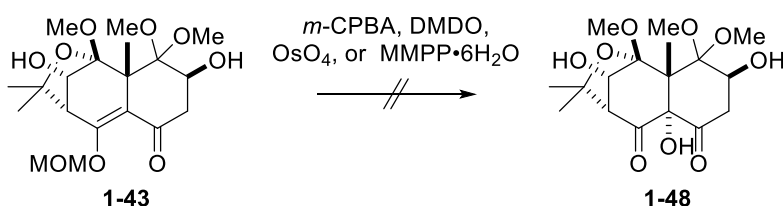


1.2.2.2 Difficulties encountered in the initial synthetic plan

1.2.2.2.1 Attempted oxidation of C5-C6 olefin

Initially, introduction of the oxygen functionality at C5-position was investigated from **1-43** (Scheme 1.6). Although various conditions were examined (*m*-CPBA, DMDO, OsO₄, or magnesium monoperoxyphthalate (MMPP)), the enol ether moiety was not oxidized.³ The steric hinderance of the adjacent quaternary carbon and the concave nature of the α -face of C5-C6 olefin due to the presence of the oxabicyclo[3.2.1]octane skeleton could be the causes of the low reactivity

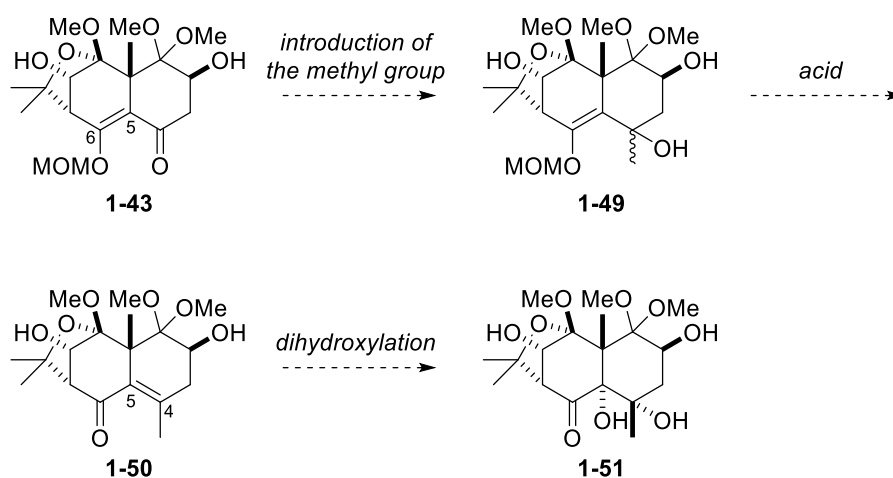
Scheme 1.6 Attempted oxidation of the enol ether



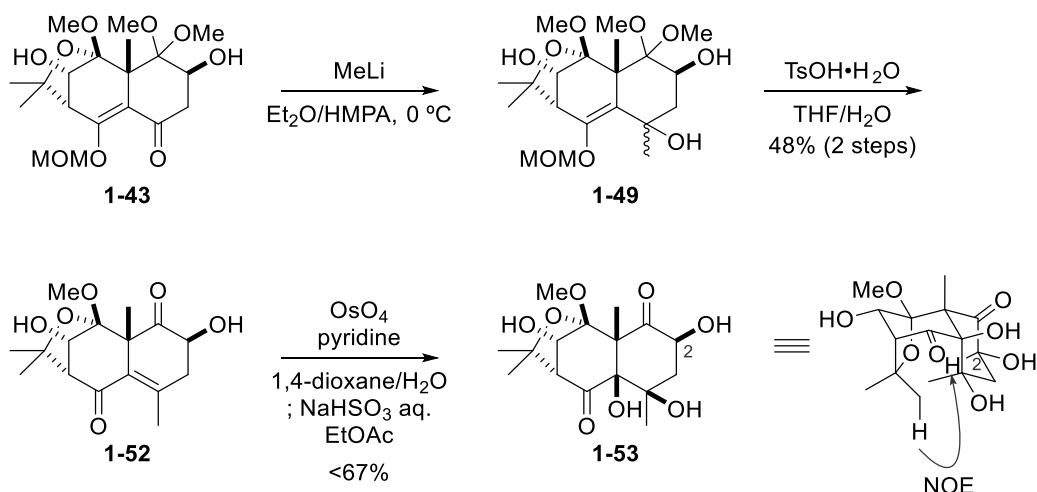
1.2.2.2.2 Attempted oxidation of C4-C5 olefin

Faced with the above difficulty, the author revised the synthetic plan (Scheme 1.7). Namely, after introduction of the methyl group to the ketone of **1-43**, compound **1-49** would be converted to α,β -unsaturated ketone **1-50** via dehydration under the acidic conditions. Although the C5-C6 olefin of **1-43** was unreactive toward several oxidation conditions, the C4-C5 olefin of **1-50** was expected to be less shielded and more reactive, because the olefin is one-carbon away from the oxabicyclo[3.2.1]octane skeleton compared to the C5-C6 olefin of **1-43**.

Scheme 1.7 Revised synthetic plan for construction of the C4- and C5-tetrasubstituted carbons



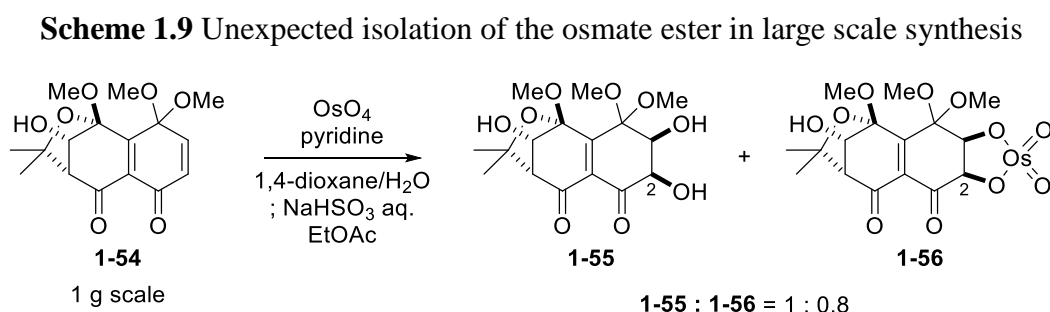
Following this consideration, the reactions in Scheme 1.8 were conducted. Introduction of the methyl group and acidic dehydration proceeded without problem to give α,β -unsaturated ketone **1-52**. The dimethyl acetal was also hydrolyzed at this point. Then, oxidation of the olefin was attempted. Although the olefin reacted smoothly with OsO₄, the product was the undesired diastereomer **1-53**. The stereochemistry was determined by NOE correlation between C2-proton and one of the methyl group of the *gem*-dimethyl structure, which would be observed only if the decaline was *cis*-fused. The concave nature of the α -face of the olefin must be the cause of the face selectivity.

Scheme 1.8 Attempted dihydroxylation of α,β -unsaturated ketone **1-52**

The above results clearly indicate the cyclic ketal structure inhibited approach of the oxidizing reagents to the α -face of the C5-position. Therefore, hydrolysis of the cyclic ketal should be conducted prior to the introduction of the C5-oxygen functionality.

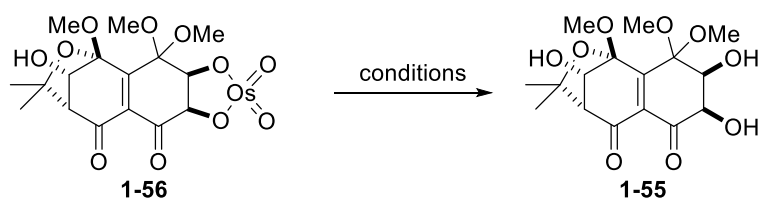
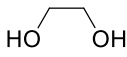
1.2.2.2.3 Reproducibility problem in dihydroxylation

While investigating the above reactions, severe problem occurred in the large scale synthesis of **1-55** (Scheme 1.9). When diketone **1-54** was subjected to the dihydroxylation conditions in 1 gram scale, a highly polar byproduct was generated along with the desired product **1-55**. The structure of the byproduct was tentatively assigned as the osmate ester **1-56** based on the ESI-MS peak pattern and large downfield shift (ca. 0.9 ppm compared to **1-55**) of the peak of the proton at C2-position in its ^1H NMR spectrum.



Aiming at confirming the structure of the osmate ester **1-56** and recovering the material, hydrolysis of the separated osmate ester was attempted (Table 1.1). Under the aqueous basic conditions, diol **1-55** was initially detected on TLC, but both the starting material and the product decomposed under the reaction conditions (entry 1). Methansulfonamide, which is known to accelerate the hydrolysis of the osmate ester in asymmetric dihydroxylation⁴, was ineffective in this case (entry 2). Finally, ethylene glycol was found to be able to liberate the diol in clean fashion. Although the result obtained here supported the structural assumption of **1-56**, the hydrolysis was very slow and seemed to require excess amount of ethylene glycol, which would be difficult to apply to the large scale synthesis.

Table 1.1 Attempted hydrolysis of the osmate ester

		
entry	conditions	results
1	K ₂ CO ₃ MeOH, H ₂ O	decomposed ^a
2	CH ₃ SO ₂ NH ₂ EtOAc/H ₂ O	no reaction
3	 EtOAc rt to 50 °C	1-56 : 1-55 = 2.5 : 1

^a **1-55** was observed on TLC at first, but seemed decomposed under the conditions.

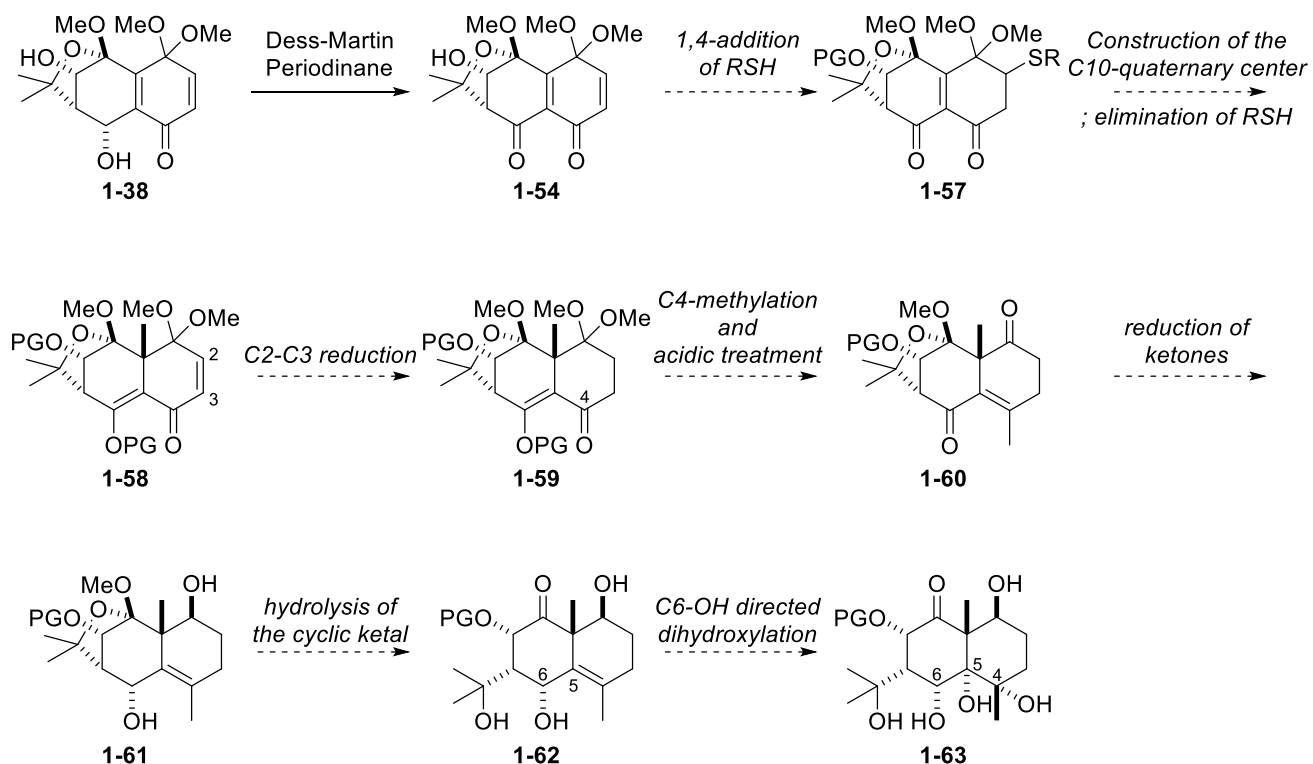
1.2.3 Revise of the plan for the model study

1.2.3.1 Revised synthetic plan

The results in the preceding section 1.2.2 disclosed the two problems. The first one was the low reactivity of the α -face of the C5-position toward oxidation (Scheme 1.6 and 1.8). This could be attributed to the *concave* nature of the α -face, and thus the cyclic ketal should be hydrolyzed prior to the C5-oxidation. The second one was the irreproducible dihydroxylation of the C2-C3 olefin of **2-7** (Scheme 1.9). This problem would be avoided by reducing the olefin instead of oxidizing it. Although the reduction of the C2-C3 olefin decreases the oxidation state of the skeleton, such simplification would be justified, since the primary aim of this model study was construction of the C10- and C5-tetrasubstituted carbons via 1,4-addition and following oxidation.

Accordingly, the revised synthetic plan was formulated in Scheme 1.10. Diketone **1-54** was obtained by the oxidation of Dr. Iwatsu's intermediate **1-38**, and was set as a starting material. 1,4-Addition of thiol was to be employed as a temporary protection of the less hindered α,β -unsaturated ketone structure. Construction of the C10-quaternary carbon via 1,4-addition to diketone **1-57** followed by elimination of the thiol would give α,β -unsaturated ketone **1-58**. The C2-C3 olefin would then be reduced to **1-59**, from which the introduction of the methyl group to C4-position, and acidic treatment would give α,β -unsaturated ketone **1-60**. After reduction of the two ketones, the cyclic ketal of **1-61** would be hydrolyzed to afford ketone **1-62**. Dihydroxylation of the C4-C5 olefin could be directed by the allylic C6-hydroxy group to yield the desired α -isomer **1-63**.

Scheme 1.10 Revised synthetic plan from 1-54

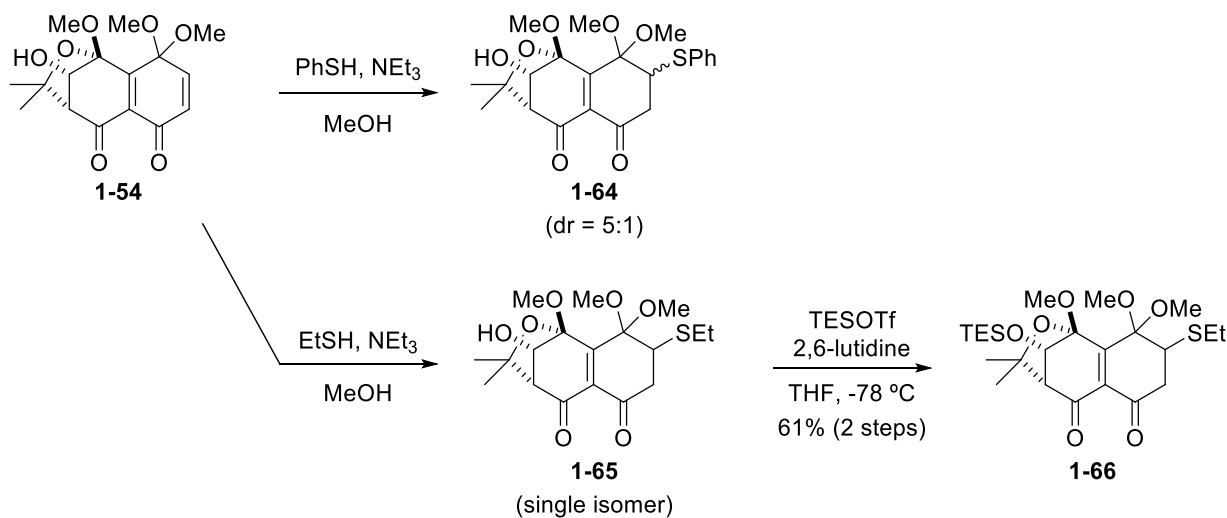


1.2.3.2 Construction of the C10-quaternary carbon

1.2.3.2.1 Synthesis of substrates for 1,4-addition

First of all, a couple of substrates for the key 1,4-addition were prepared (Scheme 1.11). 1,4-Addition of thiophenol or ethanethiol to the less-hindered α,β -unsaturated carbonyl group of **1-54** yielded β -thioketones **1-64** and **1-65**, respectively. The secondary alcohol of the latter was protected as a TES ether to give **1-66**.

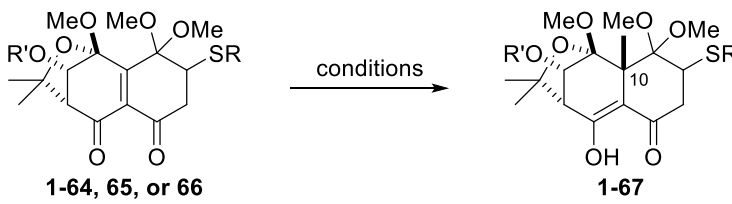
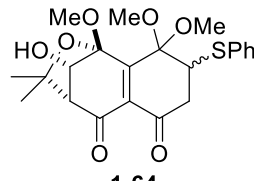
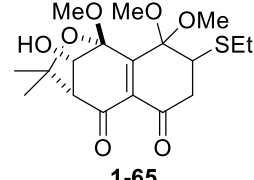
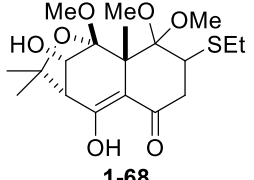
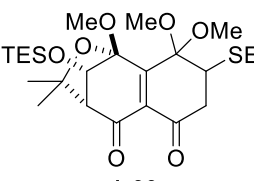
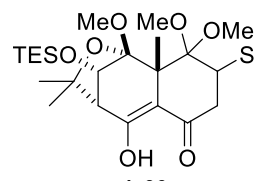
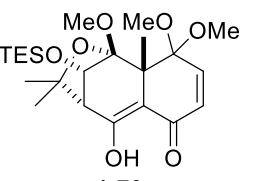
Scheme 1.11 Preparation of precursors for 1,4-addition



1.2.3.2.2 Construction of the C10-quaternary carbon by 1,4-addition

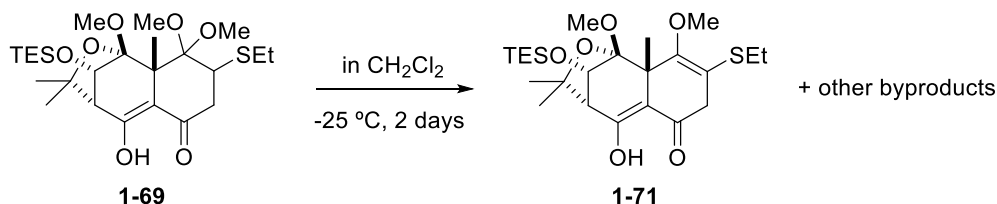
Next, 1,4-addition of the methyl group to these substrates was investigated (Table 1.2). Phenylsulfide **1-64** decomposed under the previously optimized reaction conditions (entry 1). In contrast, ethyl sulfide **1-65** did give the desired product **1-68** in low yield (entry 2). TES protection of the secondary alcohol was found to increase the yield of 1,4-adduct **1-69** (entry 3), and further optimization revealed $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the more effective Lewis acid, yielding **1-69** in higher yield (53%, entry 4).^{5, 6}

Table 1.2 1,4-addition of the methyl cuprate

 1-64, 65, or 66 1-67			
entry	substrate	conditions	result
1	 1-64	MeLi, CuCN TMSCl Et ₂ O -78 °C to -50 °C	decomposed
2	 1-65	MeLi, CuCN TMSCl Et ₂ O -78 °C to -50 °C	 1-68 <26%
3	 1-66	MeLi, CuCN TMSCl Et ₂ O -78 °C to -50 °C	 1-69 32%  1-70 9%
4	1-66	MeLi, CuCN $\text{BF}_3 \cdot \text{Et}_2\text{O}$ Et ₂ O -78 °C to -50 °C	1-69 : 53%

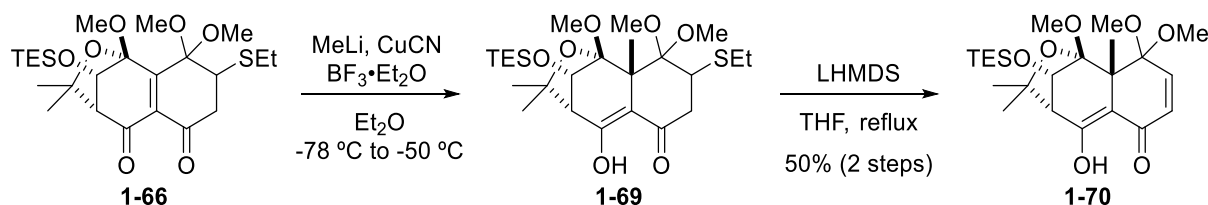
Although the desired 1,4-adduct was obtained, the yield was still moderate. Careful investigation of the product revealed the instability of the dimethyl acetal moiety of **1-69** (Scheme 1.12).

Scheme 1.12 Spontaneous decomposition of the 1,4-adduct **1-69**



Therefore, in the optimized procedure, 1,4-adduct **1-69** was immediately treated with base to unveil the stable α,β -unsaturated ketone **1-70** (Scheme 1.13). Through the sequence, compound **1-70** bearing the C10-quaternary carbon was successfully synthesized.

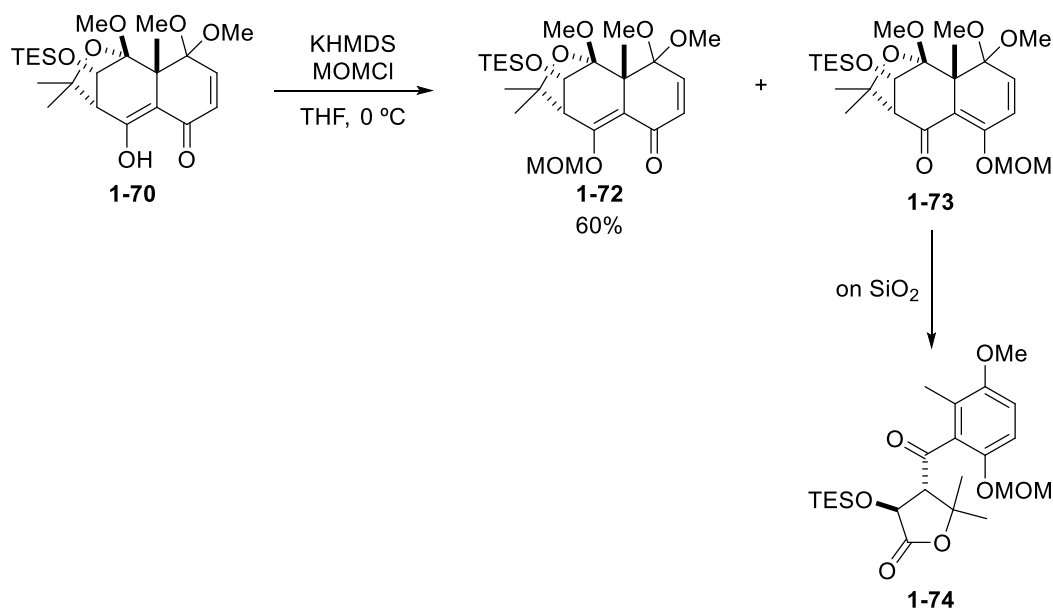
Scheme 1.13 Successful 1,4-addition combined with E1cB elimination



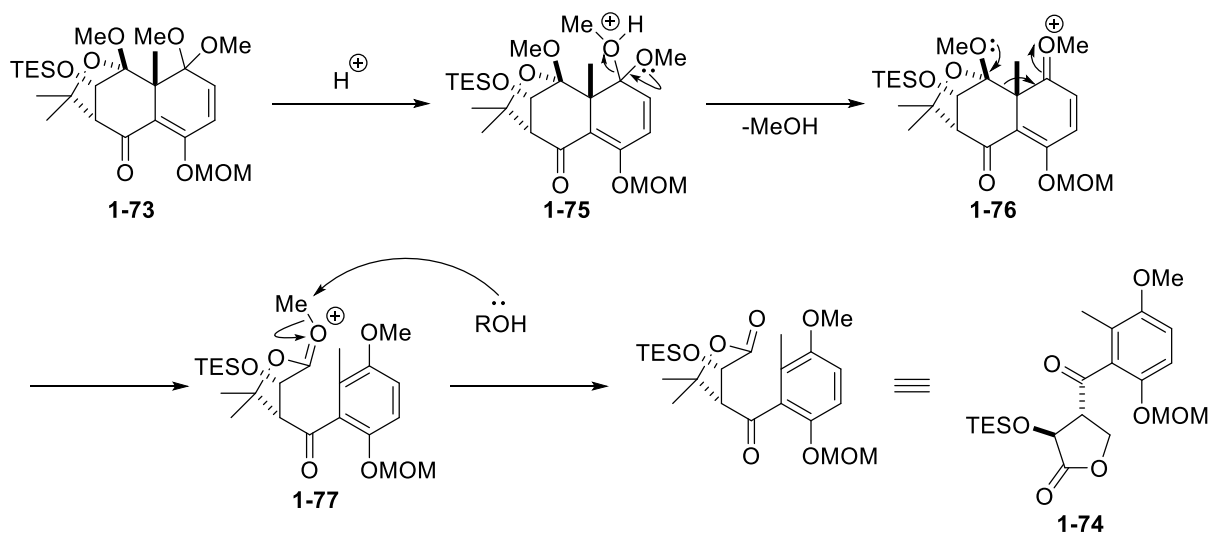
1.2.3.3 Synthesis of the substrates for the hydrolysis of the cyclic ketal

1.2.3.3.1 Protection of the enol

Transformations toward the hydrolysis of the cyclic ketal was then investigated. Protection of the enol proceeded in moderate regioselectivity to give **1-72**, and the undesired regioisomer **1-73** was spontaneously converted to the aromatic compound **1-74** (Scheme 1.14).

Scheme 1.14 Protection of the enol moiety

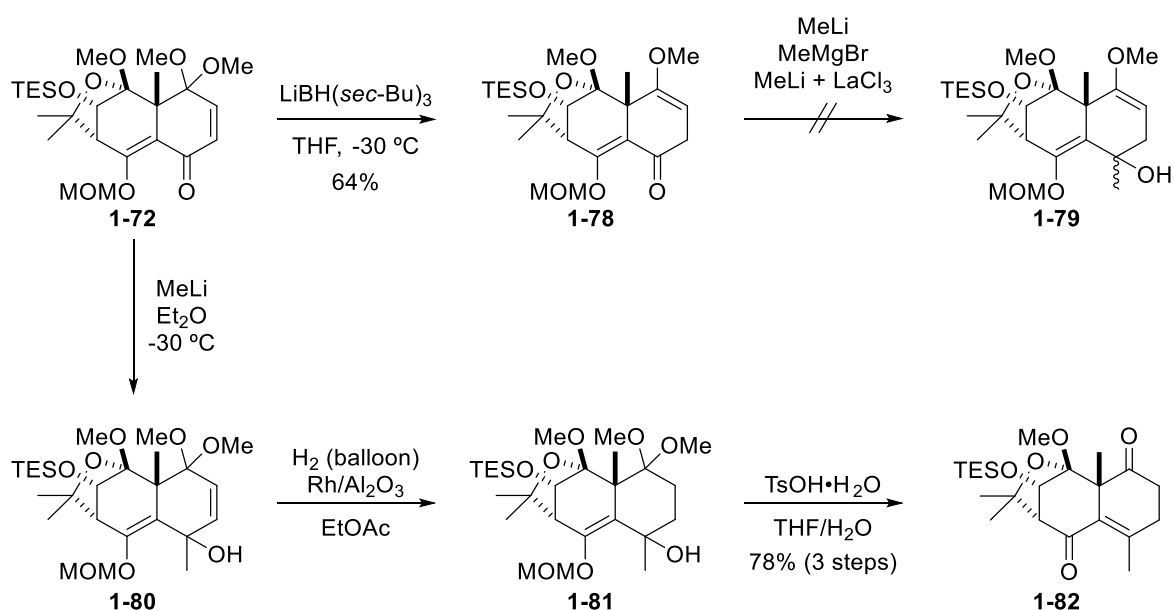
The proposed mechanism of the aromatization is shown in Scheme 1.15. The dimethyl acetal of 1,3-diene **1-73** was activated on silica gel to give **1-75**. Elimination of methanol yielded **1-76**, from which C-C bond cleavage occurred to give another oxonium cation **1-77**. The driving force of the C-C bond cleavage must be the aromatization of the right ring. Finally the methyl group was removed by some nucleophiles to afford the observed lactone **1-74**.

Scheme 1.15 Proposed mechanism for the aromatization of **1-73** to **1-74**

1.2.3.3.2 Reduction of the C2-C3 olefin and introduction of the methyl group at C4-position

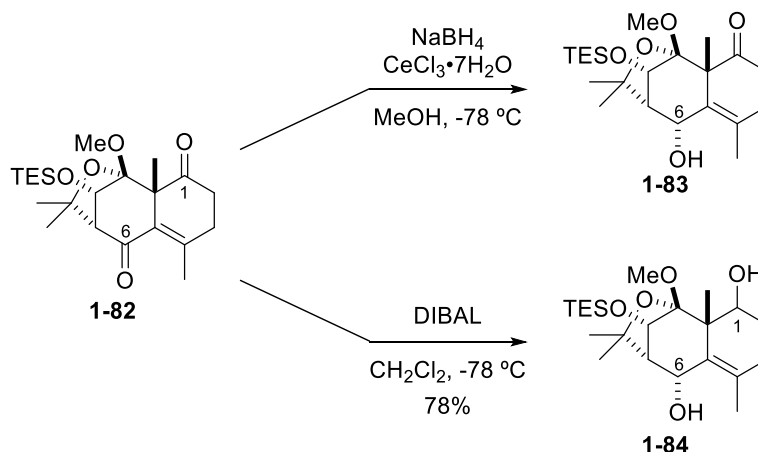
The 1,4-reduction of **1-72** smoothly proceeded with $\text{LiBH}(\text{sec-Bu})_3$ (Scheme 1.16). At the same time, one molecule of methanol was eliminated to give methyl enol ether **1-78** as a stable product. But the introduction of the methyl group to **1-78** did not proceed under various reaction conditions. Thus, the methyl group was introduced first to **1-72**, and then the olefin was reduced by hydrogenation over $\text{Rh}/\text{Al}_2\text{O}_3$ (**1-72** to **1-80** to **1-81**).⁷ Acidic treatment of the tertiary alcohol **1-81** cleanly afforded diketone **1-82**.⁸

Scheme 1.16 Synthesis of C2-C3-reduced diketone **1-82**



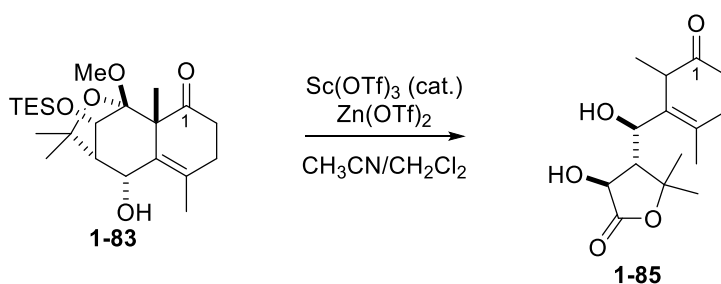
1.2.3.3.3 Reduction of ketones at C1- and C6-position

Toward the hydrolysis of the cyclic ketal, two substrates were prepared by reduction of ketones of **1-82** (Scheme 1.17). First, C6-ketone was regioselectively reduced under the Luche reduction conditions⁹ to ketone **1-83**. On the other hand, reduction with DIBAL afforded diol **1-84** as a single isomer. The stereochemistries of C6-positions of **1-83** and **1-84** were confidently proposed as shown based on the previous results, whereas that of C1-position of **1-84** was not determined since the following steps were unsuccessful (*vide infra*).

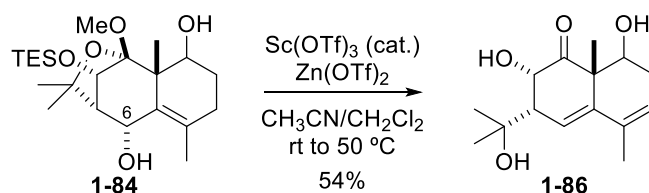
Scheme 1.17 Preparation of two substrates for the hydrolysis of the cyclic ketal

1.2.3.4 Hydrolysis of the cyclic ketal

Next, thus obtained two substrates were subjected to various acidic hydrolysis conditions. When ketone **1-83** was subjected to the previously optimized conditions using catalytic $\text{Sc}(\text{OTf})_3$, C-C bond cleavage occurred again to give **1-85**, even in the absence of the driving force of aromatization (Scheme 1.18). Highly congested nature of the quaternary carbon and anion stabilizing effect of C1-ketone could be causes of this undesired reaction.

Scheme 1.18 Unexpected C-C bond cleavage

On the other hand, the cyclic ketal of diol **1-84** was smoothly hydrolyzed under the same conditions (Scheme 1.19). However, C6-hydroxy group at the allylic position was eliminated at the same time to give diene **1-86**. Various attempts to suppress the undesired dehydration met with no success.

Scheme 1.19 Hydrolysis of C9-ketal using diol **1-84**

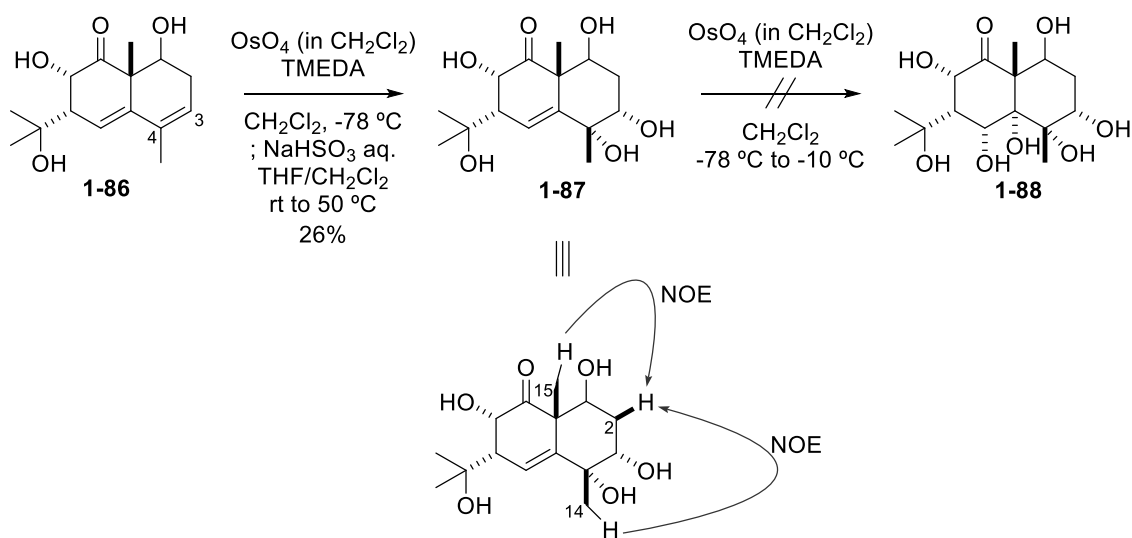
Other attempted conditions:

 $\text{Sc}(\text{OTf})_3$ in THF, $(\text{CH}_2\text{Cl})_2$, MeOH, or $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ $\text{Sc}(\text{OTf})_3$ with buffering base

TfOH, HCl, Nafion

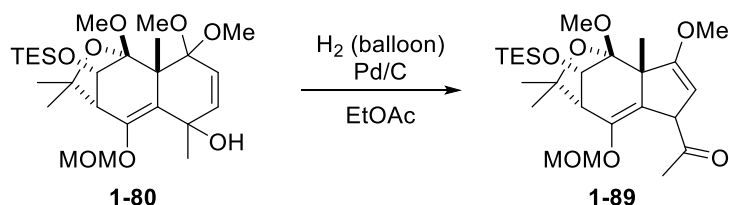
TMSCl, $\text{TiCl}_4 + \text{LiI}$, $\text{BF}_3 \cdot \text{Et}_2\text{O} + \text{NaI}$, $\text{Yb}(\text{OTf})$ **1.2.3.5 Attempted construction of the C5-tetrasubstituted carbon on the bicyclic system**

In any case, hydrolysis of the cyclic ketal was achieved, and the stage was set for introduction of the C5-oxygen functionality. When diene **1-86** was treated with OsO_4 with TMEDA in CH_2Cl_2 ¹⁰, only the C3-C4 olefin reacted to give diol **1-87** (Scheme 1.20). The stereochemistry was determined by combining NOE correlations $\text{H}_{14}\text{-H}_{2\beta}$ and $\text{H}_{15}\text{-H}_{2\beta}$ as shown in the scheme. Although the yield was unsatisfactory, C4-tetrasubstituted carbon was successfully constructed. Finally, pentaol **1-87** was subjected to the same conditions at higher temperature, with the expectation that the allylic hydroxy group would direct the approach of the oxidant. But none of the desired product was obtained. Although protection of some hydroxy groups might improve the result of the second dihydroxylation, in the light of inefficiency of functionalization sequence developed herein, this route was abandoned.

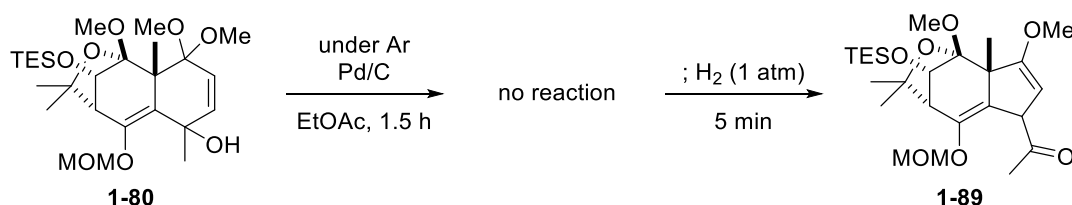
Scheme 1.20 Unsuccessful oxidation of the C5-C6 olefin

1.2.4 References and notes for section 1.2

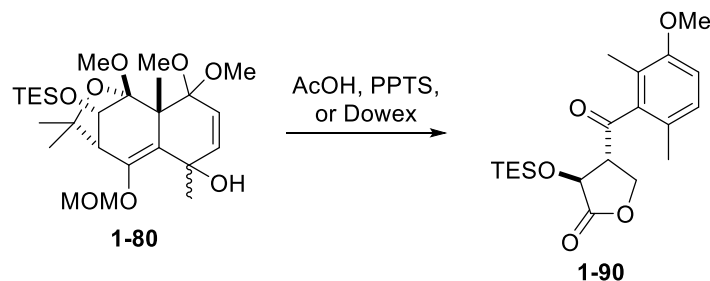
- ¹ Todoroki, H. Master Thesis, The University of Tokyo, 2012.
- ² Numbering system used in ref 14(a) of section 1.1 is employed in this dissertation.
- ³ *m*-CPBA yielded Bayer-Villiger oxidation product.
- ⁴ Shrapless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
- ⁵ (a) For review on the mechanism of the nucleophilic reactions of organocuprates, see: Yoshikai, N.; Nakamura, E. *Chem Rev.* **2011**, *112*, 2339.
- ⁶ For the role of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, see: Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351.
- ⁷ Hydrogenation of **1-80** on Pd/C effected ring contraction to **1-89**.



Although the mechanism of the reaction seemed to be acid-mediated 1,2-alkyl shift, control experiment showed hydrogen gas was required for the transformation, thus indicating involvement of some palladium hydride species.



- ⁸ Acidic treatment before the hydrogenation of **1-80** induced the aromatization similar to that shown in Scheme 1-14 and 1-15.



- ⁹ (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
- ¹⁰ Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J.; *Tetrahedron Lett.* **1999**, *38*, 5027.

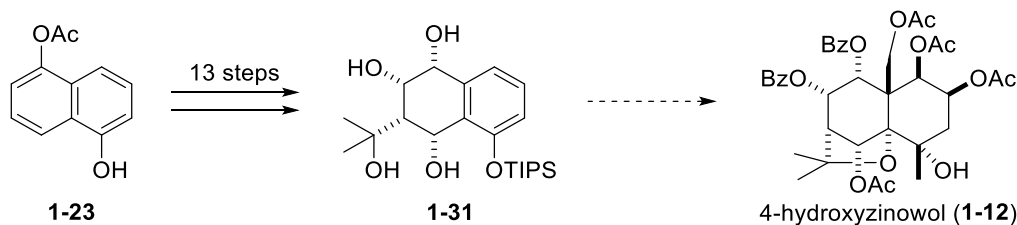
1.3 Oxidative dearomatization and Diels-Alder reaction

1.3.1 Revise of the synthetic plan

1.3.1.1 Synthetic consideration

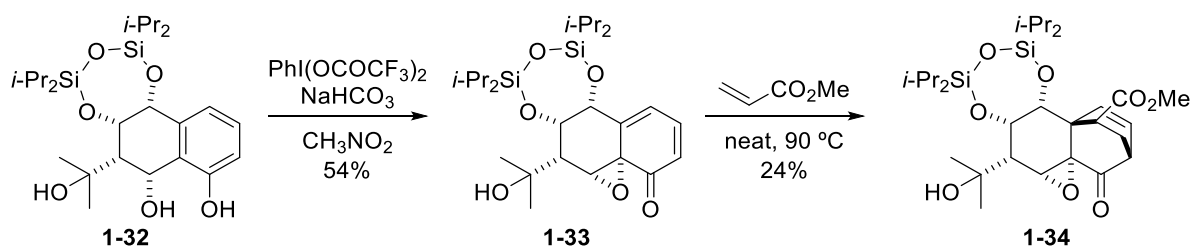
The author identified two difficulties in the above model study: hydrolysis of the cyclic ketal at the C9-position with highly functionalized intermediates, and construction of the C5-tetrasubstituted carbon by using external oxidant. Thus, the synthetic plan was revised to start from Dr. Iwatsu's intermediate **1-31** whose cyclic ketal had already been hydrolyzed (Scheme 1.21).

Scheme 1.21 Revise of the starting point



Construction of the C10-quaternary carbon by 1,4-addition to substrates synthesized from **1-31** had already been investigated by the author and had resulted in failure (not shown),¹ oxidative dearomatization and Diels-Alder reaction was chosen as a key reaction for the construction of C5- and C10-tetrasubstituted carbons. Although the results reported by Dr. Iwatsu were discouraging in terms of the low yields and the difficulty of further functionalizations (Scheme 1.22), there seemed to be a room for improvement by modifying the reaction conditions and substrates.

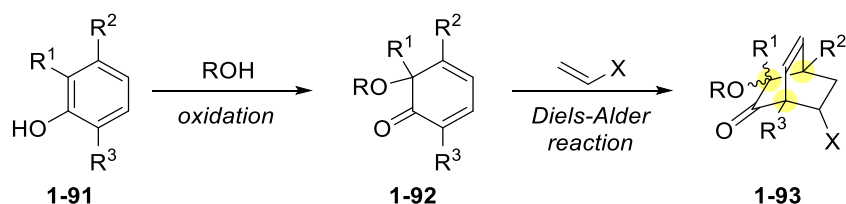
Scheme 1.22 Results obtained by Dr. Iwatsu



1.3.1.2 General features of oxidative dearomatization and Diels-Alder reaction

Oxidative dearomatization of *ortho*-substituted phenols **1-91** and the following Diels-Alder reaction of the resulting diene **1-92** with alkenes is a powerful strategy for construction of highly-functionalized bicyclo[2.2.2]octane skeleton (Scheme 1.23).²

Scheme 1.23 Oxidative dearomatization and Diels-Alder reaction with alkenes



Not only the high level of oxidation state of the obtained skeleton, but also the possibility of construction of multiple tetrasubstituted carbons (highlighted in yellow in Scheme 1.23) appeals many synthetic chemists, resulting in the wide application of this strategy in the total synthesis of complex natural products. Selected recent examples are shown in Scheme 1.24.

Liao and co-workers reported the total synthesis of magellanine (**1-97**) in 2002 (Scheme 1.24a).³ Intermolecular Diels-Alder reaction of *in-situ* generated diene **1-95** and cyclopentadiene was employed as a first step of the synthesis to give the adduct **1-96**. Linear triquinane **1-97** was synthesized by the following 13 steps.

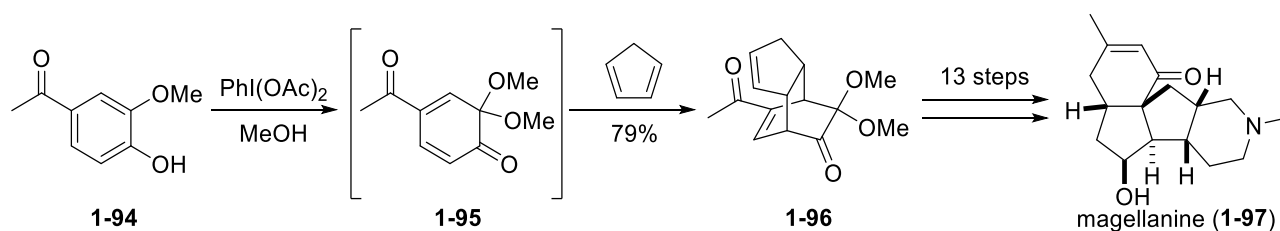
On the other hand, in 2013 Zakarian and co-workers reported the total synthesis of maeocrystal V (**1-102**) utilizing the intramolecular Diels-Alder reaction (Scheme 1.24b).⁴ Phenol **1-99**, which was obtained from alcohol **1-98** in 7 steps, was oxidized to construct the diene moiety of **1-100**. After the incorporation of vinyl silane moiety as a dienophile, intramolecular Diels-Alder reaction under the heating conditions yielded **1-101** bearing the tricyclic core structure of maeocrystal V. The synthesis was accomplished in 14 steps from this intermediate.

Scheme 1.24 Recent applications of oxidative dearomatization and Diels-Alder reaction strategy

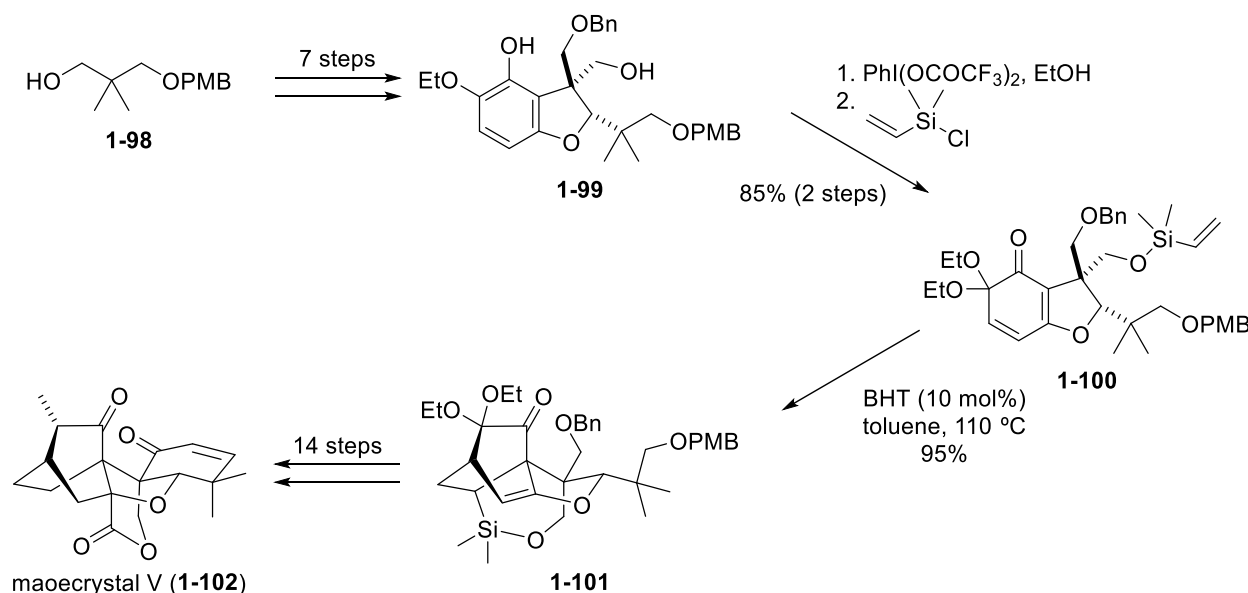
a. Total synthesis of magellanine by Liao and co-workers using intermolecular Diels-Alder reaction

b. Total synthesis of maoecrystal V by Zakarian and co-workers using intramolecular Diels-Alder reaction

a.

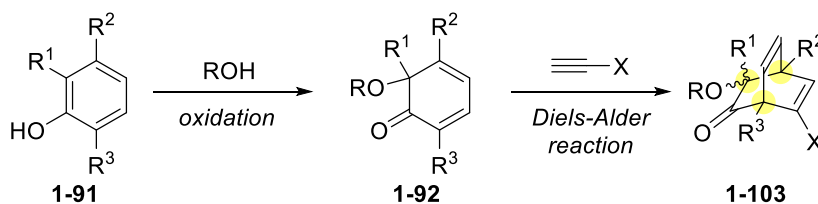


b.

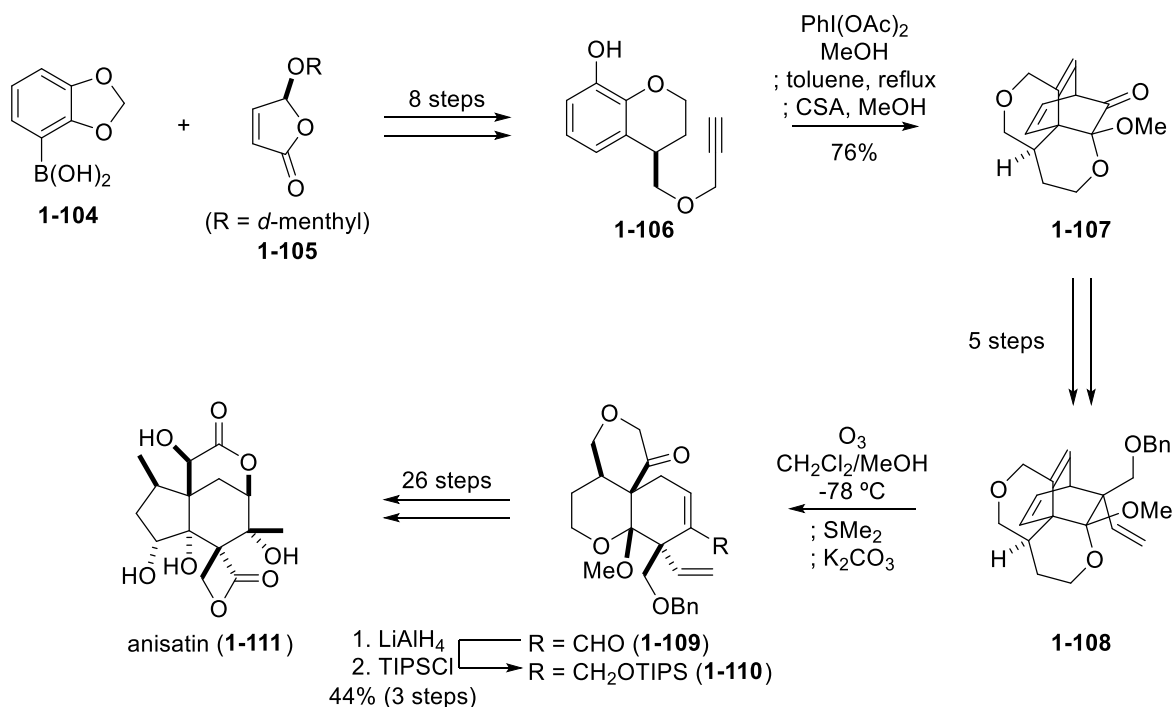


1.3.1.3 Use of alkyne as a dienophile

It can be simply deduced that the use of an alkyne as a dienophile would give more oxidized bicyclo[2.2.2]octadiene **1-103** and increase the value of the product as a highly oxidized building block (Scheme 1.25).

Scheme 1.25 Oxidative dearomatization and Diels-Alder reaction with alkynes

To fully utilize the product, it is inevitable to distinguish the resulting two olefins in further transformations. As demonstrated by Fukuyama and co-workers in their total synthesis of anisatin (Scheme 1.26),⁵ it is possible to distinguish the olefins by subtle difference of electron density or strain of olefins. Specifically, alkynyl phenol **1-106**, which was prepared from two fragments **1-104** and **1-105**, were subjected to the oxidation and then heated to give the Diels-Alder adduct **1-107** after the acid-mediated epimerization. After the conversion to **1-108**, the putatively more electron-rich and more strained trisubstituted olefin was chemoselectively oxidized by ozone to give the aldehyde, the remained olefin of which was isomerized under the basic conditions to give **1-109**. Reduction of the aldehyde and protection of the resulting primary hydroxy group, followed by 26-step sequence completed the total synthesis of anisatin (**1-111**).

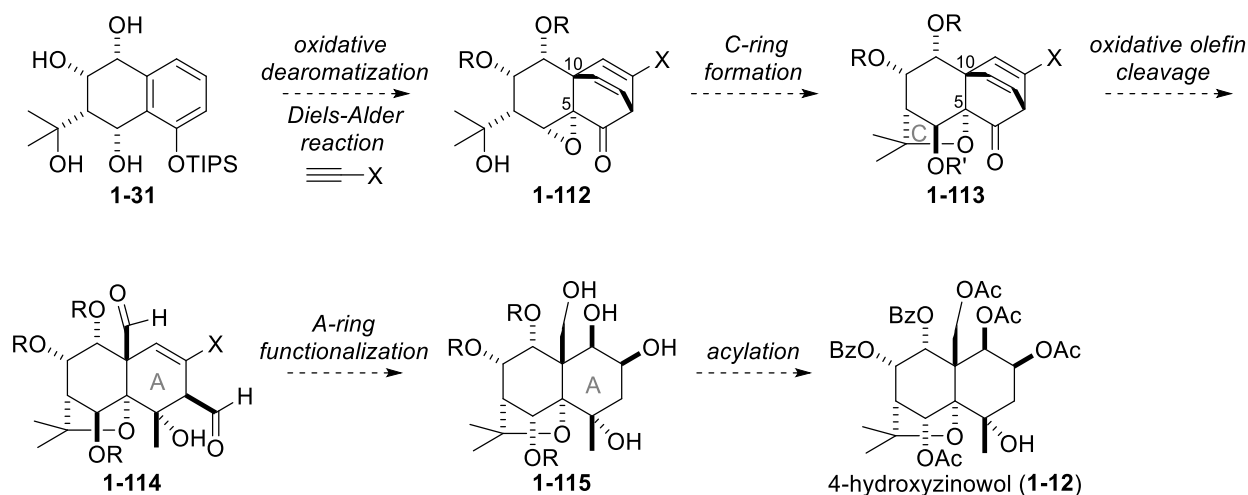
Scheme 1.26 Total synthesis of anisatin by Fukuyama *et al.*

Application of alkynes bearing electron withdrawing groups enables chemoselective transformations of two olefins of the product, thus would be more general and reliable. Surprisingly, despite apparent simplicity of the strategy, the examples using such alkynes in the synthesis of highly oxygenated molecule is scarce.⁶

1.3.1.4 Revised synthetic plan

The detailed revised synthetic plan is depicted in Scheme 1.27. After the initial key reactions, epoxide of diene **1-112** was intended to be opened by oxygen nucleophile, instead of the sulfur nucleophile, to let the future inversion of the stereochemistry be more feasible. After the C-ring formation, chemoselective oxidative cleavage of the electron-rich olefin of **1-113** would give dialdehyde **1-114**, from which functionalization of the A-ring would afford polyol **1-115**. Finally, the regioselective introduction of multiple acyl groups would afford 4-hydroxyzinowol (**1-12**).

Scheme 1.27 Revised synthetic plan from **1-31**

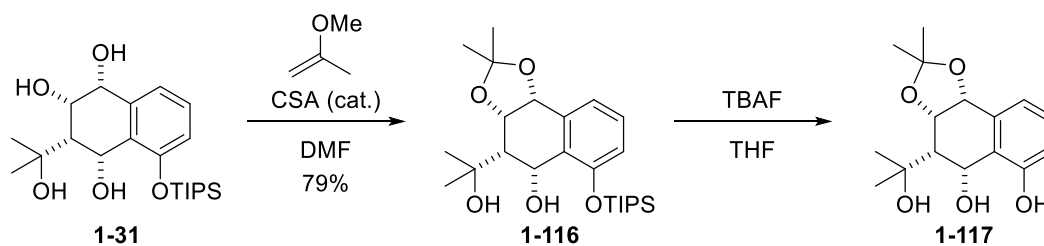


1.3.2 Oxidative dearomatization

1.3.2.1 Preparation of the substrate

Starting from tetraol **1-31**, 1,2-diol was selectively protected as acetonide in the presence of the 1,3-diol moiety (Scheme 1.28). Then the TIPS group of **1-116** was removed without problem to give phenol **1-117**.

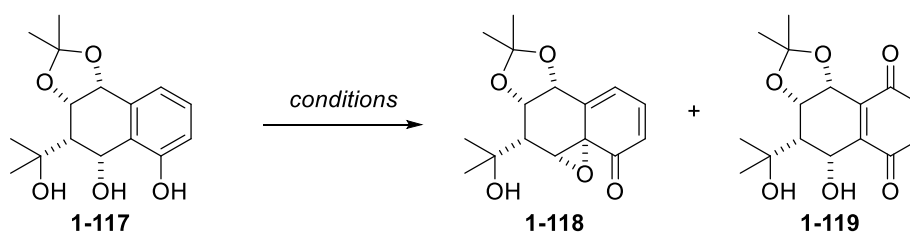
Scheme 1.28 Preparation of the substrate for the oxidative dearomatization



1.3.2.2 Condition screening of the oxidative dearomatization

Next, screening of the reaction conditions was performed towards construction of the C5-tetrasubstituted carbon by the oxidative dearomatization of phenol **1-117** (Table 1.3). Initially, previous best condition was applied (entry 1). As a result, the desired epoxide **1-118** was obtained in only 3% yield along with *p*-quinone **1-119** as a major product. Use of hexafluoro-2-propanol, one of the perfluoroalcohol known as a good solvent for oxidative dearomatization,⁷ complicated the reaction in entry 2. Finally, NaIO₄⁸ was found to be the effective oxidant yielding **1-118** in almost quantitative yield. Some 2,4-cyclohexadienones derived from phenols are reported to be highly unstable and prone to dimerization by the self Diels-Alder reaction.⁹ However, **1-118** was stable enough to be purified by silica gel chromatography or recrystallization, suggesting the congested surrounding functional groups increased the stability of diene **1-118**.

Table 1.3 Oxidative dearomatization of the phenol **1-117**



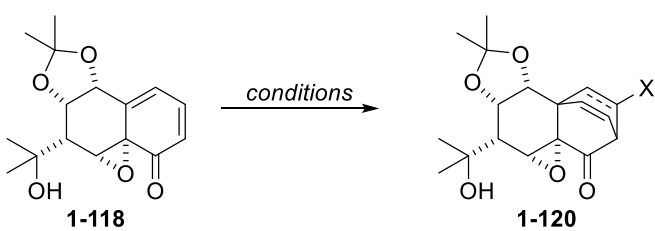
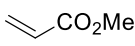
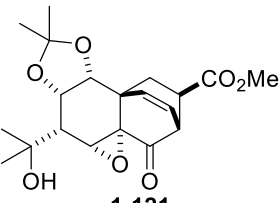
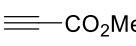
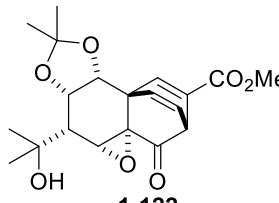

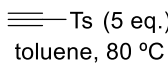
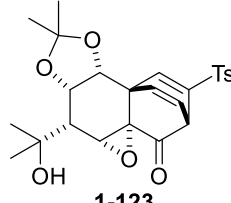
entry	conditions	results
1	PhI(OCOCF ₃) ₂ NaHCO ₃ MS 3A, CH ₃ NO ₂	1-118 : 3% 1-119 : <29%
2	PhI(OCOCF ₃) ₂ NaHCO ₃ MS 3A, (CF ₃) ₂ CHOH	complex mixture
3	NaIO ₄ MeOH/H ₂ O	1-118 : 97% (2 steps from 1-116)

1.3.3 Diels-Alder reaction

1.3.3.1 Substrate scope

Now the stable diene **1-118** in hand, construction of the C10-quaternary carbon was attempted by Diels-Alder reaction with various dienophiles (Table 1.4). First, methyl acrylate was used under neat condition for comparison with the previous synthetic study (entry 1). Surprisingly, two components reacted in the regio- and stereoselective manner to give the adduct **1-121** in high yield. On the other hand, 1-cyanovinyl acetate, which is a ketene equivalent, did not afford any Diels-Alder adduct presumably due to the steric hinderance of 1,1-disubstitution of the dienophile (entry 2). To alleviate the steric hinderance without lowering the oxidation state, attention was next turned to alkynes. As can be seen in entry 3, the reaction with methyl propiolate under neat conditions cleanly yielded **1-122**. The stereo- and regioselectivity was the same as that of entry 1. Vinyl ester part of **1-122** could be used as a functional handle for further functionalization, but the robust methoxycarbonyl group had to be removed in later stage. Thus the easily removable tosyl group was chosen as an electron withdrawing group in entry 4. The reactivity as a dienophile was also improved by substitution with the tosyl group: only 5 equivalents of dienophile in toluene was sufficient to achieve high yielding formation of the adduct **1-123**.

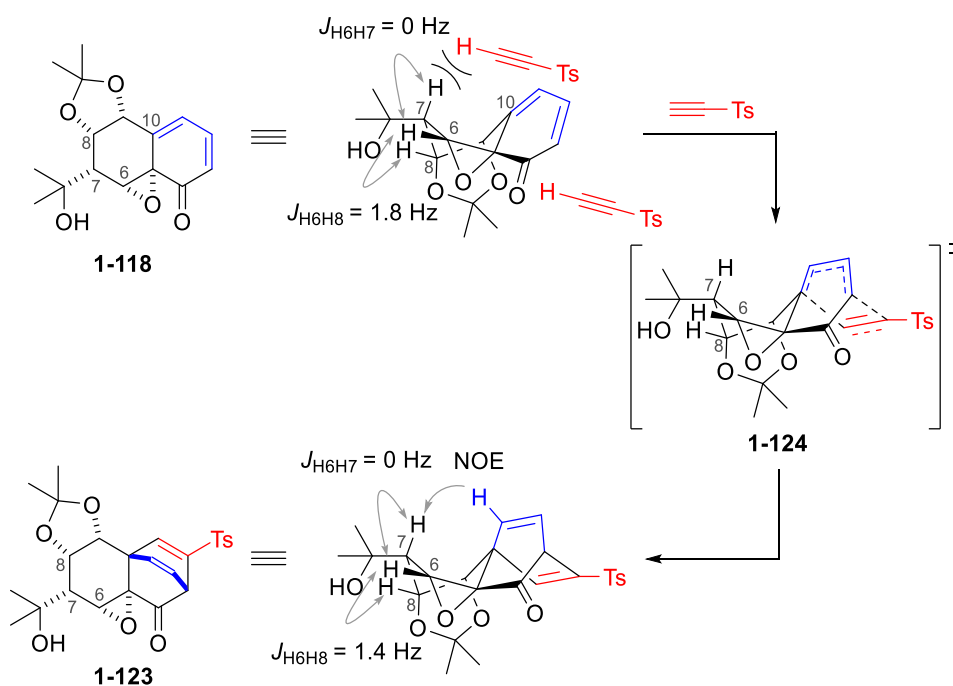
Table 1.4 Diels-Alder reaction of **1-118**

					
entry	conditions	results	entry	conditions	results
1	 (neat) 80 °C	 1-121 79%	3	 (neat) 80 °C	 1-122 81%
2	 (neat) 80 °C to 140 °C	decomposed	4	 toluene, 80 °C	 1-123 70%

1.3.3.2 Rationale for the diastereoselectivity and regioselectivity of the Diels-Alder reaction

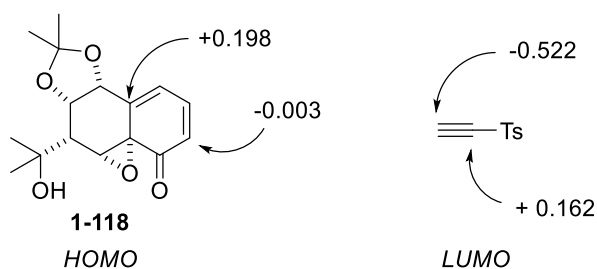
The proposed rationale for the face selectivity of the Diels-Alder reaction is shown in the Scheme 1.29. In the ^1H NMR spectrum of diene **1-118**, the ^1H - ^1H coupling between H6 and H7 was not observed ($J_{\text{H6H7}} = 0$ Hz), whereas the long-range coupling constant between H6 and H8 was relatively large ($J_{\text{H6H8}} = 1.8$ Hz). These data indicates that the left 6-membered ring of **1-118** adopts twist-boat conformation as shown. Product **1-123** showed similar coupling pattern ($J_{\text{H6H7}} = 0$ Hz and $J_{\text{H6H8}} = 1.8$ Hz), possibly adopting the same twist-boat conformation. Furthermore, NOE correlation was observed between C15-proton and C7-proton of the product. By combining these spectral data, it was speculated that H7 was positioned close to the reaction center (C10) in the parent diene **1-118**. The steric shielding by this proton should have directed the α -face approach of the dienophile, producing the observed product **1-123** via transition state **1-124**.

Scheme 1.29 Rationale for the stereoselective Diels-Alder reaction



As for the regioselectivity, it can be simply explained by regarding the reaction as a *normal-electron-demand* Diels-Alder reaction (i.e. HOMO of diene and LUMO of dienophile). Although similar tendencies were reported in many experiments,^{9,10} there are also some contracting examples in literature. For example, calculation on similar diene system indicated that they reacts by using their LUMOs even with electron deficient alkenes.¹¹ There is also the case in which no regioselectivity was observed.¹² Thus the generalization of the reactivity pattern of 2,4-cycloheadienone is difficult as of today, and contributing factors have to be carefully investigated case by case. In this case, the complete regioselectivity could be attributed to the steric repulsion between the generating quaternary carbon and the tosyl group. Furthermore, the regioselectivity could also be rationalized from the frontier orbital interaction of the diene and the dienophile. In order to clarify the origin of this selectivity in more detail, the DFT calculation of the orbital energies (B3LYP/6-31G*) of **1-118** and ethynyl-*p*-tolyl sulfone was performed.¹³ As a result, $\text{HOMO}_{\text{diene}} = -6.47 \text{ eV}$ and $\text{LUMO}_{\text{diene}} = -2.22 \text{ eV}$, whereas $\text{HOMO}_{\text{dienophile}} = -7.53 \text{ eV}$ and $\text{LUMO}_{\text{dienophile}} = -1.49 \text{ eV}$ were obtained. The results clearly shows this reaction proceeds *normal-electron-demand* manner. Thus, the atomic orbital coefficients of HOMO of the diene and LUMO of the dienophile were also calculated with the same method (Figure 1.4). The regioselectivity could be explained by considering the reaction occurred between the atoms bearing the larger coefficient in each reaction component.

Figure 1.4 Atomic orbital coefficients of HOMO of the diene and LUMO of the dienophile



1.3.4 References and notes for section 1.3

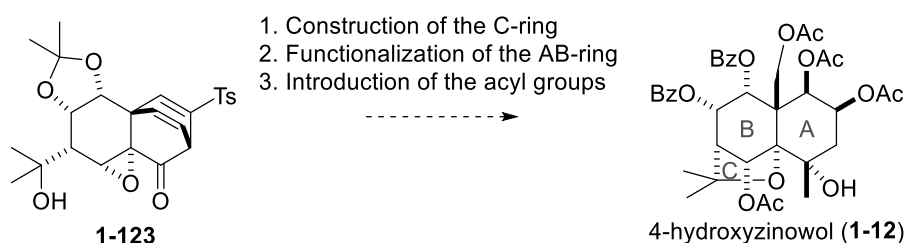
- ¹ Todoroki, H. Master Thesis, The University of Tokyo, 2012.
- ² For reviews on synthetic applications of the oxidative dearomatization and the following Diels-Alder reaction, see: (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (b) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221. (c) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (d) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.
- ³ Yen, C.-F.; Liao, C.-C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4090.
- ⁴ Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552.
- ⁵ Ogura, A.; Yamada, K.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2012**, *14*, 1632.
- ⁶ For the limited examples, see: (a) Takeshita, M.; Tsuzuki, M.; Tashiro, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2076. (b) Ganga, V. B.; Sreeja, T.; Suresh, E.; Varma, R. L. *Tetrahedron* **2007**, *63*, 4134.
- ⁷ Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119.
- ⁸ Becker, H.-D.; Bremholt, T.; Adler, E. *Tetrahedron Lett.* **1972**, *13*, 4205.
- ⁹ Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 6102.
- ¹⁰ For the recent selected example, see: Surasani, S. R.; Parumala, S. K. R.; Peddinti, R. K. *Org. Biomol. Chem.* **2014**, *12*, 5656. and references cited therein.
- ¹¹ Dory, Y. L.; Roy, A.-L.; Soucy, P.; Deslongchamps, P. *Org. Lett.* **2009**, *11*, 1197.
- ¹² Chang, C.-P.; Chen, C. H.; Chuang, G. J.; Liao, C.-C. *Tetrahedron Lett.* **2009**, *50*, 3414.
- ¹³ Initial structure was obtained by MacroModel ver. 10.4. Conditions are as follows. Force Field: MM2*, Solvent: none, Minimization Method: PRCG, Maximum Iteration: 2500, CSearch Method: Mixed Torsional/Low-mode Sampling. DFT calculation was then performed at the B3LYP/6-31G* level of theory.

1.4 Total synthesis of 4-hydroxyzinowol

1.4.1 Overview of the remaining tasks

In section 1.3, two consecutive tetrasubstituted carbons at C5- and C10-positions were successfully constructed. Toward the total synthesis of 4-hydroxyzinowol, there remains the three major tasks (Scheme 1.30): construction of the C-ring, introduction of the oxygen functionalities onto the AB-ring with proper stereochemistry, and introduction of the acyl groups. In this section, study towards construction of the C-ring is described in section 1.4.2, introduction of the oxygen functionalities onto AB-ring is described in section 1.4.3, and regioselective acylation to 4-hydroxyzinowol is described in section 1.4.4.

Scheme 1.30 The remaining tasks toward the total synthesis of 4-hydroxyzinowol



1.4.2 Construction of the C-ring

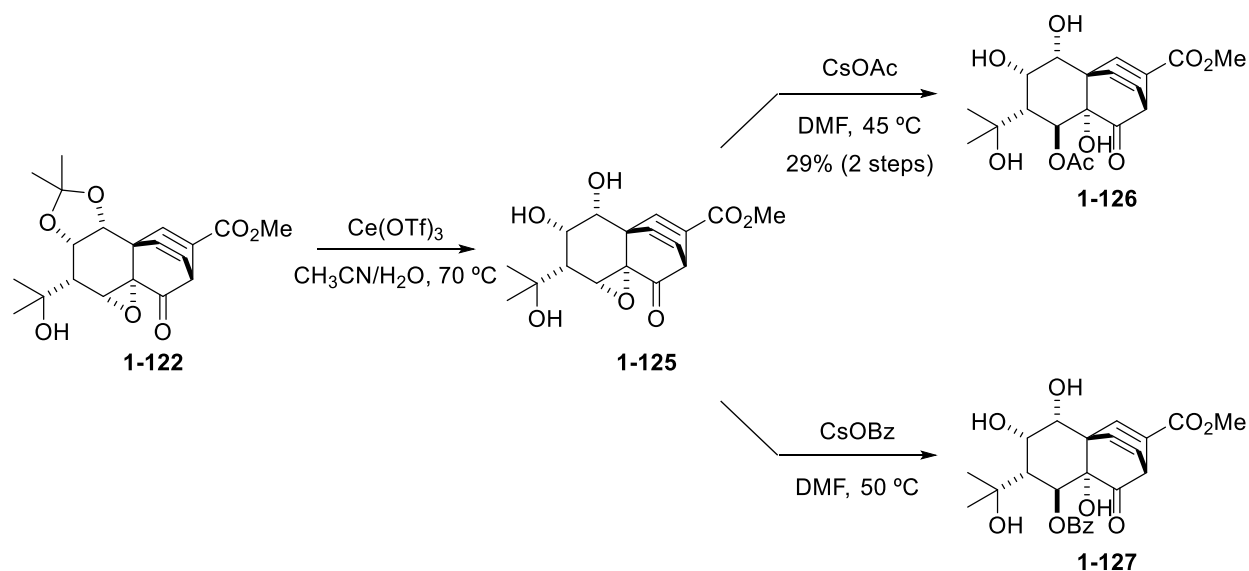
1.4.2.1 Model study of C-ring construction

From the Diels-Alder adduct, the C-ring formation was investigated first. In doing so, the model study was conducted.

1.4.2.1.1 Preparation of model substrates

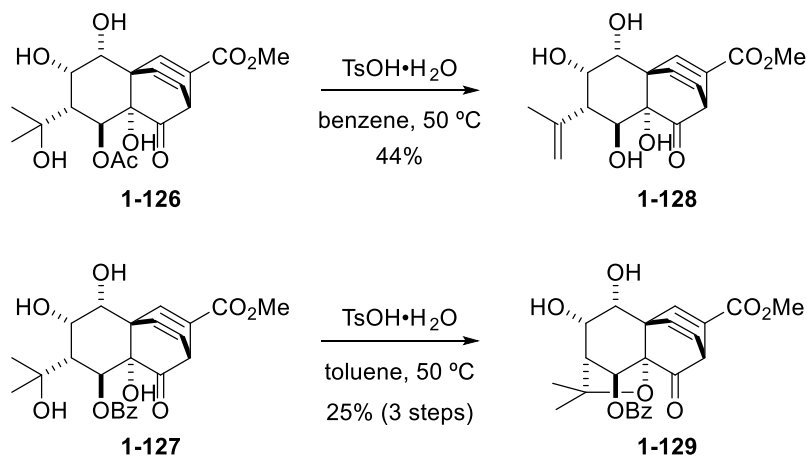
Diels-Alder adduct **1-122** was selected as a starting material of the model study. As shown in Scheme 1.31, two tetraols **1-126** and **1-127** were prepared by removal of the acetonide¹ followed by nucleophilic opening of the epoxide with cesium carboxylates.²

Scheme 1.31 Preparation of two model substrates



1.4.2.1.2 Attempts for C-ring formation using model substrates

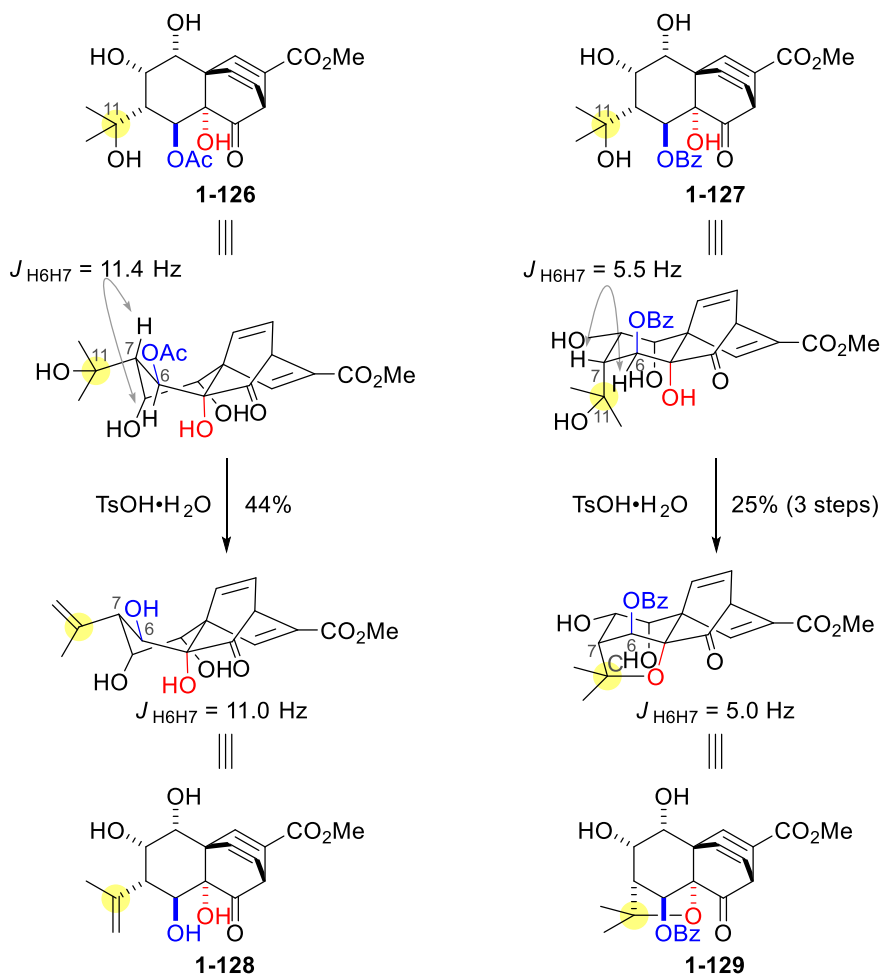
Two model substrates were treated with Brønsted acid under the same conditions (Scheme 1.32). With acetate **1-126**, elimination of the tertiary hydroxy group was the major reaction path to give *exo*-olefin **1-128**.³ In contrast, benzoate **1-127** afforded five-membered ring ether **1-129** in clean fashion.

Scheme 1.32 Contrasting reactivity of acetate **1-126** and benzoate **1-127**

1.4.2.1.3 Rationale for the different reactivity of the model substrates

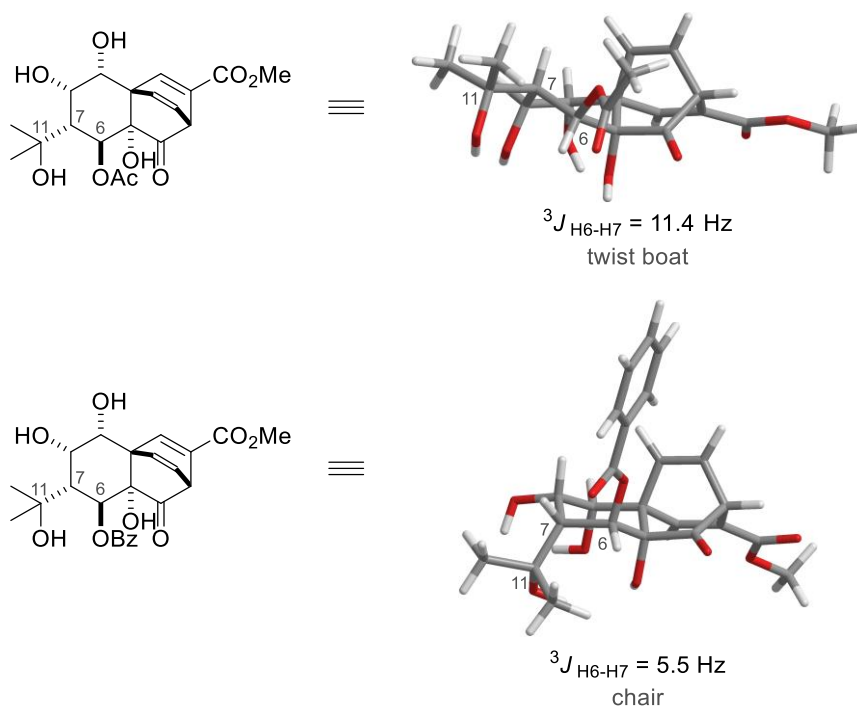
To rationalize the above contrasting reactivity, ^1H NMR analysis was conducted, which revealed the difference of conformational preference between two substrates (Scheme 1.33). The H6-H7 coupling constant of acetate **1-126** was 11.4 Hz, indicating the diaxial relationship of these protons. Taking into account of the bulkiness of the branched substituent at C7-position, the 6-membered ring should have the twist boat conformation. In this conformation, two reaction centers (C11 and C5-OH) are positioned far away from each other. Therefore the elimination was the major reaction path instead of the desired etherification. In contrast, the H6-H7 coupling constant of benzoate **1-127** was 5.5 Hz. The relatively small J value suggested that contribution of the chair-like conformation greatly increased in case of **1-127**. Aforementioned two reaction centers are positioned in the 1,3-diaxial relationship in this conformation, which were smoothly connected under the acidic conditions to give 5-membered ether ring.

Scheme 1.33 Conformational preference of two substrates



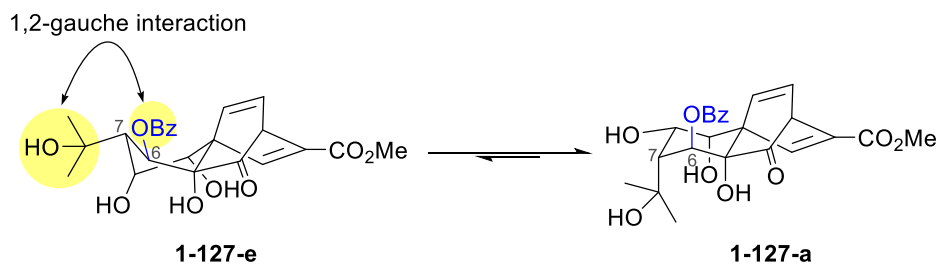
These conformational preferences were also supported from the search of the most stable conformation (MacroModel ver. 10.4, Force Field: MM2*, Solvent: none, Minimization Method: PRCG, Maximum Iteration: 2500, CSearch Method: Mixed Torsional/Low-mode Sampling. (Figure 1.5).

Figure 1.5 Calculated conformation of two model substrates (in vacuum)



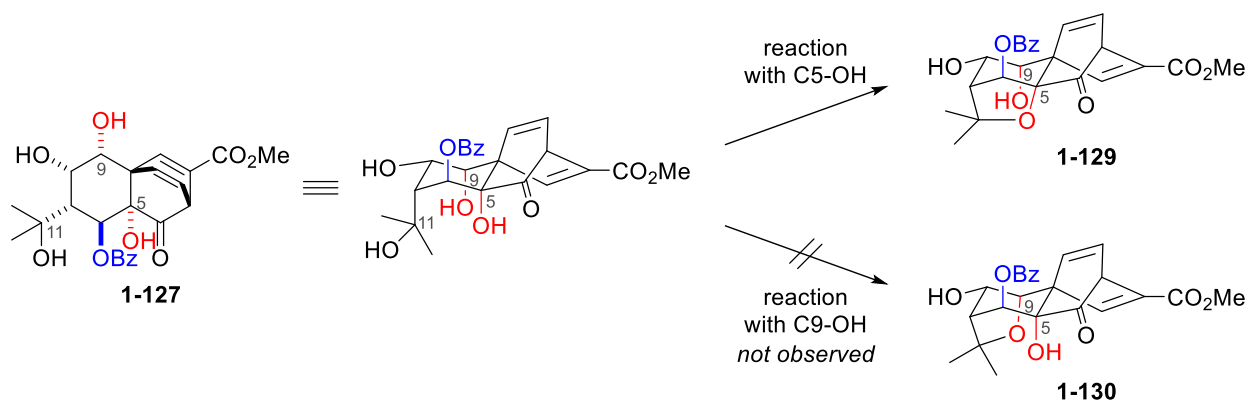
The different preferences of conformations could be explained by invoking possible 1,2-gauche interaction⁴ between the benzoyl group and the C7-substituent in the twist boat conformation (**1-127-e**) (Scheme 1.34).⁵

Scheme 1.34 Possible explanation for conformational preference of benzoate **1-127**



1.4.2.1.4 Rationale for the selectivity between C5- and C9-OH

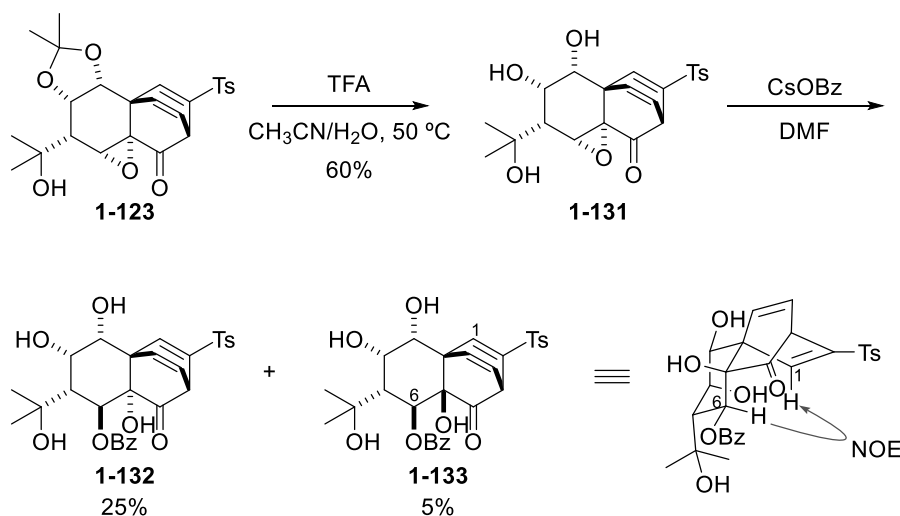
In the preferred conformation of benzoate **1-127**, C5- and C9-OH seemed to exist in the same position relative to the reaction center at the C11-carbon. Therefore it was possible that C9-OH reacted instead of C5-OH to give another 5-membered ring ether **1-130** (Scheme 1.35). The selective formation of **1-129** could be rationalized by considering the rigidity of the conformation. Namely, the orientation of C5-OH is completely fixed to axial due to the presence of the bicyclo[2.2.2]octadiene skeleton, whereas that of C9-OH had some flexibility. Thus the C5-OH always exists near the reaction center at C11-position and the reaction with C5-OH occurred much faster than with C9-OH, resulting in the selective formation of **1-129**.

Scheme 1.35 Possible two reaction paths from **1-127**

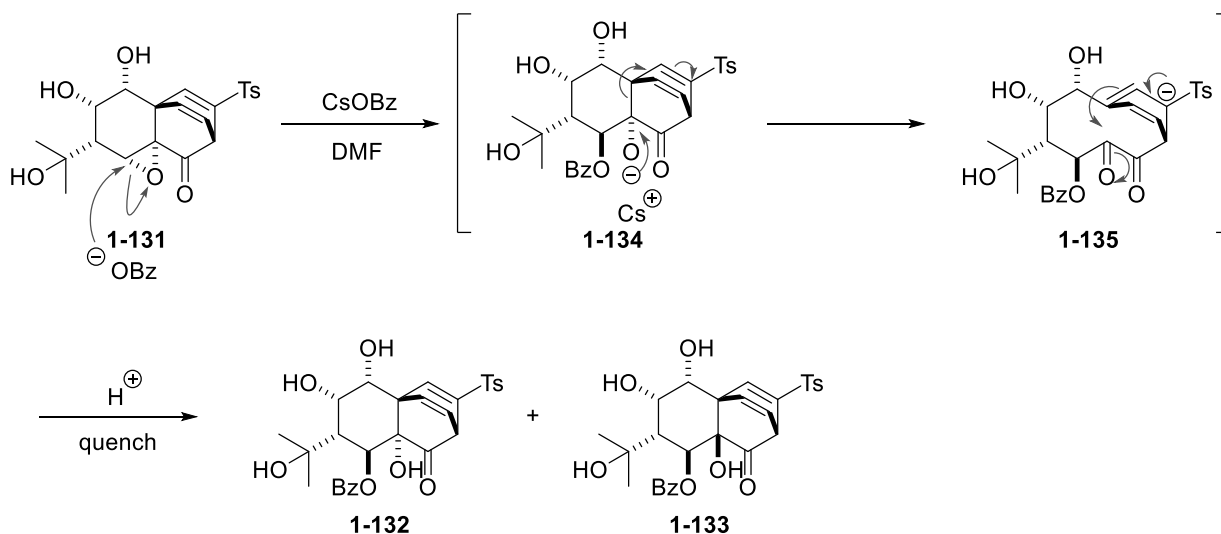
1.4.2.2 Construction of the C-ring from the Diels-Alder adduct bearing tosyl group

Based on the model study of the previous section, the established sequence was applied to Diels-Alder adduct **1-123** (Scheme 1.36). Acetonide was smoothly removed by TFA. When epoxide **1-131** was treated with CsOBz, complex mixture of products was obtained, from which the desired benzoate **1-132** was isolated only in 25% yield. Careful examination of byproducts revealed formation of the unexpected C5-diastereomer **1-133** as a minor product, the stereochemistry of which was determined by the NOE correlation shown in Scheme 1.36.

Scheme 1.36 Unexpected epimerization of C5-stereocenter

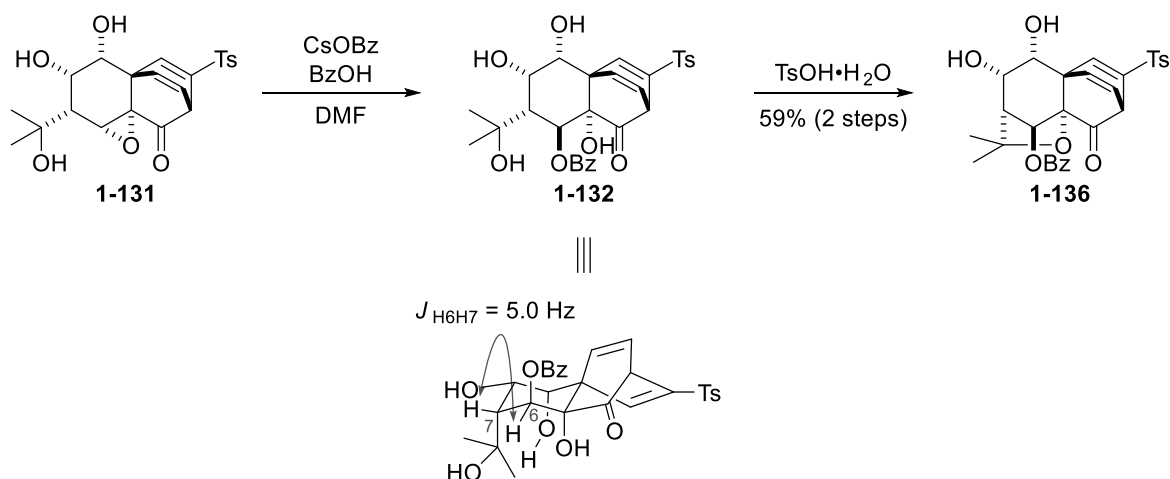


Proposed mechanism for generation of **1-133** is delineated in scheme 1.37. After the epoxide opening, C5-C10 bond could be cleaved from the highly basic cesium alkoxide **1-134** in DMF. The generated pentadienyl carbanion **1-135** is further stabilized by the tosyl group. C5-epimer could be formed by the re-addition of this anion to the C5-ketone. Because such reaction was not observed in the model study, the stronger electron withdrawing ability of the tosyl group must have been the cause of this side reaction.

Scheme 1.37 Proposed mechanism of the epimerization at C5-position

The above analysis indicates that, in order to suppress the side reactions, the generated cesium alkoxide should be protonated as soon as possible, ideally *in situ*. Thus, benzoic acid was chosen as a proton source which would not interfere the expected reaction.

As a result, the epoxide opening proceeded smoothly to give tetraol **1-132**, which could be isolated at this point in about 80% yield (Scheme 1.38). The coupling constant between C6-proton and C7-proton of **1-132** was 5.0 Hz. In the same manner as the model study, acidic treatment of **1-132** cleanly generated the desired 5-membered ring ether **1-136** in high yield.

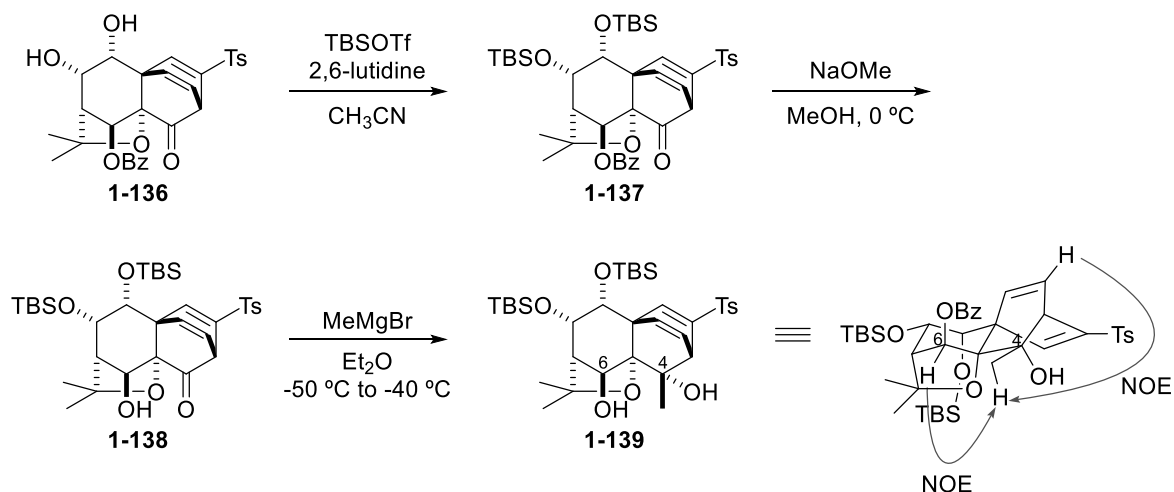
Scheme 1.38 Successful construction of the C-ring

1.4.3 Functionalization of the AB-ring

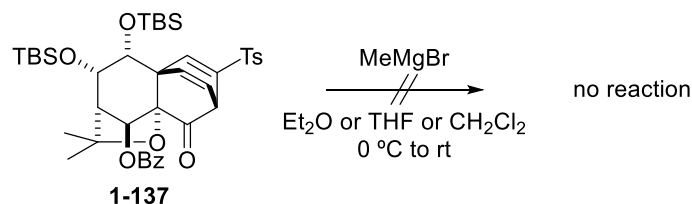
1.4.3.1 Construction of the tetrasubstituted carbon at C4-position

With the construction of the BC-ring structure completed, functionalization of the A-ring was next surveyed. Before transformation of the bicyclo[2.2.2]octadiene structure of **1-136**, the tetrasubstituted carbon at C4 was installed (Scheme 1.39). 1,2-Diol of **1-136** was protected as their TBS ethers, and the benzoyl group of **1-137** was cleaved with NaOMe. Care have to be paid to keep the temperature at 0 °C in this reaction, otherwise the 1,4-addition of sodium methoxide to the α,β -unsaturated sulfone occurred. Then, obtained β -hydroxyketone **1-138** was treated with excess amount of methyl magnesium bromide to give rise to the addition product **1-139** in a highly diastereoselective manner.

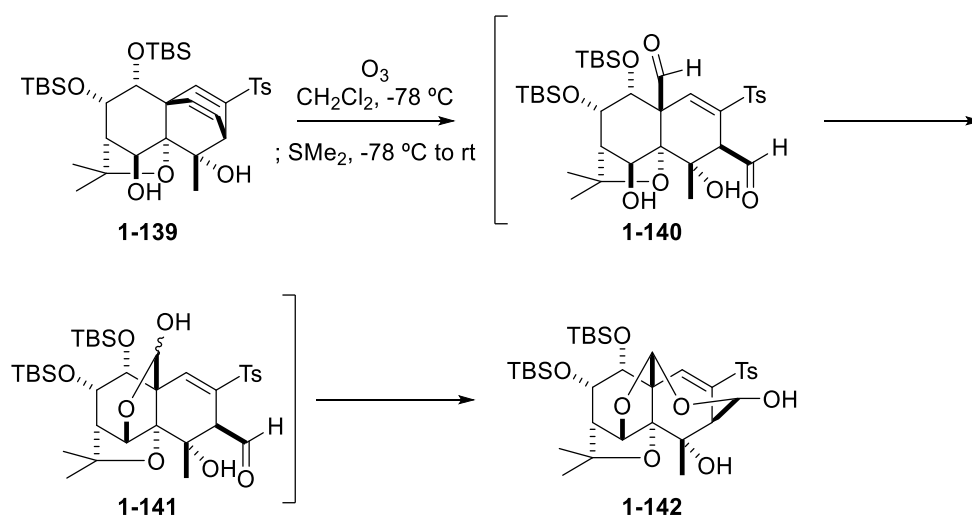
Scheme 1.39 Construction of the tetrasubstituted carbon at C4-position



As for the high diastereoselectivity, both face of ketone **1-138** can be regarded as *concave* due to the presence of the bicyclo[2.2.2]octadiene skeleton and oxabicyclo[3.2.1]octane (BC-ring). Thus it could be hypothesized that the β -hydroxy group acted as a directing group, which resulted in the high diastereoselectivity.⁶ Although the exact role of the hydroxy group is still elusive, the negligible reactivity of benzoate **1-137** to Grignard reagent may support the hypothesis (Scheme 1.40).

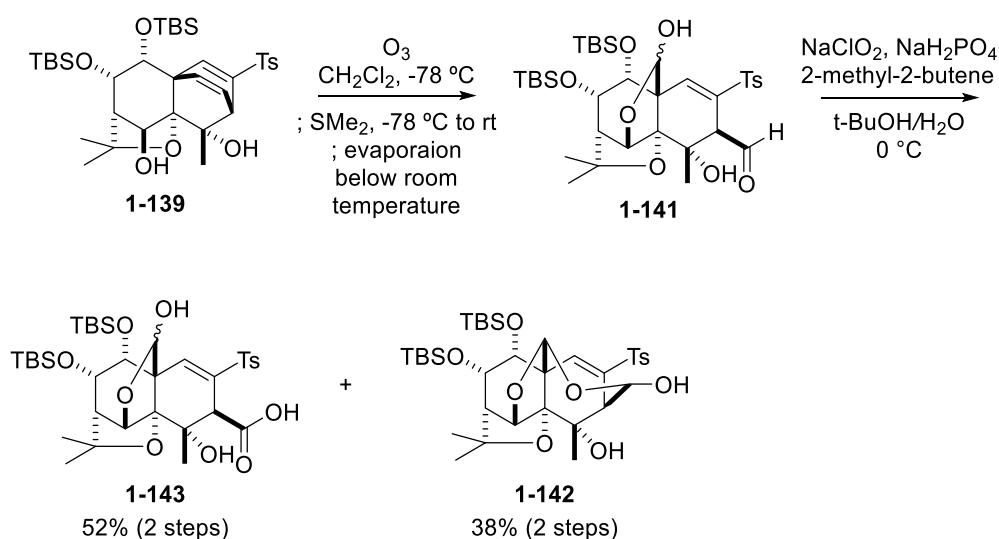
Scheme 1.40 Attempted Grignard reaction to benzoate **1-137****1.4.3.2 Oxidative cleavage of the olefin**

The stage was set for the key oxidative cleavage of the olefin (Scheme 1.41). Although the ozone chemoselectively cleaved the more electron-rich olefin of diene **1-139**, the product was not the expected dialdehyde **1-140** but hemiacetal **1-141** (not isolated). Furthermore, second acetalization occurred spontaneously to give pentacyclic compound **1-142** as a stable product. The structure of **1-142** was tentatively assigned at this point, but later verified by chemical conversions (*vide infra*)

Scheme 1.41 Spontaneous acetalization of ozonolysis products

Since the hemiacetal formation can be regarded as a temporary protection of the aldehyde, mono-hemiacetal **1-141** seemed to be the useful product for further transformations. Thus the experimental procedure was optimized, and it was found that direct oxidation of crude **1-141** with NaClO_2^7 afforded carboxylic acid **1-143** along with hemiacetal **1-142** (Scheme 1.42). Although the yield of carboxylic acid **1-143** was not perfect, hemiacetal **1-142** can also be converted to the synthetic route via simple transformations (*vide infra*); hence the overall efficiency of the chemoselective oxidative cleavage of the olefin was excellent.

Scheme 1.42 Two-step procedure toward the carboxylic acid **1-143**

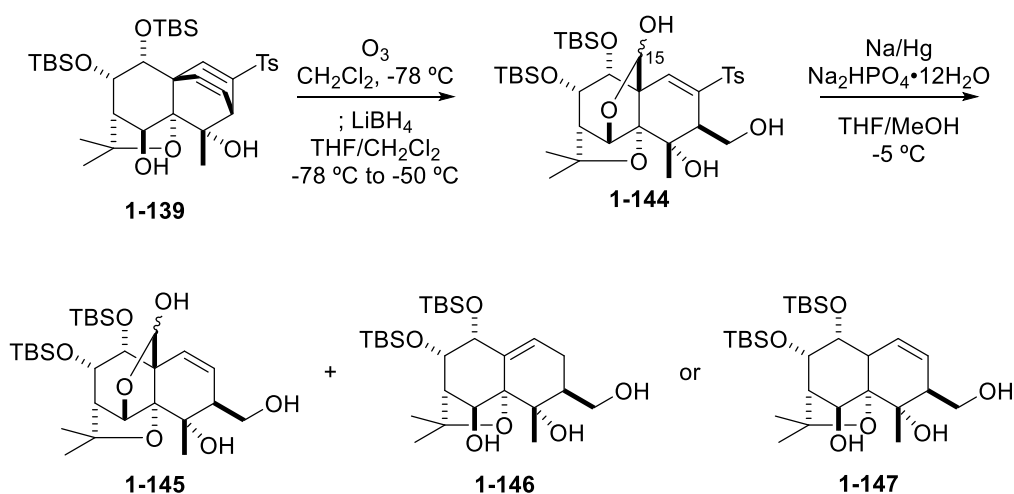


1.4.3.3 Removal of one carbon unit at C3-position

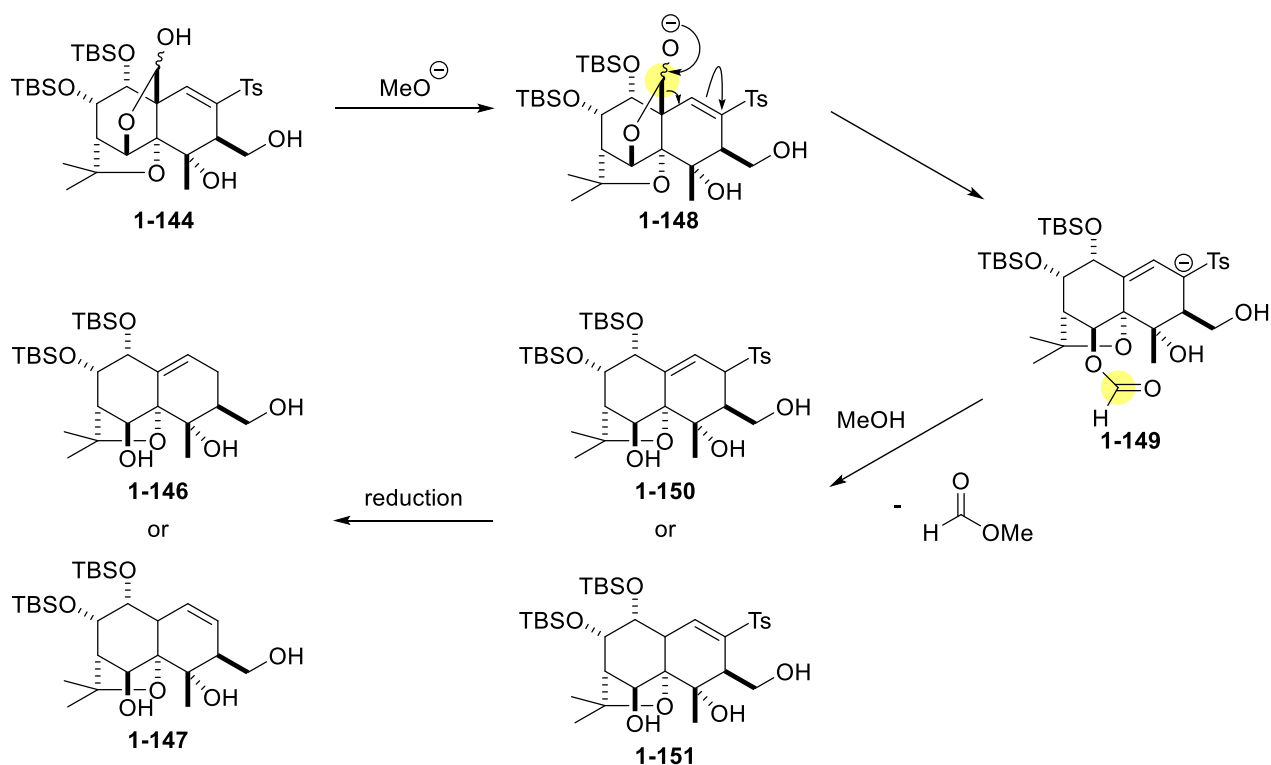
1.4.3.3.1 Removal of the tosyl group

Before one-carbon truncation, tosyl group was removed first. The preliminary investigation was done using the model substrate **1-144** which was obtained by the reductive work-up of the ozonolysis step from **1-139** (Scheme 1.43). Although the tosyl group was chosen as a removable electron withdrawing group, well-established buffered reduction using sodium amalgam⁸ unexpectedly resulted in the desired reduction accompanied by the loss of the C15-carbon atom.

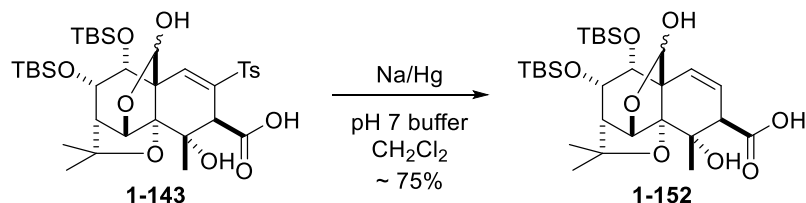
Scheme 1.43 Preliminary result of the removal of the tosyl group



The proposed mechanism is shown in the Scheme 1.44. The hydroxy group of the hemiacetal of **1-144** was deprotonated under the basic conditions to give **1-148**. Due to the strong electron withdrawing ability of the tosyl group, C-C bond cleavage occurred from **1-148** to give the highly stabilized carbanion **1-149**. Formyl ester derived from the C15-carbon atom was then cleaved under the basic conditions to give **1-150** or **1-151**. Final reductive cleavage of the tosyl group afforded the observed product.

Scheme 1.44 Proposed mechanism for the removal of C15-carbon atom

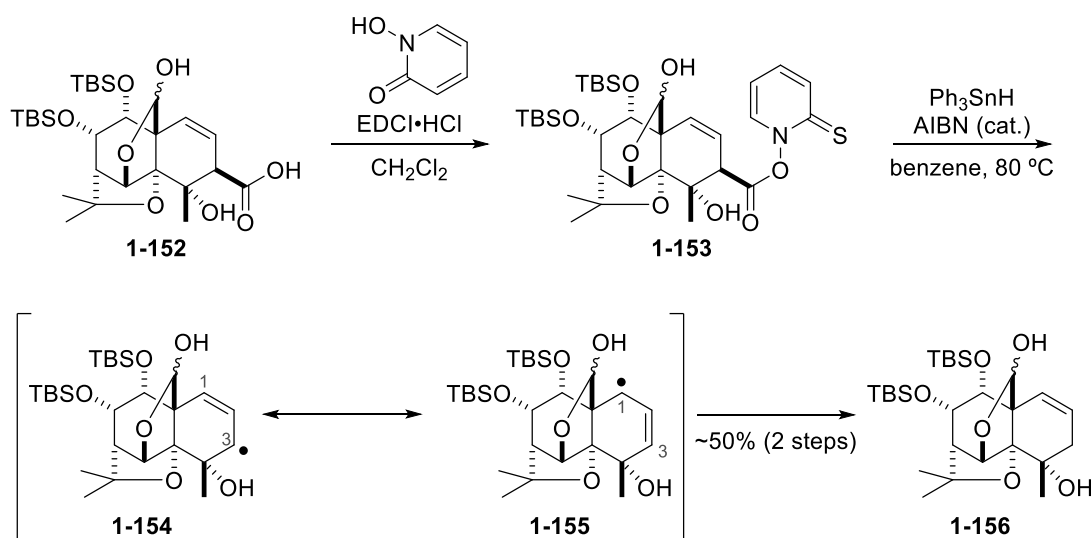
In order to make the system as neutral as possible and avoid the side reaction, the conditions were employed using Na/Hg in CH_2Cl_2 and pH 7 buffer biphasic system.⁹ In this procedure, the pH of aqueous phase was kept below 9~10 by constantly adding the buffer solution. Application of those conditions to the above model substrate resulted in the successful clean removal of the tosyl group (not shown). Thus the conditions were applied to carboxylic acid **1-143** to give the desired product **1-152** (Scheme 1.45). The yield was determined by the weight of the roughly purified material and its ^1H NMR. Determination of the precise yield was difficult due to the presence of the hemiacetal diastereomers.

Scheme 1.45 Successful removal of the tosyl group

1.4.3.3.2 Barton decarboxylation

β,γ -Unsaturated carboxylic acid **1-152** was next decarboxylated under the radical conditions (Scheme 1.46). Barton ester **1-153** was prepared from carboxylic acid **1-152** by using EDCI as a condensation reagent, and it was heated with triphenyltinhydride and AIBN.¹⁰ The generated allyl radical **1-154** can be drawn as the resonance form **1-155**, hence the hydrogenation could occur at either C1- or C3-position. But in this case, C3-position was hydrogenated regioselectively, presumably owing to the steric hinderance of the C1-position by the adjacent quaternary center. The yield of **1-156** was determined by the weight of the roughly purified material and its ¹H NMR for the same reason as that for **1-152**.

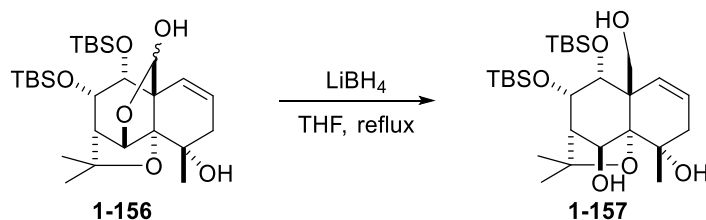
Scheme 1.46 Barton decarboxylation



1.4.3.4. Completion of the synthesis of the tricyclic skeleton of 4-hydroxyzinowol

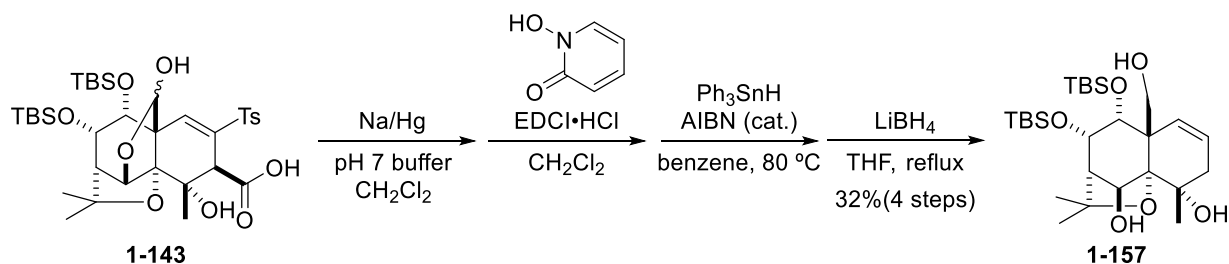
Finally, hemiacetal, or protected aldehyde, of **1-156** was reduced to afford triol **1-157** (Scheme 1.47).

Scheme 4.17 Reduction of the hemiacetal



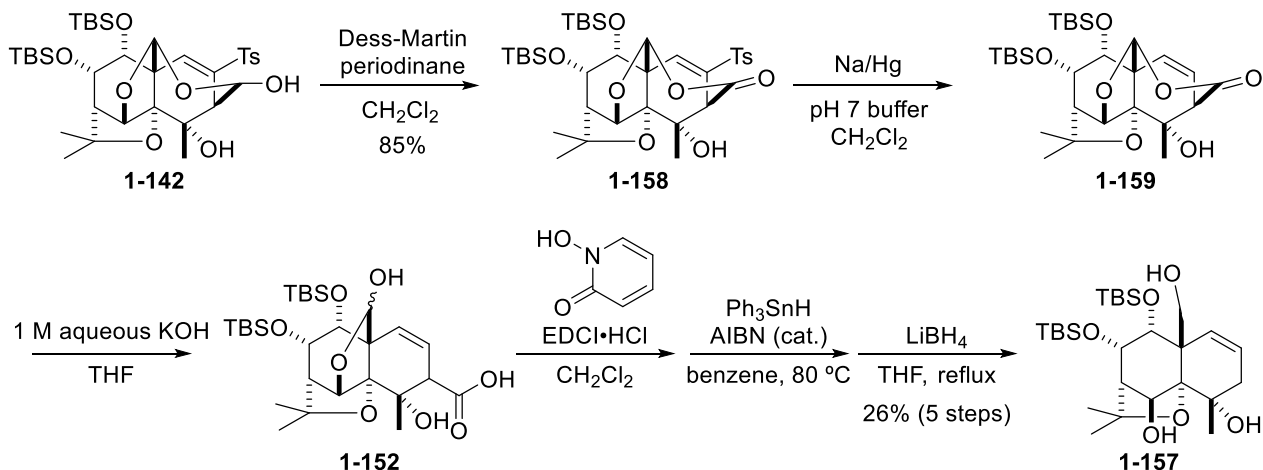
Practically, these 4 steps from carboxylic acid **1-143** were conducted without intensive purification of each products, affording the triol **1-157** in 32% yield over 4 steps (average 75%/step) (Scheme 1.48). At this point, tricyclic scaffold of the dihydro- β -agarofuran skeleton was successfully constructed.

Scheme 1.48 4-Step sequence to triol **1-157**



Hemiacetal **1-142**, the byproduct obtained in the ozonolysis step (Scheme 1.42), was also converged to the same triol **1-157** via six-step sequence (Scheme 1.49). First, the hemiacetal was oxidized to lactone **1-158**. After the reductive removal of the tosyl group, lactone **1-159** was hydrolyzed to carboxylic acid **1-152**, which was converted to triol **1-157** in the same manner. Furthermore, the tentatively assigned structure of **1-142** was confirmed by the sequence.

Scheme 1.49 Conversion of the byproduct of ozonolysis to the triol **1-157**



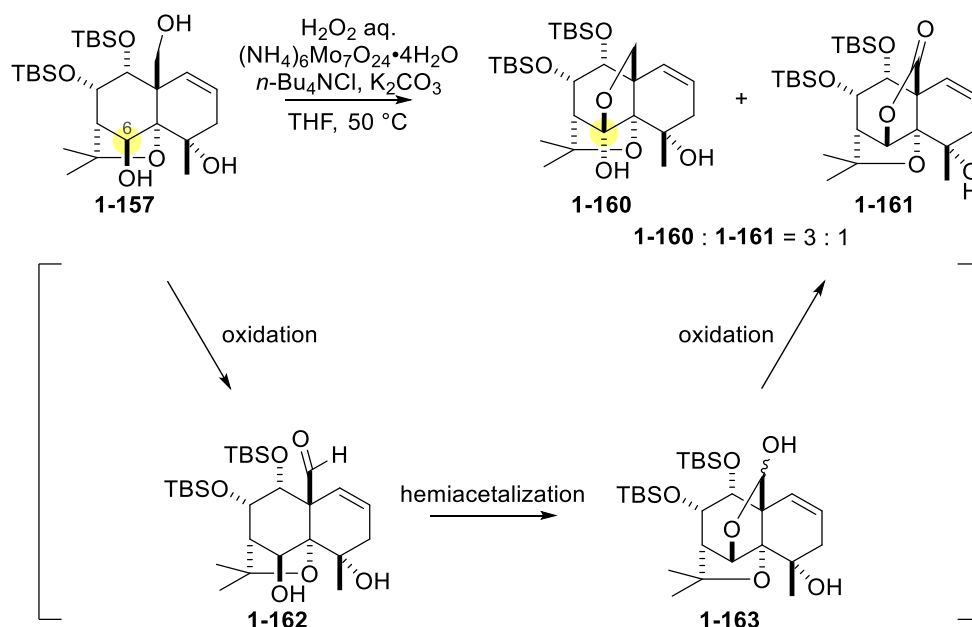
1.4.3.5 Introduction of the three remained stereocenters at C1-, C2-, and C6-positions

1.4.3.5.1 Oxidation of the C6-secondary alcohol

After introduced by the epoxide opening in Scheme 1.38, the C6- β -oxygen functionality had played the pivotal roles in controlling the conformation of the precursor for the C-ring formation, directing the course of the addition in construction of the C4-tetrasubstituted carbon, and protecting the angular aldehyde as the hemiacetal during the A-ring functionalization. As it has completed its roles, the stereochemistry has to be inverted at this stage. Although there are some examples realizing direct inversion of secondary alcohols on cyclic systems,¹¹ it seemed impossible to apply them to the C6-secondary alcohol within the oxabicyclo[3.2.1]octane (BC-ring structure). Therefore the oxidation-reduction strategy was employed in this case.

To avoid protecting group manipulation, selective oxidation of the secondary alcohol was attempted in the presence of the primary hydroxy group (Scheme 1-50). By applying the conditions developed by Trost and co-workers¹², the desired oxidation of **1-157** was realized to give the stable hemiacetal **1-160**. The byproduct was lactone **1-161**, which was generated via oxidation of the primary alcohol to aldehyde **1-162**, hemiacetalization to **1-163** and further oxidation of the hemiacetal.

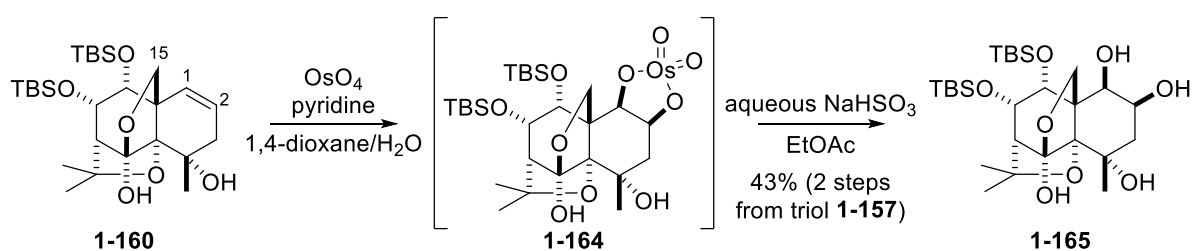
Scheme 1-50 Selective oxidation of the secondary alcohol



1.4.3.5.2 Dihydroxylation of the C1-C2 olefin

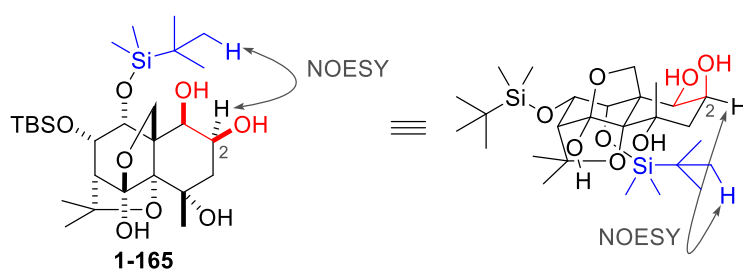
The steric hinderance around the β -face of the C1-C2 olefin would be minimized by the cyclic hemiacetal structure of **1-160**. Thus it was determined to oxidize the olefin before the reduction of the hemiacetal. As shown in Scheme 1.51, although the stoichiometric amount of osmium tetroxide was necessary, desired oxidation proceeded with complete face selectivity to yield osmate ester **1-164** (not isolated), which was reductively cleaved with aqueous NaHSO₃ to give 1,2-diol **1-165**.

Scheme 1.51 Stereoselective dihydroxylation



In determining the stereochemistry of the product, interesting NOESY correlation was observed (Figure 1.6), indicating one of the TBS groups resides near H₂. From this spectral data, it was suggested that two TBS groups repulse each other, and that one of the TBS group (shown in blue) resides below the C1-C2 olefin, inhibiting the approach of the osmium tetroxide.

Figure 1.6 NOESY correlation of **1-165**

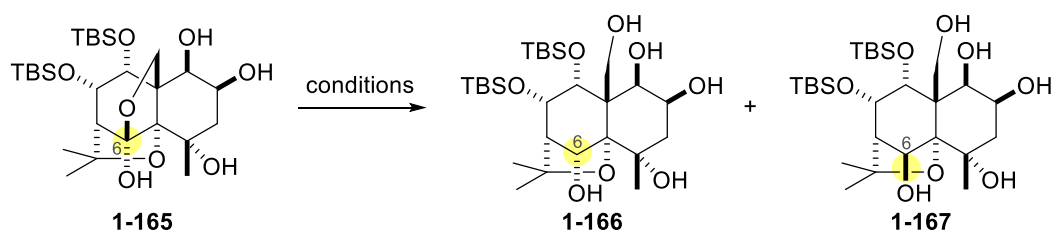


1.4.3.5.3 Reduction of the C6-hemiacetal

Five consecutive stereocenters having been constructed, construction of the final stereocenter at C6 was next investigated, which was found to be the difficult task. Since its formation through Trost oxidation, the C6-hemiacetal had always existed intact, and the equilibrium with the hydroxy ketone had never been observed in ^1H NMR. This fact indicated some kind of acid or harsh condition would be required to unveil the C6-ketone. Various conditions were investigated, and part of them were shown in Table 1.5.¹³

Standard hydride sources in entry 1 and 2 did not react at all, with the starting hemiacetal recovered intact. In the presence of the Brønsted acid with $\text{Al}(\text{O}i\text{-Pr})_3$,¹⁴ removal of the TBS group was observed without any clue of the desired reduction (entry 3). Interestingly, among the various reducing reagents, only LiBH_4 could reduce C6-position (entry 4). To improve the yield and the diastereoselectivity, conditions were further varied in entries 5-8. Aiming at the generation of reportedly more reactive alkoxyborohydride,¹⁵ the limited amount of methanol was added in entry 5, but the undesired isomer was obtained as a major product. In contrast, the reaction in refluxing 1,2-dichloroethane realized good diastereoselectivity and acceptable isolated yield (entry 6). To improve the solubility of the reagent, THF was used as a cosolvent in entry 7, which resulted in the disappearance of the diastereoselectivity. $n\text{-Bu}_4\text{NBH}_4$ is known to be more soluble than metal borohydrides in chlorinated organic solvents,¹⁶ thus higher reactivity was expected. However, no reaction occurred in entry 8. Overall, the conditions in entry 6 was selected as the optimal one.

The stereochemistry at C6-position was determined by comparing the coupling constant between the protons at C6- and C7-positions of **1-166** and **1-167**: $J_{\text{H6H7}} = 0$ Hz in **1-166** whereas $J_{\text{H6H7}} = 3.6$ Hz in **1-167**. The former is the characteristic value of the dihydro- β -agarofuran skeleton, and also the same value as that of 4-hydroxyzinowol.

Table 1.5 Reduction of the hemiacetal at C6-position

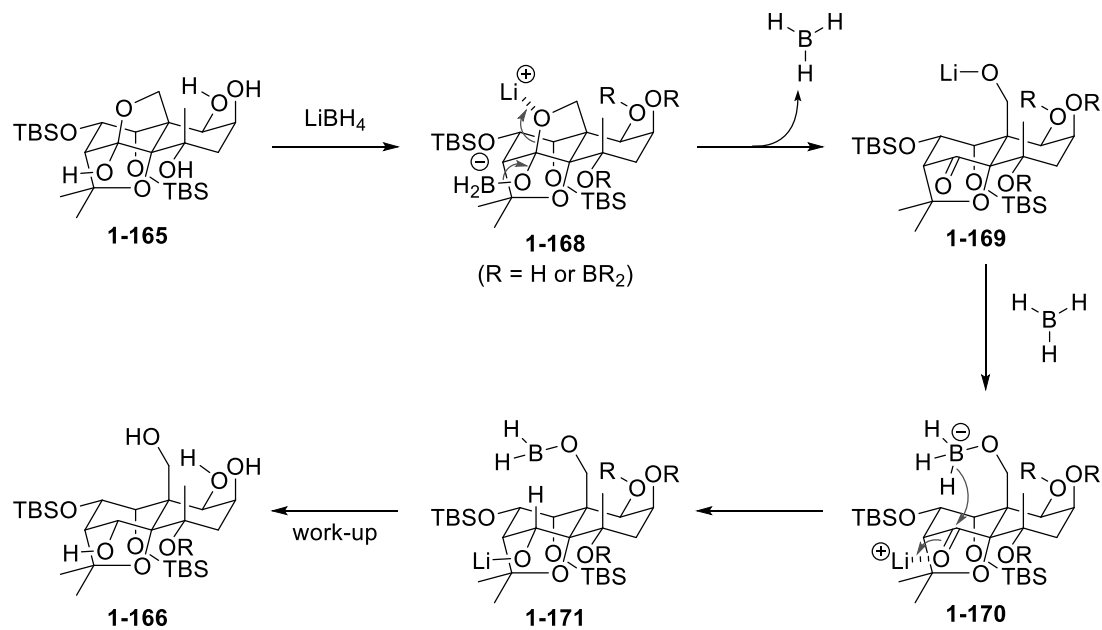
entry	conditions ^a	results	entry	conditions ^a	results
1	NaBH ₄ , CeCl ₃ ·7H ₂ O MeOH	no reaction	5 ^b	LiBH ₄ , MeOH THF, reflux	1-166 : 1-167 = 1:3
2	LiAlH ₄ THF, reflux	no reaction	6 ^c	LiBH ₄ 1,2-dichloroethane reflux	1-166 : 36% 1-166 : 1-167 = >5:1 recovery of 1-165 : 15%
3	Al(O <i>i</i> -Pr) ₃ C ₆ F ₅ OH 1,2-dichloroethane rt to 70 °C	no reduction removal of the TBS group was observed	7 ^d	LiBH ₄ 1,2-dichloroethane/THF reflux	1-166 : 1-167 = 1:1
4	LiBH ₄ THF, reflux	1-166 : 23% 1-166 : 1-167 = 1:1	8	<i>n</i> -BuN ₄ BH ₄ 1,2-dichloroethane reflux	no reaction

^a Reagents were used in large excess. ^b LiBH₄ : MeOH = 1:1 ^c 2 M THF solution of LiBH₄ was used. Solid LiBH₄ showed almost the same selectivity. ^d 1,2-dichloroethane : THF = 3:1

The optimal conditions in hand, the rationale for the high reactivity and diastereoselectivity of entry 6 is discussed below (Scheme 1.52). First of all, comparison of entry 1 and 4, or entry 6 and 8, clearly illustrates the importance of the lithium cation, which was probably required to open the hemiacetal (**1-168** to **1-169**) and allow the reduction to proceed. Next, as for the diastereoselectivity, there is a possibility that external borohydrides were not the true reductant. Borohydrides are known to produce the borane by reacting with alkyl halides like 1,2-dichloroethane.¹⁷ Although borane itself could act as an external reducing agent of the ketone, the more plausible scenario is that the generated borane reacted with lithium alkoxide **1-169**¹⁸ generated from the hemiacetal opening. The intramolecular hydride transfer from the resultant alkoxyborohydride **1-170** would yield **1-171**, from which the major diastereomer **1-166** would be generated after the work-up.¹⁹

The reverse or loss of the diastereoselectivity in entry 5 or 7 could be explained by considering the solubility of the LiBH₄ in these reaction conditions. In the absence of the polar solvent (MeOH or THF), LiBH₄ is hardly soluble in the less polar 1,2-dichloroethane, and thus its reactivity would be greatly decreased. In that case, the intramolecular hydride reduction (**1-170** to **1-171**) would become the major reaction path. On the other hand, in the presence of the polar solvent, LiBH₄ would become more soluble in the solvent. In that case, reduction of ketone **1-170** by external hydride sources could become faster. Since the α - and β -faces of the ketone seems sterically not differentiated, such intermolecular reaction would not be stereoselective, which resulted in the low selectivity observed in entry 5 or 7.

Scheme 1.52 Plausible explanation for the stereoselectivity of the hemiacetal reduction

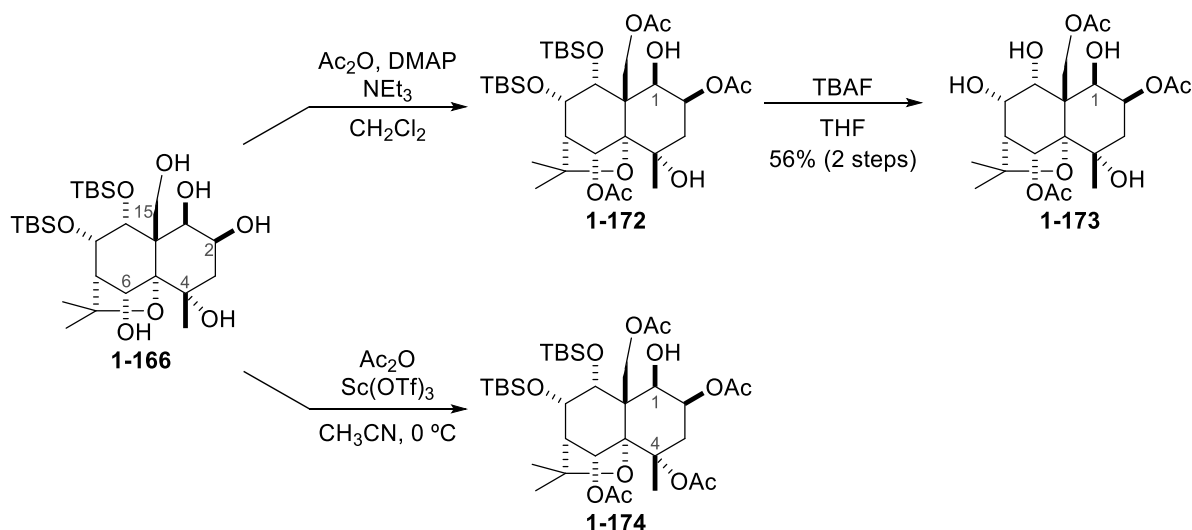


1.4.4 Regioselective acylation

1.4.4.1 Attempted acetylation of the C1-OH

Fully functionalized dihydro- β -agarofuran skeleton in hand, acylation of hydroxy groups was finally investigated. Optimally, tetra-acetylation of pentaol **1-166** followed by TBS removal and bis-benzoylation would complete the total synthesis of 4-hydroxyzinowol. Thus the pentaol was first subjected to acetylation conditions (Scheme 1.53). In the presence of NEt_3 and DMAP, Ac_2O introduced three acetyl groups on C2-, C6-, and C15-OH groups to afford **1-172**. All of the methine peaks in ^1H NMR spectra of **1-166** and **1-172** were well-separated, and the position of acetyl groups were unambiguously determined by observing the downfield shift of the corresponding peaks. C1-OH did not react at all under the reaction conditions. On the other hand, under the $\text{Sc}(\text{OTf})_3$ -mediated acidic conditions, tetra-acetylation did occur, in which the C4-tertiary OH was acetylated instead of the C1-OH to afford **1-174**. The assignment was based on the ESI-MS value and unchanged chemical shift of C1-proton. Exposure of pentaol **1-166** to the solvent mixture of Ac_2O and pyridine resulted in the complex mixture of products (not shown). The low reactivity of the C1-OH could be attributed to the bulkiness of the TBS group, thus two TBS groups were removed from **1-172**, and regioselective benzoylation of **1-173** was investigated in the next section.

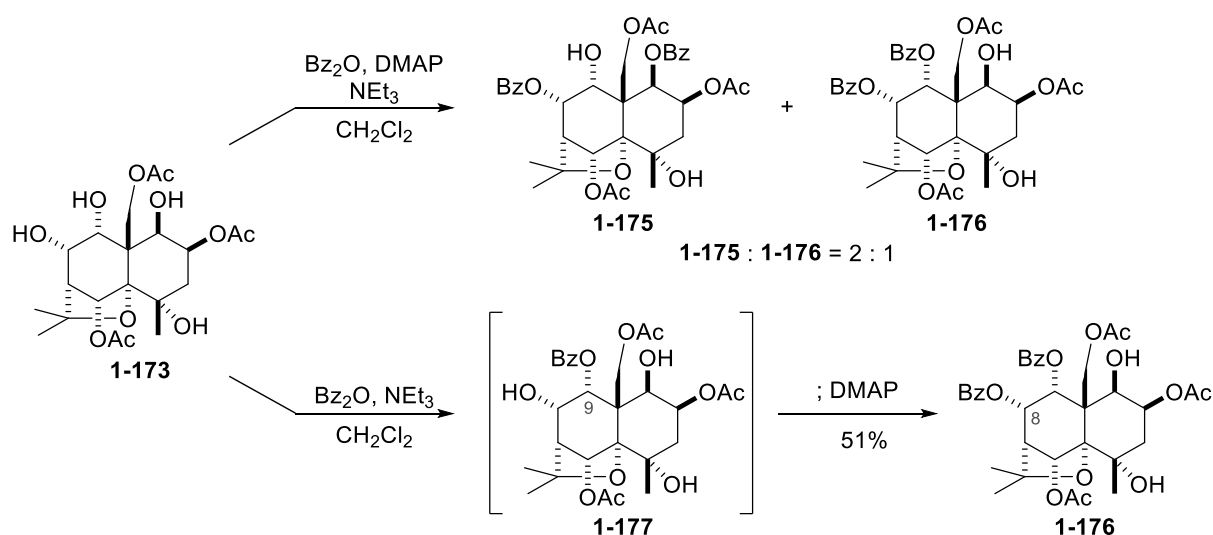
Scheme 1-53 Attempted tetra-acetylation of the pentaol **1-166**.



1.4.4.2 Regioselective benzylation

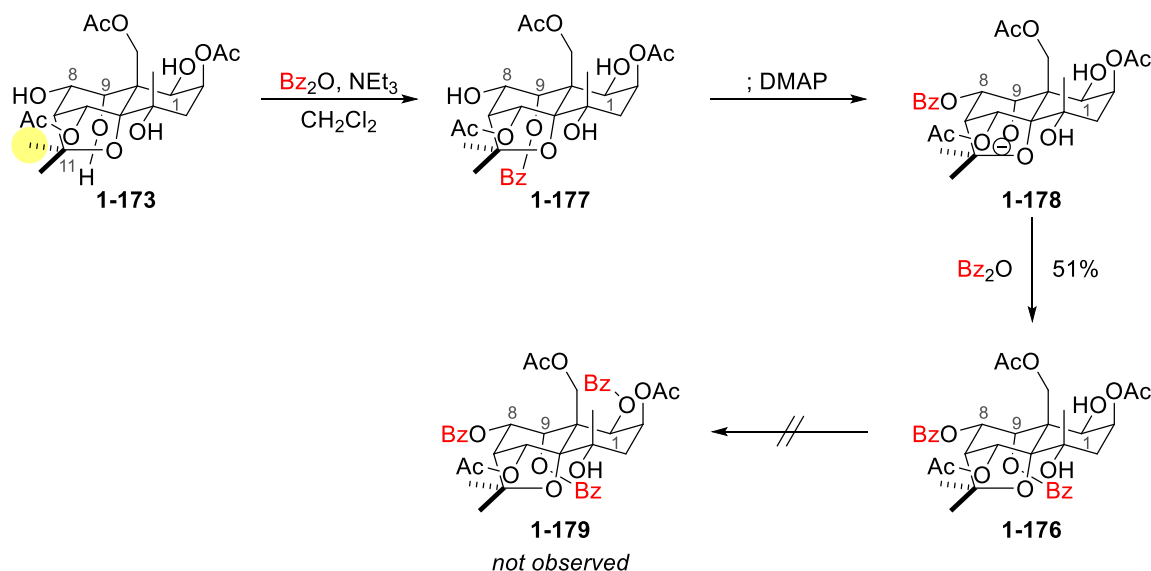
Disappointingly, attempted benzylation of tetraol **1-173** under the similar conditions as the previous acetylation afforded the undesired bis-benzoate **1-175** as a major product with the desired bis-benzoate **1-176** (Scheme 1.54, upper scheme). In order to control the reactivity, DMAP was removed from the reaction conditions (lower scheme). Surprisingly, C9-OH was acylated regioselectively under the reaction conditions. The generated **1-177** can be isolated, but more conveniently, addition of DMAP to the reaction mixture resulted in the second regioselective benzylation at C8-OH with complete regioselectivity. Although the isolated yield of **1-176** was moderate, it can be justified because remained mono-benzoate **1-177** was recovered approximately in 20% yield. The position of acylated hydroxy groups was determined by the chemical shifts of ^1H NMR peaks as before.

Scheme 1.54 Regioselective benzylation



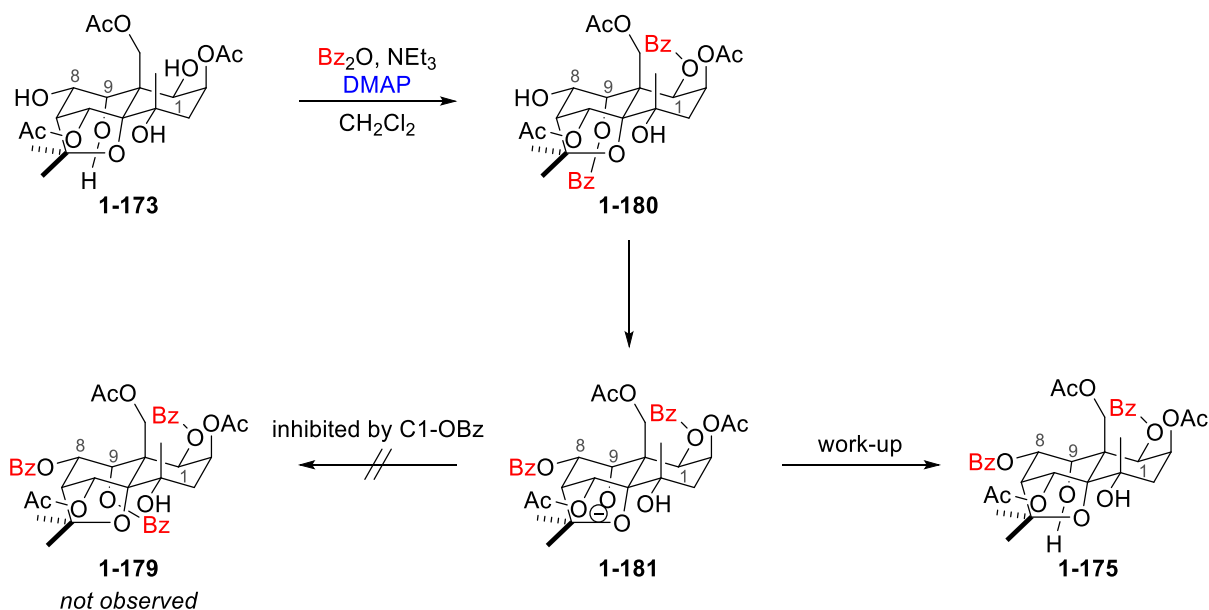
The persuasive explanation for the regioselectivity is still elusive due to the lack of sufficient control experiments, but it is worth estimating of this curious selectivity. Clean generation of C9-benzoate **1-177** in the absence of DMAP suggested C9-OH was the most reactive even though it is at the neopentyl position (Scheme 1.55). Approach of the reagent to the seemingly less-crowded C8-OH could be inhibited by the presence of one of the methyl groups attached to the C11-carbon atom (highlighted in yellow). After the addition of DMAP, it was possible that the benzoyl group of **1-177** migrated from C9-OH to C8-OH, and then the generated C9-alkoxide **1-178** was benzoylated again. The two benzoyl groups of **1-176** might repulse each other as in the case of the bis-TBS ether (see Figure 1.6 in p.52), and thus C9-benzoyl group could reside near the C1-position, inhibiting the third benzoylation at C1-OH.

Scheme 1.55 Proposed reaction path of the optimized benzoylation



Although the possibility of the direct benzylation of C8-OH could not be excluded, the preferred formation of **1-175** (C9-OH was not acylated) corroborated the hypothesis (Scheme 1.56). Namely, C9-OH should be acylated first also under this more forcing reaction conditions (DMAP was added from the beginning). No acylation on C9-OH of the final product **1-175** indicated the initially introduced acyl group went possibly to the adjacent C8-OH. Re-acylation of C9-alkoxide **1-181** could be suppressed by the benzoyl group at C1-OH, which could be introduced much faster in this reaction conditions.

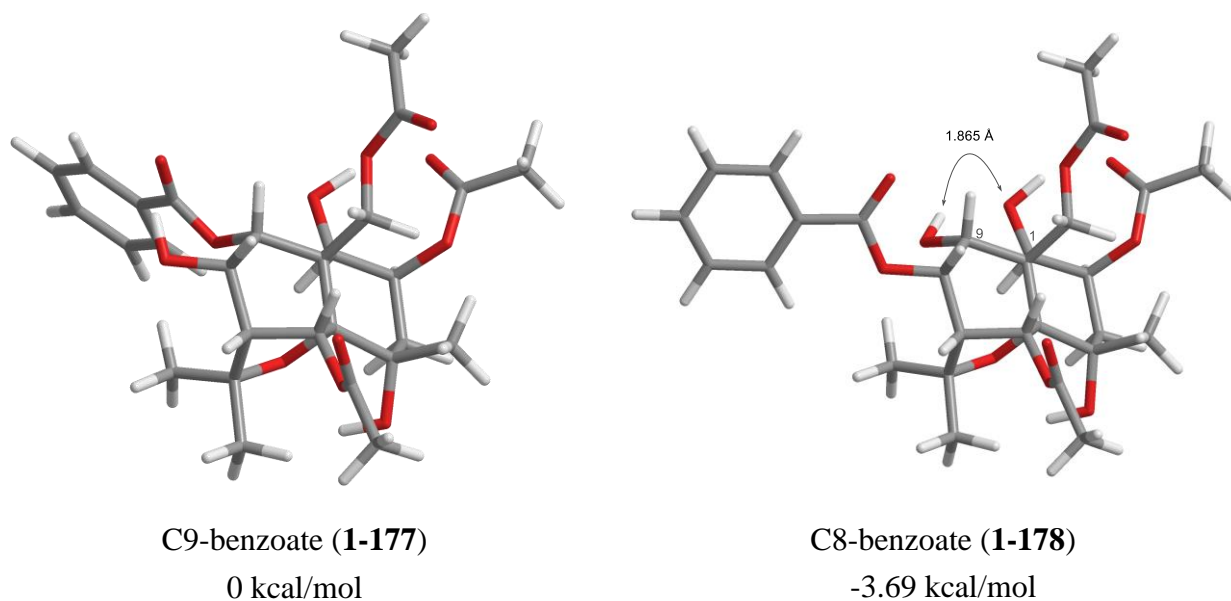
Scheme 1.56 Proposed reaction path toward the undesired bis-benzoate **1-175**



On the other hand, C1-OH and C2-OAc seemed to exist in the similar relationship. Thus it seemed possible that the migration of acetyl group occur, although such reaction was not observed. This could be explained by comparing the coupling constant between C1- and C2-protons ($J_{H1H2} = 3.2$ Hz) and the coupling constant between C8- and C9-protons ($J_{H8H9} = 6.4$ Hz), indicating the latter combination was more eclipsed, which could result in the higher propensity of acyl migration.

To rationalize the direction of migration (C9-OH to C8-OH), ground state energies of the two benzoates in CH₂Cl₂ were calculated by DFT (B3LYP/6-31G*).²¹ The result clearly shows the C8-benzoate **1-178** is much more stable than C9-benzoate **1-177** (Figure 1.7). This large energy difference could be attributed to the possible hydrogen bonding between C9-OH and C1-OH in **1-178**, which would be disturbed in C9-benzoate **1-177**.

Figure 1.7 Comparison of relative stability of C9- and C8-benzoates (DFT, in CH₂Cl₂)



1.4.4.3 Total synthesis of 4-hydroxyzinowol

Finally, the remained secondary hydroxy group was acetylated under the same conditions as the previous acetylation to give the natural product, 4-hydroxyzinowol (Scheme 1.55). All of the analytical data (^1H NMR, ^{13}C NMR, IR, and $[\alpha]_{\text{D}}$) of the synthetic sample matched well with those of the sample isolated from the natural source (Table 1.6).²⁰

Scheme 1.57 Total synthesis of 4-hydroxyzinowol

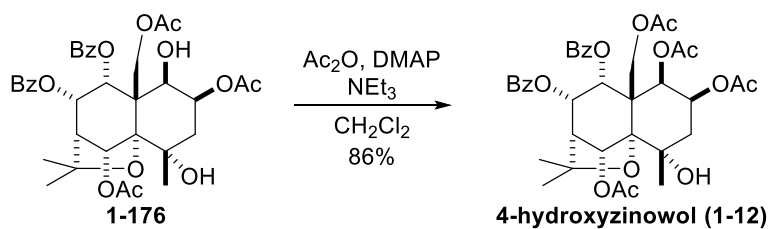


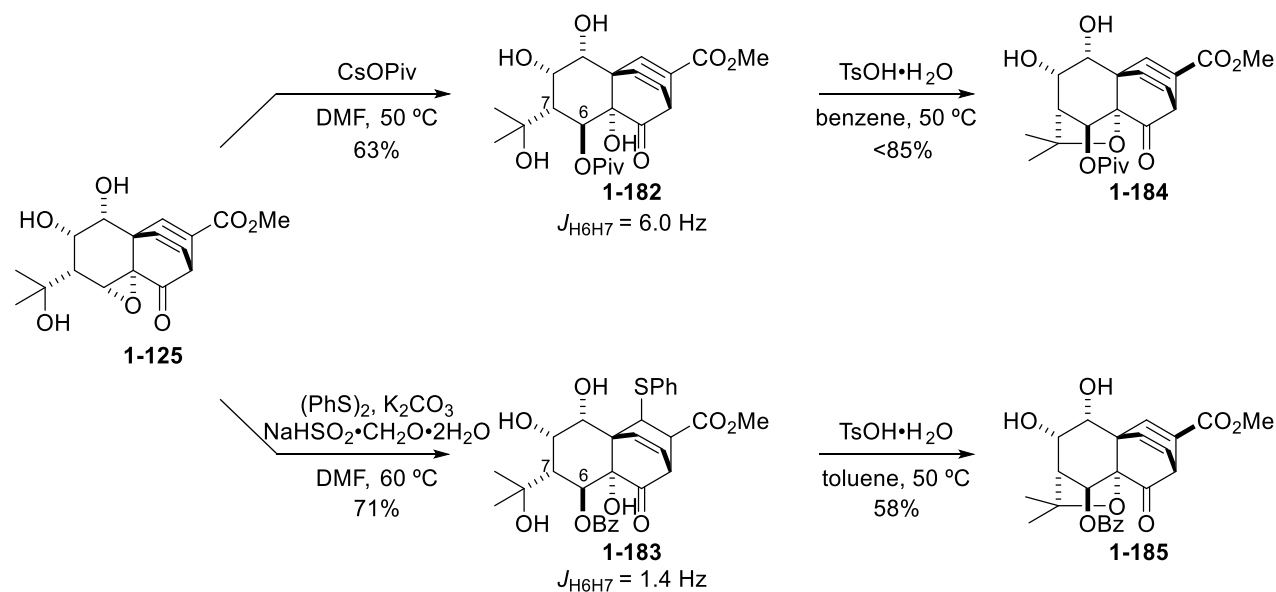
Table 1.6 Comparison of the spectral data of synthetic and natural 4-hydroxyzinowol

No.	natural		synthetic	
	¹ H [δ, multi. <i>J</i> (Hz)]	¹³ C (δ)	¹ H [δ, multi. <i>J</i> (Hz)]	¹³ C (δ)
1	5.64 (d, 3.6)	70.1	5.65 (d, 3.4)	70.1
2 ^a	5.52 (ddd, 3.3, 3.3, 3.3)	68.0	5.52 (ddd, 3.4, 3.4, 3.4)	68.0
3a	2.03 (dd, 15.1, 2.9)	42.0	2.03 (dd, 15.5, 3.4)	42.0
3b	2.15 (m)		2.20 (dd, 15.5, 3.4)	
4		69.8		69.8
5		91.0		91.0
6	6.19 (s)	76.0	6.19 (s)	76.0
7	2.59 (d, 3.3)	53.9	2.59 (d, 4.0)	53.8
8	6.06 (dd, 6.5, 3.5)	70.6	6.06 (dd, 6.9, 4.0)	70.6
9	5.77 (d, 6.5)	68.2	5.77 (d, 6.9)	68.1
10		54.0		54.0
11		84.9		84.9
12	1.60 (s)	29.9	1.60 (s)	30.0
13	1.80 (s)	26.5	1.80 (s)	26.6
14	1.52 (s)	25.0	1.52 (s)	25.0
15a	4.48 (d, 13.0)	64.6	4.48 (d, 13.2)	64.6
15b	4.90 (d, 13.0)		4.90 (d, 13.2)	
4-OH	2.89 (s)		2.88 (s)	
1-OAc	1.61 (s)	20.2, 169.2	1.62 (s)	20.3, 169.2
2-OAc	2.12 (s)	21.1, 169.5	2.12 (s)	21.1, 169.6
6-OAc	2.14 (s)	21.2, 169.8	2.14 (s)	21.3, 169.9
15-OAc	2.40 (s)	21.3, 170.5	2.41 (s)	21.4, 170.6
OBz x 2	7.22 (2H, m)	128.2, 128.3	7.22 (2H, dd, 7.5, 7.5)	128.26, 128.31
	7.44 (3H, m)	128.8, 129.2	7.42 (2H, dd, 7.5, 7.5)	128.8, 129.2
		129.5, 130.3	7.47 (2H, dd, 7.5, 7.5)	129.5, 130.3
	7.58 (1H, m)	133.1, 133.5	7.59 (2H, dd, 7.5, 7.5)	133.2 133.6
	7.70 (1H, d, 7.5)	164.8, 165.4	7.70 (1H, d, 7.5)	164.8, 165.4
	7.89 (1H, d, 7.5)		7.89 (1H, d, 7.5)	

^a Jiménez, Gamarro, and co-workers reported the coupling pattern of H2 as dd (*J* = 6.5, 3.3 Hz) in the original paper. Judging from their ¹H NMR spectrum, the coupling pattern should be described as ddd (*J* = 3.3, 3.3, 3.3 Hz).

1.4.5 References and notes for section 1.4

- ¹ For Ce(III)-mediated removal of acetone, see: Xiao, X.; Bai, D. *Synlett* **2001**, 535.
- ² (a) Kruizinga, W. H.; Strijfveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, 46, 4321. (b) Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron* **1993**, 49, 5067. (c) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, 70, 6045.
- ³ Further heating of **1-128** resulted in the removal of the acetyl group, and no etherification was observed.
- ⁴ (a) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, 35, 5181. (b) Eliel, E. L.; Satıcı, H. *J. Org. Chem.* **1994**, 59, 688. (c) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, 37, 663. (d) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, 40, 5573.
- ⁵ Two more substrates **1-182** and **1-183** were prepared, both of which have the “small” *J* value, and as expected smoothly afforded the cyclized product **1-184** and **1-185**.



- ⁶ Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127.
- ⁷ Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091.
- ⁸ Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 17, 3477.
- ⁹ Wade, P. A.; Bereznak, J. F. *J. Org. Chem.* **1987**, 52, 2973.
- ¹⁰ Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939.
- ¹¹ (a) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, 37, 6145. (b) Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2000**, 65, 8379. (c) Shi, X.-X.; Shen, C.-L.; Yao, J.-Z.; Nie, L.-D.; Quan, N. *Tetrahedron: Asymmetry* **2010**, 21, 277.

- ¹². (a) Trost, B. M.; Masuyama, Y. *Tetrahedron Lett.* **1984**, 25, 173. For the recent synthetic application, see: (b) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, 305, 495.
- ¹³. Other attempted reagents include: Red-Al, BH₃•THF, LiBH₄+LiCl, LiEt₃BH, all of which resulted in no reaction.
- ¹⁴. Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, 115, 10695.
- ¹⁵. (a) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, 92, 6894. (b) Wuesthoff, M. T. *Tetrahedron* **1973**, 29, 791.
- ¹⁶. Raber, D. J.; Guida, W. C. *Synthesis* **1974**, 808.
- ¹⁷. (a) Brändström, A.; Junggren, U.; Lamm, B. *Tetrahedron Lett.* **1972**, 31, 3173. (b) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, 41, 690. (c) Periasamy, M.; Muthukumaragopal, G. P.; Sanjeevakumar, N. *Tetrahedron Lett.* **2007**, 48, 6966.
- ¹⁸. Generation of alkoxy borohydride via the reaction of borane with metal alkoxide is a known process. See: Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, 113, 3085.
- ¹⁹. Similar directed reduction is well-documented when NaBH(OAc)₃ is used: (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, 24, 273. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, 110, 3560.
- ²⁰. Muñoz-Martínez, F.; Mendoza, C. R.; Bazzocchi, I. L.; Castanys, S.; Jiménez, I. A.; Gamarro, F. *J. Med. Chem.* **2005**, 48, 4226.
- ²¹. Initial structure was obtained by MacroModel ver. 10.4. Conditions are as follows. Force Field: MM2*, Solvent: none, Minimization Method: PRCG, Maximum Iteration: 2500, CSearch Method: Mixed Torsional/Low-mode Sampling. DFT calculation was then performed at the B3LYP/6-31G* level of theory.

Chapter 2
Synthetic study of talatisamine

2.1 Introduction

2.1.1 Diterpene alkaloids

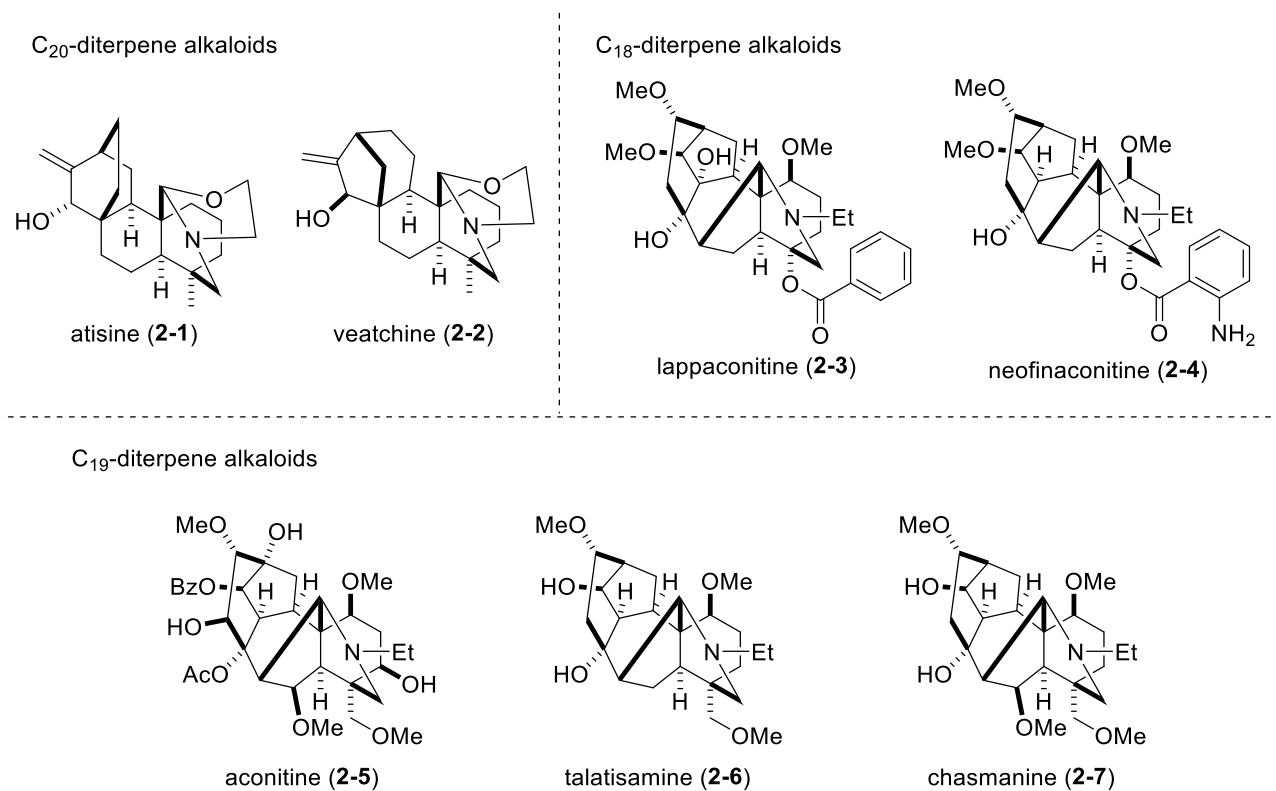
“Alkaloids” refers to the natural products derived from amino acid precursors. In contrast, the skeletons of “terpenoid-alkaloids” are constructed from the prenyl units.¹ Nitrogen atoms of these pseudo-alkaloids are incorporated at some stage of the biosynthesis of terpenoids as simple alkyl amine units. Reflecting the biosynthetic origin, these alkaloids are classified by its parent terpenoid skeletons such as triterpenoid-alkaloids, diterpenoid-alkaloids, and so on. Among those, diterpenoid-alkaloids, or generally called as diterpene alkaloids, share the highly complex fused polycyclic skeleton consisting of 18, 19, or 20 carbon atoms with one characteristic bridging nitrogen atom.² Diterpene alkaloids are widely distributed in various families of plants, among which Ranunculaceae is one of the main source. The selected examples of C₁₈-, C₁₉-, and C₂₀-diterpene alkaloids are shown in the Figure 2.1.

Atisine (**2-1**) and veatchine (**2-2**)³ belong to the C₂₀-diterpene alkaloids and their skeletons constitute the starting point of biosynthesis of related diterpene alkaloids (*vide infra*).

C₁₈- and C₁₉-diterpene alkaloids have much more complicated hexacyclic skeleton compared to that of C₂₀-counterparts. Lappaconitine (**2-3**)⁴ and neofinaconitine (**2-4**)⁵ are examples of C₁₈-diterpene alkaloids. Lappaconitine is commercialized as an antiarrhythmic drug.⁶

Among nearly one thousand natural products of this class isolated to date, more than half belong to C₁₉-diterpene alkaloids. The representative example is aconitine (**2-5**)⁷ which is well known for its toxicity (toxic component of genus *aconitum*). Talatisamine (**2-6**)⁸ and chasmanine (**2-7**)⁹ are related natural products.

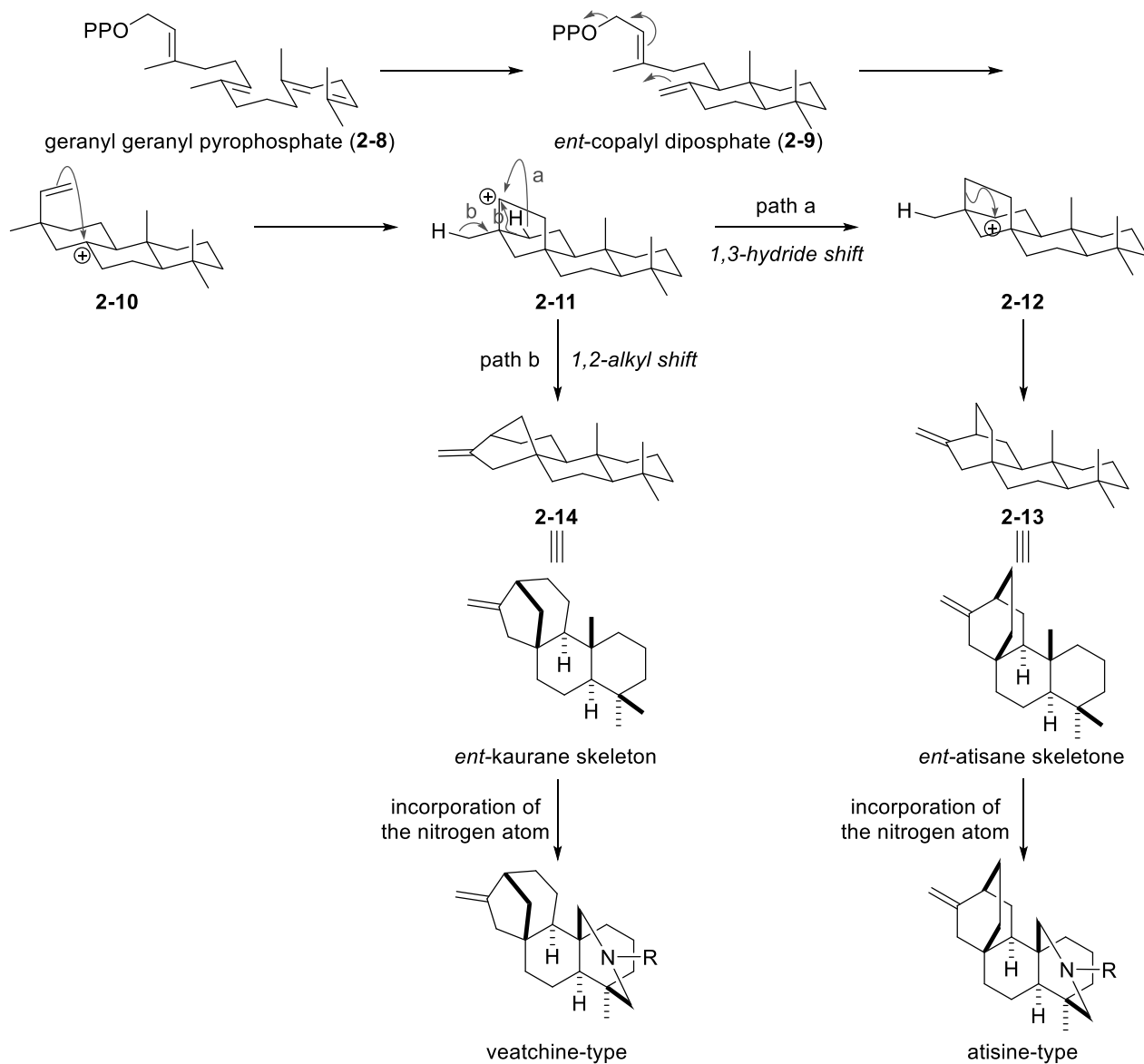
Figure 2.1 Examples of diterpene alkaloids.



2.1.2 Biosynthetic hypothesis

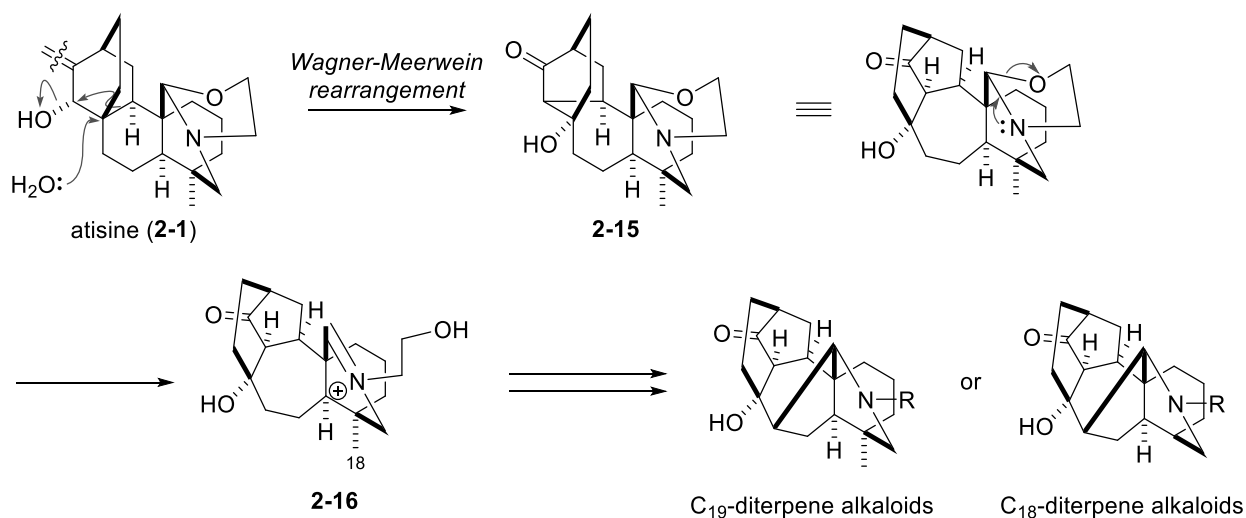
All diterpene alkaloids are proposed to be synthesized from geranylgeranyl pyrophosphate (**2-8**) (Scheme 2.1).¹⁰ Initially, cyclization from **2-8** affords *ent*-copalyl diphosphate (**2-9**). Formation of the third ring accompanies the loss of the pyrophosphate anion to give tertiary cation **2-10**, from which Prins cyclization occurs to yield secondary cation **2-11**.¹¹ 1,3-Hydride shift from **2-11** (path a) gives another secondary cation **2-12**, and the following 1,2-alkyl shift gives rise to *ent*-atisane skeleton **2-13**. Finally, the introduction of the nitrogen atom¹² furnishes the skeleton of the atisine-type diterpene alkaloids. On the other hand, 1,2-alkyl shift from the secondary cation **2-11** (path b) gives another tetracyclic scaffold called *ent*-kaurane skeleton (**2-14**), which leads to veatchine-type C₂₀-diterpene alkaloids by incorporation of the nitrogen atom.

Scheme 2.1 Biosynthetic hypothesis of C₂₀-diterpene alkaloids



Hexacyclic skeleton of C₁₉- and C₁₈-diterpene alkaloids are proposed to be generated from atisine (**2-1**) (Scheme 2.2).¹ Oxidative cleavage of the one-carbon atom of the *exo*-olefin and the Wagner-Meerwein rearrangement affords pentacyclic skeleton **2-15** consisting of 19 carbon atoms. Opening of the *N,O*-acetal yields iminium cation **2-16**, and the following cyclization to the carbon atom of the iminium cation leads to the characteristic hexacyclic skeleton of C₁₉-diterpene alkaloids. Further loss of the C18-carbon atom affords the skeleton of C₁₈-diterpene alkaloids.

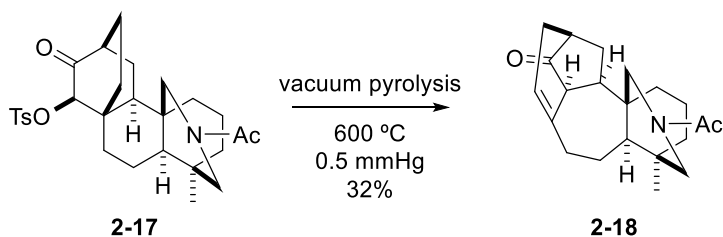
Scheme 2.2 Biosynthetic hypothesis of C₁₉- and C₁₈-diterpene alkaloids



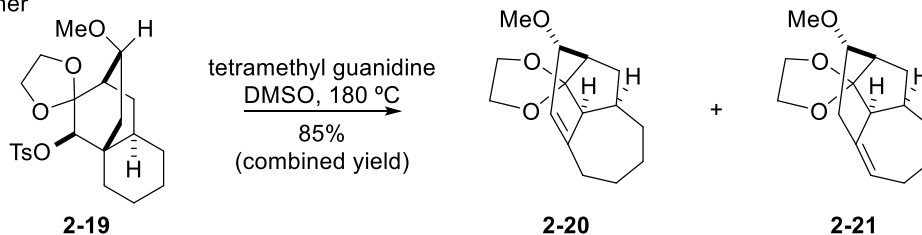
Although the order of these reactions have not been established yet, the plausibility of these reactions were verified in model systems. Overton and co-workers performed pyrolysis of simple pentacyclic tosylate **2-17** to obtain the rearranged product **2-18** (Scheme 2.3a).¹³ Wiesner and co-workers also obtained the rearrangement product **2-20** and **2-21** using the more oxygenated model system **2-19**. (Scheme 2.3b).¹⁴ Additionally, Edwards achieved the last ring formation of **2-24** by oxidation of the amine **2-22** to the iminium cation **2-23** with Hg(OAc)₂, followed by Mannich reaction (Scheme 2.3c).¹⁵ Wiesner and co-workers collectively utilized these insights in their total synthesis of diterpene alkaloids (*vide infra*).

Scheme 2.3 Biomimetic transformations in model compounds

a. Overton

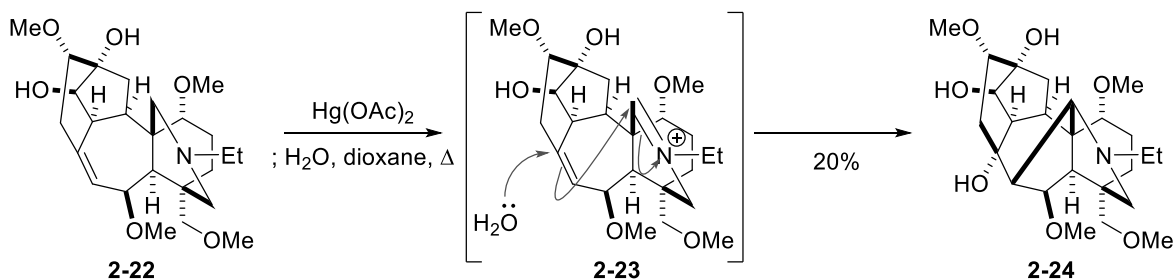


b. Wiesner



2-20 : 2-21 = 1 : 1

c. Edwards

**2.1.3 Biological activities of diterpene alkaloids**

The plants of *Aconitum* and *Delphinium* family (Ranunculaceae), the major sources of diterpene alkaloids, has been widely used as folk medicine in China and Japan.¹⁶ They are mainly used as analgesics and antiarrhythmic agents. Attempts toward identification of bioactive components of these medicinal plants lead to isolation of various diterpene alkaloids such as those shown above. The expected antiarrhythmic and analgesic activities were found, for example, in lappaconitine (**2-3**) which blocks the Na^+ channels.^{2, 3b} It was also found that some of the congeners like aconitine (**2-5**) instead induce arrhythmia by activation of the Na^+ channels.² Although many diterpene alkaloids act on the Na^+ channels,¹⁷ there are also K^+ channel modulators. For example, talatisamine (**2-6**) is reported to selectively inhibit K^+ channel and show antiarrhythmic effect.¹⁸

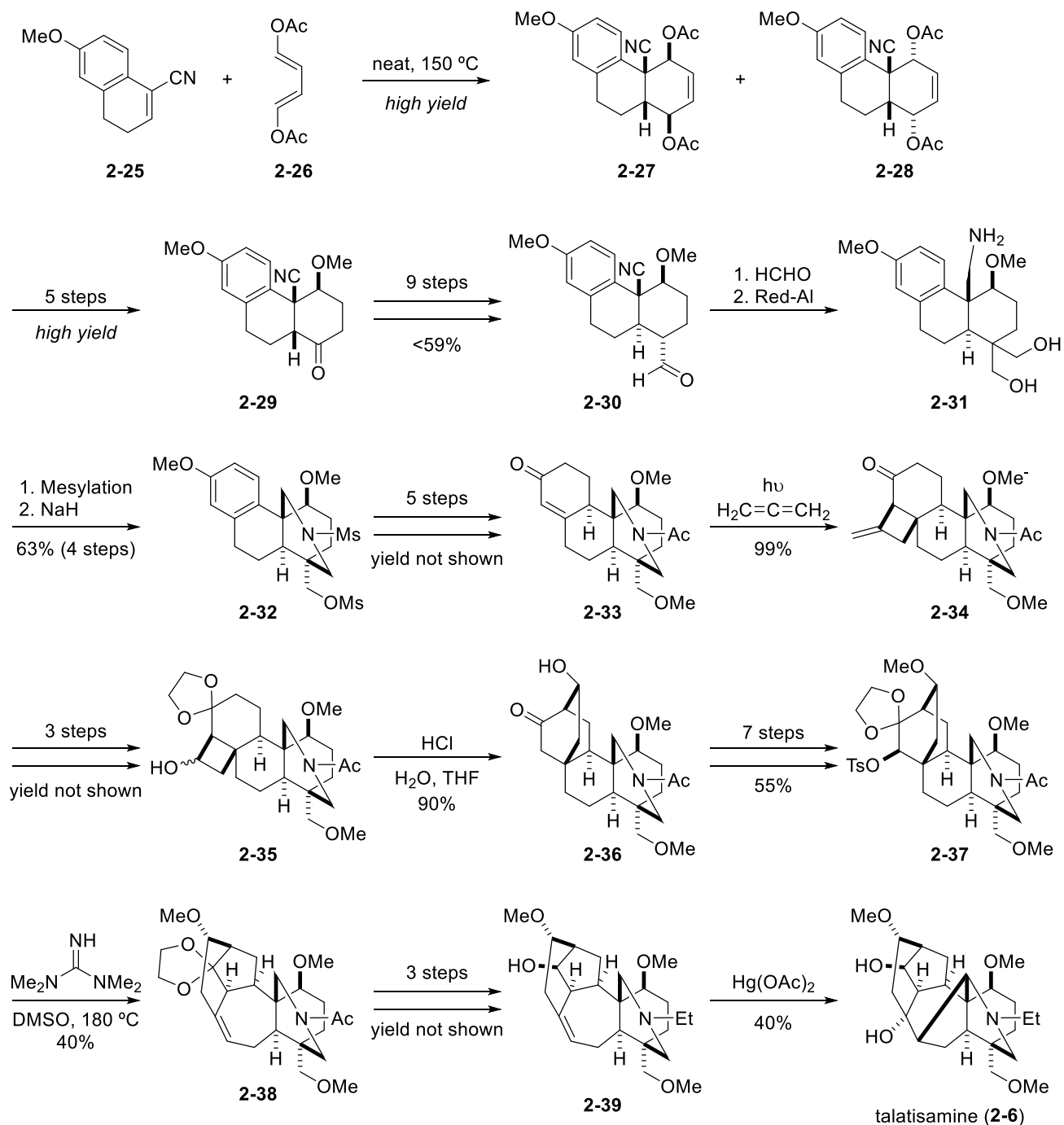
2.1.4 Synthetic studies

2.1.4.1 Synthetic studies by other groups

Attracted by its intriguing structure and biological activities, synthetic studies of diterpene alkaloids have been conducted since 1960s. Successful total synthesis of C₂₀ series have been reported by many groups,¹⁹ whereas that of relatively more complicated C₁₉ and C₁₈ series are not so many.^{20,21} Selected examples of the total syntheses of C₁₉- and C₂₀-diterpene alkaloids are described in the following sections with focusing on the construction of bicyclo[2.2.2]octane skeleton.

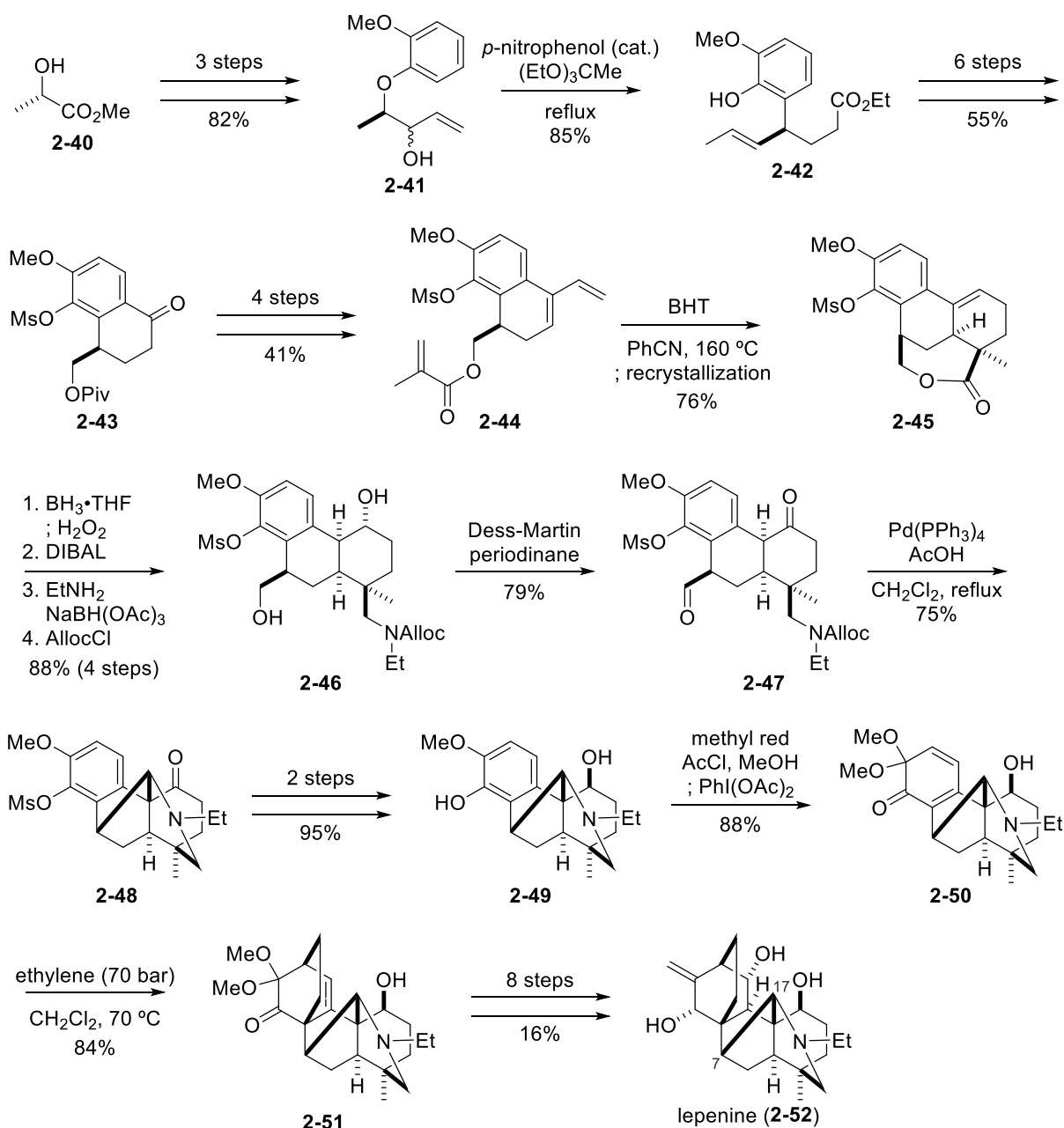
2.1.4.1.1 Total synthesis of talatisamine by Wiesner and co-workers

Wiesner and co-workers have completed the total synthesis of talatisamine (**2-6**) in 1974.¹⁴ Their synthetic strategy was based on the biosynthetic hypothesis. Namely, Wagner-Meerwein rearrangement of the bicyclo[2.2.2]octane skeleton was exploited to construct the carbon skeleton of talatisamine. The synthesis started from the Diels-Alder reaction of nitrile **2-25** and diene **2-26** to afford a 1 to 1 mixture of diastereomers of the adduct **2-27** and **2-28** (Scheme 2.4). Both compounds were converged to the same ketone **2-29** over five steps. Isomerization of *cis*-decalin to *trans*-decalin and one-carbon homologation through the nine-step sequence afforded aldehyde **2-30**. Aminodiol **2-31** was then obtained by the aldol reaction of **2-30** with formaldehyde and the following reduction. Piperidine ring of **2-32** was constructed from **2-31** by tri-mesylation and the following S_N2 reaction. Next, toward construction of the bicyclo[2.2.2]octane skeleton, the aromatic ring of **2-32** was converted to the α,β -unsaturated ketone of **2-33**. [2+2]-Photocycloaddition with the allene gave rise to cyclobutane **2-34**. After three steps, acid-mediated retro-aldol reaction cleaved the cyclobutane ring. The ensuing aldol reaction under the same conditions furnished bicyclo[2.2.2]octane **2-36**, which was converted to **2-37**, the substrate for the key rearrangement. Pentacyclic compound **2-38** was successfully generated from **2-37** under the previously established conditions (see Scheme 2.3b) through the biomimetic rearrangement.²² Finally the last ring was constructed over four steps via **2-39** to accomplish the total synthesis of talatisamine (**2-6**).

Scheme 2.4 Total synthesis of talatisamine by Wiesner and co-workers

2.1.4.1.2 Total synthesis of lepenine by Fukuyama and co-workers

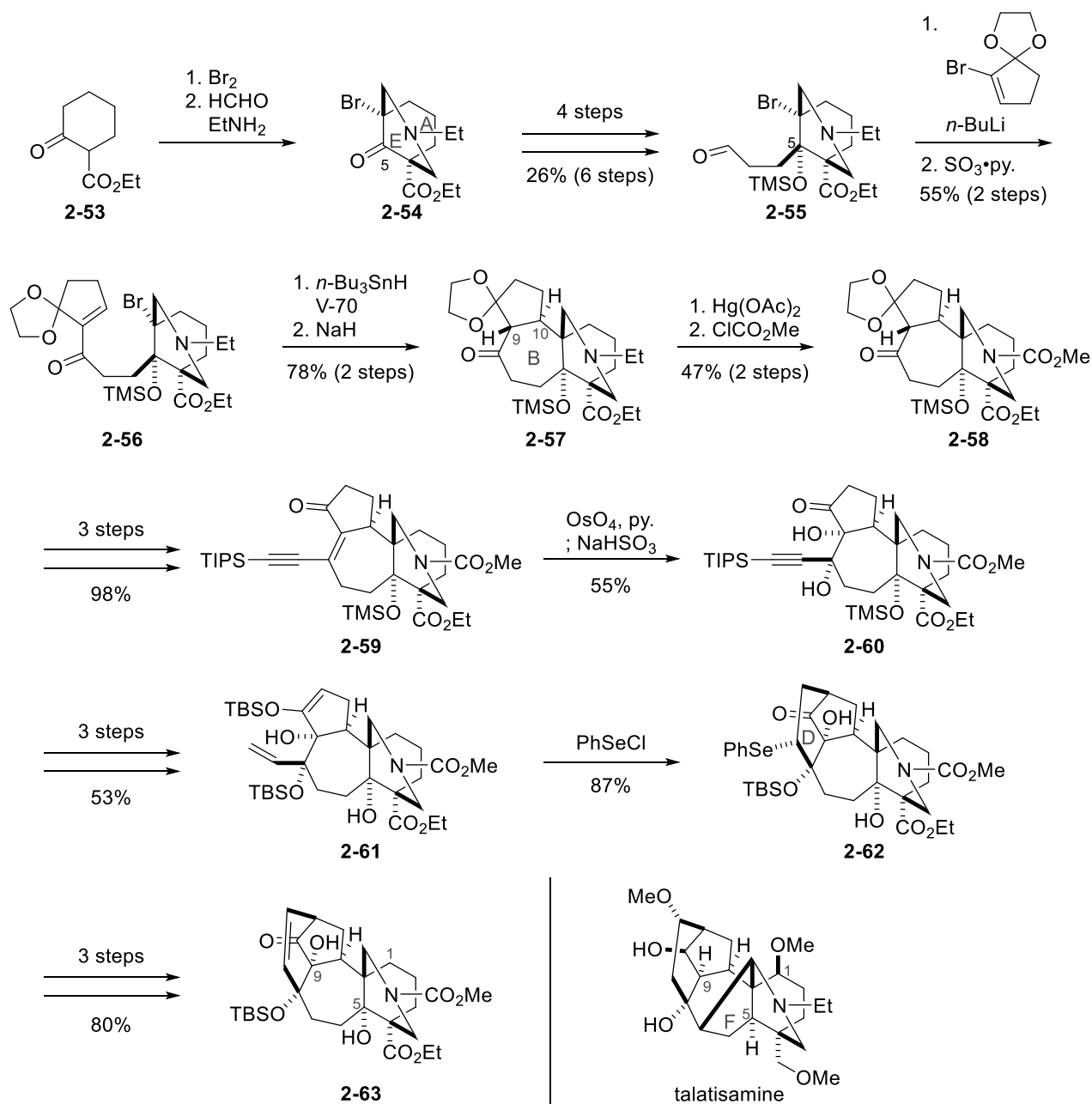
Recently, Fukuyama and co-workers completed the total synthesis of lepenine, C₂₀-diterpene alkaloid possessing the bicyclo[2.2.2]octane skeleton and characteristic C7-C17 bridge (Scheme 2.5).^{19q} Starting from enantiomerically pure L-lactic acid methyl ester (**2-40**), three step transformations led to the diastereomixture of allylic alcohols **2-41**. The Johnson-Claisen and ensuing Claisen rearrangements of **2-41** afforded ester **2-42** with complete control of the stereochemistry. Tetralone **2-43** was synthesized in six steps from **2-42**, and then 1,3-diene and *exo*-olefin were installed in 4 steps. Intramolecular Diels-Alder reaction of **2-44** went smoothly under heating conditions to construct two more stereocenters in **2-45**. Alloc-protected aminodiol **2-46** was obtained through the four step redox reactions, and then oxidized to diketone **2-47**. The key Mannich reaction was effected by Alloc deprotection in the presence of acetic acid to furnish pentacyclic compound **2-48**. After two steps, the oxidative dearomatization of phenol **2-49** afforded diene **2-50**. Diels-Alder reaction of **2-50** with ethylene yielded **2-51**, realizing construction of the bicyclo[2.2.2]octane skeleton in the late stage of the synthesis. **2-51** was converted to the natural product lepenine (**2-52**) by further eight steps.

Scheme 2.5 Total synthesis of lepenine by Fukuyama and co-workers

2.1.4.2 Synthetic study in our laboratory

Recently our group have established the efficient strategy for construction of the pentacyclic skeleton of talatisamine by employing the radical cyclization as a key step (Scheme 2.6).²³

The synthesis commenced from bromination of the commercially available ketoester **2-53**. The following double Mannich reaction using ethylamine afforded bicyclic amine **2-54**,²⁴ which corresponds to the AE-ring of talatisamine. The attachment of three-carbon chain at C5, followed by introduction of the cyclopentene unit to **2-55** and oxidation of the resulting alcohol afforded the substrate **2-56** for radical cyclization. Using the radical initiator V-70, the key cyclization of the bridgehead radical²⁵ constructed the seven-membered B-ring to give **2-57** in high yield. The C10-stereochemistry was installed correctly, while that of C9 was wrong. After exchange of the protecting group at the nitrogen atom, high-yielding three-step sequence from **2-58** gave enyne **2-59** with erasing the wrong C10-stereochemistry. Dihydroxylation of the olefin afforded α -oriented diol **2-60**, which was converted to silyl enol ether **2-61** in 3 steps. Treatment of **2-61** with PhSeCl selectively activated the terminal olefin, and the following nucleophilic attack of the silyl enol ether completed the construction of the D-ring. Thus introduced selenide atom was then eliminated to give olefin **2-63**, being posed to construction of the remained F-ring.

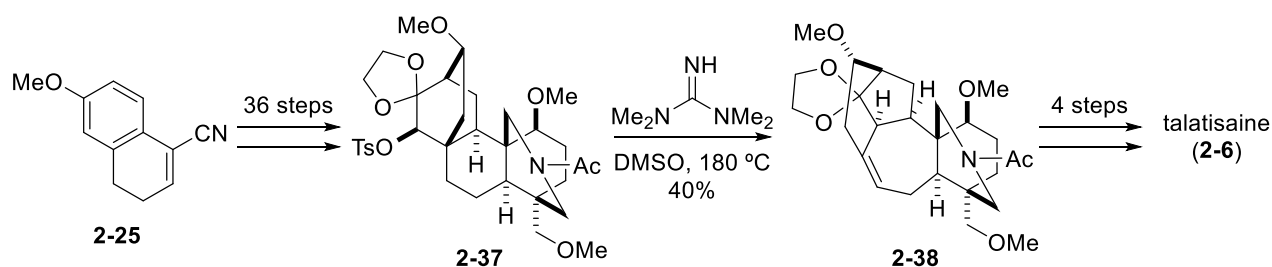
Scheme 2.6 Construction of the pentacyclic skeleton of talatisamine by Dr. Tabuchi

Although the pentacyclic ring system of C_{19} -diterpene alkaloid was elegantly constructed in the sequence, there remains to be done toward the total synthesis of talatisamine, especially adjustment of the oxidation state of the skeleton: C5- and C9-deoxygenation and C1-oxidation. Among those, introduction of the oxygen functionality at C1-position from **2-63** seems quite difficult.

2.1.5 Synthetic plan

Talatisamine (**2-6**) has twelve consecutive stereocenters including three tetrasubstituted carbons on its complex hexacyclic skeleton. Total synthesis of this molecule is highly challenging even today. Wiesner and co-workers synthesized the pentacyclic substrate for the skeletal rearrangement (**2-37**) in 36 steps (Scheme 2.7). The fascinating reaction sequence consisting of the skeletal rearrangement and the oxidative cyclization remains to be improved concerning the yields and scope of the reactions.

Scheme 2.7 Summary of the total synthesis of talatisamine by Wiesner and co-workers

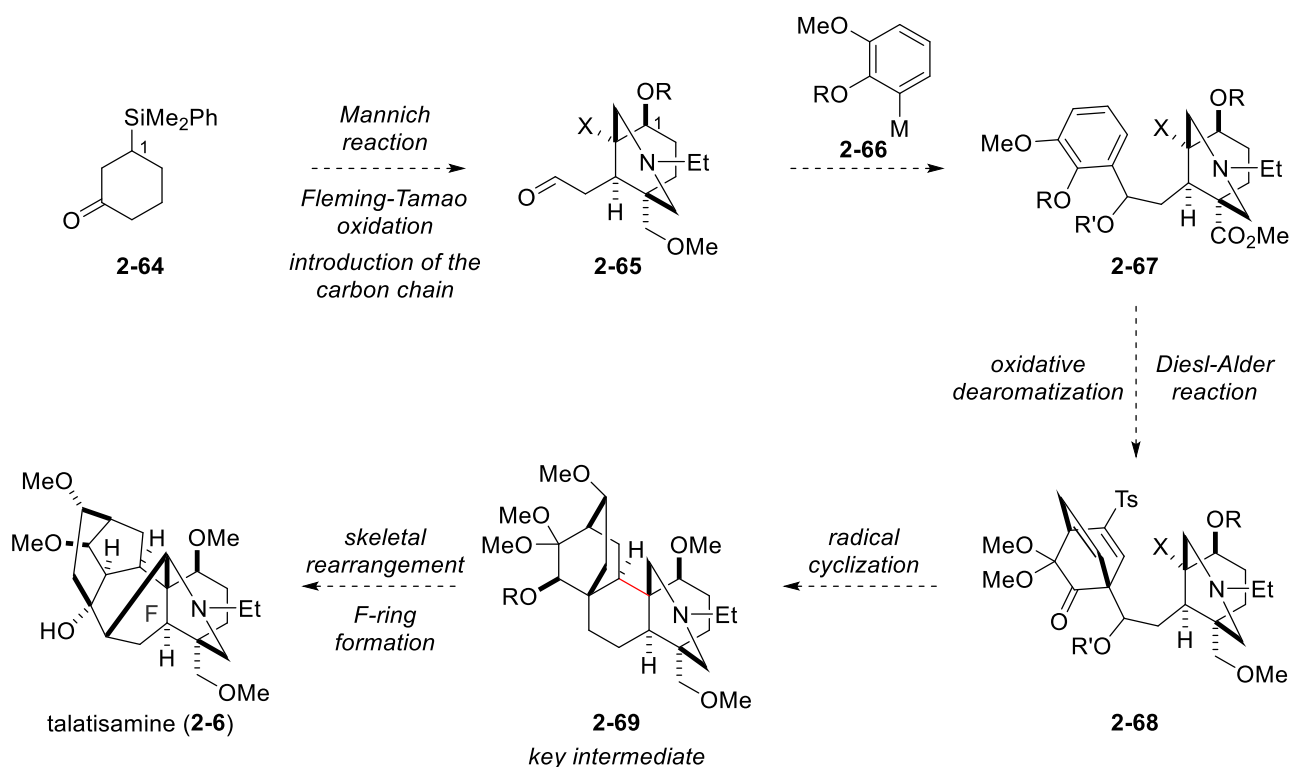


Thus the author set the substrate of the rearrangement **2-37** or its derivative as a key intermediate, and determined to establish the more efficient synthetic route toward the key intermediate by combining the strategies developed in our laboratory: oxidative dearomatization and Diels-Alder reaction sequence, and the bridgehead radical cyclization.

Specifically, **2-37** bears bicyclo[2.2.2]octane skeleton connected with the bicyclic amine moiety at its bridgehead position. Possibility of preparation of bicyclo[2.2.2]octane moiety by oxidative dearomatization and Diels-Alder reaction sequence was demonstrated in the synthesis of lepenine by Fukuyama and co-workers. Furthermore, the utility of the bridgehead radical generated from the bicyclic amine moiety was shown in our group's previous study. However, the AE-ring unit used in our group's previous study did not have the appropriate oxidation state, hence it should be replaced with the properly functionalized one to realize the more convergent synthesis. Taking into account of these, the synthetic route of talatisamine was planned as depicted in Scheme 2.8.

The known silyl ketone **2-64**²⁶ was selected as a starting compound. The silyl group could be regarded as a stable surrogate of the C1-oxygen functionality since its conversion to the hydroxy group by Fleming-Tamao oxidation²⁷ is a well-established process. In addition, the asymmetric synthesis of **2-64** is documented²⁸, thus the asymmetric total synthesis would be possible. Four contiguous stereocenters on the cyclohexane ring of **2-65** would be constructed via Mannich reaction, Fleming-Tamao oxidation, and introduction of the carbon chain. **2-65** has the same oxidation state as that of the AE-ring of talatisamine. Then introduction of the aromatic ring would be achieved by addition of aryl metal species **2-66** to aldehyde **2-65**. Thus obtained **2-67** would then be subjected to the oxidative dearomatization and Diels-Alder reaction sequence to give diene **2-68**. Two olefins of **2-68** would be differentiated by the effect of the electron withdrawing group as in the total synthesis of 4-hydroxyzinowol. Therefore the radical cyclization could afford the key intermediate **2-69** with correct stereochemistry. Finally, the Wagner-Meerwein rearrangement and oxidative F-ring formation would complete the total synthesis of talatisamine (**2-6**).

Scheme 2.8 Synthetic plan of talatisamine



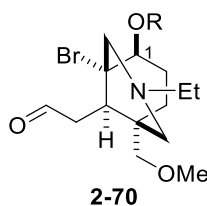
2.2 Synthesis of the AE-ring bearing the proper oxidation state

2.2.1 Construction of the piperidine ring

2.2.1.1 Attempted introduction of the bromide atom at the bridgehead position

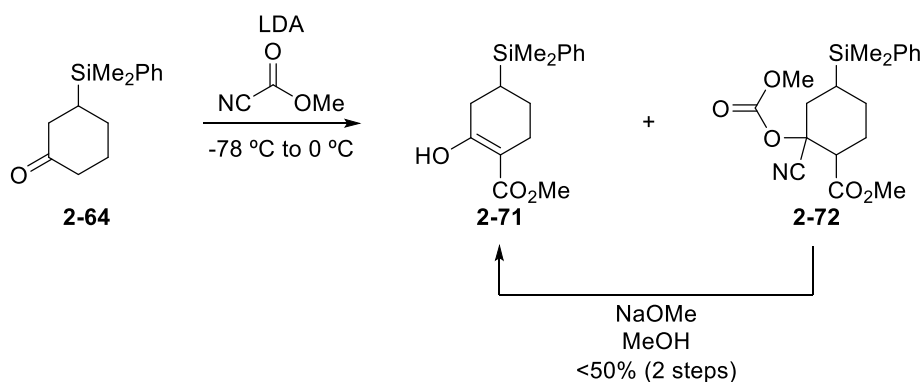
Based on the previous synthetic study, the bromide atom at the bridgehead position can be considered as a good precursor for the bridgehead radical. Thus, the brominated bicyclic amine **2-70** was initially set as a targeted AE-ring fragment.

Figure 2.2 Initially designed AE-ring fragment



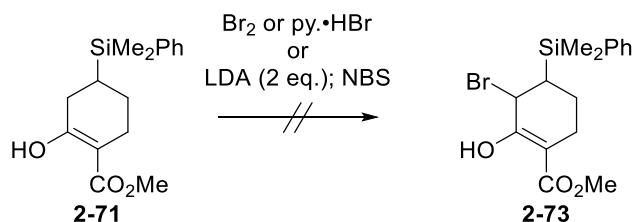
Regioselective deprotonation of **2-64** by LDA followed by treatment of the enolate with Mander's reagent²⁹ afforded enol **2-71** (Scheme 2.9). Although a considerable amount of methoxycarbonylcyanohydrin **2-72**³⁰ was also generated from **2-71** *in situ*, it was efficiently converted back to **2-71** by treating with sodium methoxide.

Scheme 2.9 Introduction of the one carbon unit at C4



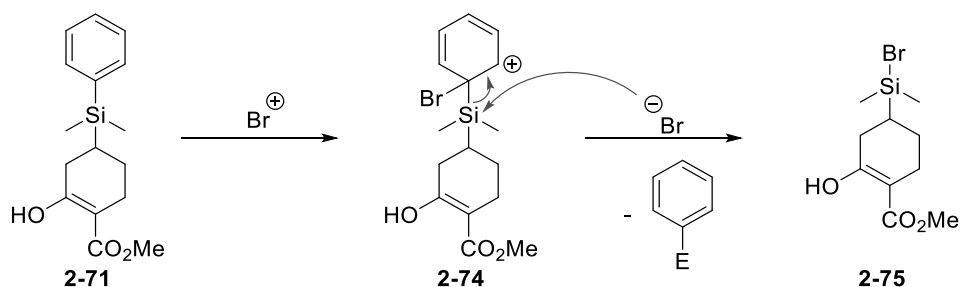
Next, introduction of the bromide atom at the other α -position was attempted (Scheme 2-10). Although a couple of conditions were attempted, the reaction became complicated in every case. None of the desired product **2-73** was obtained.

Scheme 2.10 Attempted bromination of **2-71**



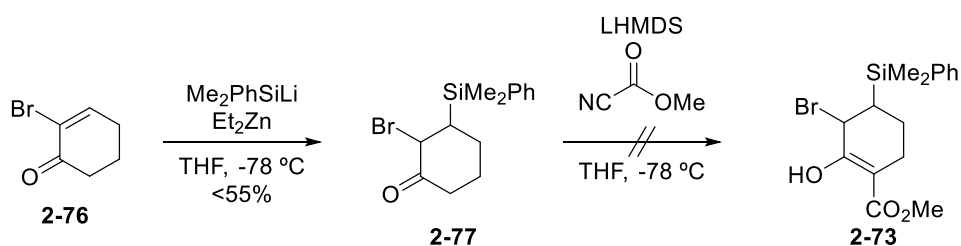
The difficulty of the bromination could be attributed to the presence of the silyl phenyl group. Other than two α -positions of the ketone, the *ipso*-position of the aromatic ring on the silicon atom is also nucleophilic. Thus it was speculated that the electrophilic *ipso*-substitution of the aromatic ring via the stabilized β -silyl cation **2-74** was the cause of the failure (Scheme 2.11).³¹

Scheme 2.11 Possible side reaction in the attempted bromination



To circumvent the problem, the order of introduction of substituents were modified (Scheme 2.12). Specifically, the silyl group was introduced by the 1,4-addition to α -bromo cyclohexenone **2-76**. Successfully obtained bromosilyl ketone **2-77** was then subjected to the base and Mander's reagent. However, the reaction became complicated again. Control experiment showed the treatment of **2-77** with LHMDs for 10 minutes at $-78\text{ }^{\circ}\text{C}$ afforded the complex mixture of products, indicating the lability of **2-77** under the strongly basic conditions.

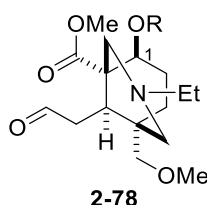
Scheme 2.12 Attempted synthesis of **2-73** from bromoketone **2-76**



2.2.1.2 Introduction of the ester functionality at the bridgehead position

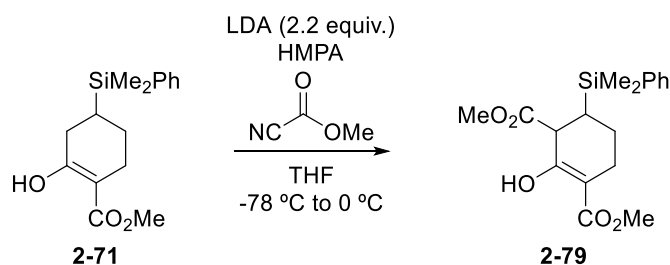
Faced with the above obstacles, the author determined to change the radical precursor from the bromide atom to the Barton ester.³² The methyl ester **2-78**, which would be reasonably stable and could be converted to the Barton ester in later stage, was chosen as its precursor (Figure 2.3).

Figure 2.3 Revised design of the AE-ring fragment



The introduction of the second methoxycarbonyl group to enol **2-71** was effected by utilizing the dianion chemistry (Scheme 2.13).³³ Ketoester **2-71** was treated with 2.2 equivalent of LDA followed by 1 equivalent of Mander's reagent and HMPA³⁴ to afford the desired diester **2-79** in clean fashion. The exact yield of **2-79** was difficult to determine since the purity of the sample could not be verified due to the presence of its diastereomers and tautomers.

Scheme 2.13 Introduction of the second methoxycarbonyl group



Next, diester **2-79** was subjected to the Mannich reaction to construct the piperidine ring (Scheme 2.14). By mixing diester **2-79** with ethylamine and formaldehyde, the desired bicyclic amine was obtained as a mixture of diastereomers at C1-position in 16% overall yield from β -silyl ketone **2-64**. The stereochemistry was determined by NOE correlation shown in figure 2.4.

Scheme 2.14 Construction of the piperidine ring

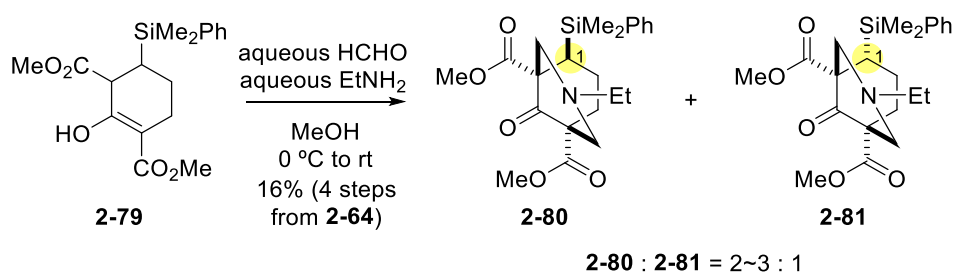
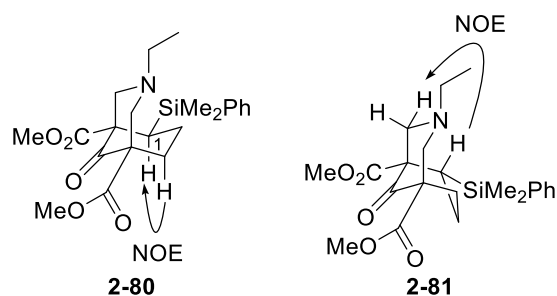


Figure 2.4 NOE correlation of **2-80** and **2-81**

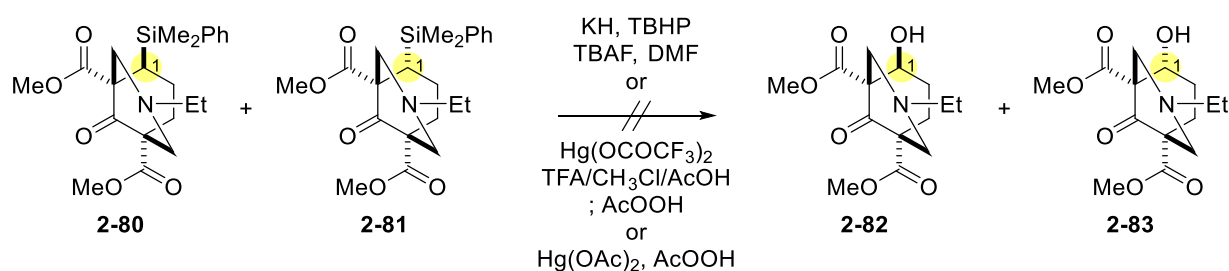


2.2.2 Introduction of the oxygen functionality at C1-position

2.2.2.1 One-pot Fleming-Tamao oxidation

The ensuing Fleming-Tamao oxidation is inherently incompatible with the electron-rich nitrogen atom. The amine could be oxidized to its *N*-oxide under the reaction conditions. There are a handful of examples in literature that realize Fleming-Tamao oxidation in the presence of the unprotected tertiary amine.³⁵ Referring to these examples, some one-pot oxidation conditions were examined in Scheme 2.15. However, desired product was obtained in neither conditions.

Scheme 2.15 Attempted one-pot Fleming-Tamao oxidation from the phenylsilanes

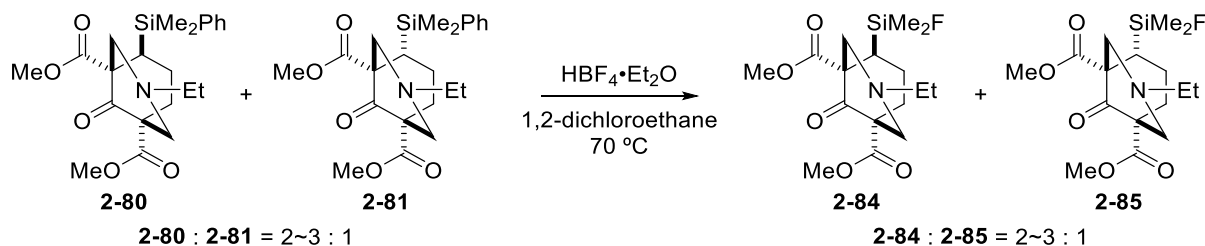


2.2.2.2 Two-pot Fleming-Tamao oxidation

2.2.2.2.1 Conversion to silyl fluoride

In order to simplify the reaction outcome, phenyl group on the silicon atom was first replaced by the fluoride atom. This reaction corresponds to the putative first step of the one-pot conditions (Scheme 2.16).³⁶

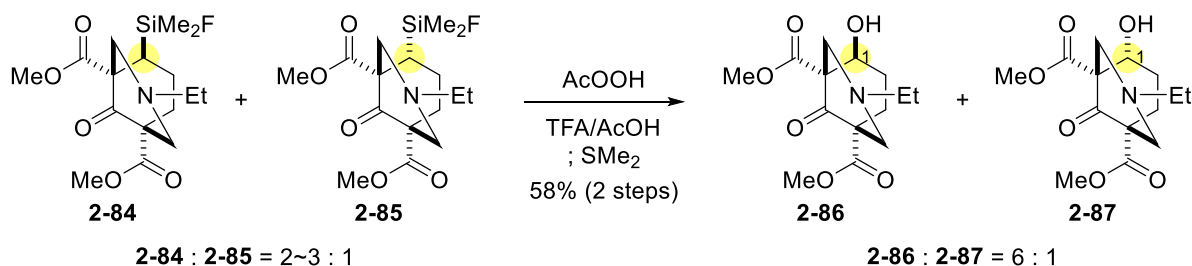
Scheme 2.16 Conversion of the phenyl group to the fluoride atom



2.2.2.2.2 Oxidation of the silyl fluoride

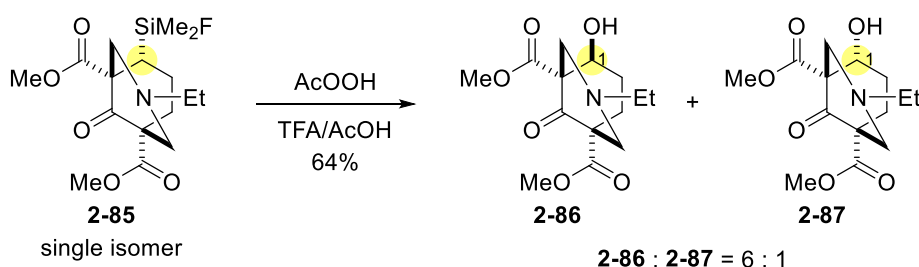
Thus obtained silyl fluorides **2-84** and **2-85**³⁷ were then subjected to the oxidation under the acidic conditions (Scheme 2.17). Owing to formation of the ammonium salt under the acidic conditions, the desired oxidation proceeded cleanly without over-oxidation of the tertiary amine. Furthermore, the diastereomeric ratio changed from $\beta : \alpha = 2\sim3 : 1$ to $\beta : \alpha = 6:1$, favoring the desired β isomer. The stereochemistry was determined by the coupling constants of C1-proton of **2-86** ($J = 10.1, 6.4$ Hz). 10.1 Hz and 6.4 Hz could be attributed to axial-axial and axial-equatorial coupling, respectively, thus the J values indicated C1-proton has axial orientation. Assuming the cyclohexane ring adopted the chair conformation, the stereochemistry at C1-position was determined to be β .

Scheme 2.17 Fleming-Tamao oxidation with epimerization of the stereochemistry



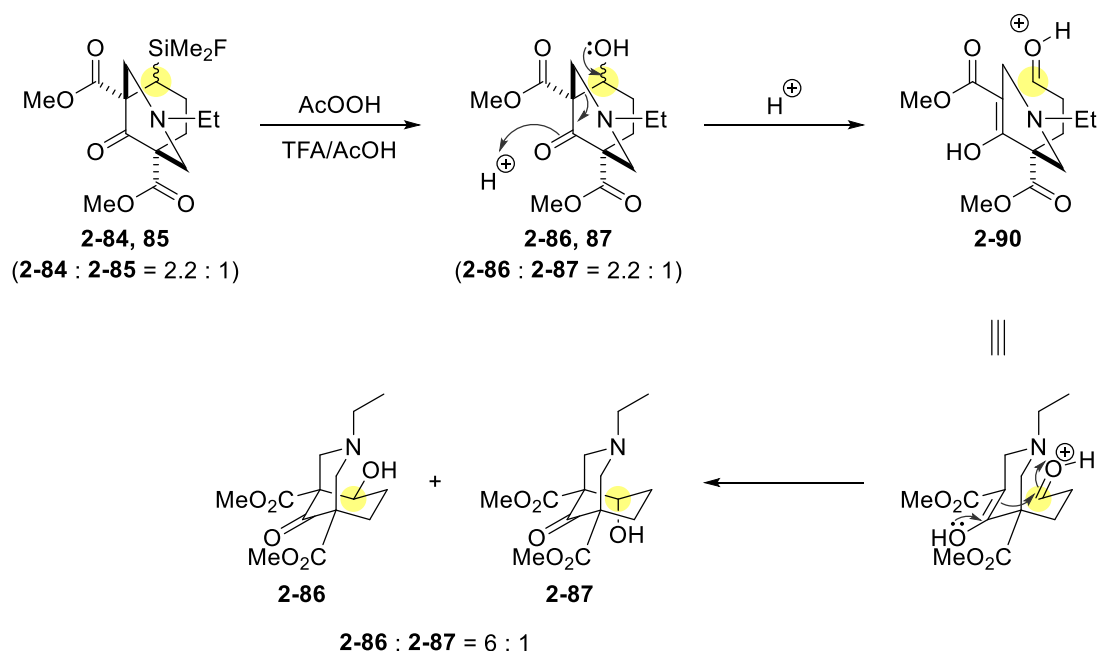
To clarify the reason for the change of the diastereomeric ratio, the control experiment was performed as shown in Scheme 2.18. When isolated single isomer of fluoride **2-85** was subjected to the same oxidation conditions, the epimerization of the stereochemistry occurred and diastereomixture of **2-86** and **2-87** was obtained in the same ratio as before. From the result, it was concluded that the stereochemistry at C1-position of the product alcohol was irrelevant to that of the starting material.

Scheme 2.18 Control experiment using single diastereomer of silyl fluoride



2.2.2.2.3 Rationale for the epimerization

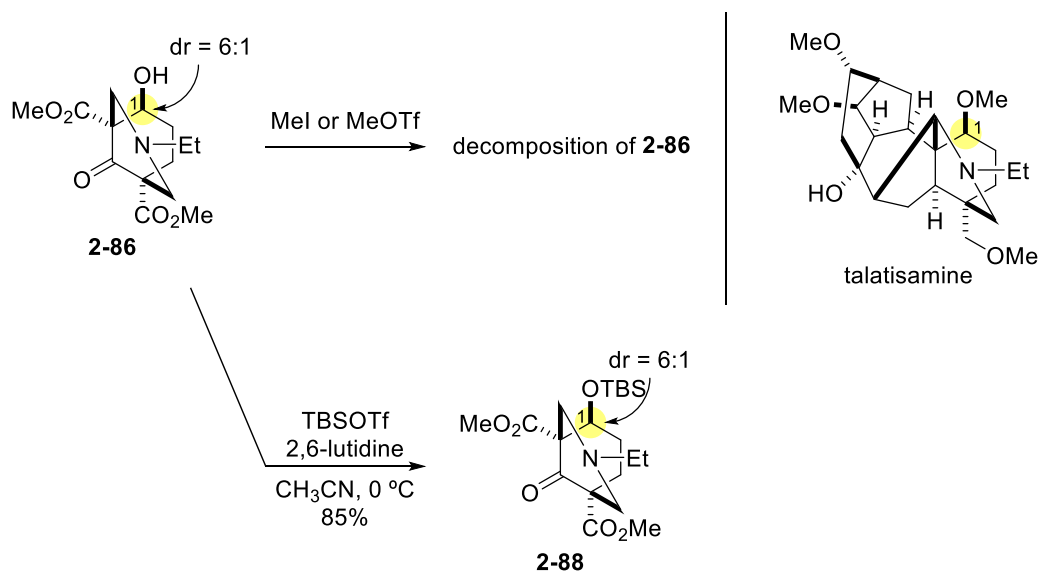
Fleming-Tamao oxidation is known to proceed with retention of configuration.³⁶ Therefore it is reasonable to surmise the epimerization shown in Scheme 2.18 occurred after the oxidation. Considering the strong acidity of the reaction conditions, the mechanism for the epimerization could be proposed as shown in Scheme 2.19. Initially, alcohols **2-86** and **2-87** would be generated with retention of configuration of the parent fluorides **2-84** and **2-85**. Under the acidic conditions, retro-aldol reaction would occur from β -hydroxyketones **2-86** and **2-87** to give enol intermediate **2-90**. The stereochemistry at C1-position disappears at this point. The following aldol reaction would regenerate the diastereomixture of alcohols. The aldol reaction would be under the thermodynamic control, and thus the β -isomer **2-86** would be the major product due to the thermodynamic stability of equatorial-alcohol **2-86** compared to axial-alcohol **2-87**.

Scheme 2.19 Proposed mechanism for the epimerization at C1-position

2.2.2.3 Protection of the introduced hydroxy group

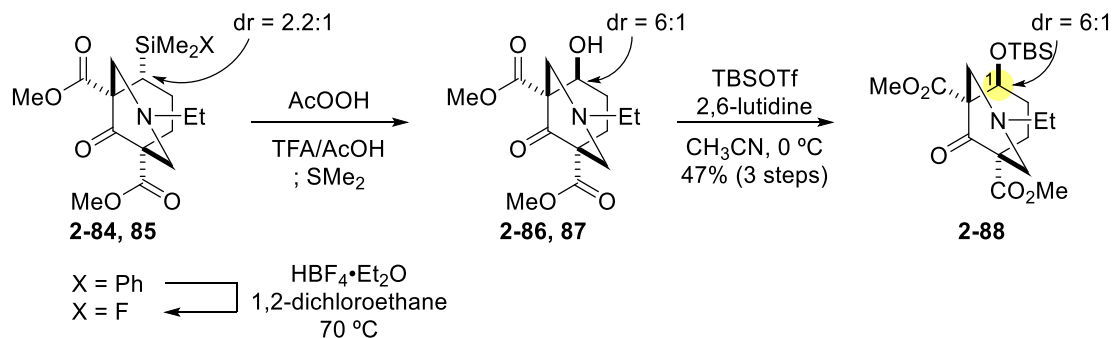
Although talatisamine bears the methyl ether at C1-position, attempts toward formation of methyl ether from **2-86** failed (Scheme 2.20). The instability of β -hydroxyketone moiety of **2-86**, which could be inferred from the above epimerization via retro-aldol/aldol sequence, could be a cause of the failure.³⁸

Thus the hydroxy group was protected as its TBS ether instead.

Scheme 2.20 Protection of C1-OH

It was found later that alcohol **2-86** was unstable even on silica gel. Attempted isolation in large scale resulted in the considerable decrease of the yield. Thus, the crude alcohol **2-86** was protected without isolation to give TBS ether **2-88** in good yield over three steps (Scheme 2.21).

Scheme 2.21 Three-step procedure to TBS ether **2-88**

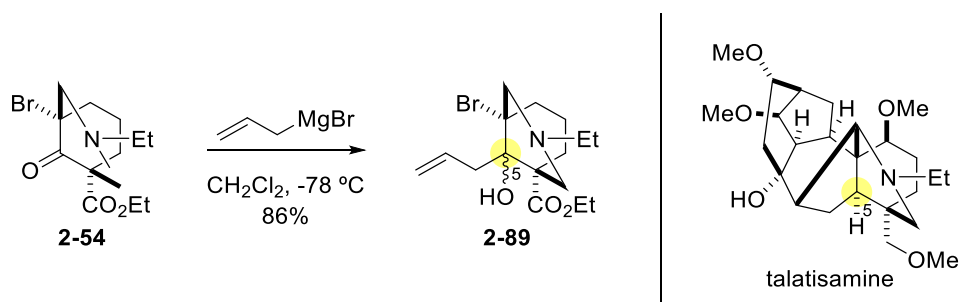


2.2.3 Introduction of carbon chain at C5-position

2.2.3.1 Synthetic consideration

The C1-oxygen functionality having been successfully constructed, introduction of carbon chain at C5-position was next investigated. Although Grignard reaction had been successfully employed for this purpose in the previous study, product **2-89** retained tertiary hydroxy group which had to be removed in later stage (Scheme 2.22)

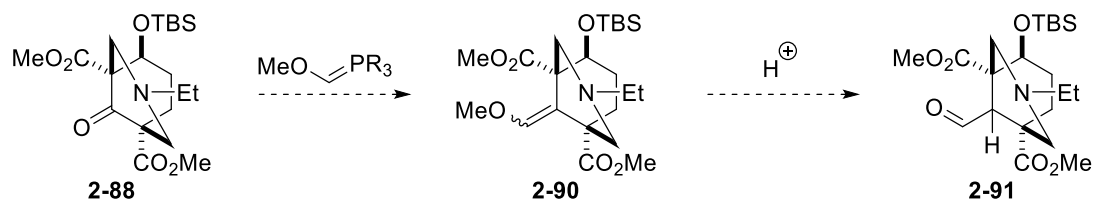
Scheme 2.22 Previous result obtained by Dr. Tabuchi



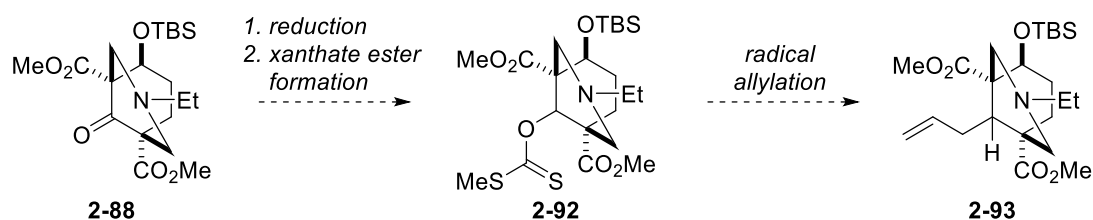
Thus the author determined to attach the carbon chain with concurrent removal of the oxygen atom. Two plans are shown in scheme 2.23. Specifically, Wittig-type reaction of **2-88** with functionalized ylide could give enol ether **2-90**. The hydrolysis of **2-90** would give aldehyde **2-91** which could be used for further homologation (Scheme 2.23a). Alternatively, the ketone of **2-88** could be reduced and the resulting alcohol could be converted to xanthate ester **2-92**, which could be allylated under the radical reaction conditions (Scheme 2.23b).

Scheme 2.23 Two plans for introduction of carbon chain at C5-position

a. Wittig reaction

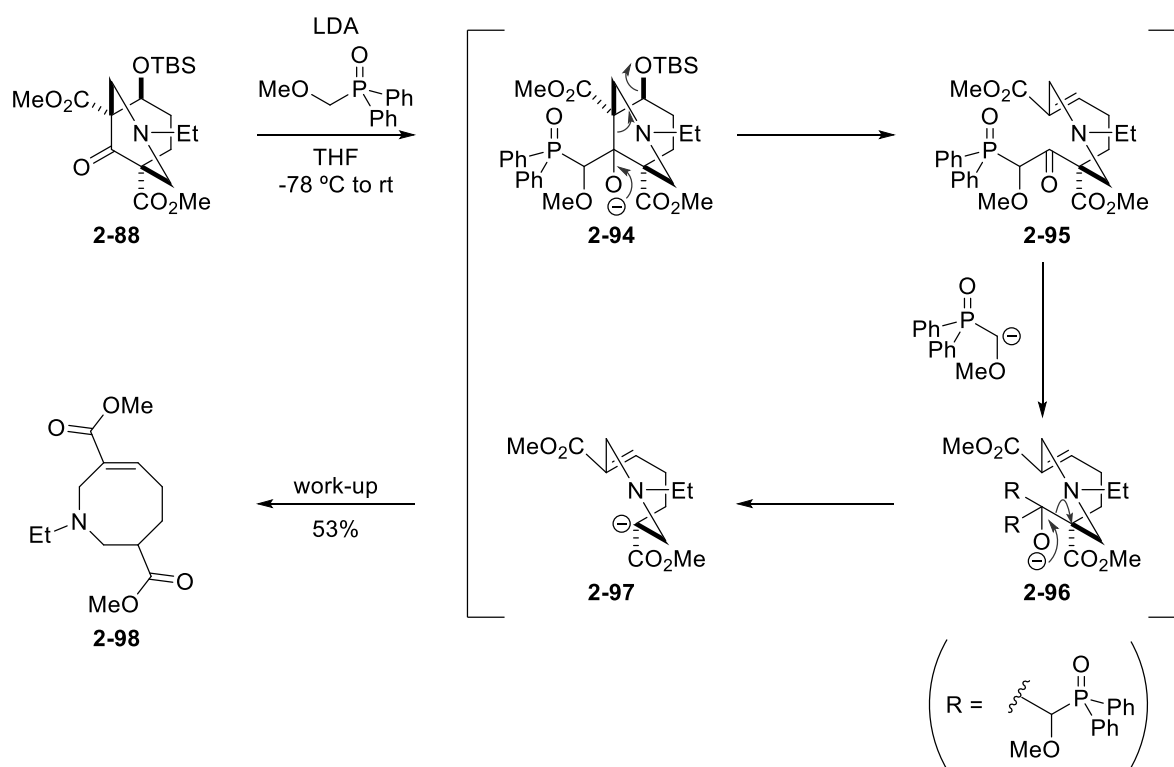


b. radical reaction



2.2.3.2 Attempted olefination

Initially Wittig-type reaction was attempted (Scheme 2.24). Although the substrate **2-88** was consumed under standard conditions, the product was eight-membered ring amine **2-98**. The proposed mechanism is also shown in the scheme. After the addition of the ylide species to the ketone, Grob-type fragmentation from **2-94** occurred to give α,β -unsaturated ester **2-95**. Second addition of the ylide species to the ketone followed by retro-aldol-type reaction of **2-96** afforded the carbanion **2-97**, which was protonated to give **2-98**. The mechanistic consideration indicated that the formation of oxaphosphetane from **2-94** was retarded presumably due to the steric congestion by the two adjacent quaternary carbons. Furthermore, the fragmentation from oxanyan **2-96** might be fast since the steric repulsion between the quaternary carbon and the phenyl rings on the phosphine atoms would be relieved by the reaction. Other attempts to suppress the side reactions resulted in similar results.³⁹

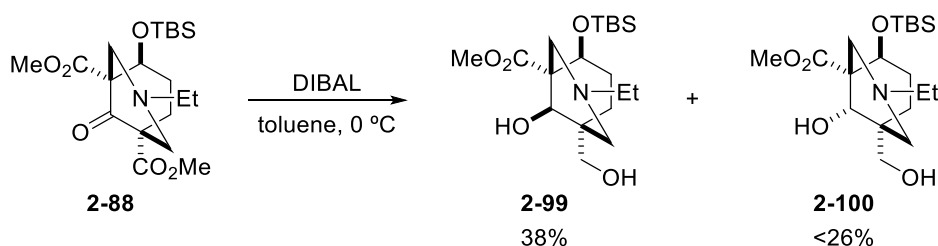
Scheme 2.24 Attempted olefination of ketone **2-88**

2.2.3.3 Radical allylation

2.2.3.3.1 Preparation of the substrate for radical allylation

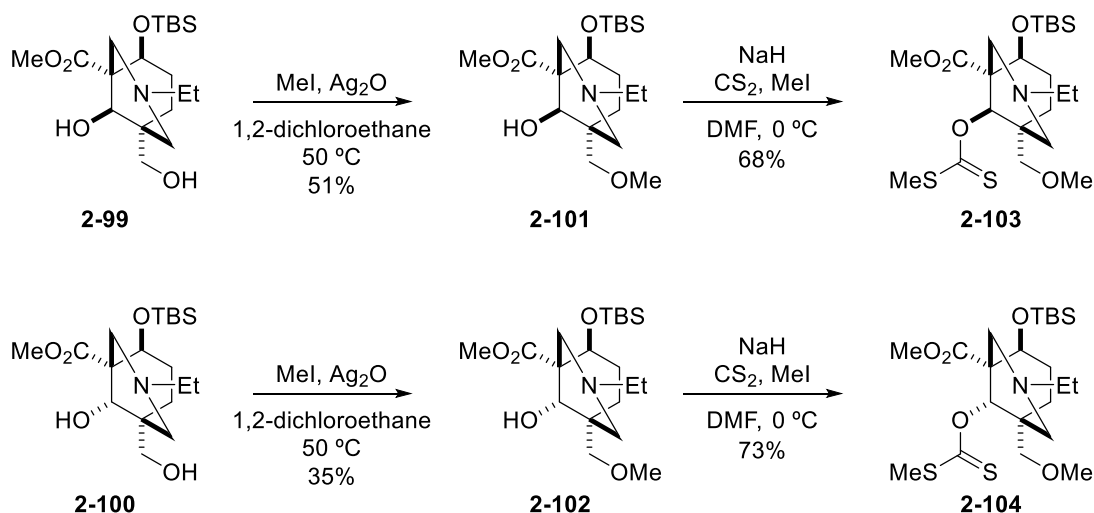
Thus, radical allylation strategy was next investigated. First of all, Treatment of **2-88** with DIBAL reduced the ketone and one of the esters in highly regioselective manner to give diols **2-99** and **2-100** (Scheme 2.25). Although the diastereoselectivity was low, this stereochemistry is inconsequential because it would disappear in generating the radical at this position.

Scheme 2.25 Regioselective reduction of ketoester **2-88**



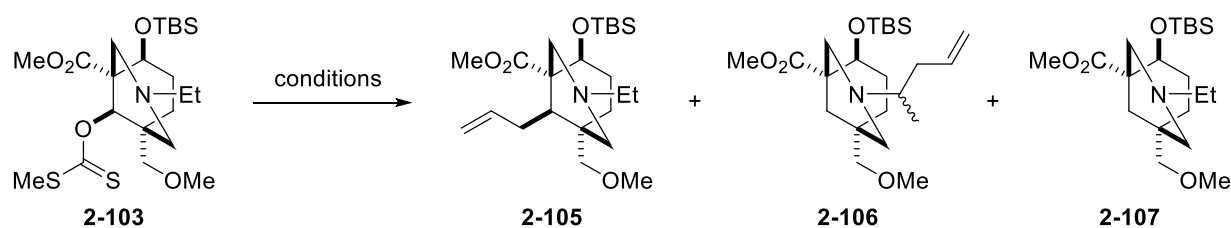
Each of the primary alcohol of diols **2-99** and **2-100** was methylated under the standard conditions (Scheme 2.26). Secondary alcohols **2-101** and **2-102** were then converted to xanthate esters **2-103** and **2-104**.

Scheme 2.26 Conversion of the diols to xanthate esters

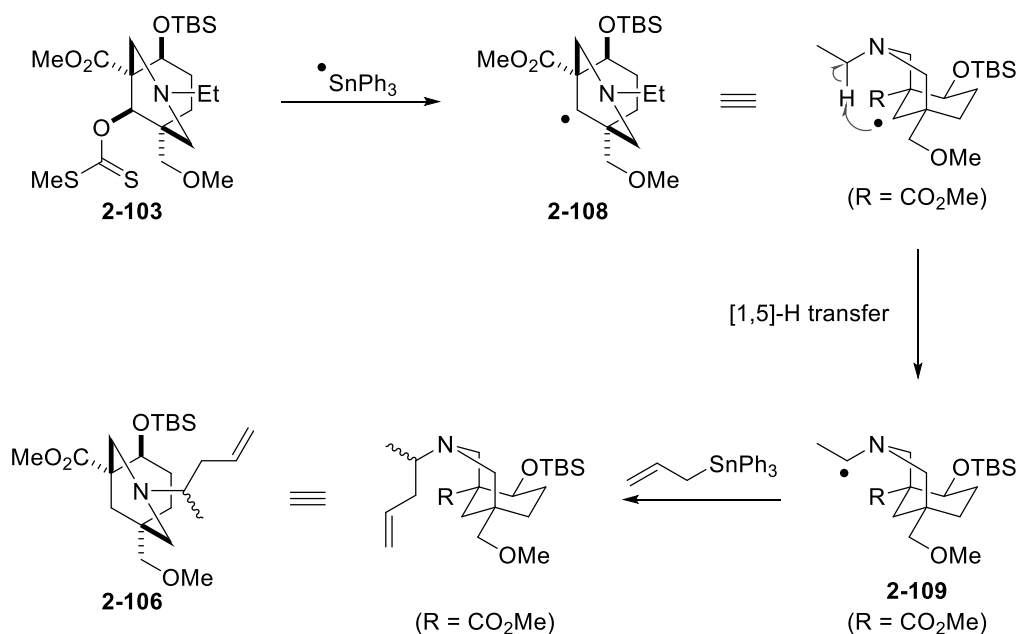


2.2.3.3.2 Condition screening of the radical allylation

Substrate for the radical allylation in hand, conditions of the radical allylation was screened using the major diastereomer **2-103** (Table 2.1). Under the standard conditions using allyltributyltin, only hydrogenated compound **2-107** was obtained (entry 1). The source of the hydrogen atom could be the benzylic hydrogen atom of the solvent or the allylic hydrogen atom of the allyltin reagent. Therefore, in entry 2, the solvent was changed to chlorobenzene and also the allyltin reagent was changed to allyltriphenyltin because the bulky phenyl groups were expected to inhibit the hydrogen abstraction from its allylic position. As a result, the desired product **2-105** was obtained in only 12 % yield as a 7:1 diastereomixture along with the unexpected allylated product **2-106** as a major product. The proposed mechanism for the generation of **2-106** is depicted in Scheme 2.27. The generated secondary alkyl radical **2-108** abstracted the hydrogen atom adjacent to the nitrogen atom via six-membered transition state to yield α -amino alkyl radical **2-109**. Allylation of this radical species would give **2-106**. The steric hinderance around the first carbon radical would inhibit the approach of the reagents and retarded the desired reaction, and this was considered to be the cause of the side reaction. The mechanistic consideration indicated the side reaction could be suppressed by accelerating the allylation of the initial alkyl radical **2-108**. Hence the reaction was conducted under neat conditions in entry 3, which minimized the side reaction and afforded the desired product **2-106** in 44% yield with the same diastereoselectivity as in entry 2.

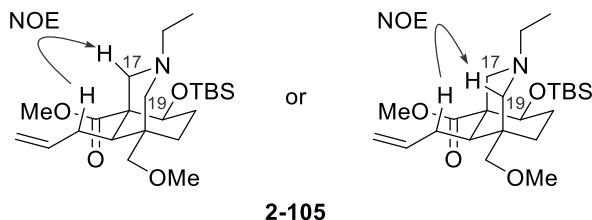
Table 2.1 Radical allylation

entry	conditions	results
1	 V-40 (cat.) xylene, 110 °C	2-107 only
2	 V-40 (cat.) chlorobenzene, 130 °C	2-105 : 12% (dr = 7:1) 2-106 : 23% (dr = 2:1) 2-107 : 16% recovery of 2-103 : 23%
3	 V-40 (cat.) neat, 130 °C	2-105 : 44% (dr = 7:1) 2-106 : 16% (dr = 2:1) recovery of 2-103 : 10%

Scheme 2.27 Proposed mechanism for the generation of **2-106**

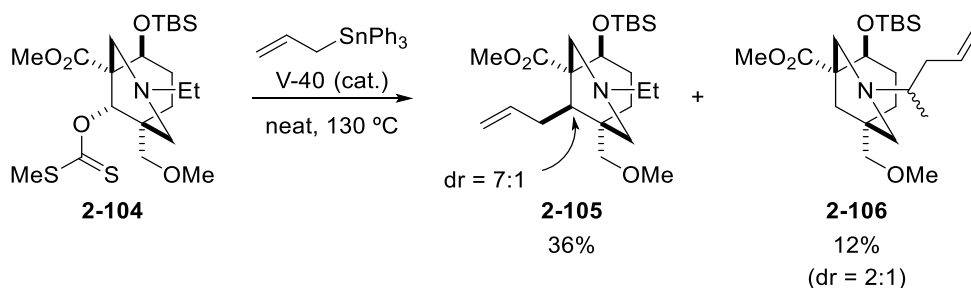
The stereochemistry of the major diastereomer of the allylated product **2-105** and was unambiguously determined by the NOE experiment (Figure 2.5). One of the protons at the allylic position showed NOE correlation with C17-proton or C19-proton.

Figure 2.5 NOE correlation of the desired allylated product **2-105**



Optimal reaction conditions in hand, the minor diastereomer of the xanthate ester **2-104** was also subjected to the same reaction conditions to afford **2-105** and **2-106** in similar yields (Scheme 2.28). The major diastereomer was again the β -isomer. As expected, the stereochemistry of the parent xanthate disappeared in the radical intermediate, and was not related to the stereochemistry of the product.

Scheme 2.28 Radical allylation of the minor diastereomer **2-104**



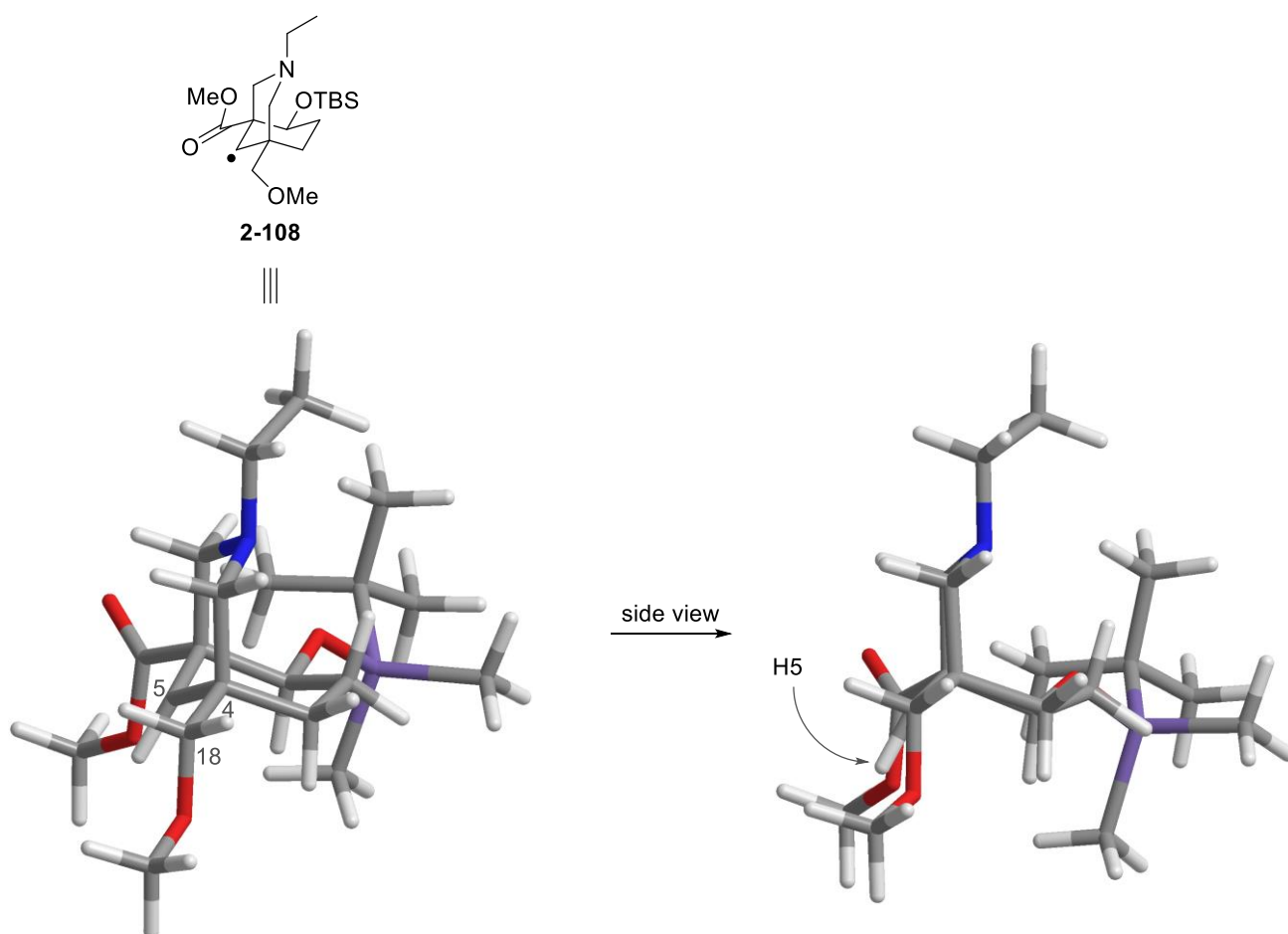
2.2.3.3.3 Rationale for the stereoselectivity

The observed high diastereoselectivity could not be explained by steric factors. Namely, assuming that both of the cyclohexane and the piperidine rings of azabicyclo[3.3.1]nonane should be in chair forms, clear difference cannot be found between the steric environment of α - and β -faces of the reaction center. In order to clarify the origin of the stereoselectivity, DFT calculation (uB3LYP/6-31G*) of the structure and the orbital energy of the radical intermediate **2-108** was performed. Thus obtained structure was depicted in Figure 2.6.

Secondary carbon radical is generally considered to be in the p -orbital of the sp^2 -hybridized carbon atom. However, as can be seen from the side view of the structure in Figure

2.6, the C5-proton slightly tilted to axial (to the cyclohexane ring) from the orientation expected for the planar structure of the sp^2 -hybridized carbon atom. The dihedral angle (C18-C4-C5-H5) was calculated to be -29.15° (around 0° if C5 is sp^2 -carbon, and $\pm 60^\circ$ if C5 is sp^3 -carbon). Therefore, the radical would have sp^3 character to some extent, and also would bear the equatorial-like orientation. Allylation of such radical would afford the β -isomer, which was the observed major product.

Figure 2.6 Calculated stable structure of the radical intermediate



The reason for the distortion revealed above can be speculated by considering the orbital interaction of the atomic orbital at C5-position. The energy of the atomic orbital at C5-position bearing the unpaired electron would be increased by orbital interactions with neighboring electron rich C-C bonds (Figure 2.7). The axial-oriented orbital (**2-108-a**) would interact with two C-C bonds (C17-C11 and C19-C4). However, both bonds are connected to the electronegative nitrogen atom, and thus the increase of the orbital energy by these bonds would be attenuated. On the other hand, equatorial-oriented orbital (**2-108-e**) would interact with the other two C-C bonds (C1-C11

and C3-C4). Although one of them (C1-C11) bears the oxygen atom, the other does not bear any electronegative atom. Therefore, the increase of the orbital energy would be greater compared to the axial-oriented orbital, hence the contribution to SOMO from the equatorial-oriented atomic orbital would also be greater than from the axial-oriented one, resulting in the distortion observed above. The calculated SOMO (HOMO) of the radical intermediate **2-108** is shown in Figure 2.8.⁴⁰ It can be seen that the phase of the orbital lobe at C5 matched with C-C bonds discussed above (blue: C3-C4 and C1-C11, red: C4-C19 and C11-C17).

Figure 2.7 Axial- and equatorial-oriented atomic orbitals

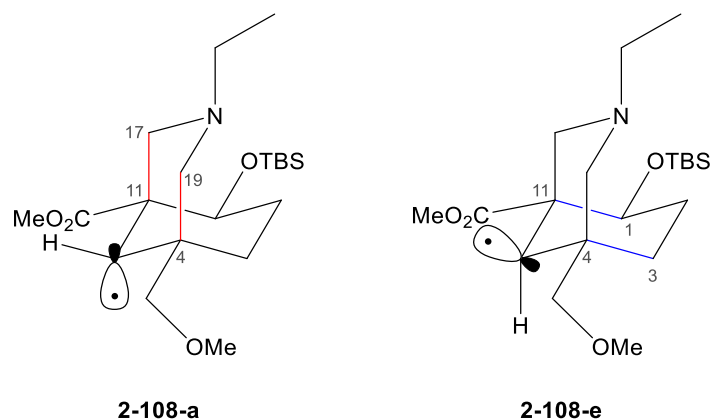
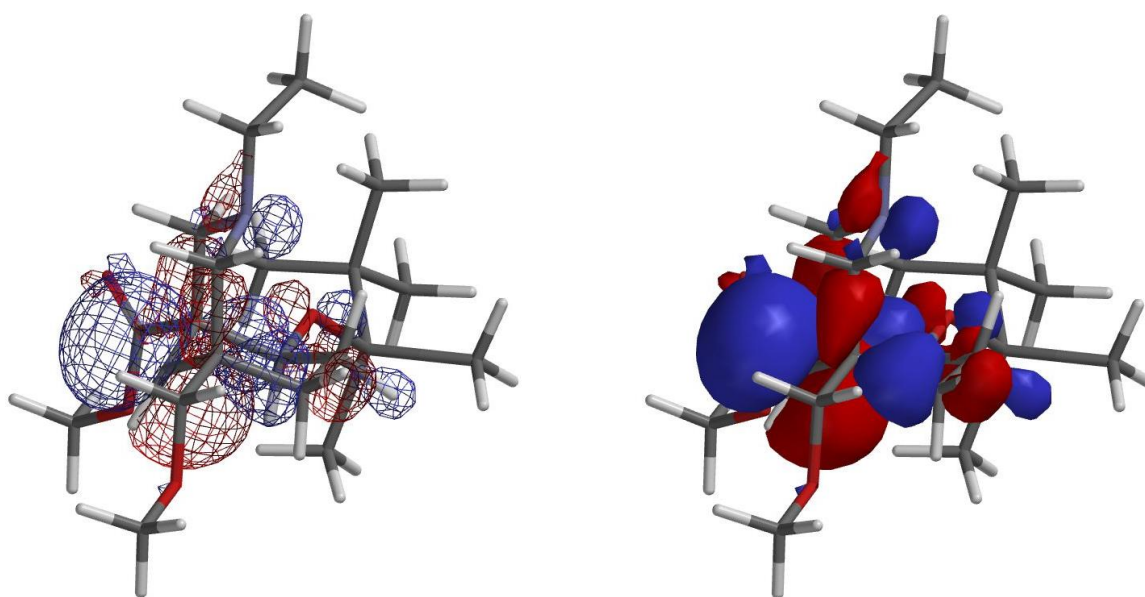


Figure 2.8 Calculated SOMO (HOMO) of the radical intermediate **2-108**

(left: mesh view, right: solid view)



2.3 Introduction of the aromatic ring

2.3.1 Ozonolysis of the terminal olefin

2.3.1.1 Unexpected formation of the zwitterionic species

Successfully introduced three-carbon unit had to be truncated toward the introduction of the aromatic ring moiety. Thus ozonolysis of the terminal olefin was investigated next (Scheme 2.29). Initially tertiary amine **2-105** was protected as its TFA salt, and then ozonolysis was performed at $-78\text{ }^{\circ}\text{C}$. The reaction proceeded cleanly without undesired oxidation of the nitrogen atom. Unexpectedly, the product was found to be a zwitterionic species **2-110**, instead of the expected aldehyde **2-111**. The structure of **2-110** was proposed based on its ESI-MS spectrum, large low-field shift of the chemical shift of the protons around the nitrogen atom (Table 2.2), and its very high polarity. C7-proton was assigned to the peak at 5.15 ppm in ^1H NMR, which is a similar value to the related literature examples (*vide infra*).

Scheme 2.29 Ozonolysis of the terminal olefin

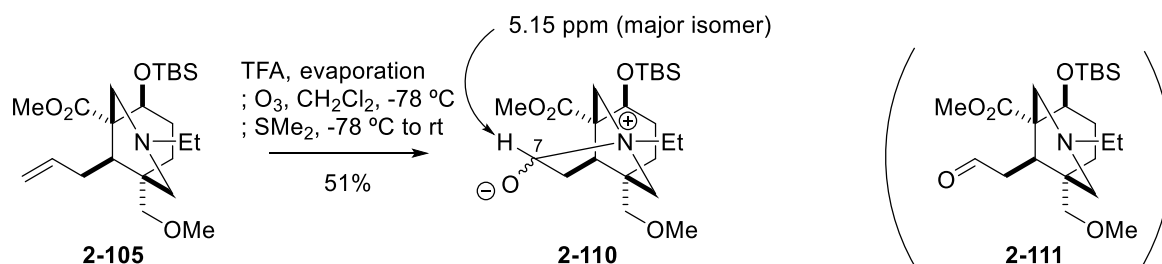


Table 2.2 Comparison of selected chemical shifts (δ) of **2-105** and **2-110**

	 2-105	 2-110 (major isomer at C7)
H17 or H19	2.05 and 2.43	2.56 and 3.32*
H17 or H19	2.16 and 3.30	3.23 and 3.90
CH_2 of N-Et	2.21-2.34 (2H)	3.30* and 3.60
CH_3 of N-Et	1.04 (3H)	1.46 (3H)

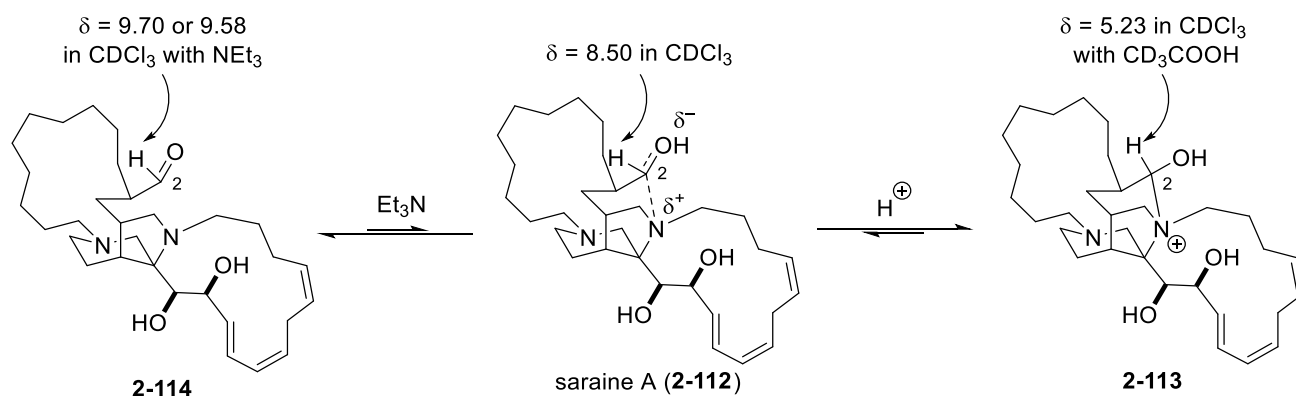
* Estimated from ^1H - ^1H cosy correlation.

2.3.1.2 Amine-aldehyde interaction in literature

Although the structure of **2-110** seemed unstable, there are a handful of examples of such zwitterionic species in literature.⁴¹ The representative example is found in the natural product saraine A (Scheme 2-30).⁴² Under neutral conditions, C2-proton of saraine A was observed at 8.50 ppm, which is shifted slightly upper field compared to normal aldehydes. This up-field shift is attributed to the interaction of the aldehyde with the lone pair of the nearby tertiary amine, and thus the structure of saraine A is generally drawn as **2-112** (middle structure), in which the tertiary amine is partially bonded to the aldehyde carbon atom. This interaction is known to be highly environment-dependent, and observation of the consistent ¹H NMR of saraine A was reported to be difficult under neutral conditions. However, when acid is present in the system, saraine A exists mostly in the stable hemiaminal cation form as shown in **2-113** (right structure) in which the ¹H NMR peak for C2-proton appears at 5.23 ppm. The structure of hemiaminal cation **2-113** was established by X-ray crystallographic analysis, and also its ¹H NMR spectrum was reproducible enough to be utilized in comparison with the synthetic sample of saraine A.⁴³ On the other hand, it was recently reported⁴⁴ that in the presence of triethylamine, C2-proton appeared around 9.6 ppm, which can be regarded as a chemical shift of “normal” aldehyde as shown in **2-114** (left structure). Although the reason for this change is still elusive, it could be speculated that the added amine scavenged residual acids in the sample, thus inhibited the activation of the aldehyde with acidic species and the formation of the aminal structure like **2-113**.

As for the reactivity of such interacting aldehyde as an electrophile, saraine A is known to unreactive toward NaBH₄⁴² or Wittig type reagents.⁴⁴ No literature example can be found in which external nucleophiles attack on such interacting aldehydes.

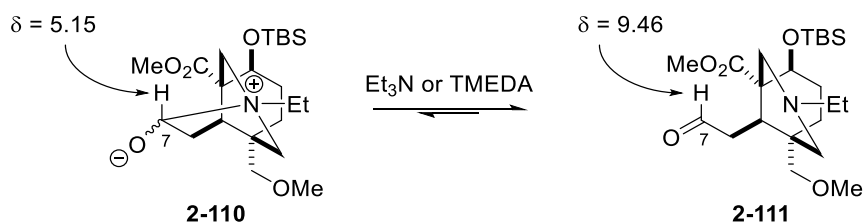
Scheme 2.30 Fluctuating structures of saraine A



2.3.1.3 Interconversion of the zwitterion and the aldehyde

These literature insights in mind, triethylamine was added to the sample of the zwitterionic species **2-110** in CDCl₃ (Scheme 2.31). As expected, aldehyde-like peak at 9.46 ppm appeared instead of the peak at 5.15 ppm in ¹H NMR. The same phenomenon was observed in the presence of TMEDA.

Scheme 2.31 Interconversion of the zwitterion and the aldehyde in CDCl_3

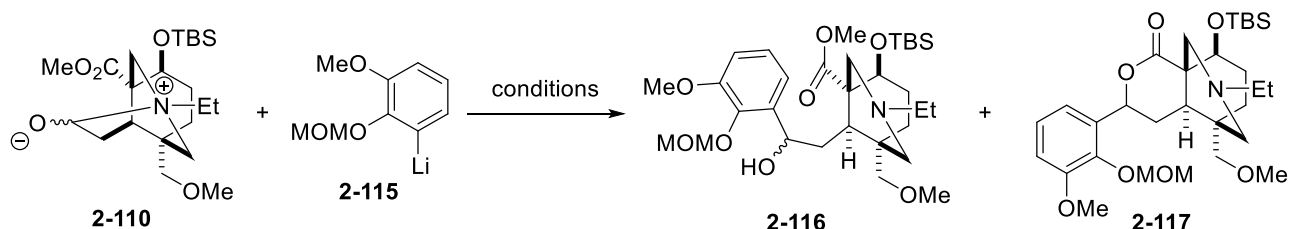


2.3.2 Introduction of the aromatic ring

The behavior of the zwitterionic species disclosed, introduction of the aromatic ring was investigated at last. Aryl lithium **2-115** was prepared according to the literature procedure,⁴⁵ and was added to zwitterion **2-110** with various additives (Table 2.3). Without any tertiary amine, the reaction did not proceed at all even in the presence of HMPA (entry 1). The reaction in the presence of triethylamine also resulted in no reaction (entry 2), although the aldehyde form of **2-110** should have been exposed under the conditions. Finally, when TMEDA was employed as an additive, the desired addition went smoothly to give adduct **2-116** (entry 3). Although the isolated yield of **2-116** was modest, considerable amount of lactone **2-117** was also generated, and thus the addition reaction itself could be regarded as effective.

Comparison of the results of these entries suggested that TMEDA should have the dual roles in this reaction. The first is to increase the reactivity of the lithium species **2-115** by decomplexation and the second is to convert the zwitterionic species to the aldehyde. Both effects seemed to be important since either decomplexation of lithium species (entry 1) or exposure of the aldehyde form (entry 2) alone did not realize the desired addition reaction.

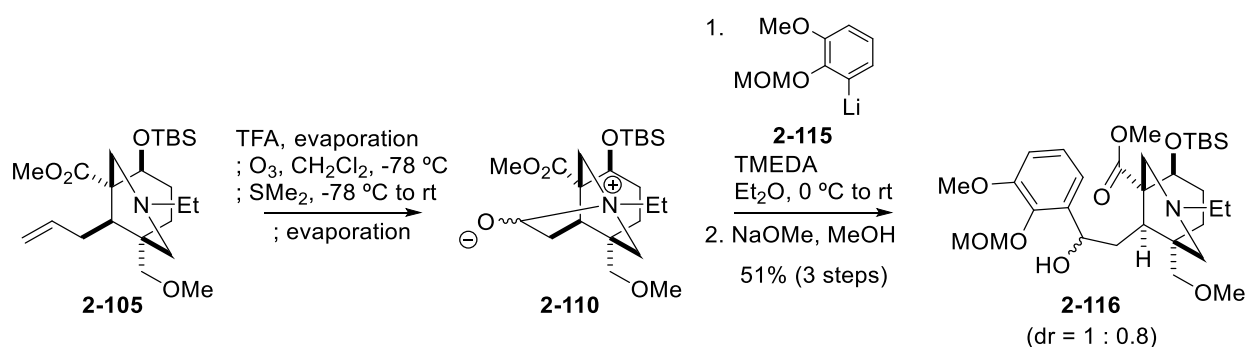
Table 2.3 Addition of aryl lithium **2-115** to the zwitterion **2-110**



entry	conditions	results
1	Et ₂ O, HMPA 0 °C	no reaction
2	Et ₂ O, NEt ₃ 0 °C to rt	no reaction
3	Et ₂ O, TMEDA 0 °C to rt	2-116 : 38% 2-117 was also observed

Practically, isolation of highly polar zwitterionic species **2-110** resulted in the low overall yield. Thus, the crude product of the ozonolysis was directly treated with the above reaction conditions (Scheme 2.32). In addition, the generated mixture of the desired product **2-116** and lactone **2-117** was treated with NaOMe to converge to alcohol **2-116**. With these modifications, adduct **2-116** was obtained in 51% yield over three steps from terminal olefin **2-105**. Although **2-116** was obtained as a diastereomixture, it is inconsequential since the hydroxy group at the benzylic position would be removed in later stage

Scheme 2.32 Practical three step sequence toward adduct **2-116**



2.4 References and notes

- ¹ For reviews on terpenoid-alkaloids, see: Cherney, E. C.; Baran, P. S. *Isr. J. Chem.* **2011**, *51*, 391.
- ² For reviews on diterpene alkaloids, see: C₂₀: Wang, F.-P.; Liang, X.-T. "The alkaloids: Chemistry and Biology" (Cordell, G. A., ed.), vol 59, pp. 1-280. Elsevier Science, New York, 2002. C₁₉-diterpene alkaloids: Wang, F.-P.; Chen, Q.-H. "The alkaloids: Chemistry and Biology" (Cordell, G. A., ed.), vol 69, pp. 1-577. Elsevier Science, New York, 2010. C₁₈-diterpene alkaloids: Wang, F.-P.; Chen, Q.-H.; Liang, X.-T. "The alkaloids: Chemistry and Biology" (Cordell, G. A., ed.), vol 67, pp. 1-78. Elsevier Science, New York, 2009. Classification of the diterpene alkaloids used in these comprehensive reviews is used in this dissertation.
- ³ For seminal work on the structure determination and chemistry of atisine, veatchine, and related simple C₂₀-diterpene alkaloids, see: (a) Pelletier, S. W. *Tetrahedron*, **1961**, *14*, 76. (b) Pelletier, S. W.; Parthasarathy, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 777. and references cited therein.
- ⁴ For structure determination of lappaconitine by X-ray crystallographic analysis, see Birnbaum, G. I. *Tetrahedron Lett.* **1969**, *10*, 2193.
- ⁵ Jiang, S.; Hong, S.; Song, B.; Zhu, Y.; Zhou, B. *Acta Chim. Sin.* **1988**, *46*, 26.
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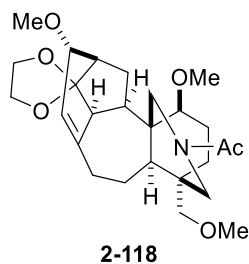
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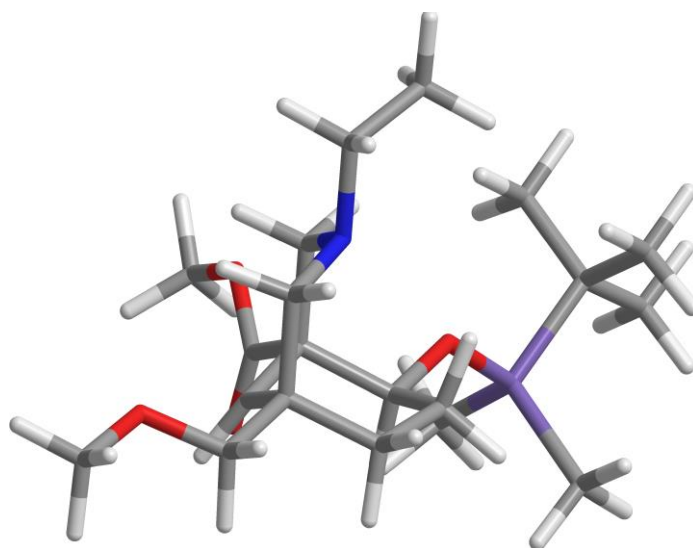
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(b) Another conformer shown below was found to have almost the similar energy (The energy difference was about 0.5 kcal/mol, the major difference was the orientation of the methoxymethyl group). C5-proton also distorted in this conformation, and thus similar discussion can be applied to explain the stereoselectivity.



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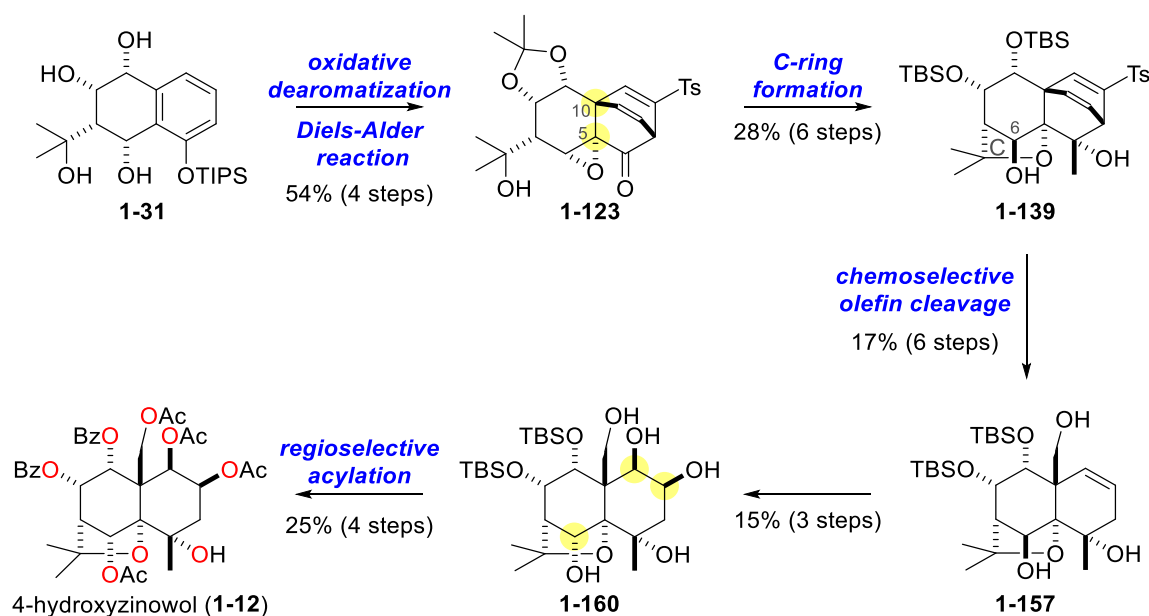
Chapter 3:

Conclusion

3.1 Total synthesis of 4-hydroxyzinowol

In chapter 1 of this dissertation, total synthesis of 4-hydroxyzinowol was described (Scheme 3.1). Starting from the tetraol **1-31**, the consecutive tetrasubstituted carbons at C5- and C10-position of **1-123** was efficiently constructed via the oxidative dearomatization and the following Diels-Alder reaction with ethynyl-*p*-tolyl sulfone. The C-ring formation was effected by the judicious choice of the acyl group of the C6-oxygen functionality to give **1-139**. Two olefins of **1-139** was completely differentiated in the oxidative cleavage step by the strategically placed electron withdrawing tosyl group to yield the tricyclic compound **1-157**. Three stereocenters were then installed onto the tricyclic skeleton of **1-157** in a highly diastereoselective manner. Finally, the regioselective acylation of the poly-hydroxylated agarofuran skeleton **1-160** was realized to achieve the total synthesis of 4-hydroxyzinowol in 23 steps from **1-31** (36 steps from the known compound).

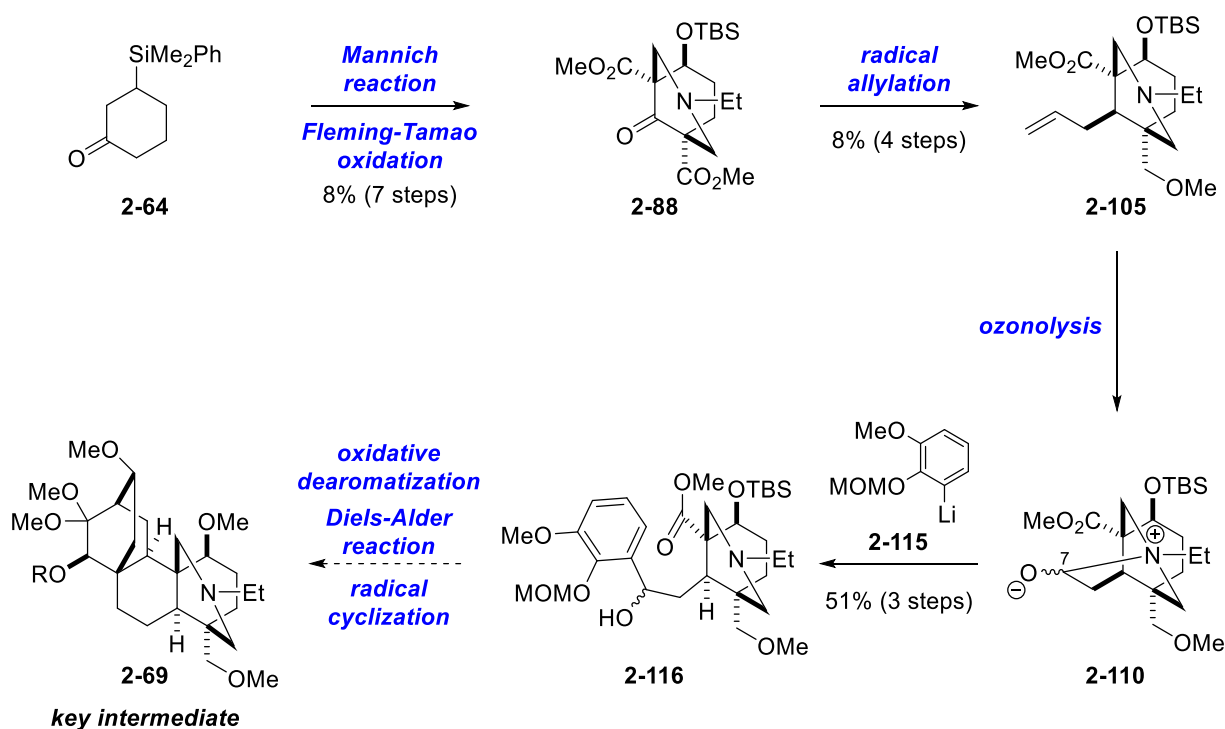
Scheme 3.1 Total synthesis of 4-hydroxyzinowol



3.2 Synthesis of the substrate for the key reaction in the synthetic study of talatisamine

In chapter 2, the synthetic study of talatisamine was conducted aiming at the more efficient synthesis of the key intermediate using the oxidative dearomatization, the Diels-Alder reaction with ethynyl-*p*-tolyl sulfone, and the bridgehead radical cyclization (Scheme 3.2). Starting from the known ketone **2-64**, four contiguous stereocenters on the cyclohexane ring of **2-105** were constructed thorough **2-88**, even though there is room for improvement of the yields. Then, aromatic ring moiety was connected to the bicyclic amine moiety to give **2-116**, with unveiling the interesting reactivity of the zwitterionic intermediate **2-110**. The key three reactions from **2-116** would give the key intermediate **2-69**, possibly constituting the highly effective total synthesis of talatisamine.

Scheme 3.2 Synthetic study of talatisamine



3.3 Summary and outlook

In summary, the total synthesis of 4-hydroxyzinowol and the synthesis of alcohol **2-116** have been achieved in the present study.

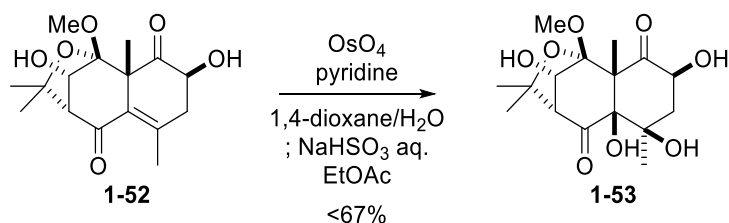
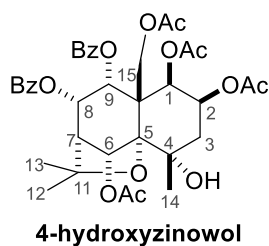
The oxidative dearomatization and the Diels-Alder reaction were established as the efficient methods for construction of the angular contiguous tetrasubstituted carbons, which are the ubiquitous structural motifs of dihydro- β -agarofurans. Furthermore, the total synthesis of 4-hydroxyzinowol is the first example of the synthesis of the highly oxygenated *and* multiply acylated dihydro- β -agarofuran sesquiterpenoid. Thus, insights obtained in the regioselective acylation would be quite valuable in synthesizing other multiply acylated congeners. Overall, the strategies developed herein will be a basis for the divergent synthesis of various agarofuran sesquiterpenes and will accelerate the future structure-activity relationship study.

Alcohol **116** consists of the AE-ring and the aromatic ring. Future work will be carried out based on the synthetic route developed herein, and also will prove the versatility of the two key reactions developed in our laboratory: the oxidative dearomatization and the following Diels-Alder reaction with ethynyl-*p*-tolyl sulfone, and the bridgehead radical cyclization. In addition, the properly functionalized AE-ring fragment would also be a useful building block for another synthetic strategy of diterpene alkaloids, namely the strategy employed in the previous study of our laboratory (see Scheme 2.4 on p. 72).

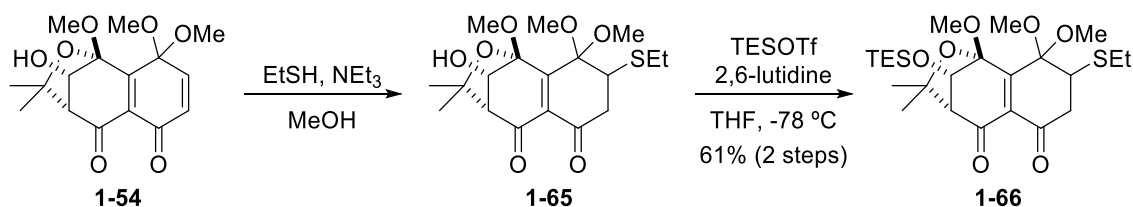
Chapter 4:
Experimental section

General Methods. All reactions sensitive to air or moisture were carried out in anhydrous solvents under argon atmosphere, unless otherwise noted. THF, CH₂Cl₂, toluene, DMF, and Et₂O were purified by a Glass Contour solvent dispensing system. CsOBz was prepared by mixing the eqimolar amount of CsOH and BzOH in H₂O followed by dried at 50 °C in vacuum. 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, or granular, neutral, 32–53 μm). Melting points are reported uncorrected. Optical rotations were measured using the sodium D line. A 0.7 mL cell, which was filled with a solution of the weighed sample prepared in a 2.00 mL volumetric flask, was used for the measurement of optical rotations. The indicated temperatures refer to those of the polarimeter's cavity. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using a FT/IR spectrometer. ¹H and ¹³C NMR spectra were recorded on 400 or 500 MHz, and 100 or 125 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to CHCl₃ (δ = 7.26 for ¹H NMR), CDCl₃ (δ = 77.0 for ¹³C NMR), CD₂HOD (δ = 3.31 for ¹H NMR), CD₃OD (δ = 49.0 for ¹³C NMR), C₆D₆ (δ = 128.0 for ¹³C NMR), and (CD₃)₂CO (δ = 29.84 for ¹³C NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. The numbering of compounds corresponds to that of the natural product. High resolution mass spectra were measured on ESI-TOF mass spectrometers.

Chapter 1: Total synthesis of 4-hydroxyzinowol



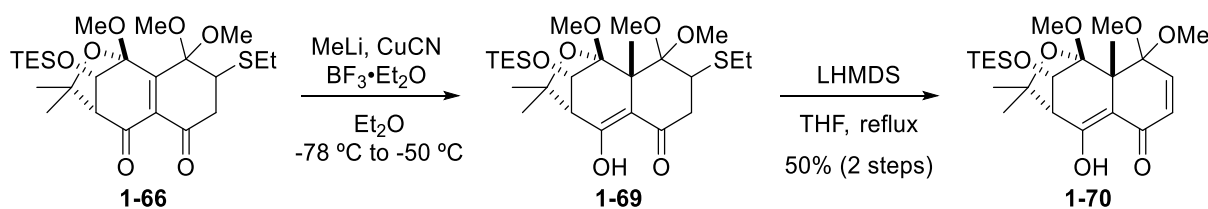
Tetraol 1-53 [HT-11-061] OsO₄ (150 μ L, 0.16 M in H₂O, 24 μ mol) was added to a solution of diketone **1-52** (3.6 mg, 12 μ mol) in pyridine (330 μ L), 1,4-dioxane (330 μ L), and H₂O (330 μ L) at room temperature. The resulting solution was stirred at room temperature for 3 h, and then saturated aqueous NaHSO₃ (3 mL) and EtOAc (1 mL) was added. The resulting mixture was further stirred at room temperature for 4 h followed by extraction with EtOAc (2 mL x4). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc = 1/1 to 1/2) to afford slightly impure tetraol **1-53** (2.7 mg, 3.2 μ mol) in 67% yield: ¹H NMR (400 MHz, CDCl₃) δ 1.01 (3H, s, H12 or H13), 1.25 (3H, s, H14), 1.44 (3H, s, H12 or H13), 1.63 (3H, s, H15), 1.71 (1H, dd, J = 15.6, 3.2 Hz, H3a), 2.46 (1H, dd, J = 15.6, 11.0 Hz, H3b), 2.70 (1H, s, OH), 3.33 (3H, s, CH₃), 4.49 (1H, dd, J = 11.0, 3.2 Hz, H2), 4.81 (1H, s, H8).



Sulfide 1-66 [HT-12-139,141] EtSH (130 μ L, 1.84 mmol) was added to a solution of diketone **1-54** (60 mg, 0.19 mmol) and NEt₃ (26 μ L, 0.18 mmol) in MeOH (4 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h, and then the solution was concentrated under reduced pressure to afford crude sulfide **1-65**. The crude material was used in the next

reaction without further purification.

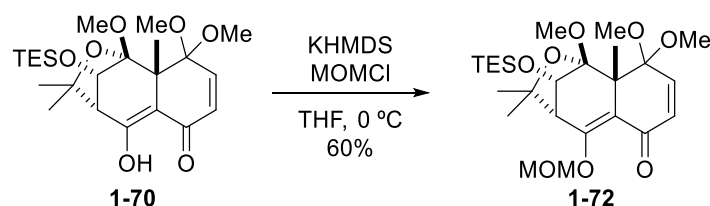
TESOTf (120 μ L, 0.552 mmol) was added to a solution of the crude sulfide **1-65** and 2,6-lutidine (90 μ L, 0.74 mmol) in THF (1.8 mL), at -78 $^{\circ}$ C. The resulting mixture was stirred at -78 $^{\circ}$ C for 20 min, and then the additional 2,6-lutidine (90 μ L, 0.74 mmol) and TESOTf (120 μ L, 0.552 mmol) were added. The resulting solution was further stirred for 10 min, and then the solution was diluted with H_2O (5 mL) and warmed to room temperature. The mixture was extracted with EtOAc (5 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc = 1/0 to 40/1 to 5/1) to afford sulfide **1-66** (57 mg, 0.11 mmol) in 61% yield over 2 steps: yellow oil; 1H NMR (400 MHz, $CDCl_3$) δ 0.65 (6H, q, J = 7.8 Hz, CH_2 of TES x3), 0.97 (9H, t, J = 7.8 Hz, CH_3 of TES x3), 1.17 (3H, s, H12, or H13), 1.23 (3H, t, J = 6.4 Hz, $-SCH_2CH_3$), 1.64 (3H, s, H12, or H13), 2.64-2.71 (3H, m, H3a and $-SCH_2CH_3$), 2.91 (1H, dd, J = 18.3, 6.4 Hz H3b), 3.02 (1H, s, H7), 3.42 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.53 (1H, dd, J = 6.4, 6.4 Hz, H2), 3.67 (3H, s, OCH_3), 4.12 (1H, s, H8).



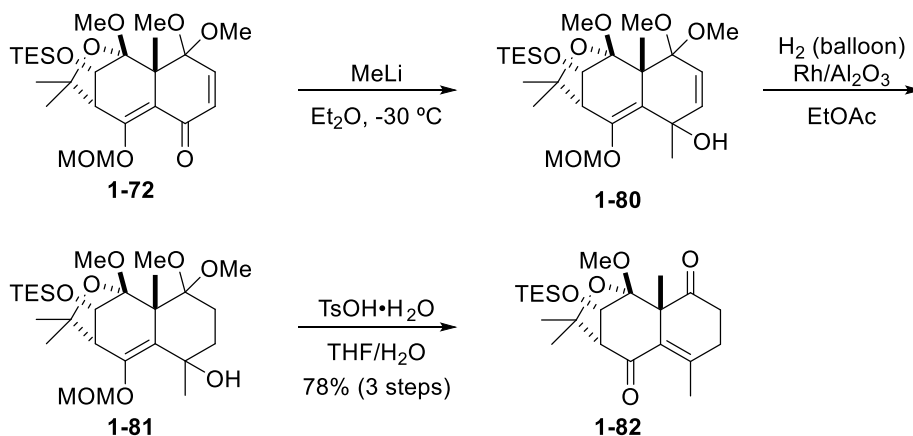
Enol 1-70 [HT-13-183, 187] CuCN (276 mg, 3.08 mmol) was azeotropically dried with toluene three times before suspended in Et_2O (6 mL). MeLi (5.6 mL, 1.1 M in Et_2O , 6.1 mmol) was added dropwise to the stirring suspension of CuCN at -78 $^{\circ}$ C. The resulting mixture was stirred at -78 $^{\circ}$ C for 2 min, and then at 0 $^{\circ}$ C for 5 min, then re-cooled to -78 $^{\circ}$ C. $BF_3 \cdot Et_2O$ (330 μ L, 2.67 mmol) was added to this mixture and the resulting solution was stirred at -78 $^{\circ}$ C for 4 min. Pre-cooled solution (-78 $^{\circ}$ C) of sulfide **1-65** (307 mg, 0.613 mmol) in Et_2O (8 mL) was added slowly to the solution via cannula. The resulting mixture was stirred at -50 $^{\circ}$ C for 12 h, and then pH 7 phosphate buffer (10 mL) was added. After warmed to room temperature, the mixture was diluted with EtOAc (10 mL) and saturated aqueous NH_4Cl (10 mL), and then this mixture was stirred until the aqueous layer got clear blue (about 20 min). This mixture was extracted with EtOAc (10 mL x3). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated to afford crude 1,4-adduct **1-69**. The crude material was used in the next reaction without further purification. 1H NMR (400 MHz, $CDCl_3$) δ 0.59-0.70 (6H, m, CH_2 of TES x3), 0.96 (9H, t, J = 7.8 Hz, CH_3 of TES x3), 1.26 (3H, t, J = 7.3 Hz, $-SCH_2CH_3$), 1.28 (3H, s, H12,

H13, or H15), 1.38 (3H, s, H12, H13, or H15), 1.59 (3H, s, H12, H13, or H15), 2.41 (1H, s, H7), 2.62-2.69 (2H, m, $-\text{SCH}_2\text{CH}_3$), 2.81 (1H, dd, $J = 18.8, 7.4$ Hz H3a), 2.92 (1H, dd, $J = 18.8, 9.6$ Hz H3b), 3.21-3.24 (1H, m, H2), 3.23 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 4.30 (1H, s, H8).

LHMDS (3.0 mL, 1 M in THF, 3.0 mmol) was added to a solution of crude 1,4-adduct **1-69** in THF (12 mL) at room temperature. The resulting solution was stirred at 75 °C for 1.5 h. After the solution was cooled to room temperature, saturated aqueous NH_4Cl (10 mL) was added. The resulting mixture was extracted with EtOAc (5 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc = 8/1) to yield enol **1-70** (140 mg, 0.308 mmol) in 50% yield over 2 steps): yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 0.61-0.71 (6H, m, CH_2 of TES x3), 0.99 (9H, t, $J = 7.8$ Hz, CH_3 of TES x3), 1.31 (6H, s, H12, H13, or H15), 1.62 (3H, s, H12, H13, or H15), 2.43 (1H, s, H7), 3.18 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 4.32 (1H, s, H8), 6.11 (1H, d, $J = 10.5$ Hz, H2 or H3), 6.43 (1H, d, $J = 10.5$ Hz, H2 or H3).



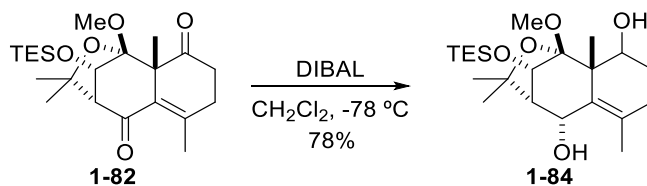
MOM ether 1-72 [HT-13-017] KHMDS (250 μL , 0.5 M in toluene, 130 μmol) and MOMCl (20 μL , 0.26 mmol) were successively added to a solution of enol **1-70** (11 mg, 25 μmol) in THF (750 μL) at 0 °C. The resulting solution was stirred at 0 °C for 10 min, and then saturated aqueous NaHCO_3 (5 mL) and H_2O (5 mL) were added. The mixture was extracted with EtOAc (3 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc = 8/1 to 5/1) yielded MOM ether **1-72** (7.4 mg, 15 μmol) in 60% yield: yellow oil; ^1H NMR (400 MHz, CDCl_3) [HT-12-191] δ 0.60-0.69 (6H, m, CH_2 of TES x3), 0.99 (9H, t, $J = 7.8$ Hz, CH_3 of TES x3), 1.29 (3H, s, H12, H13, or H15), 1.40 (3H, s, H12, H13, or H15), 1.62 (3H, s, H12, H13, or H15), 2.68 (1H, s, H7), 3.22 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 4.22 (1H, s, H8), 4.95 (1H, d, $J = 6.9$ Hz CH_2 of MOM), 4.98 (1H, d, $J = 6.9$ Hz CH_2 of MOM), 5.99 (1H, d, $J = 10.6$ Hz, H2 or H3), 6.57 (1H, d, $J = 10.6$ Hz, H2 or H3).



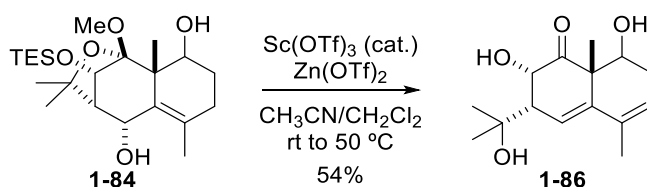
Diketone 1-82 [HT-14-047, 049, 051] MeLi (240 μL 1.1 M in Et_2O , 0.26 mmol) was added to a solution of MOM ether **1-72** (27 mg, 54 μmol) in Et_2O (1 mL) at $-30\text{ }^\circ\text{C}$. The resulting solution was stirred at $-30\text{ }^\circ\text{C}$ for 30 min, and then saturated aqueous NH_4Cl (5 mL) was added. The resulting mixture was extracted with EtOAc (3 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated to afford crude alcohol **1-80**.

$\text{Rh/Al}_2\text{O}_3$ (27 mg) was suspended in a solution of the crude alcohol **1-80** in EtOAc (1 mL). The flask was evacuated and then flushed with hydrogen gas (balloon) three times, and the solution was stirred at room temperature for 11 h under hydrogen atmosphere. Rh catalyst was removed by Celite filtration and the cake was washed with EtOAc (3 mL x3). The filtrate was concentrated to afford crude alcohol **1-81**.

$p\text{-TsOH}\cdot\text{H}_2\text{O}$ (52 mg, 0.27 mmol) was added to a solution of the crude alcohol **1-81** in THF (500 μL) and H_2O (500 μL) at room temperature. The resulting solution was stirred at room temperature for 50 min, and then saturated aqueous NaHCO_3 (5 mL) was added. The resulting mixture was extracted with EtOAc (5 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/ EtOAc = 5/1) to afford diketone **1-82** (17 mg, 42 μmol) in 78% yield over 3 steps: yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 0.60-0.68 (6H, m, CH_2 of TES x3), 0.95 (9H, t, J = 7.3 Hz, CH_3 of TES x3), 1.17 (3H, s, H12, H13, or H15), 1.28 (3H, s, H12, H13, or H15), 1.58 (3H, s, H12, H13, or H15), 2.25 (1H, d, J = 0.9 Hz, H14), 2.31-2.40 (2H, m, H2 and/or H3), 2.55 (1H, dd, J = 15.1, 5.9 Hz, H2 or H3), 2.69 (1H, s, H7), 2.74-2.84 (1H, m, H2 or H3), 3.61 (3H, s, OCH_3), 4.18 (1H, s, H8).

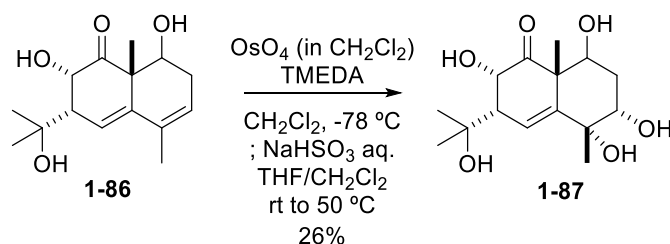


Diol 1-84 [HT-14-097] DIBAL (20 μL , 1.5 M in toluene, 29.5 μmol) was added to a solution of diketone **1-82** (2.4 mg, 5.9 μmol) in CH_2Cl_2 (590 μL), at -78°C . The resulting solution was stirred at this temperature for 40 min before the additional amount of DIBAL (30 μL , 1.5 M in toluene, 44.3 μmol) was added. The resulting solution was stirred at this temperature for 30 min, and then saturated aqueous potassium sodium tartrate (10 mL) and CH_2Cl_2 (5 mL) were added. The resulting mixture was further stirred for 30 min, and then extracted with EtOAc (5 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc = 7/1 to 1/1) to yield diol **1-84** (1.9 mg, 4.6 μmol , 78%): yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 0.62-0.69 (6H, m, CH_2 of TES x3), 1.00 (9H, t, $J = 7.8$ Hz, CH_3 of TES x3), 0.97 (3H, s, H12, H13, or H15), 1.51 (3H, s, H12, H13, or H15), 1.56 (3H, s, H12, H13, or H15), 1.64-1.71 (1H, m, H2a), 1.81-1.89 (2H, m, H2b, H3a), 1.93 (3H, s, H4), 2.12 (1H, $J = 3.2$ Hz, H7), 2.36-2.42 (1H, m, H3b), 3.61 (3H, s, OCH_3), 4.15 (1H, s, H8), 4.18 (1H, d, $J = 3.2$ Hz, H6), 4.70 (1H, broad, H1), 5.10 (1H, d, $J = 1.8$ Hz, C1-OH).

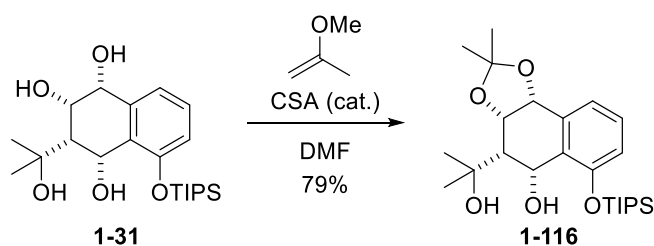


Diene 1-86 [HT-14-081] Sc(OTf)_3 (0.3 mg, 0.6 μmol) and Zn(OTf)_2 (1.8 mg, 5.0 μmol) were successively added to a solution of diol **1-84** (1.5 mg, 3.5 μmol) in CH_3CN (300 μL) and CH_2Cl_2 (100 μL) at room temperature. The resulting solution was stirred at 50°C for 30 min and then, saturated aqueous NaHCO_3 (3 mL) was added. The resulting mixture was extracted with EtOAc (1 mL x3). Combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by PTLC (hexane/EtOAc = 1/2) to afford diene **1-86** (0.5 mg, 1.9 μmol , 77%): yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 1.06 (3H, s, H12, H13, or H15), 1.23 (3H, s, H12, H13, or H15), 1.32 (3H, s, H12, H13, or H15), 1.92 (3H, d, $J = 1.4$ Hz, H14), 2.26-2.33 (1H, m, H2 α), 2.51-2.59 (1H, m, H2 β), 3.32 (1H, dd, $J = 7.8, 5.5$ Hz, H7), 4.13 (1H, d, $J = 2.7$ Hz, C8-OH), 4.41-4.43 (1H, m, H1), 4.98 (1H, dd, $J = 7.8, 2.7$ Hz, H8), 5.49-5.53 (1H, m, H3), 5.87 (1H,

d, $J = 5.5$ Hz, H6); ^{13}C NMR (100 MHz, CDCl_3) δ 20.0, 25.0, 26.6, 29.7, 30.7, 51.6, 52.7, 68.2, 72.6, 74.5, 121.5, 121.6, 130.1, 138.0, 213.7.

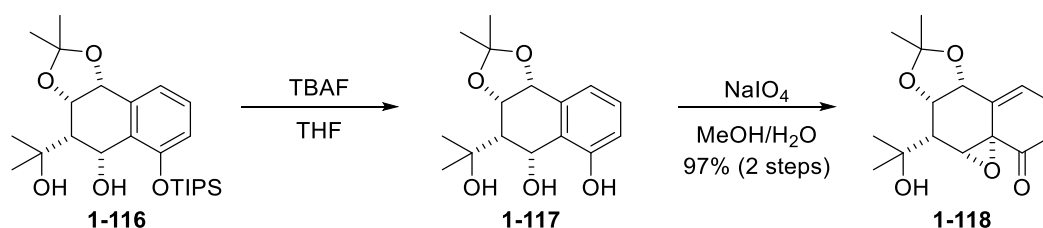


Pentaol 1-87 [HT-14-193] OsO_4 (840 μL , 0.02 M in CH_2Cl_2 , 17 μmol) was added slowly to a solution of diene **1-86** (3.7 mg, 14 μmol) and TMEDA (2.5 μL , 17 μmol) in CH_2Cl_2 (150 μL) at -78°C . The resulting solution was stirred at -78°C for 40 min, and then saturated aqueous NaHSO_3 (3 mL) and THF (1.2 mL) was added. The resulting mixture was further stirred at room temperature for 11 h and then for 6 h at 50°C . Additional aqueous NaHSO_3 (2 mL) was added to the mixture, and it was further stirred for 2.5 h at 50°C . The mixture was extracted with EtOAc (3 mL x4). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (EtOAc/*i*-PrOH = 5/1) to afford pentaol **1-87** (1.1 mg, 3.7 μmol) in 26% yield: ^1H NMR (500 MHz, CDCl_3) δ 1.04 (3H, s, H12 or H13), 1.35 (3H, s, H12 or H13), 1.39 (3H, s, H15), 1.44 (3H, s, H14), 2.17 (1H, ddd, $J = 16.0, 2.9, 2.9$ Hz, H2a), 2.34 (1H, ddd, $J = 16.0, 2.9, 2.9$ Hz, H2b), 3.26 (1H, dd, $J = 6.9, 4.6$ Hz, H7), 3.62 (1H, br H3), 4.41 (1H, br, H1), 4.95 (1H, d, $J = 6.9$ Hz, H8), 6.47 (1H, d, $J = 4.6$ Hz).



Acetonide 1-116 [HT-20-015] CSA (57 mg, 0.25 mmol) was added to a solution of tetraol **1-31** (3.29 g, 8.01 mmol, a 18:1 diastereomeric mixture at the C9 position) and 2-methoxypropene (1.2 mL, 13 mmol) in DMF (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then 2-methoxypropene (0.38 mL, 4.0 mmol) was added. The reaction mixture was stirred at room temperature for further 30 min, and then saturated aqueous NaHCO_3 (50 mL) was added. The resultant solution was diluted with H_2O (150 mL) and extracted with EtOAc (50 mL x4). The combined organic layers were washed with brine (100 mL), dried over

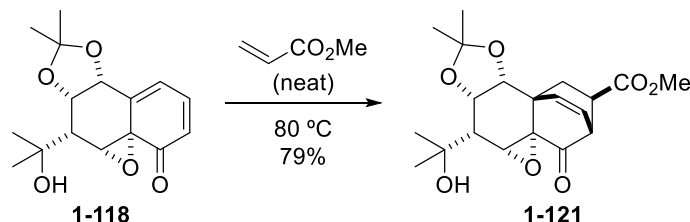
Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane/EtOAc 6/1 to 3/1 to 1/2 to 0/1) to afford acetonide **1-116** (2.84 g, 6.30 mmol) in 79% yield: colorless oil; $[\alpha]_D^{24} +3.30$ (c 1.27, CHCl₃); IR (neat) ν 3520, 2944, 2868, 1587, 1463, 1278, 1230, 1058, 992 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.11 (9H, d, J = 7.8 Hz, CH₃CHCH₃ of TIPS \times 3), 1.14 (9H, d, J = 7.8 Hz, CH₃CHCH₃ of TIPS \times 3), 1.29 (3H, s, CH₃), 1.33 (3H, septet, J = 7.8 Hz, CH(CH₃)₂ of TIPS \times 3), 1.45 (3H, s, CH₃), 1.48 (3H, s, CH₃), 1.54 (3H, s, CH₃), 1.67 (1H, dd, J = 2.8, 2.8 Hz, H7), 4.96 (1H, ddd, J = 5.6, 2.8, 1.8 Hz, H8), 5.17 (1H, d, J = 5.6 Hz, H9), 5.54 (1H, m, H6), 6.81 (1H, d, J = 8.2 Hz, H3), 7.02 (1H, d, J = 7.8 Hz, H1), 7.20 (1H, dd, J = 8.2, 7.8 Hz, H2); ¹³C NMR (100 MHz, CDCl₃) δ 12.9, 17.99, 18.03, 25.8, 27.5, 29.0, 29.3, 47.8, 63.2, 73.0, 73.9, 76.4, 109.8, 118.2, 122.0, 129.0, 129.2, 135.5, 153.7; HRMS (ESI) calcd for C₂₅H₄₂O₅SiNa 473.2694 [M + Na]⁺, found 473.2693.



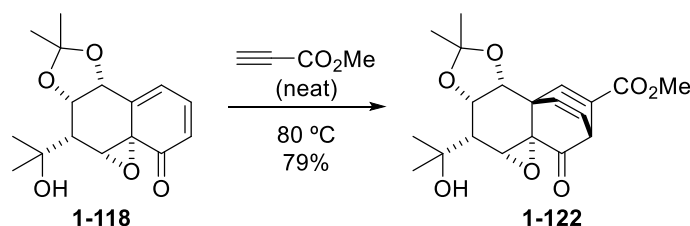
Epoxide 1-118 [HT-20-021, 023] *n*-Bu₄NF (8.0 mL, 1.0 M in THF, 8.0 mmol) was added to a solution of diol **1-116** (2.95 g, 6.55 mmol) in THF (60 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min, and then saturated aqueous NH₄Cl (150 mL) and H₂O (50 mL) were successively added. The resultant solution was extracted with EtOAc (80 mL \times 4), and the combined organic layers were washed with saturated aqueous NH₄Cl (50 mL \times 3) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated to afford the crude phenol **1-117**, which was used in the next reaction without further purification.

NaIO₄ (7.02 g, 32.8 mmol) was added to a suspension of the above crude phenol **1-117** in a mixture of MeOH (90 mL) and H₂O (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then H₂O (200 mL) was added. The resultant solution was extracted with CHCl₃ (100 mL \times 4), and the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by recrystallization from hexane/CHCl₃ to afford diene **1-118** (1.85 g, 6.33 mmol) in 97% yield over 2 steps: white solid; m.p. 180-181 °C; $[\alpha]_D^{24} = +490$ (c 0.80, CDCl₃); IR (neat) ν 3448, 2969, 2918, 1659, 1630, 1366, 1209, 1142, 1031 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (3H, s, CH₃), 1.40 (3H, s, CH₃), 1.47 (1H, d, J = 4.1 Hz, H7), 1.56 (3H, s, CH₃), 1.99 (1H, d, J = 3.7 Hz, H7), 3.06 (1H, br s, OH), 3.87 (1H, d, J = 1.8 Hz, H6), 4.73-4.79 (2H, m, H8 and 9), 6.27 (1H, d, J =

10.5 Hz, H3), 6.60 (1H, d, $J = 5.4$ Hz, H1), 7.18 (1H, dd, $J = 10.5, 5.4$ Hz, H2); ^{13}C NMR (100 MHz, CDCl_3) δ 23.6, 26.0, 28.5, 29.0, 46.0, 59.4, 71.5, 72.4, 75.2, 75.3, 110.4, 127.16, 127.25, 140.7, 145.0, 194.6; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 315.1203, found 315.1209.

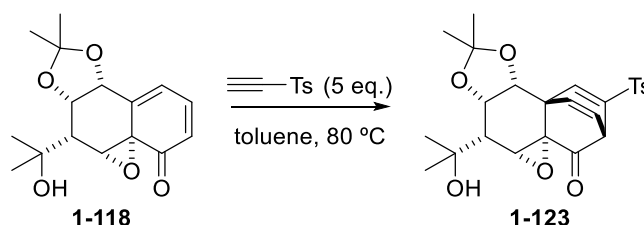


Cycloadduct 1-121 [HT-15-077] A mixture of epoxide **1-118** (9.7 mg, 33 μmol) and methyl acrylate (1.5 mL) was heated to 80 °C and was stirred for 12 h. After being cooled to roomtemperature, the mixture was concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 1/1 to 1/2) to afford cycloadduct **1-121** (9.8 mg, 26 μmol) in 79% yield: white solid; m.p. 215 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.78 (1H, d, $J = 4.6$ Hz, H7), 2.06 (1H, dd, $J = 14.2, 4.1$ Hz, H1a), 2.64 (1H, dd, $J = 14.2, 10.5$ Hz, H1b), 3.12-3.18 (1H, m, OH), 3.16 (1H, ddd, $J = 10.5, 4.1, 2.3$ Hz, H2), 3.42 (1H, d, $J = 1.4$ Hz, H6), 3.70 (3H, s, COOCH_3), 3.76 (1H, ddd, $J = 5.5, 2.3, 2.3$ Hz, H3), 4.39 (1H, d, $J = 8.2$ Hz, H9), 4.73 (1H, ddd, $J = 8.2, 4.6, 1.4$ Hz, H8), 6.24 (1H, dd, $J = 8.2, 5.5$ Hz, H3'), 6.28 (1H, dd, $J = 8.5, 2.3$ Hz, H15); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3, 26.1, 27.9, 28.4, 28.8, 40.5, 42.2, 43.6, 50.6, 52.5, 58.0, 60.2, 72.3, 72.4, 76.7, 108.9, 128.1, 136.8, 172.8, 204.8. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_7$ $[\text{M}+\text{Na}]^+$ 401.1571, found 401.1573.

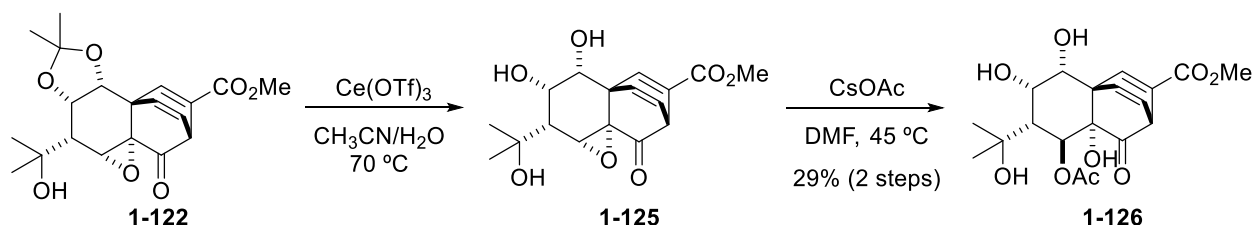


Cycloadduct 1-122 [HT-16-145] According to the synthetic procedure of **1-121**, cycloadduct **1-122** (289 mg, 0.768 mmol) was synthesized from **1-118** (279 mg, 0.954 mmol) and methyl propiolate (9.0 mL) in 81% yield. The residue was purified by flash column chromatography on silica gel (15 g, hexane/EtOAc 1/0 to 2/1 to 1/1 to 1/2 to 0/1) to afford impure cycloadduct **1-122**. The impure material was further purified by flash column chromatography on silica gel (15 g, hexane/EtOAc 1/0 to 2/1 to 1/1 to 1/2 to 0/1): pale yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.79 (1H, d, $J = 4.1$

Hz, H7), 3.06 (1H, s, OH), 3.44 (1H, d, $J = 1.4$ Hz, H6), 3.81 (3H, s, COOCH_3), 4.69 (1H, d, $J = 8.2$ Hz, H9), 4.78–4.82 (2H, m, H3 and 8), 6.32 (1H, dd, $J = 7.3, 1.8$ Hz, H15), 6.69 (1H, dd, $J = 7.3, 6.0$ Hz, H3'), 7.84 (1H, d, $J = 2.3$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ 23.4, 26.1, 28.4, 28.8, 43.3, 49.1, 52.2, 54.2, 56.0, 57.0, 72.0, 72.4, 74.2, 109.3, 133.2, 134.3, 135.0, 146.2, 163.7, 196.1; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_7$ $[\text{M} + \text{Na}]^+$ 399.1414, found 399.1414.



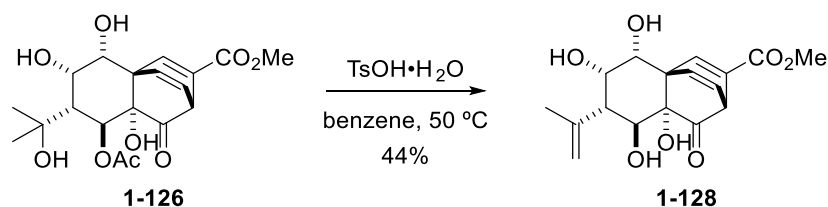
Cycloadduct 1-123 [HT-20-025] A mixture of **1-118** (1.85 g, 6.33 mmol) and ethynyl *p*-tolyl sulfone (5.0 g, 28 mmol) in toluene (60 mL) was heated to 80 °C and was stirred for 20 h. After being cooled to room temperature, the mixture was concentrated. The resultant residue was purified by flash column chromatography on silica gel (60 g, hexane/EtOAc 2/1 to 1/1 to 1/2) to afford cycloadduct **1-123** (2.09 g, 4.42 mmol) in 70% yield: pale yellow solid; mp 232–234 °C; $[\alpha]_{\text{D}}^{24} +9.0$ (c 1.2, CHCl_3); IR (neat) ν 3531, 2980, 2935, 1743, 1319, 1212, 1155, 1088 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.76 (1H, d, $J = 4.1$ Hz, H7), 2.43 (3H, s, ArCH_3), 3.36 (1H, d, $J = 1.4$ Hz, H6), 4.39 (1H, ddd, $J = 6.0, 2.3, 1.8$ Hz, H3), 4.67 (1H, d, $J = 8.2$ Hz, H9), 4.77 (1H, ddd, $J = 8.2, 4.1, 1.4$ Hz, H8), 6.34 (1H, dd, $J = 7.3, 1.8$ Hz, H15), 6.63 (1H, dd, $J = 7.3, 6.0$ Hz, H3'), 7.34 (2H, d, $J = 7.8$ Hz, aromatic), 7.74 (2H, d, $J = 7.8$ Hz, aromatic), 7.87 (1H, d, $J = 2.3$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 23.4, 26.1, 28.4, 28.7, 43.3, 49.5, 54.1, 55.7, 57.0, 71.9, 72.4, 74.1, 109.6, 127.9, 130.2, 132.2, 135.5, 135.8, 143.6, 144.5, 145.1, 194.3; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{28}\text{O}_7\text{SNa}$ $[\text{M} + \text{Na}]^+$ 495.1448, found 495.1434.



Acetate 1-126 [HT-15-185, 191] $\text{Ce}(\text{OTf})_3$ (49 mg, 83 μmol) was added to a solution of cycloadduct **1-122** (6.2 mg, 16 μmol) in a mixture of CH_3CN (540 μL) and H_2O (270 μL) at room temperature. The reaction mixture was heated to 70 °C and was stirred for 14 h. After the mixture

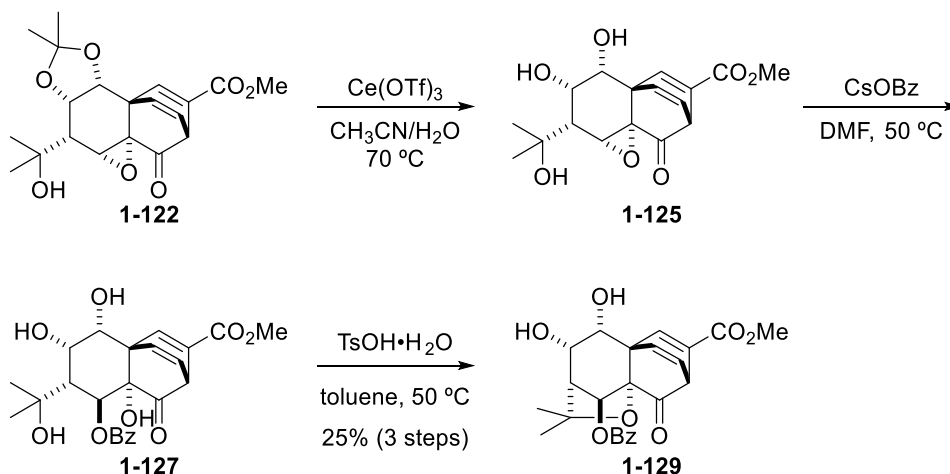
was cooled to room temperature, saturated aqueous NaHCO_3 (5 mL) was added. The resultant mixture was extracted with EtOAc (2 mL x8), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, EtOAc/i-PrOH 1/0 to 5/1) to afford crude triol **1-125**, which was used in the next reaction without further purification.

CsOAc (16 mg, 83 μmol) was added to a solution of the above crude **1-125** in DMF (550 μL) at room temperature. The reaction mixture was heated to 45 $^\circ\text{C}$ and was stirred for 18 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (5 mL) was added. The resultant mixture was extracted with EtOAc (2 mL x8), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, EtOAc/i-PrOH 1/0 to 5/1) to afford acetate **1-126** (1.8 mg, 4.6 μmol) in 29% yield over 2 steps: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (3H, s, H12), 1.41 (3H, s, H13), 2.08 (3H, s, CH_3 of Ac), 2.43 (1H, dd, $J = 11.4, 2.7$ Hz, H7), 2.88 (1H, br, OH), 3.81 (3H, s, OCH_3), 4.29 (1H, d, $J = 3.6$ Hz, H9), 4.62 (1H, m, Hz, H8), 4.66 (1H, d, $J = 6.4$ Hz, H3), 5.14 (1H, d, $J = 11.4$ Hz, H6), 6.48–6.55 (2H, m, H3' and 15), 7.93 (1H, s, H1); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 29.8, 30.8, 46.2, 52.3, 54.0, 56.5, 68.5, 69.3, 71.4, 72.8, 73.5, 129.4, 133.7, 137.6, 144.4, 163.9, 170.6, 201.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{24}\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$ 419.1313, found 419.1316.



Compound 1-128 [HT-15-187] *p*-tol $\text{SO}_3\text{H}\cdot\text{H}_2\text{O}$ (5.1 mg, 27 μmol) was added to a solution of **1-126** (2.3 mg, 5.9 μmol) in benzene (550 μL) at room temperature. The reaction mixture was heated to 50 $^\circ\text{C}$ and was stirred for 2.5 h. After the mixture was cooled to room temperature, saturated aqueous NaHCO_3 (3 mL) was added. The resultant mixture was extracted with EtOAc (2 mL x3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford **1-128** (1.0 mg, 2.6 μmol) in 44% yield: colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 1.88 (3H, br s, H12), 2.25 (1H, d, $J = 0.9$ Hz, OH), 2.69 (1H, dd, $J = 11.0, 2.8$ Hz, H7), 2.76 (1H, d, $J = 9.6$ Hz, OH), 3.20 (1H, d, $J = 1.4$ Hz, OH), 3.28 (1H, s, OH), 3.80 (3H, s, OCH_3), 3.81 (1H, dd, $J = 11.0, 1.4$ Hz, H6), 4.18 (1H, m, H3), 4.40 (1H, dd, $J = 9.6, 4.1$ Hz, H9), 4.69 (1H, m, H8), 4.96 (1H, m, H13a), 5.20 (1H, dd, $J = 1.8, 1.4$ Hz, H13b), 6.58 (2H, d, $J = 3.7$ Hz, H3' and 15), 7.86 (1H, d, $J = 1.8$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3)

δ 23.3, 48.6, 52.3, 53.8, 55.6, 68.5, 68.7, 70.7, 70.8, 114.1, 128.3, 134.3, 137.0, 141.7, 146.1, 163.7, 204.4; HRMS (ESI) calcd for $C_{17}H_{20}O_7Na$ $[M + Na]^+$ 359.1101, found 359.1107.

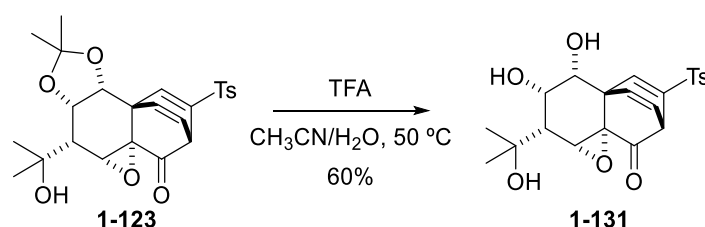


Compound 1-129 [HT-16-091, 093, 097] Ce(OTf)_3 (510 mg, 0.869 mmol) was added to a solution of cycloadduct **1-122** (97 mg, 0.26 mmol) in a mixture of CH_3CN (2 mL) and H_2O (1 mL) at room temperature. The reaction mixture was heated to 70°C and was stirred for 12 h. After the mixture was cooled to room temperature, saturated aqueous NaHCO_3 (10 mL) was added. The resultant mixture was extracted with EtOAc (10 mL x8), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was passed through a pad of silica gel (5 g, hexane/ EtOAc 1/2 to 0/1) to afford crude triol **1-125**, which was used in the next reaction without further purification.

CsOBz (117 mg, 0.461 mmol) was added to a solution of the above crude **1-125** in DMF (1.5 mL) at room temperature. The reaction mixture was heated to 50°C and was stirred for 14 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with EtOAc (5 mL x6), and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was passed through a pad of silica gel (2 g, hexane/ EtOAc 1/2 to 0/1) to afford crude tetraol **1-127**, which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ 1.33 (3H, s, H12), 1.50 (3H, s, H13), 2.04 (1H, dd, $J = 5.5, 3.2$ Hz, H7), 3.74 (3H, s, OCH_3), 4.45 (1H, d, $J = 4.1$ Hz, H9), 4.54 (1H, ddd, $J = 6.4, 2.3, 1.4$ Hz, H3), 4.75 (1H, m, H8), 4.78 (1H, br s, OH), 5.96 (1H, d, $J = 5.5$ Hz, H6), 6.32 (1H, dd, $J = 6.4, 1.4$ Hz, H15), 6.44 (1H, br, OH), 6.56 (1H, dd, $J = 6.4, 6.4$ Hz, H3'), 7.40 (2H, dd, $J = 7.8, 7.8$ Hz, aromatic), 7.54 (1H, dd, $J = 7.8, 7.8$ Hz, aromatic), 7.88 (2H, d, $J = 7.8$ Hz, aromatic), 7.94 (1H, d, $J = 2.3$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ 28.8, 30.5, 51.2, 52.1, 53.9, 55.9, 68.8, 70.3, 72.0, 72.1, 72.6, 128.4, 129.5, 129.7, 130.0, 133.1, 133.3,

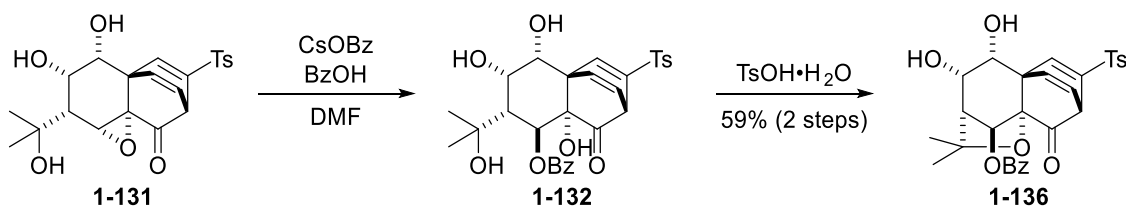
138.1, 146.1, 164.3, 164.7, 197.8; HRMS (ESI) calcd for $C_{24}H_{26}O_9Na$ $[M + Na]^+$ 481.1469, found 481.1459.

p-tolSO₃H·H₂O (56 mg, 0.29 mmol) was added to a solution of the above crude tetraol **1-127** in toluene (2.5 mL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 2.5 h. After the mixture was cooled to room temperature, saturated aqueous NaHCO₃ (10 mL) was added. The resultant mixture was extracted with EtOAc (5 mL x4), and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 2/1 to 1/1 to 1/2) to afford **1-129** (29 mg, 65 μmol) in 25% yield over 3 steps: white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.47 (3H, s, H12), 1.67 (3H, s, H13), 2.71 (1H, br s, OH), 2.74 (1H, dd, *J* = 5.0, 4.6 Hz, H7), 3.05 (1H, br d, *J* = 5.0 Hz, OH), 3.77 (3H, s, OCH₃), 4.59 (1H, dd, *J* = 6.4, 4.6 Hz, H9), 4.66 (1H, ddd, *J* = 6.0, 1.8, 1.8 Hz, H3), 4.80 (1H, m, H8), 5.65 (1H, d, *J* = 5.0 Hz, H6), 6.05 (1H, dd, *J* = 7.3, 1.8 Hz, H15), 6.12 (1H, dd, *J* = 7.3, 6.0 Hz, H3'), 7.48 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.62 (1H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.95 (2H, d, *J* = 7.8 Hz, aromatic), 7.96 (1H, d, *J* = 1.8 Hz, H1); ¹³C NMR (100 MHz, CDCl₃) δ 26.0, 31.1, 51.3, 52.1, 53.1, 57.0, 68.4, 70.2, 74.5, 75.4, 81.7, 126.3, 128.8, 129.1, 129.6, 133.4, 133.7, 136.3, 145.7, 164.1, 164.5, 194.7; HRMS (ESI) calcd. for $C_{24}H_{24}O_8Na$ $[M + Na]^+$ 463.1363, found 463.1362.



Triol 1-131 [HT-19-037] A solution of cycloadduct **1-123** (1.25 g, 2.65 mmol) in a mixture of CH₃CN (27 mL), TFA (14 mL), and H₂O (14 mL) was heated to 50 °C and was stirred for 13 h. After being cooled to 0 °C, the mixture was neutralized with aqueous saturated NaHCO₃ (200 mL). The resultant solution was extracted with EtOAc (50 mL x4), and the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 1/3 to 0/1) to afford impure triol **1-131**. The impure material was further purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 1/3 to 0/1) to afford triol **1-131** (685 mg, 1.58 mmol) in 60% yield: brown amorphous; $[\alpha]_D^{24}$ -52 (c 0.83, CHCl₃); IR (neat) ν 3479, 1746, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.42 (3H, s, H12), 1.46 (3H, s, H13), 2.02 (1H, d, *J* = 3.7 Hz, H7), 2.41 (3H, s, ArCH₃), 2.74 (1H, br s, OH), 3.31 (1H, d, *J* = 11.0 Hz, OH), 3.85 (2H, m, H6

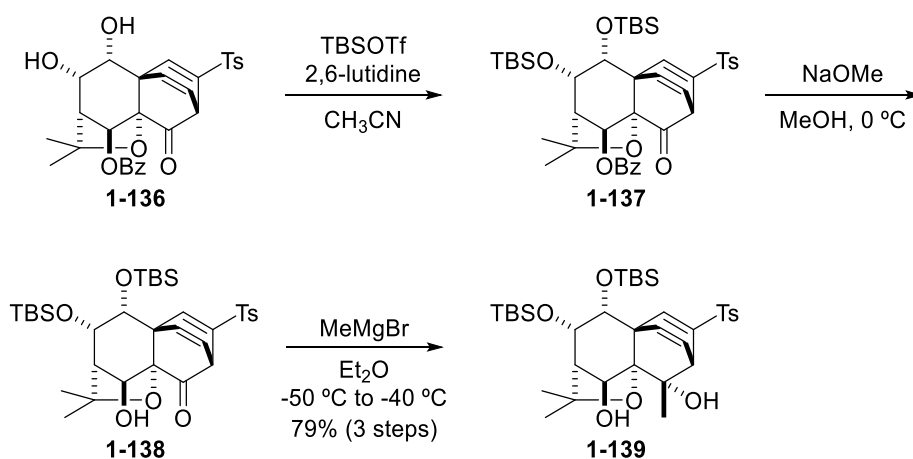
and OH), 4.16 (1H, m, H9), 4.23 (1H, m, H8), 4.41 (1H, ddd, $J = 6.4, 1.8, 1.4$ Hz, H3), 6.40 (1H, dd, $J = 6.9, 1.4$ Hz, H15), 6.61 (1H, dd, $J = 6.9, 6.4$ Hz, H3'), 7.32 (2H, d, $J = 8.2$ Hz, aromatic), 7.72 (2H, d, $J = 8.2$ Hz, aromatic), 7.89 (1H, d, $J = 1.8$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 28.7, 29.1, 45.6, 50.5, 53.7, 56.3, 59.8, 69.9, 72.5, 72.9, 127.9, 130.2, 130.9, 135.2, 140.8, 143.0, 143.5, 145.2, 191.7; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{24}\text{O}_7\text{SNa}$ $[\text{M} + \text{Na}]^+$ 455.1135, found 455.1119.



Compound 1-136 [HT-19-089, 097] CsOBz (532 mg, 2.09 mmol) was added to a solution of triol **1-131** (302 mg, 0.698 mmol) and BzOH (256 mg, 2.10 mmol) in DMF (7 mL) at room temperature. The reaction mixture was stirred at room temperature for 48 h, and then H_2O (35 mL) was added. The resultant solution was extracted with Et_2O (15 mL x9), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 1/2) to afford impure benzoate **1-132**, which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ 1.32 (3H, s, H12), 1.49 (3H, s, H13), 2.00 (1H, dd, $J = 6.0, 2.3$ Hz, H7), 2.38 (3H, s, ArCH_3), 4.14 (1H, m, H3), 4.51 (1H, d, $J = 4.1$ Hz, H9), 4.78 (1H, br s, H8), 5.92 (1H, d, $J = 6.0$ Hz, H6), 6.21 (1H, br s, OH), 6.36 (1H, d, $J = 7.3$ Hz, H15), 6.49 (1H, dd, $J = 7.3, 6.4$ Hz, H3'), 7.28 (2H, d, $J = 8.7$ Hz, aromatic), 7.37 (2H, dd, $J = 7.8, 7.8$ Hz, aromatic), 7.52 (1H, dd, $J = 7.8, 7.8$ Hz, aromatic), 7.72 (2H, d, $J = 8.7$ Hz, aromatic), 7.82 (2H, d, $J = 7.8$ Hz, aromatic), 7.97 (1H, d, $J = 1.8$ Hz, H1); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{CO}$) δ 21.5, 30.6, 31.2, 52.8, 54.7, 57.8, 69.7, 69.8, 72.4, 73.1, 73.6, 128.6, 129.35, 129.43, 130.3, 130.8, 130.9, 133.9, 137.6, 140.3, 142.8, 145.4, 145.8, 165.1, 195.5; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{30}\text{O}_9\text{SNa}$ $[\text{M} + \text{Na}]^+$ 577.1503, found 577.1511.

$p\text{-tolSO}_3\text{H}\cdot\text{H}_2\text{O}$ (321 mg, 1.69 mmol) was added to a solution of the above crude benzoate **1-132** in toluene (40 mL) at room temperature. The reaction mixture was heated to 50°C and was stirred for 16 h. After the mixture was cooled to 0°C , saturated aqueous NaHCO_3 (20 mL) and H_2O (50 mL) were successively added. The resultant solution was extracted with EtOAc (30 mL x3), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on

silica gel (10 g, hexane/EtOAc 1/1) to afford **1-136** (222 mg, 0.414 mmol) in 59% yield over 2 steps: white solid; mp 223 °C; $[\alpha]_D^{23} +59$ (c 1.2, CHCl₃); IR (neat) ν 3490, 2978, 2951, 1739, 1717, 1268, 1254, 1119, 1068 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (3H, s, H12), 1.65 (3H, s, H13), 2.41 (3H, s, ArCH₃), 2.69 (1H, dd, J = 5.0, 4.1 Hz, H7), 3.23 (1H, d, J = 7.8 Hz, OH), 4.00 (1H, J = 5.0 Hz, OH), 4.15 (1H, ddd, J = 6.9, 1.8, 1.4 Hz, H3), 4.65 (1H, dd, J = 6.9, 5.0 Hz, H9), 4.78 (1H, m, H8), 5.53 (1H, d, J = 5.0 Hz, H6), 5.95 (1H, dd, J = 6.9, 6.9 Hz, H3'), 6.07 (1H, dd, J = 6.9, 1.4 Hz, H15), 7.28 (2H, d, J = 7.8 Hz, aromatic), 7.43 (2H, dd, J = 7.8, 7.8 Hz, aromatic), 7.57 (1H, dd, J = 7.8, 7.8 Hz, aromatic), 7.70 (2H, d, J = 7.8 Hz, aromatic) 7.89 (2H, d, J = 7.8 Hz, aromatic), 8.01 (1H, d, J = 1.8 Hz, H1); ¹³C NMR (100 MHz, CDCl₃) δ 21.7, 26.0, 31.1, 51.0, 52.9, 57.7, 67.8, 69.3, 74.4, 75.1, 81.9, 124.6, 127.9, 128.8, 128.9, 129.6, 129.9, 133.7, 135.4, 137.4, 140.7, 144.8, 145.8, 164.6, 193.1; HRMS (ESI) calcd for C₂₉H₂₈O₈SNa [M + Na]⁺ 559.1397, found 559.1374.

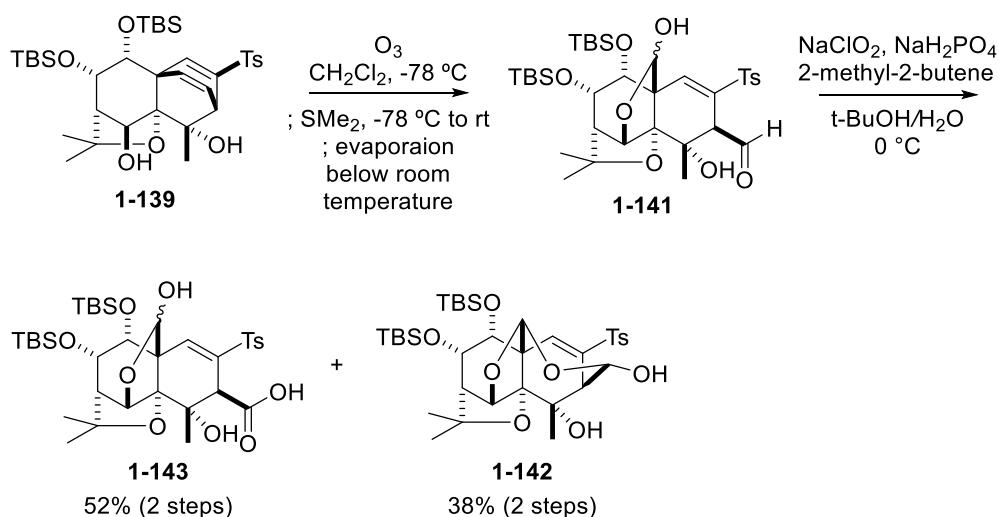


Compound 1-139 [HT-20-055, 057, 063] TBSOTf (860 μ L, 3.7 mmol) was added to a solution of **1-136** (502 mg, 0.936 mmol) and 2,6-lutidine (650 μ L, 5.6 mmol) in CH₃CN (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 3.5 h. After the mixture was cooled to 0 °C, H₂O (20 mL) was added. The resultant solution was extracted with EtOAc (10 mL x3), and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated to afford the crude bis-TBS ether **1-137**, which was used in the next reaction without further purification.

NaOMe (640 μ L, 25 wt% in MeOH, 3.0 mmol) was added to a solution of the above crude **1-137** in MeOH (28 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then saturated aqueous NH₄Cl (10 mL) was added. The resultant solution was extracted with EtOAc (10 mL x3), and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was passed through a pad of silica gel (10 g,

hexane/EtOAc 1/1) to afford impure ketone **1-138** (578 mg), which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ -0.01 (3H, s, CH_3 of TBS), 0.135 (3H, s, CH_3 of TBS), 0.137 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 0.99 (9H, s, *t*-Bu of TBS), 1.19 (3H, s, H12), 1.63 (3H, s, H13), 2.30 (1H, dd, J = 5.0, 3.2 Hz, H7), 2.40 (3H, s, ArCH_3), 4.21 (1H, ddd, J = 6.4, 1.8, 1.4 Hz, H3), 4.38 (1H, d, J = 6.9 Hz, H9), 4.49 (1H, d, J = 5.0 Hz, H6), 4.80 (1H, dd, J = 6.9, 3.2 Hz, H8), 6.07 (1H, dd, J = 7.3, 6.4 Hz, H3'), 6.27 (1H, dd, J = 7.3, 1.4 Hz, H15), 7.27 (2H, d, J = 7.3 Hz, aromatic), 7.70 (2H, d, J = 7.3 Hz, aromatic), 7.83 (1H, d, J = 1.8 Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ -4.2, -4.1, -4.0, -3.2, 18.3, 18.4, 21.6, 26.0, 26.2, 26.3, 31.1, 52.7, 53.2, 58.5, 68.2, 72.4, 73.2, 77.6, 81.6, 123.0, 127.9, 129.7, 136.3, 139.4, 139.7, 144.3, 146.6, 195.6; HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{52}\text{O}_7\text{SSi}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 683.2864, found 683.2853.

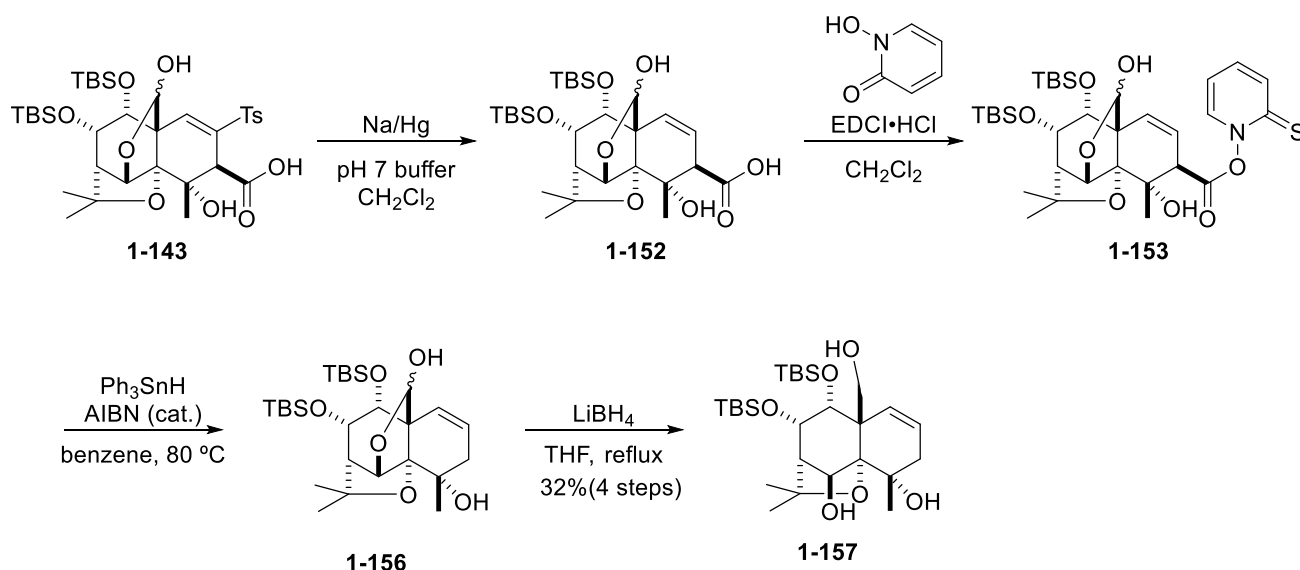
MeMgBr (2.5 mL, 3 M in Et_2O , 7.5 mmol) was added over 5 min to a stirred suspension of the above crude ketone **1-138** in Et_2O (15 mL) at $-50\text{ }^\circ\text{C}$. After the suspension became clear, the reaction mixture was warmed to $-40\text{ }^\circ\text{C}$ and stirred for 1.5 h. Then saturated aqueous NH_4Cl (10 mL) was added. The resultant solution was diluted with H_2O (10 mL), and was extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 1/1) to afford **3** (499 mg, 0.737 mmol) in 79% yield over 3 steps: colorless oil; $[\alpha]_{\text{D}}^{23}$ -47 (c 1.1, CHCl_3); IR (neat) ν 3476, 2953, 2930, 2858, 1146, 1107, 917 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ -0.04 (3H, s, CH_3 of TBS), 0.126 (3H, s, CH_3 of TBS), 0.134 (3H, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.01 (9H, s, *t*-Bu of TBS), 1.13 (3H, s, H12), 1.23 (3H, s, H14), 1.65 (3H, s, H13), 2.30 (1H, dd, J = 5.0, 3.6 Hz, H7), 2.39 (3H, s, ArCH_3), 3.75 (1H, ddd, J = 6.4, 2.3, 1.4 Hz, H3), 4.37 (1H, d, J = 6.8 Hz, H9), 4.48 (1H, d, J = 5.0 Hz, H6), 4.85 (1H, dd, J = 6.8, 3.6 Hz, H8), 5.91 (1H, dd, J = 7.3, 1.4 Hz, H15), 6.03 (1H, dd, J = 7.3, 6.4 Hz, H3'), 7.26 (2H, d, J = 8.2 Hz, aromatic), 7.71 (2H, d, J = 8.2 Hz, aromatic), 7.77 (1H, d, J = 2.3 Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ -4.3, -4.1, -4.0, -3.2, 18.3, 18.4, 21.6, 26.07, 26.11, 26.3, 26.5, 31.1, 51.9, 53.7, 59.8, 68.1, 72.1, 72.7, 75.6, 80.6, 86.5, 128.1, 129.4, 130.9, 136.5, 137.5, 143.6, 144.8, 145.3; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{56}\text{O}_7\text{SSi}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 699.3177, found 699.3158.



Carboxylic acid 1-143 and hemiacetal 1-142. [HT-20-067, 069] Ozone was bubbled through a suspension of **1-139** (499 mg, 0.737 mmol) in CH_2Cl_2 (15 mL) at $-78\text{ }^\circ\text{C}$ until the solution color turned to purple. Then oxygen gas was bubbled into the reaction mixture for 5 min. After Me_2S (ca. 3 mL) was added, the mixture was warmed to room temperature, stirred for 5 min, and then concentrated. The remaining solvents were removed under Ar stream for 5 minutes to afford the crude aldehyde **1-141**, which was used in the next reaction without further purification.

NaClO_2 (1.33 g, 14.7 mmol) was added to a solution of the above crude aldehyde **1-141** in a mixture of *t*-BuOH (3.5 mL) and 2-methyl-2-butene (7 mL) at $0\text{ }^\circ\text{C}$. Then a cooled solution of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (4.65 g, 29.8 mmol) in H_2O (7 mL) at $0\text{ }^\circ\text{C}$ was added to over 5 min. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 16 h, and then H_2O (15 mL) was added. The resultant solution was extracted with Et_2O (10 mL x5), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/ EtOAc 3/1 to 2/1 to 1/2) to afford carboxylic acid **1-143** (280 mg, 0.386 mmol, a 4:1 diastereomeric mixture at the C15 position) in 52% over 2 steps and hemiacetal **1-142** (201 mg, 0.283 mmol) in 38% over 2 steps. Carboxylic acid **1-143**: white amorphous; ^1H NMR (400 MHz, CDCl_3); δ 0.14 (3H x1/5, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.156 (3H x4/5, s, CH_3 of TBS), 0.162 (3H, s, CH_3 of TBS), 0.25 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.13 (3H x4/5, s, CH_3), 1.23 (3H x4/5, s, CH_3), 1.26 (3H x1/5, s, CH_3), 1.67 (3H x1/5, s, CH_3), 1.72 (3H x4/5, s, CH_3), 2.31 (1H x4/5, dd, $J = 5.5, 4.6\text{ Hz}$, H7), 2.38 (3H x1/5, s, ArCH_3), 2.40 (3H x4/5, s, ArCH_3), 3.88 (1H x1/5, d, $J = 2.8\text{ Hz}$, H3), 3.89 (1H x4/5, d, $J = 2.8\text{ Hz}$, H3), 4.29 (1H x1/5, d, $J = 5.0\text{ Hz}$, H9), 4.33 (1H x1/5, dd, $J = 5.0\text{ Hz}$, H8), 4.75 (1H x4/5, d, $J = 5.5\text{ Hz}$, H9), 4.84 (1H x4/5, d, $J = 5.5\text{ Hz}$, H6), 4.88 (1H x4/5, dd, $J = 5.5, 4.6\text{ Hz}$, H8), 5.03 (1H x1/5, d, $J = 5.0\text{ Hz}$, H6), 5.24 (1H x1/5, s, H15), 5.32 (1H x4/5, s, H15), 7.01 (1H x1/5, d, $J = 3.2\text{ Hz}$, H1), 7.05 (1H x4/5, d, $J = 2.8\text{ Hz}$, H1), 7.23 (2H

x1/5, d, $J = 8.2$ Hz, aromatic), 7.28 (2H x4/5, d, $J = 8.2$ Hz, aromatic), 7.70 (1H x4/5, d, $J = 8.2$ Hz, aromatic), 7.75 (1H x1/5, d, $J = 8.2$ Hz, aromatic); ^{13}C NMR (100 MHz, CDCl_3) δ -5.22, -5.15, -4.7, -4.6, -3.4, -3.3, -2.0, 14.2, 18.0, 18.4, 18.7, 18.8, 21.1, 21.7, 26.4, 26.5, 26.6, 26.9, 29.7, 29.9, 51.6, 53.9, 54.1, 57.1, 60.5, 70.4, 72.5, 72.7, 73.3, 80.2, 85.6, 89.1, 101.5, 126.8, 127.4, 128.3, 129.2, 129.4, 138.5, 140.6, 140.7, 143.5, 173.8 (Some of ^{13}C peaks of the minor isomer were not observed); HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{55}\text{O}_{10}\text{SSi}_2\text{Na}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 769.2844, found 769.2830. Hemiacetal **1-142**: white solid; $[\alpha]_{\text{D}}^{21}$ -200 (c 0.95, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.12 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS) 0.18 (3H, s, CH_3 of TBS), 0.24 (3H, s, CH_3 of TBS), 0.93 (9H, s, t -Bu of TBS), 0.95 (9H, s, t -Bu of TBS), 1.18 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.25 (1H, br dd, $J = 5.5, 4.1$ Hz, H7), 2.43 (3H, s, ArCH_3), 2.81 (1H, d, $J = 1.4$ Hz, H3), 3.06 (1H, s, OH), 4.13 (1H, d, $J = 5.5$ Hz, H9), 4.18 (1H, br dd, $J = 5.5, 4.1$ Hz, H8), 4.83 (1H, s, H15) 4.90 (1H, d, $J = 5.5$ Hz, H6), 4.93 (1H, d, $J = 13.3$ Hz, H3'), 5.07 (1H, d, $J = 13.3$ Hz, C3'-OH), 7.17 (1H, d, $J = 1.4$ Hz, H1), 7.31 (2H, d, $J = 8.2$ Hz, aromatic), 7.72 (2H, d, $J = 8.2$ Hz, aromatic); ^{13}C NMR (100 MHz, CDCl_3) δ -5.6, -4.8, -3.6, -2.1, 18.68, 18.71, 21.7, 23.1, 25.8, 26.4, 30.6, 53.6, 53.8, 57.6, 70.1, 71.1, 74.8, 82.3, 83.5, 86.9, 88.5, 102.3, 129.0, 129.5, 133.3, 137.6, 139.5, 144.8; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{56}\text{O}_9\text{SSi}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 731.3076, found 731.3078.



Triol 1-157 [HT-19-127, 131, 133] Na/Hg (446 mg, 10 wt% Na, 1.94 mmol for Na) was added to a solution of carboxylic acid **1-143** (70 mg, 97 μmol) in a mixture of CH_2Cl_2 (2 mL) and pH 7 phosphate buffer (4 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then Na/Hg (368 mg, 10 wt% Na, 1.60 mmol for Na) was added. The reaction mixture was stirred for 40 min, and then Na/Hg (550 mg, 10 wt% Na, 2.39 mmol for Na)

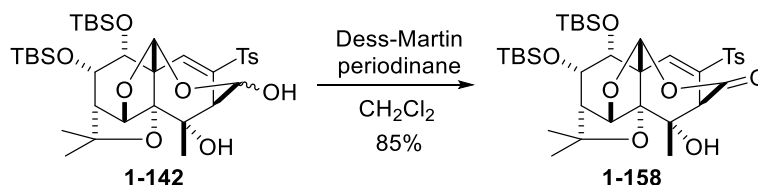
was added again. The reaction mixture was stirred for further 70 min. During performing the reaction, pH 7 phosphate buffer was continuously added to keep the pH of the aqueous layer of reaction mixture below 9 (approximately 20 mL of buffer was added). Then saturated aqueous NH_4Cl (15 mL) was added. The mixture was filtered through a pad of cotton with EtOAc. The filtrate was extracted with EtOAc (10 mL x3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was passed through a pad of silica gel (5 g, hexane/EtOAc 1/1) to afford impure **1-152**, which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) *major isomer*: δ 0.051 (3H, s, CH_3 of TBS), 0.11 (3H, s, CH_3 of TBS), 0.12 (3H, s, CH_3 of TBS), 0.13 (3H, s, CH_3 of TBS), 0.83 (9H, s, *t*-Bu of TBS), 0.94 (9H, s, *t*-Bu of TBS), 1.27 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.28 (1H, dd, $J = 5.5, 4.1$ Hz, H7), 3.38 (1H, m, H3), 4.52 (1H, d, $J = 5.0$ Hz, H9), 4.80 (1H, dd, $J = 5.0, 4.1$ Hz, H8), 4.84 (1H, d, $J = 5.5$ Hz, H6), 5.28 (1H, s, H15), 5.50 (1H, dd, $J = 10.5, 2.8$ Hz, H2), 6.11 (1H, dd, $J = 10.5, 1.8$ Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) *major isomer*: δ -4.9, -4.8, -3.5, -2.4, 17.6, 18.4, 18.6, 26.4, 26.5, 26.6, 30.2, 49.6, 53.9, 56.0, 70.3, 71.8, 72.4, 79.6, 85.5, 89.4, 102.6, 127.3, 172.7; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{49}\text{O}_8\text{Si}_2\text{Na}_2$ $[\text{M-H}+2\text{Na}]^+$ 615.2756, found 615.2751.

A flask charged with the above crude **1-152**, mercaptopyridine *N*-oxide (30 mg, 0.24 mmol) and CH_2Cl_2 (1.4 mL) was wrapped with aluminum foil. Then EDCI·HCl (45 mg, 0.23 mmol) was added to the solution. After being stirred at room temperature for 30 min, the reaction mixture was concentrated to afford the crude Barton ester **1-153**, which was used in the next reaction without purification.

AIBN (1.4 mg, 8.6 μmol) was added to the above crude residue. Then a solution of Ph_3SnH (270 mg, 0.769 mmol) in benzene (1.4 mL), which was degassed by freeze-thaw procedure (x3), was added to the mixture. After the aluminum foil was removed, the reaction mixture was heated to 80 $^\circ\text{C}$, and was stirred under room light for 1.5 h. After the mixture was cooled to room temperature, H_2O (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL x3), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was passed through a pad of short column, which was consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 2 g, with eluents (CH_2Cl_2 to hexane/EtOAc 10/1 to 5/1) to afford impure **1-156**, which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) *major isomer*: δ 0.06 (3H, s, CH_3 of TBS), 0.11 (3H, s, CH_3 of TBS), 0.12 (3H, s, CH_3 of TBS), 0.13 (3H, s, CH_3 of TBS), 0.86 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.23 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.01

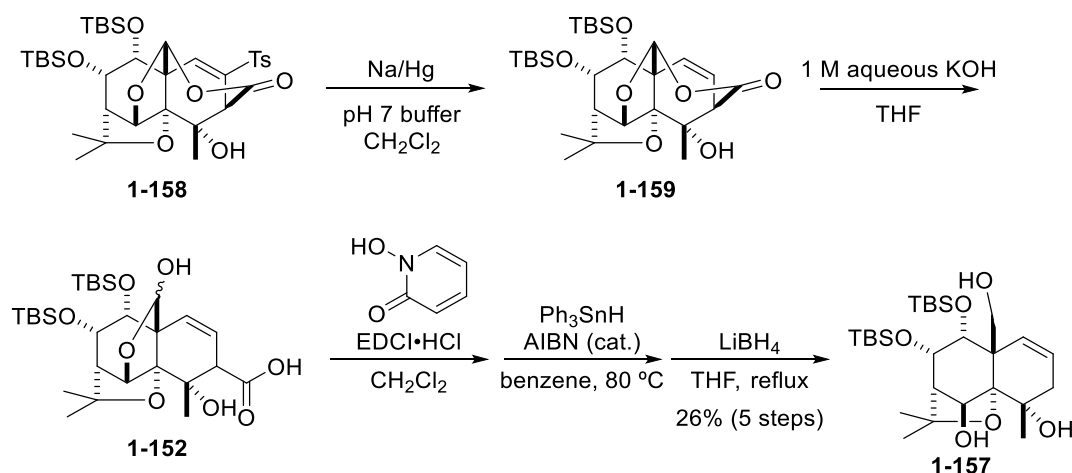
(1H, dd, $J = 17.4, 6.4$ Hz, H3a), 2.23 (1H, dd, $J = 5.5, 3.7$ Hz, H7), 2.29 (1H, br d, $J = 17.4$ Hz, H3b), 2.99 (1H, d, $J = 0.9$ Hz, OH), 3.21 (1H, d, $J = 4.1$ Hz, OH), 4.47 (1H, d, $J = 5.0$ Hz, H9), 4.78 (1H, dd, $J = 5.0, 3.7$ Hz, H8), 4.84 (1H, d, $J = 5.5$ Hz, H6), 5.31 (1H, d, $J = 4.1$ Hz, H15), 5.36 (1H, dd, $J = 10.1, 3.2$ Hz, H1), 5.73 (1H, ddd, $J = 10.1, 6.4, 1.8$ Hz, H2); ^{13}C NMR (100 MHz, CDCl_3) *major isomer*: δ -4.9, -4.7, -3.5, -2.3, 18.5, 18.6, 21.9, 26.47, 26.51, 26.7, 30.2, 38.3, 53.9, 55.6, 68.9, 70.7, 72.6, 79.9, 84.4, 89.2, 103.0, 126.0, 128.6; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 549.3038, found 549.3047.

LiBH_4 (125 μL , 2 M in THF, 0.250 mmol) was added to a solution of the above crude **1-156** in THF (1.2 mL) at room temperature. The reaction mixture was heated to reflux temperature, and was stirred for 18 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (5 mL) and H_2O (5 mL) were successively added. The resultant solution was extracted with EtOAc (5 mL x3), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 4/1 to 3/1 to 2/1) to afford triol **1-157** (16 mg, 31 μmol) in 32% yield over 4 steps: colorless oil; $[\alpha]_{\text{D}}^{21} +6.9$ (c 0.80, CHCl_3); IR (neat) ν 3304, 2953, 2929, 2857, 1472, 1254, 1104, 1070 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.128 (3H, s, CH_3 of TBS), 0.134 (9H, s, CH_3 of TBS x3), 0.90 (9H, s, $t\text{-Bu}$ of TBS), 0.94 (9H, s, $t\text{-Bu}$ of TBS), 1.30 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.10 (1H, dd, $J = 4.6, 2.8$ Hz, H7), 2.12 (1H, dd, $J = 17.8, 4.6$ Hz, H3a), 2.27 (1H, br d, $J = 17.8$ Hz, H3b), 3.31 (1H, d, $J = 12.4$ Hz, H15a), 3.84 (1H, d, $J = 12.4$ Hz, H15b), 4.28 (1H, d, $J = 6.0$ Hz, H9), 4.60 (1H, dd, $J = 6.0, 2.8$ Hz, H8), 5.13 (1H, d, $J = 4.6$ Hz, H6), 5.38 (1H, dd, $J = 10.5, 1.0$ Hz, H1), 5.48 (1H, ddd, $J = 10.5, 4.6, 2.3$ Hz, H2); ^{13}C NMR (100 MHz, CDCl_3) δ -4.7, -4.6, -3.0, -2.2, 18.6, 18.8, 24.0, 26.5, 26.7, 26.8, 31.3, 41.6, 54.3, 54.7, 66.4, 69.9, 70.8, 70.9, 75.0, 78.4, 85.2, 123.0, 129.9; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{52}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 551.3195, found 551.3194.



Lactone 1-158 [HT-20-081] Dess-Martin periodinane (360 mg, 0.849 mmol) was added to a solution of hemiacetal **1-142** (201 mg, 0.283 mmol) in CH_2Cl_2 (2.8 mL) at room temperature. The resulting suspension was stirred at room temperature for 1 h, and then saturated aqueous NaHCO_3 (10 mL) and saturated aqueous Na_2SO_3 (10 mL) were successively added. The resultant solution was extracted with CH_2Cl_2 (10 mL x3). The combined organic layers were dried over Na_2SO_4 ,

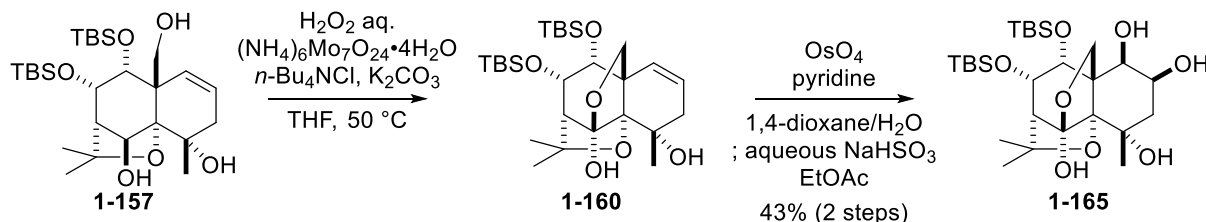
filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 3/1) to afford lactone **1-158** (171 mg, 0.242 mmol) in 85% yield: $[\alpha]_D^{21}$ -241 (*c* 1.29, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.14 (3H, s, CH₃ of TBS), 0.16 (3H, s, CH₃ of TBS), 0.21 (3H, s, CH₃ of TBS), 0.30 (3H, s, CH₃ of TBS), 0.94 (9H, s, *t*-Bu of TBS), 0.98 (9H, s, *t*-Bu of TBS), 1.22 (3H, s, CH₃), 1.38 (3H, s, CH₃), 1.64 (3H, s, CH₃), 2.34 (1H, ddd, *J* = 6.0, 2.8, 1.8 Hz, H7), 2.42 (3H, s, ArCH₃), 3.39 (1H, s, OH), 3.76 (1H, d, *J* = 2.3 Hz, H3), 4.26-4.27 (2H, m, H8 and H9), 4.96 (1H, d, *J* = 6.0 Hz, H6), 5.16 (1H, s, H15), 7.28 (1H, d, *J* = 2.3 Hz, H1), 7.30 (2H, d, *J* = 8.2 Hz, aromatic), 7.74 (2H, d, *J* = 8.2 Hz, aromatic); ¹³C NMR (100 MHz, CDCl₃) δ -5.3, -4.7, -3.5, -1.9, 18.7, 18.8, 21.7, 24.4, 25.7, 26.4, 26.5, 30.4, 52.8, 55.4, 57.4, 70.2, 71.2, 74.5, 82.3, 85.3, 88.4, 104.4, 128.8, 129.7, 134.3, 135.8, 142.4, 144.9, 165.5; HRMS (ESI) calcd for C₃₅H₅₄O₉SSi₂Na [M+Na]⁺ 729.2919, found 729.2908.



Triol 1-157 from lactone 1-158 [HT-20-027,031, 033, 035] Na/Hg (321 mg, 10 wt% Na, 1.39 mmol for Na) was added to a solution of lactone **1-59** (99 mg, 0.14 mmol) in a mixture of CH₂Cl₂ (1.8 mL) and pH 7 phosphate buffer (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then Na/Hg (183 mg, 10 wt% Na, 0.796 mmol for Na) was added. The reaction mixture was stirred for 40 min, and then Na/Hg (308 mg, 10 wt% Na, 1.34 mmol for Na) was added again. The reaction mixture was stirred for 2 h, and then Na/Hg (315 mg, 10 wt% Na, 1.37 mmol for Na) was added again. The reaction mixture was stirred for further 15 h. During performing the reaction, pH 7 phosphate buffer was continuously added to keep the pH of the aqueous layer of reaction mixture below 9 (approximately 15 mL of buffer was added). Then saturated aqueous NH₄Cl (20 mL) was added. The mixture was filtered through a pad of cotton with EtOAc. The filtrate was extracted with EtOAc (10 mL x3), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was passed through a pad of silica gel (3 g, hexane/EtOAc 1/1) to afford crude lactone **1-159**, which was used in the next reaction

without further purification: ^1H NMR (400 MHz, CDCl_3) δ 0.14 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS) 0.17 (3H, s, CH_3 of TBS), 0.19 (3H, s, CH_3 of TBS), 0.91 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.28 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.33 (1H, dd, $J = 6.0, 4.1$ Hz, H7), 3.66 (1H, dd, $J = 6.4, 1.8$ Hz, H3), 3.77 (1H, br, OH), 4.15 (1H, d, $J = 5.0$ Hz, H9), 4.27 (1H, dd, $J = 5.0, 4.1$ Hz, H8), 4.98 (1H, d, $J = 6.0$ Hz, H6), 5.08 (1H, s, H15), 6.16 (1H, dd, $J = 9.1, 1.8$ Hz, H1), 6.21 (1H, dd, $J = 9.1, 6.4$ Hz, H2); ^{13}C NMR (100 MHz, CDCl_3) δ -5.6, -4.6, -3.5, -1.7, 18.8, 18.9, 25.1, 25.6, 26.48, 26.51, 30.6, 53.0, 56.2, 56.5, 70.5, 71.1, 74.8, 82.0, 84.9, 88.3, 104.2, 129.3, 129.5, 168.5; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{48}\text{O}_7\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 575.2831, found 575.2847.

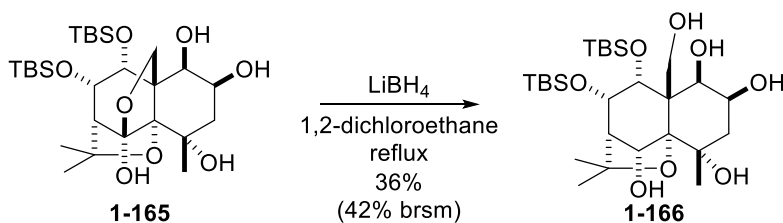
1 M aqueous KOH solution (1.4 mL) was added to a solution of the above crude lactone **1-159** in THF (1.4 mL). The reaction mixture was stirred at room temperature for 1 h, and then saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with EtOAc (3 mL x5). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 1/1 to 1/2) to afford impure carboxylic acid **1-152**. The crude carboxylic acid **1-152** was transformed in the same procedure as before to afford **1-157** (19 mg, 36 μmol) in 26% yield over 5 steps.



Hemiacetal 1-165. [HT-20-119, 125] H_2O_2 (105 μL , 30 wt% in H_2O , 0.926 mmol) was added to a solution of triol **1-157** (27 mg, 51 μmol), *n*- Bu_4NCl (69 mg, 0.25 mmol), K_2CO_3 (6.5 mg, 47 μmol), and $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (67 mg, 54 μmol) in THF (1.0 mL) at room temperature. The reaction mixture was heated to 50 $^\circ\text{C}$, and was stirred for 19 h. H_2O_2 (105 μL , 30 wt% in H_2O , 0.926 mmol) was added to the mixture, and then the reaction mixture was stirred at 50 $^\circ\text{C}$ for 24 h. H_2O_2 (105 μL , 1.03 mmol) was added again, and the mixture was stirred for further 9 h. After the mixture was cooled to room temperature, saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and Et_2O (5 mL) were successively added. The resultant solution was extracted with Et_2O (5 mL x3), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 4/1 to 2/1) to afford the crude **1-160**, which was used in the next reaction without further purification: ^1H NMR (400 MHz, CDCl_3) δ 0.05 (3H, s, CH_3 of TBS), 0.12 (3H, s, CH_3 of TBS), 0.14 (3H, s, CH_3 of TBS),

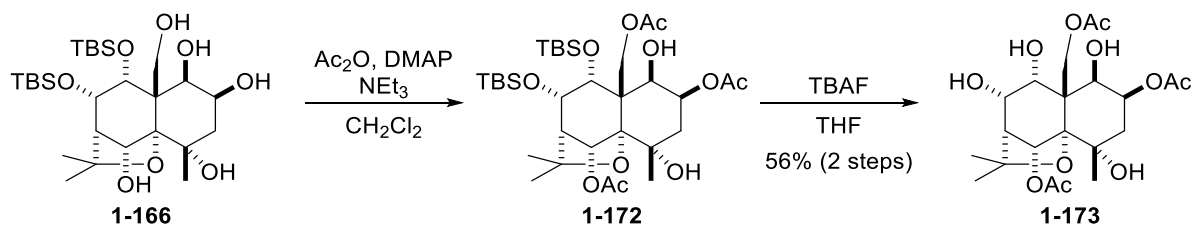
0.15 (3H, s, CH_3 of TBS), 0.87 (9H, s, $t\text{-Bu}$ of TBS), 0.95 (9H, s, $t\text{-Bu}$ of TBS), 1.53 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.97 (1H, dd, $J = 16.6, 6.9$ Hz, H3a), 2.12 (1H, d, $J = 3.5$ Hz, H7), 2.38 (1H, br d, $J = 16.6$ Hz, H3b), 3.27 (1H, br s, OH), 3.47 (1H, d, $J = 9.2$ Hz, H15a), 3.89 (1H, d, $J = 5.2$ Hz, H9), 3.93 (1H, d, $J = 9.2$ Hz, H15b), 4.50 (1H, dd, $J = 5.2, 3.5$ Hz, H8), 4.74 (1H, br s, OH), 5.24 (1H, dd, $J = 10.3, 3.5$ Hz, H1), 5.72 (1H, ddd, $J = 10.3, 6.9, 2.3$ Hz, H2); HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 549.3038, found 549.3041.

OsO_4 (350 μL , 0.16 M in H_2O , 56 μmol) was added to a solution of the above crude **1-160** in a mixture of pyridine (200 μL), H_2O (200 μL), and 1,4-dioxane (400 μL). The reaction mixture was stirred at room temperature for 3 h, and then saturated aqueous NaHSO_3 (4 mL) was added. The resultant solution was diluted with EtOAc (4 mL). After being vigorously stirred at room temperature for 53 h, the solution was extracted with EtOAc (5 mL x4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 1/1 to 1/2) to afford hemiacetal **1-165** (13 mg, 22 μmol) in 43% yield over 2 steps: colorless oil; $[\alpha]_{\text{D}}^{21} -1.8$ (c 0.40, CHCl_3); IR (neat) ν 3443, 2955, 2929, 2857, 1257, 1092, 1000 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.151 (3H, s, CH_3 of TBS), 0.154 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.20 (3H, s, CH_3 of TBS), 0.91 (9H, s, $t\text{-Bu}$ of TBS), 0.95 (9H, s, $t\text{-Bu}$ of TBS), 1.51 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.81 (1H, dd, $J = 14.7, 3.2$ Hz, H3a), 1.85 (3H, s, CH_3), 1.96 (1H, dd, $J = 14.7, 4.1$ Hz, H3b), 1.95-2.01 (1H, br s, OH), 2.12 (1H, d, $J = 3.6$ Hz, H7), 2.19-2.21 (1H, br s, OH), 3.45 (1H, d, $J = 10.1$ Hz, H15a), 3.54 (1H, s, OH), 3.79 (1H, d, $J = 4.1$ Hz, OH), 4.06 (1H, d, $J = 5.5$ Hz, H9), 4.20 (1H, m, H2), 4.36 (1H, dd, $J = 6.4, 5.5$ Hz, H1), 4.49 (1H, dd, $J = 5.5, 3.6$ Hz, H8), 4.50 (1H, d, $J = 10.1$ Hz, H15b); ^{13}C NMR (100 MHz, C_6D_6) δ -5.5, -4.4, -3.0, -1.5, 19.0, 19.3, 25.4, 26.7, 27.2, 28.2, 31.6, 44.6, 56.5, 60.3, 66.1, 69.2, 69.5, 72.4, 72.8, 77.6, 86.0, 88.5, 113.0; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{52}\text{O}_8\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 583.3093, found 583.3107.



Pentaol 1-166 [HT-20-163] LiBH_4 (140 μL , 2 M in THF, 0.28 mmol) was added to a solution of hemiacetal **1-165** (7.9 mg, 14 μmol) in 1,2-dichloroethane (5 mL) at room temperature. The reaction mixture was heated to reflux temperature, and was stirred for 28 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (3 mL) and H_2O (3 mL) were successively

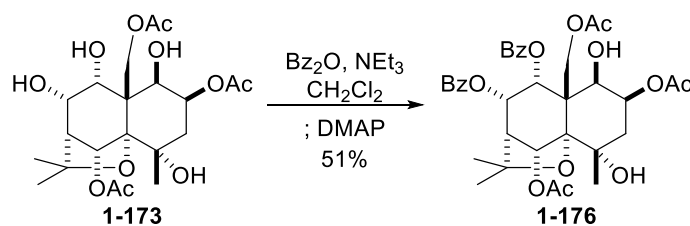
added. The resultant solution was extracted with EtOAc (5 mL x4), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford the borate ester of **1-166**. For the methanolysis of the borate ester and the azeotropic removal of trimethyl borate, the residue was dissolved in MeOH (5-10 mL) and the resultant solution was concentrated at 60 °C. The procedure was repeated 8 times. Then the resultant residue was purified by flash column chromatography on silica gel (1 g, CHCl₃/acetone 3/1) and preparative-TLC (CH₂Cl₂/acetone 3/1) to afford pentaol **1-166** (2.8 mg, 5.0 μmol) and **1-165** (1.2 mg, 2.1 μmol) in 36% and 15% yields, respectively. The yield of **1-166** was calculated to be 42% based on the recovered **1-165**: colorless oil; $[\alpha]_D^{20}$ -9.2 (*c* 0.21, CHCl₃); IR (neat) ν 3394, 2954, 2928, 2856, 1472, 1253, 1137, 1071, 835 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.15 (3H, s, CH₃ of TBS), 0.16 (3H, s, CH₃ of TBS), 0.17 (3H, s, CH₃ of TBS), 0.22 (3H, s, CH₃ of TBS), 0.93 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.50 (3H, s, CH₃), 1.73 (3H, s, CH₃), 1.75 (3H, s, CH₃), 1.90 (1H, dd, *J* = 14.2, 3.6 Hz, H3a), 2.05 (1H, dd, *J* = 14.2, 2.8 Hz, H3b), 2.31 (1H, d, *J* = 2.3 Hz, H7), 3.56 (1H, d, *J* = 11.9 Hz, H15a), 4.11 (1H, dd, *J* = 5.5, 2.3 Hz, H8), 4.14 (1H, m, H6), 4.19 (1H, ddd *J* = 4.1, 3.6, 2.8 Hz, H2), 4.43 (1H, d, *J* = 5.5 Hz, H9), 4.53 (1H, d, *J* = 4.1 Hz, H1), 4.62 (1H, d, *J* = 11.9 Hz, H15b), 5.12 (1H, br s, OH); ¹³C NMR (125 MHz, C₆D₆) δ -5.6, -4.5, -2.7, -0.3, 19.1, 19.7, 25.4, 26.9, 27.6, 28.1, 31.2, 43.5, 53.5, 58.5, 66.9, 70.6, 71.6, 73.0, 74.1, 74.2, 78.5, 84.7, 91.4; HRMS (ESI) calcd for C₂₇H₅₄O₈Si₂Na [M+Na]⁺ 585.3249, found 585.3270.



Tetraol 1-173 [HT-20-165, 167] DMAP (1.0 mg, 8.1 μmol) was added to a solution of pentaol **1-166** (4.1 mg, 7.3 μmol) in a mixture of Et₃N (150 μL), Ac₂O (75 μL) and CH₂Cl₂ (750 μL) at room temperature. The reaction mixture was stirred at room temperature for 9 h, and then aqueous NH₄Cl (5 mL) was added. The resultant solution was extracted with EtOAc (3 mL x5), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, hexane/EtOAc 1/1) to afford impure triacetate **1-172**, which was used in the next reaction without further purification.

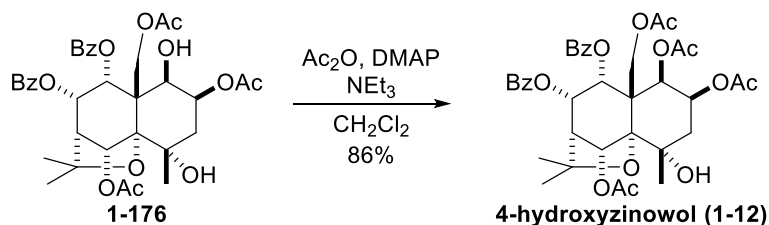
n-Bu₄NF (24 μL, 1 M in THF, 24 μmol) was added to a solution of the above crude triacetate **1-172** in THF (620 μL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then aqueous NH₄Cl (3 mL) was added. The resultant solution was

extracted with EtOAc (3 mL x4), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/3) to afford tetraol **1-173** (1.9 mg, 4.1 μmol) in 56% yield over 2 steps: colorless oil; [α]_D²³ -16 (c 0.095, CHCl₃); IR (neat) ν 3480, 2926, 1739, 1367, 1240, 1148, 1097, 1036 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.41 (3H, s, CH₃), 1.51 (3H, s, CH₃), 1.73 (3H, s, CH₃), 2.00-2.01 (2H, m, H3), 2.10 (3H, s, CH₃ of Ac), 2.170 (3H, s, CH₃ of Ac), 2.172 (3H, s, CH₃ of Ac), 2.44 (1H, d, *J* = 3.7 Hz, H7), 2.89 (1H, br s, OH), 3.30 (1H, br s, OH), 4.10 (1H, br d, *J* = 6.4 Hz, H9), 4.33-4.36 (1H, m, H8), 4.35 (1H, d, *J* = 12.8 Hz, H15a), 4.67 (1H, d, *J* = 3.6 Hz, H1), 4.74 (1H, d, *J* = 12.8 Hz, H15b), 5.30 (1H, td, *J* = 3.6, 3.2 Hz, H2), 5.81 (1H, s, H6); ¹³C NMR (125 MHz, CDCl₃) δ 21.1, 21.3, 21.5, 25.0, 26.3, 30.3, 42.5, 54.0, 55.7, 65.2, 69.70, 69.73, 70.4, 71.7, 72.5, 76.5, 84.0, 90.7, 170.0, 170.5, 172.1; HRMS (ESI) calcd for C₂₁H₃₂O₁₁Na [M+Na]⁺ 483.1837, found 483.1816.



Diol 1-178 [HT-20-169] Bz₂O (4.7 mg, 21 μmol) was added to a solution of tetraol **1-173** (1.9 mg, 4.1 μmol) in a mixture of Et₃N (410 μL) and CH₂Cl₂ (410 μL) at room temperature. The reaction mixture was stirred at room temperature for 7.5 h, and then Bz₂O (4.2 mg, 19 μmol) was added. After the reaction mixture was stirred for 15 h, DMAP (1.3 mg, 11 μmol) was added. The reaction mixture was stirred at room temperature for further 29 h, and then pH 7 phosphate buffer (5 mL) was added. The resultant solution was extracted with CH₂Cl₂ (3 mL x3), and the combined organic layers were washed with saturated aqueous NaHCO₃ solution (4 mL x3), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative-TLC (hexane/EtOAc 1/2) to afford diol **1-176** (1.4 mg, 2.1 μmol) in 51% yield: colorless oil; [α]_D²² -20 (c 0.07, CHCl₃); IR (neat) ν 3515, 2919, 2849, 1733, 1235, 1097, 1044 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.50 (3H, s, CH₃), 1.60 (3H, s, CH₃), 1.85 (3H, s, CH₃), 2.04 (1H, dd, *J* = 14.9, 2.9 Hz, H3a), 2.12-2.14 (1H, m, H3b), 2.13 (3H, s, CH₃ of Ac), 2.14 (3H, s, CH₃ of Ac), 2.36 (3H, s, CH₃ of Ac), 2.62 (1H, d, *J* = 3.5 Hz, H7), 2.90 (1H, s, OH), 4.48 (1H, d, *J* = 13.1 Hz, H15a), 4.70 (1H, d, *J* = 2.9 Hz, H1), 4.77 (1H, d, *J* = 13.1 Hz, H15b), 5.29 (1H, ddd, *J* = 2.9, 2.9, 2.9 Hz, H2), 5.80 (1H, d, *J* = 6.3 Hz, H9), 6.05 (1H, dd, *J* = 6.3, 3.5 Hz, H8), 6.14 (1H, s, H6), 7.27 (2H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.45-7.49 (3H, m, aromatic), 7.61 (1H, m, aromatic), 7.78 (2H, dd, *J* = 8.1, 1.4 Hz

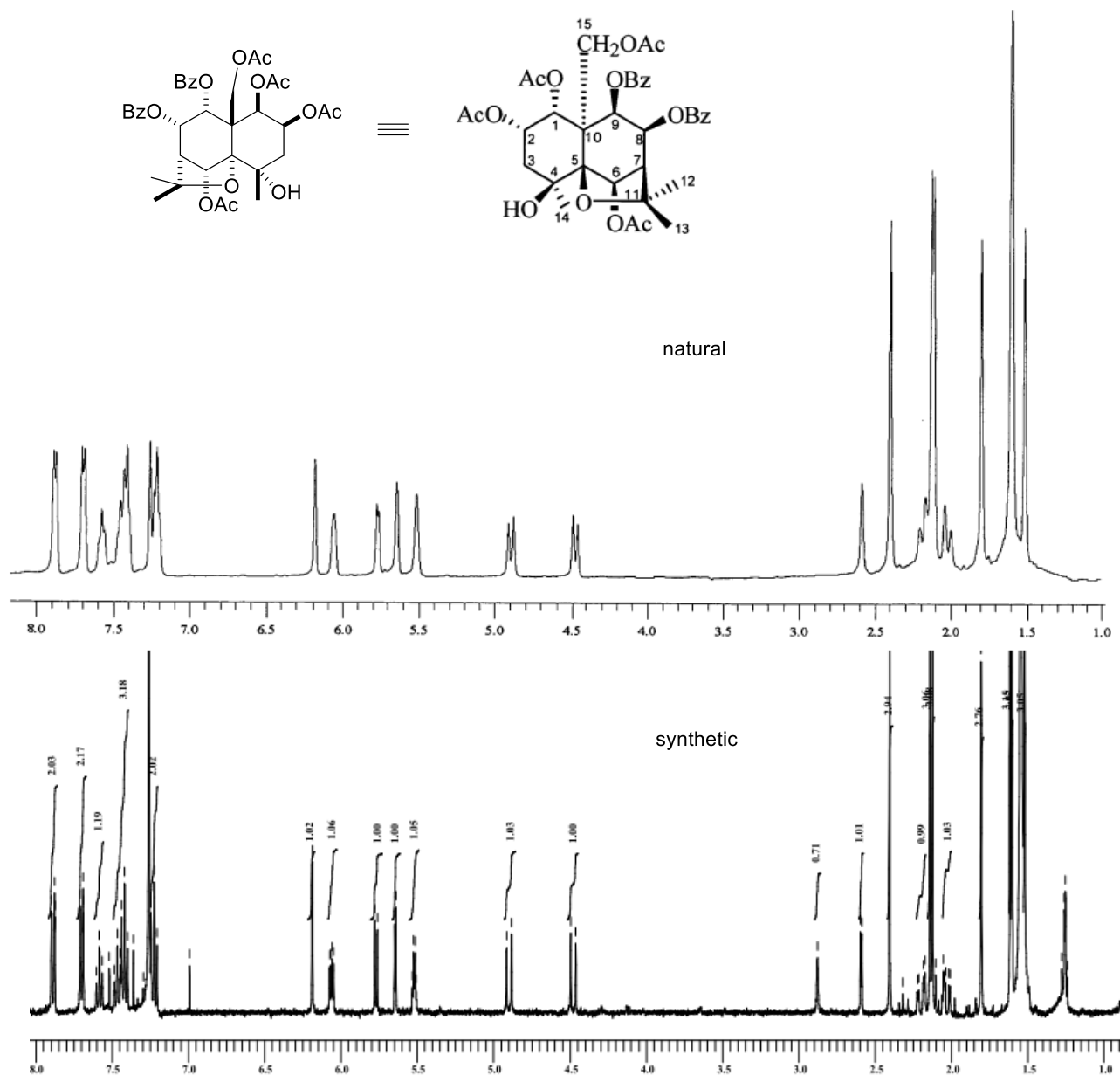
aromatic), 8.00 (2H, d, $J = 8.1$ Hz, aromatic) ; ^{13}C NMR (125 MHz, CDCl_3) δ 21.2, 21.3, 21.4, 25.1, 26.6, 30.0, 42.1, 53.8, 55.2, 64.1, 68.4, 68.8, 69.7, 70.8, 72.0, 76.2, 84.7, 91.0, 128.3, 128.6, 129.4, 129.6, 129.7, 130.0, 133.1, 133.3, 164.9, 165.1, 169.8, 170.7, 171.7; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{40}\text{NaO}_{13}$ $[\text{M}+\text{Na}]^+$ 691.2361, found 691.2343.



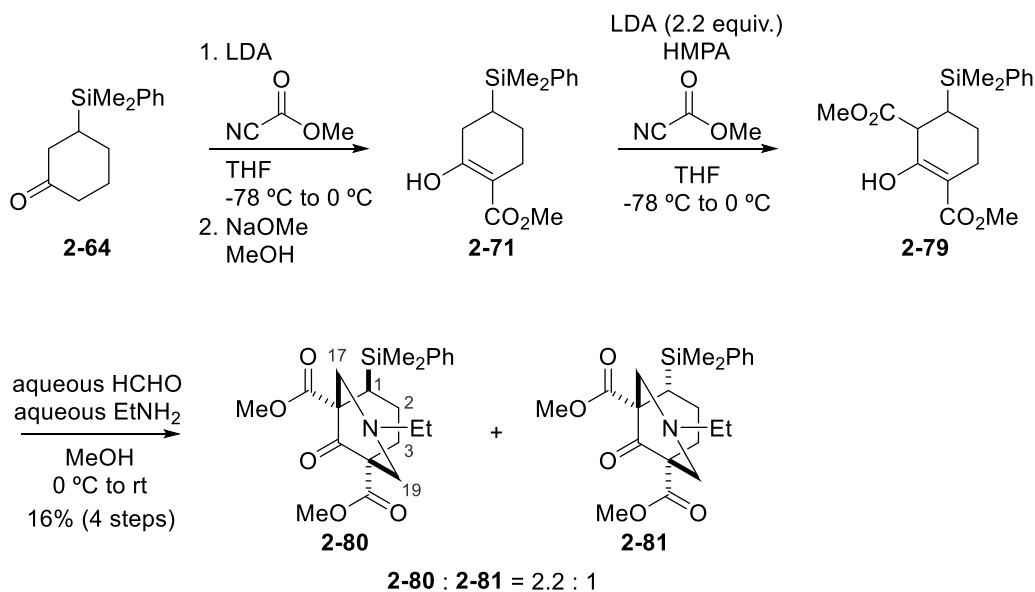
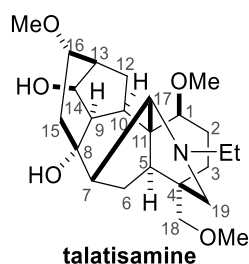
4-Hydroxyzinowol (1-12) [HT-20-171] DMAP (0.5 mg, 4.1 μmol) was added to a solution of triol **1-176** (1.4 mg, 2.1 μmol) in a mixture of Et_3N (85 μL), Ac_2O (42 μL), and CH_2Cl_2 (420 μL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then pH 7 phosphate buffer (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL x3), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by preparative-TLC (hexane/ EtOAc 1/1) to afford 4-hydroxyzinowol **1-12** (1.3 mg, 1.8 μmol) in 86% yield: colorless oil; $[\alpha]_{\text{D}}^{21}$ -11 (c 0.065, CHCl_3); IR (neat) ν 3550, 2923, 2850, 1747, 1368, 1280, 1229, 1093, 1045, 757, 709 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.52 (3H, s, H14), 1.60 (3H, s, H12), 1.62 (3H, s, CH_3 of Ac), 1.80 (3H, s, H13), 2.03 (1H, dd, $J = 15.5, 3.4$ Hz, H3a), 2.12 (3H, s, CH_3 of Ac), 2.14 (3H, s, CH_3 of Ac), 2.20 (1H, dd, $J = 15.5, 3.4$ Hz, H3b), 2.41 (3H, s, CH_3 of Ac), 2.59 (1H, d, $J = 4.0$ Hz, H7), 2.88 (1H, s, OH), 4.48 (1H, d, $J = 13.2$ Hz, H15a), 4.90 (1H, d, $J = 13.2$ Hz, H15b), 5.52 (1H, ddd, $J = 3.4, 3.4, 3.4$ Hz, H2), 5.65 (1H, d, $J = 3.4$ Hz, H1), 5.77 (1H, d, $J = 6.9$ Hz, H9), 6.06 (1H, dd, $J = 6.9, 4.0$ Hz, H8), 6.19 (1H, s, H6), 7.22 (2H, dd, $J = 7.5, 7.5$ Hz, aromatic), 7.42 (2H, dd, $J = 7.5, 7.5$ Hz, aromatic), 7.47 (1H, dd, $J = 7.5, 7.5$ Hz, aromatic), 7.59 (1H, dd, $J = 7.5, 7.5$ Hz, aromatic), 7.70 (2H, d, $J = 7.5$ Hz, aromatic), 7.89 (2H, d, $J = 7.5$ Hz, aromatic); ^{13}C NMR (125 MHz, CDCl_3) δ 20.3, 21.1, 21.3, 21.4, 25.0, 26.6, 30.0, 42.0, 53.8, 54.0, 64.6, 68.0, 68.1, 69.8, 70.1, 70.6, 76.0, 84.9, 91.0, 128.26, 128.31, 128.8, 129.2, 129.5, 130.3, 133.2, 133.6, 164.9, 165.4, 169.2, 169.6, 169.9, 170.6; HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{42}\text{O}_{14}\text{Na}$ $[\text{M}+\text{Na}]^+$ 733.2467, found 733.2485.

Comparison of ^1H NMR spectra of natural and synthetic sample of 4-hydroxyzinowol

^1H NMR SPECTRUM OF COMPOUND 11



Chapter 2: Synthetic study of talatisamine

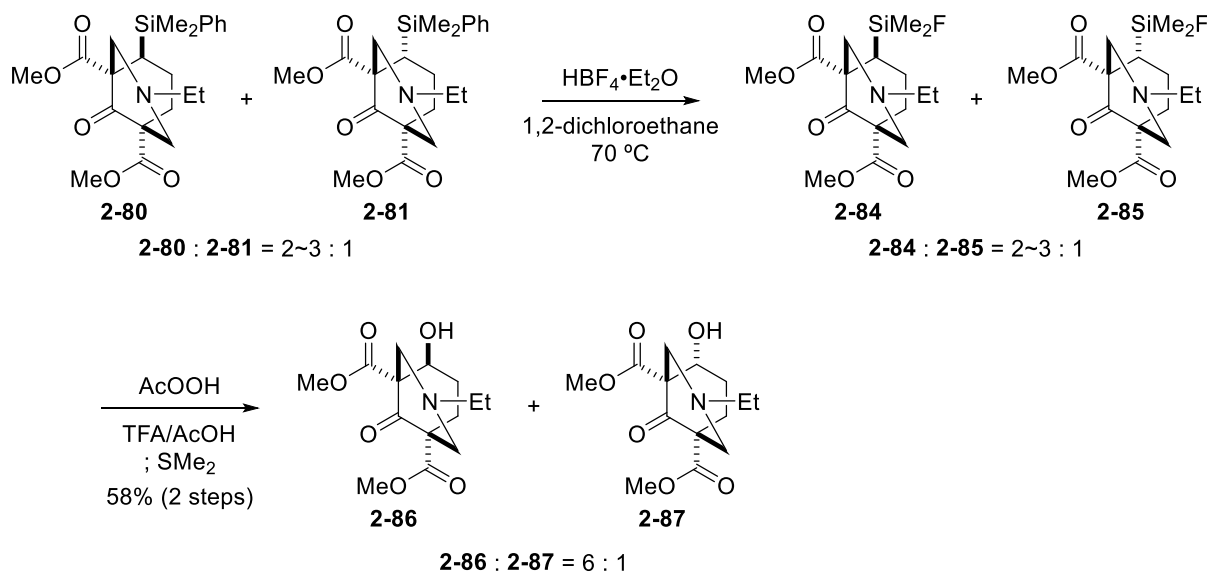


Bicyclic amines 2-80 and 2-81 [HT-21-151, 157, 159] *n*-BuLi (3.8 mL, 1.6 M in hexane, 6.1 mmol) was added to a solution of *i*-Pr₂NH (930 μ L, 6.60 mmol) in THF (11 mL) at -78 $^\circ$ C. The resulting solution was stirred at 0 $^\circ$ C for 30 min, and then cooled to -78 $^\circ$ C. Ketone **2-64** (1.18 g, 5.08 mmol) in THF (4 mL) was added to the solution via cannula, and the flask was washed with THF (1 mL) two times. The resulting solution was stirred at -78 $^\circ$ C for 30 min, and then Mander's reagent (600 μ L, 7.62 mmol) was added and the mixture was warmed to 0 $^\circ$ C. The resulting mixture was stirred at 0 $^\circ$ C for 20 min before the addition of saturate aqueous NH₄Cl (20 mL). The resulting mixture was extracted with Et₂O (20 mL \times 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was then dissolved in MeOH (17 mL). NaOMe (1.2 mL, 25 wt% in MeOH, 5.3 mmol) was added to the solution at 0 $^\circ$ C. The resulting solution was stirred at 0 $^\circ$ C for 3 h, and then aqueous NH₄Cl (20 mL) was added. The resulting mixture was extracted with Et₂O (20 mL \times 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (15 g,

hexane/EtOAc 10/1) to afford crude ester **2-71** (837 mg), which was used in the next reaction without further purification.

A solution of LDA was prepared as above from *n*-BuLi (4.3 mL, 1.6 M in hexane, 6.9 mmol) and *i*-Pr₂NH (1.0 mL, 7.2 mmol) in THF (10 mL). Crude ester **2-71** in THF (3 + 1 mL) was added to the solution via cannula at -78 °C. The resulting solution was stirred at 0 °C for 1 h, and then HMPA (500 µL, 2.88 mmol) and Mander's reagent (340 µL, 4.28 mmol) was added successively. The resulting solution was stirred at 0 °C for 2 h, and then aqueous NH₄Cl (30 mL) was added. The resulting mixture was extracted with Et₂O (30 mL × 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 1/1) to afford crude diester **2-79** (1.03 g).

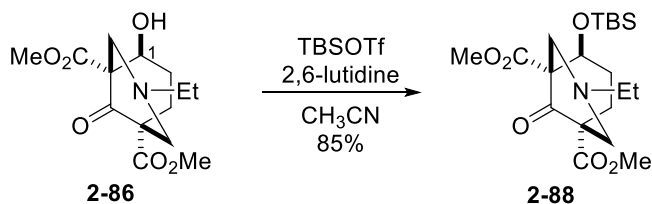
A solution of crude diester **2-79** and HCHO (2.6 mL, 37 wt% in H₂O, 36 mmol) in MeOH (18 mL) was cooled to 0 °C. EtNH₂ (710 µL, 70 wt% in H₂O, 8.9 mmol) was added to the solution dropwise over 5 min. The resulting mixture was warmed to room temperature and stirred for 22 h. The solution was diluted with H₂O (30 mL) and brine (60 mL). The resulting mixture was extracted with Et₂O (40 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel twice (10 g, hexane/EtOAc 10/1) to afford a diastereomixture of bicyclic amines **2-80** and **2-81** (345 mg, 0.826 mmol) in 16% yield over 4 steps (dr = 2.2:1). **Major isomer:** ¹H NMR (400 MHz, CDCl₃) δ 0.28 (3H, s, SiCH₃), 0.38 (3H, s, SiCH₃), 1.01 (3H, t, *J* = 7.3 Hz, -NCH₂CH₃), 1.52-1.59 (1H, m, H1, H2, or H3), 2.22-2.41 (5H, m, -NCH₂CH₃ and H1 or H2 or H3), 2.61 (1H, dddd, *J* = 13.7, 13.7, 6.4, 1.8 Hz, H3), 2.93 (1H, dd, *J* = 11.4, 2.3 Hz, H17 or H19), 2.97 (1H, dd, *J* = 11.9, 1.8 Hz, H17 or H19), 3.10 (1H, dddd, *J* = 13.7, 13.7, 13.7, 6.0 Hz), 3.22 (1H, dd, *J* = 11.4, 2.3 Hz, H17 or H19), 3.32 (1H, dd, *J* = 11.9, 1.8 Hz, H17 or H19), 7.34-7.37 (3H, m, SiPh), 7.50-7.53 (2H, m, SiPh) ; HRMS (ESI) calcd for C₂₂H₃₁NNaO₅Si [M+Na]⁺ 440.1864, found 440.1866.



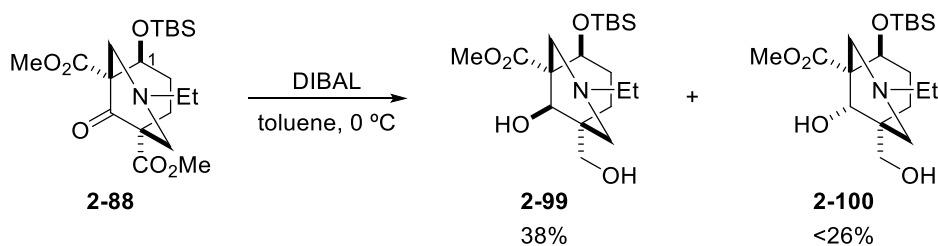
Alcohol 2-86 [HT-21-187, 195] $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ (510 μL , 3.75 mmol) was added to a solution of the 2.2:1 diastereomixture of bicyclic amines **2-80** and **2-81** (158 mg, 0.378 mmol) in 1,2-dichloroethane (3.8 mL) at room temperature. The resulting mixture was stirred at 70 $^{\circ}\text{C}$, and then aqueous NaHCO_3 (20 mL) was added slowly at 0 $^{\circ}\text{C}$. The resulting mixture was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The obtained crude silyl fluorides **2-84** and **2-85** (128 mg) were used in the next reaction without further purification.

A solution of the crude silyl fluorides in TFA (3.6 mL) was stirred at room temperature for 1 h. AcOOH (9% in AcOH , ca. 3 mL, ca. 3.7 mmol) was added to the solution and the resulting mixture was stirred at room temperature for 2.5 h. The solution was cooled to 0 $^{\circ}\text{C}$, and then Me_2S (ca. 3 mL) was added slowly. After stirred for 15 min at room temperature, the solution was concentrated and the residue was dissolved in EtOAc (10 mL). The organic layer was washed with aqueous NaHCO_3 (5 mL \times 2) and brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/ EtOAc 2/1 to 1/1) to afford a diastereomixture of alcohols **2-86** and **2-87** (66 mg, 0.22 mmol) in 58% yield over 2 steps (dr = 6:1). **2-86**: ^1H NMR (400 MHz, CDCl_3) δ 1.13 (3H, t, J = 7.3 Hz, $-\text{NCH}_2\text{CH}_3$), 1.98 (1H, dddd, 13.3, 6.4, 6.4, 3.6 Hz, H2), 2.16 (1H, ddd, J = 14.2, 6.4, 3.7 Hz, H3), 2.35-2.42 (1H, m, H3), 2.43-2.54 (2H, m, $-\text{NCH}_2\text{CH}_3$), 2.88 (1H, br d, J = 11.0 Hz, H17 or H19), 2.89-2.95 (1H, m, H2), 3.04 (1H, dd, J = 11.4, 1.8 Hz, H17 or H19), 3.19 (1H, dd, J = 11.4, 2.3 Hz, H17 or H19), 3.60 (1H, dd, J = 11.4, 2.3 Hz, H17 or H19), 3.75 (3H, s, COOMe), 3.78 (3H, s, COOMe), 4.61 (1H, dd, J = 10.1, 6.4 Hz, H1); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{NNaO}_6$

$[M+Na]^+$ 322.1261, found 322.1252.

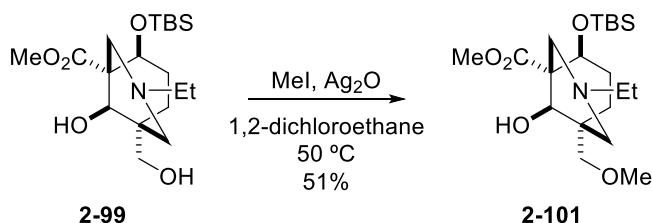


TBS ether 2-88 [HT-21-197] TBSOTf (150 μ L, 0.651 mmol) was added to a solution of alcohol **2-86** (66 mg, 0.22 mmol, 6:1 diastereomixture at C1-position) and 2,6-lutidine (130 μ L, 1.12 mmol) in CH_3CN (2.2 mL) at room temperature. The resulting solution was stirred at room temperature for 1.5 h, and then H_2O (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (5 mL \times 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 20/1 to 10/1) to afford TBS ether **2-88** (76 mg, 0.19 mmol) in 85% yield as a diastereomixture at C1-position (dr = 6:1). **Major isomer:** ^1H NMR (400 MHz, CDCl_3) δ -0.01 (3H, s, CH_3 of TBS), 0.07 (3H, s, CH_3 of TBS), 0.84 (9H, s, t -Bu of TBS), 1.11 (3H, t, $J = 7.3$ Hz, $-\text{NCH}_2\text{CH}_3$), 1.90 (1H, br ddd, $J = 12.8, 6.4, 6.4$ Hz, H2), 2.08 (1H, br dd, 14.2, 5.5 Hz, H3), 2.28-2.53 (3H, m, $-\text{NCH}_2\text{CH}_3$ and H3), 2.74 (1H, d, $J = 11.9$ Hz, H17 or H19), 3.06 (1H, dd, $J = 11.4, 1.8$ Hz, H17 or H19), 3.10-3.15 (1H, m, H2), 3.19 (1H, dd, $J = 11.4, 2.3$ Hz, H17 or H19), 3.70-3.74 (1H, m, H17 or H19), 3.74 (6H, s, $\text{COOCH}_3 \times 2$), 4.64 (1H, dd, $J = 10.5, 6.9$ Hz, H1) ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{35}\text{NNaO}_6\text{Si}$ $[M+Na]^+$ 436.2126, found 436.2129.



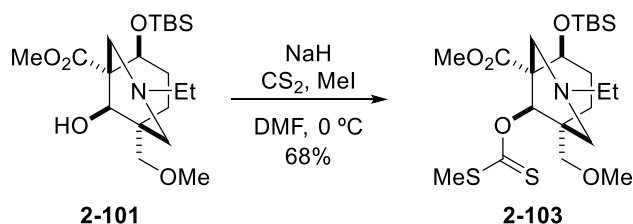
Diols 2-99 and 2-100 [HT-22-109] DIBAL (2.9 mL, 1.5 M in toluene, 4.4 mmol) was added to a solution of ketone **2-88** (510 mg, 1.23 mmol, 6:1 diastereomixture at C1-position) in toluene (13 mL) at 0 $^\circ\text{C}$. The resulting solution was stirred at 0 $^\circ\text{C}$ for 4 h, and then pH 7 phosphate buffer (30 mL), aqueous Rochelle's salt (250 mL), and brine (200 mL) was added in this order. The resulting mixture was stirred at room temperature for 2 h, and then extracted with EtOAc (100 mL \times 4). The combined organic layers were washed with brine (200 mL) dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel

(15 g, hexane/EtOAc 1/0 to 3/1 to 2/1) to afford diol **2-99** (180 mg, 0.464 mmol) in 38% yield and slightly impure diol **2-100** (124 mg, 0.320 mmol) in 26% yield. The yields are based on the major diastereomer of the starting material. **2-99**: white solid; ^1H NMR (500 MHz, CDCl_3) δ -0.04 (3H, s, CH_3 of TBS), 0.02 (3H, s, CH_3 of TBS), 0.83 (9H, s, *t*-Bu of TBS), 1.10 (3H, t, J = 7.3 Hz, $-\text{NCH}_2\text{CH}_3$), 1.23-1.30 (1H, m, H3), 1.34 (1H, dddd, J = Hz, H3), 1.67 (1H, dddd, 13.2, 5.7, 5.7, 1.8, H2), 2.24 (1H, d, J = 11.4 Hz, H17 or H19), 2.28-2.45 (3H, m, $-\text{NCH}_2\text{CH}_3$ and H2), 2.79 (1H, d, J = 11.4 Hz, H17 or H19), 2.90 (1H, d, J = 12.4 Hz, H17 or H19), 3.01 (1H, d, J = 12.4 Hz, H17 or H19), 3.50 (1H, d, J = 11.0 Hz, H18), 3.55 (1H, d, J = 11.0 Hz, H18), 3.72 (3H, s, OCH_3), 3.78 (1H, s, H5), 4.08 (dd, J = 11.0, 6.4 Hz, H1); ^{13}C NMR (100 MHz, CDCl_3) δ -5.3, -4.0, 12.6, 17.8, 25.6, 28.8, 29.9, 38.9, 47.8, 51.6, 52.0, 54.5, 55.8, 70.4, 73.9, 75.7, 174.5; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{37}\text{NNaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 410.2333, found 410.2337. **2-100**: clear oil; ^1H NMR (400 MHz, CDCl_3) δ -0.05 (3H, s, CH_3 of TBS), 0.04 (3H, s, CH_3 of TBS), 0.85 (9H, s, *t*-Bu of TBS), 1.06 (3H, t, J = 7.3 Hz, $-\text{NCH}_2\text{CH}_3$), 1.38 (1H, br dd, J = 14.2, 6.8 Hz, H3), 1.77 (1H, ddd, J = 11.9, 6.4, 6.4 Hz, H2), 1.92 (1H, dd, J = 11.0, 1.8 Hz, H17 or H19), 1.93 (1H, d, J = 11.4 Hz, H17 or H19), 2.10-2.36 (3H, m, $-\text{NCH}_2\text{CH}_3$ and H3), 2.60 (1H, dd, J = 11.0, 1.4 Hz, H17 or H19), 2.71-2.82 (1H, m, H2), 3.36 (1H, d, J = 11.0 Hz, H18), 3.47 (1H, d, J = 11.0 Hz, H18), 3.57 (1H, dd, J = 11.4, 1.8 Hz, H17 or H19), 3.70 (3H, s, OCH_3), 3.80 (1H, s, H5), 4.38 (1H, s, OH), 4.46 (dd, J = 10.5, 6.9 Hz, H1).

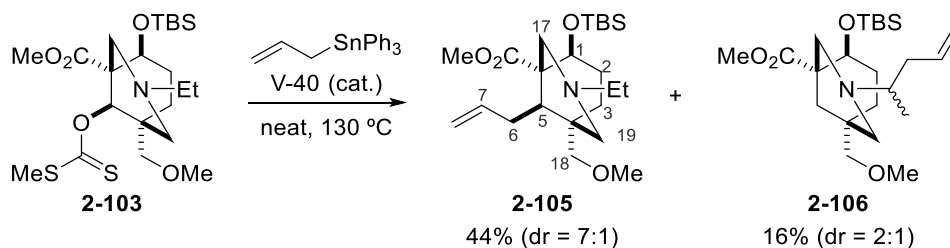


Methyl ether 2-101 [HT-22-113] MeI (145 μL , 2.32 mmol, passed thorough alumina silica gel before use) was added to the suspension of diol **2-99** (180 mg, 0.464 mmol) and Ag_2O (216 mg, 0.928 mmol) in 1,2-dichloroethane at room temperature. The resulting suspension was stirred at 50 $^\circ\text{C}$ in the dark for 12 h, and then additional MeI (145 μL , 2.32 mmol) was added. The resulting mixture was further stirred at 50 $^\circ\text{C}$ in the dark for 12 h, and then the mixture was filtered through a pad of Celite. The cake was washed with EtOAc (15 mL \times 3) and the combined organic layers were concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 1/0 to 15/1 to 10/1) to afford methyl ether **2-101** (95 mg, 0.24 mmol) in 51% yield: ^1H NMR (400 MHz, CDCl_3) δ -0.05 (3H, s, CH_3 of TBS), 0.01 (3H, s, CH_3 of TBS), 0.83 (9H, s, *t*-Bu of TBS), 1.07 (3H, t, J = 7.3 Hz, $-\text{NCH}_2\text{CH}_3$), 1.31 (1H, dddd, J = 13.7, 7.8, 6.0, 1.8 Hz, H3),

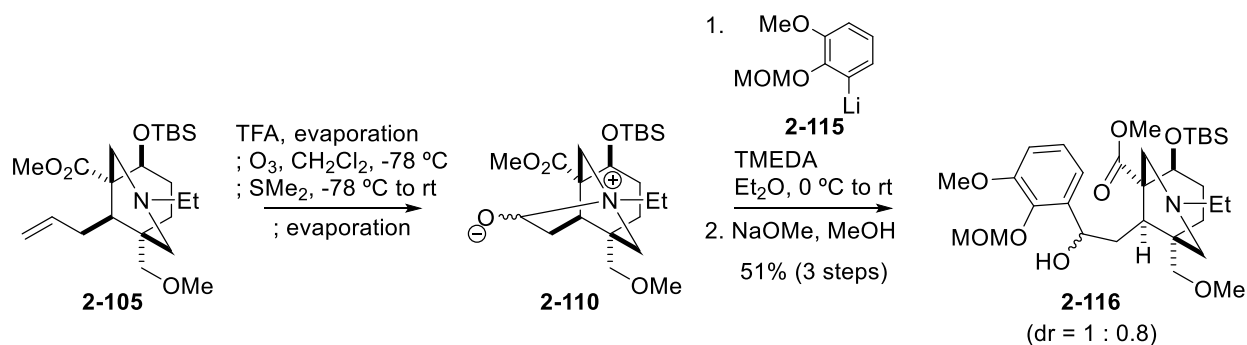
1.48 (1H, br dd, $J = 13.7, 6.9$ Hz, H3), 1.64 (1H, dddd, $J = 12.8, 6.4, 6.4, 1.4$ Hz, H2), 2.26-2.41 (3H, m, $\text{-NCH}_2\text{CH}_3$ and H17 or H19), 2.59 (1H, br d, $J = 11.0$ Hz, H17 or H19), 2.55-2.65 (1H, m, H2), 2.67 (1H, d, $J = 11.9$ Hz, H17 or H19), 3.10 (1H, d, $J = 11.9$ Hz, H17 or H19), 3.23 (1H, d, $J = 9.1$ Hz, H18), 3.29 (1H, d, $J = 9.1$ Hz, H18), 3.31 (3H, s, CH_2OCH_3), 3.70 (3H, s, COOCH_3), 3.78 (1H, s, H5), 4.12 (dd, $J = 11.0, 6.4$ Hz, H1) ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{39}\text{NNaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$ 424.2490, found 424.2490.



Xanthate ester 2-103 [HT-22-159] NaH (13 mg, 50-70 wt% dispersion in mineral oil, 0.27-0.38 mmol) was added to the solution of methyl ether **2-101** (36 mg, 90 μmol) and CS_2 (55 μL , 0.90 mmol) in DMF (900 μL) at 0°C . The resulting suspension was stirred at 0°C for 15 min, and then MeI (55 μL , 0.90 mmol, passed thorough alumina silica gel before use) was added. The resulting mixture was further stirred at 0°C for 30 min, and then aqueous NH_4Cl (2 mL) and H_2O (5 mL) were added. The resultant solution was extracted with Et_2O (3 mL \times 3), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/ EtOAc 1/0 to 70/1 to 20/1) to afford xanthate ester **2-103** (30 mg, 61 μmol) in 68% yield: ^1H NMR (400 MHz, CDCl_3) δ -0.05 (3H, s, CH_3 of TBS), 0.03 (3H, s, CH_3 of TBS), 0.84 (9H, s, $t\text{-Bu}$ of TBS), 1.08 (3H, t, $J = 7.3$ Hz, $\text{-NCH}_2\text{CH}_3$), 1.54-1.63 (1H, m, H3), 1.69 (1H, ddd, $J = 12.4, 6.4, 6.4$ Hz, H2), 1.89 (1H, dd, $J = 14.2, 6.4$ Hz, H3), 2.29-2.42 (3H, m, $\text{-NCH}_2\text{CH}_3$ and H17 or H19), 2.47 (1H, d, $J = 11.9$ Hz, H17 or H19), 2.52 (3H, s, SCH_3), 2.72 (1H, d, $J = 11.0$ Hz, H17 or H19), 2.86 (1H, dddd, 12.4, 11.9, 11.4, 5.5 Hz, H2), 3.05 (1H, d, $J = 9.2$ Hz, H18), 3.10 (1H, d, $J = 9.2$ Hz, H18), 3.21 (3H, s, CH_2OCH_3), 3.40 (1H, d, $J = 11.9$ Hz, H17 or H19), 3.58 (3H, s, COOCH_3), 4.30 (dd, $J = 11.0, 6.9$ Hz, H1), 5.99 (1H, s, H5) ; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{41}\text{NNaO}_5\text{S}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 514.2088, found 514.2084.



Terminal olefin 2-105 [HT-22-183] xanthate ester **2-103** (24 mg, 49 μmol) was azeotropically dried with benzene three times before use. A mixture of the dried **2-103**, V-40 (1.4 mg, 5.8 μmol), and allyltriphenyltin (196 mg, 0.501 mmol, m.p. 72-75 $^\circ\text{C}$) was heated at 130 $^\circ\text{C}$. After the liquid became homogeneous, the stirring started and continued at 130 $^\circ\text{C}$ for 13 h. After cooled to room temperature, the resulting mixture was purified by flash column chromatography (a column consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 6 g, hexane/EtOAc 70/1 to 20/1) to afford the mixture of **2-105**, **2-106**, and the starting material **2-103** (15.2 mg combined) in 44%, 16%, and 10% yield respectively. Since separation of these compounds were difficult on preparative scale, yields were calculated based on the integrations in ^1H NMR of the mixture. NMR chart of **2-105** was obtained by using a part of the sample further purified by preparative TLC (hexane/EtOAc 10/1). **2-105**: ^1H NMR (400 MHz, CDCl_3) δ -0.06 (3H, s, CH_3 of TBS), 0.01 (3H, s, CH_3 of TBS), 0.82 (9H, s, $t\text{-Bu}$ of TBS), 1.04 (3H, t, $J = 7.3$ Hz, $-\text{NCH}_2\text{CH}_3$), 1.61-1.81 (5H, m, H2, H3 x2, H5, and H6a), 2.05 (1H, d, $J = 11.9$ Hz, H17 or H19), 2.16 (1H, d, $J = 11.9$ Hz, H17 or H19), 2.21-2.34 (3H, m, $-\text{NCH}_2\text{CH}_3$ and H6b), 2.43 (1H, d, $J = 11.0$ Hz, H17 or H19), 2.76-2.85 (1H, m, H2), 2.95 (1H, d, $J = 9.2$ Hz, H18), 3.07 (1H, d, $J = 9.2$ Hz, H18), 3.24 (3H, s, CH_2OCH_3), 3.30 (1H, d, $J = 11.9$ Hz, H17 or H19), 3.58 (3H, s, COOCH_3), 4.17 (1H, dd, $J = 11.0, 6.4$ Hz, H1), 4.85 (1H, dd, $J = 10.0, 1.4$, $\text{CH}_2=\text{CH}-$), 4.89 (1H, dd, $J = 16.9, 1.4$, $\text{CH}_2=\text{CH}-$), 5.62-5.72 (1H, m, H7).



Preparation of lithium species 2-115. [HT-23-107] Methoxymethyl guaiacol (67 mg, 0.39 mmol) was azeotropically dried with benzene three times, and then dissolved in Et_2O (1.7 mL).

n-BuLi (1.6 M in hexane, 200 μ L, 0.32 mmol) was added to the stirring solution at room temperature. White solid precipitated immediately after the addition of *n*-BuLi. Further stirring for 3 h afforded the suspension of aryl lithium **2-115**.

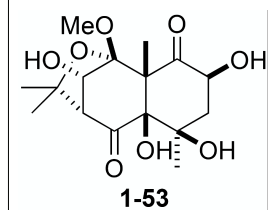
Alcohol 2-116. [HT-23-103, 107, 111] TFA (ca. 1 mL) was added to terminal olefin **2-105** (17 mg, 39 μ mol, calculated amount) and then the solution was concentrated under reduced pressure. The procedure was repeated three times. Thus obtained residue was dissolved in CH₂Cl₂ (1.2 mL) and cooled to -78 °C. Ozone was bubbled via needle to the stirring solution until the color of the solution turned to blue (for about 20 seconds). The resulting solution was stirred for about 3 minutes at -78 °C. And then oxygen gas was bubbled via needle into the reaction mixture until the blue color disappeared (for 30 seconds), followed by addition of Me₂S (ca. 1 mL). The mixture was warmed to room temperature, stirred for 9 h, and then concentrated to afford crude zwitterion **2-110**, which was azeotropically dried with benzene three times. Et₂O (500 μ L) and TMEDA (65 μ L) was added at room temperature and the resulting suspension was sonicated for about 1 min. Suspension of aryl lithium **2-115** in Et₂O was added to the suspension of **2-110** via cannula at 0 °C. The resulting mixture was stirred at room temperature for 13 h, and then aqueous NH₄Cl (3 mL) was added. The resultant solution was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford the mixture of alcohol **2-115** and lactone **2-116**. The mixture was dissolved in MeOH (1.3 mL) and NaOMe (25 wt% in MeOH, 29 μ L, 0.13 mmol) was added. The resulting mixture was stirred at room temperature for 2 h, and then aqueous NH₄Cl (3 mL) and H₂O (10 mL) were added. The resultant solution was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 1/0 to 10/1 to 5/1 to 3/1) to afford alcohol **2-116** (12 mg, 20 μ mol) in 51% yield over 3 steps as a mixture of diastereomers (dr = 1 : 0.8). **Major isomer:** ¹H NMR (400 MHz, CDCl₃) δ -0.04 (3H, s, CH₃ of TBS), 0.02 (3H, s, CH₃ of TBS), 0.84 (9H, s, *t*-Bu of TBS), 1.02 (3H, t, *J* = 7.3 Hz, -NCH₂CH₃), 1.05-1.12 (1H, m, H6), 1.69-1.81 (3H, m, H2a, H3 x2), 1.96-2.10 (3H, m, H6b, H17 or H19 x2), 2.11 (1H, br d, *J* = 7.3 Hz, H5), 2.14-2.29 (2H, m, -NCH₂CH₃), 2.46 (1H, d, *J* = 11.4 Hz, H17 or H19), 2.79-2.88 (1H, m, H2), 3.06 (1H, d, *J* = 9.2 Hz, H18), 3.17 (1H, d, *J* = 4.6 Hz, OH), 3.25 (1H, d, *J* = 9.2 Hz, H18), 3.31-3.34 (1H, m, H17 or H19), 3.34 (3H, s, CH₃), 3.53 (3H, s, CH₃), 3.70 (3H, s, CH₃) 3.84 (3H, s, CH₃), 4.20-4.24 (1H, m, H1), 4.93 (1H, ddd, *J* = 11.0, 4.6, 2.8, H7), 5.12 (1H, d, *J* = 5.5 Hz, CH₃OCH₂O-), 5.15 (1H, d, *J* = 5.5 Hz, CH₃OCH₂O-), 6.82 (1H, dd, *J* = 8.2, 1.4 Hz, *Ph*), 6.97 (1H, dd, *J* = 8.2, 1.4 Hz, *Ph*), 7.07 (1H, dd, *J* = 8.2, 8.2 Hz, *Ph*); ¹³C NMR (100 MHz, CDCl₃) δ -5.3, -3.8, 12.5, 17.8, 25.59, 25.63, 31.0, 33.9,

36.6, 38.3, 39.1, 48.2, 51.7, 52.2, 54.8, 55.4, 55.7, 57.9, 59.0, 68.1, 76.1, 78.3, 98.9, 111.0, 118.5, 124.6, 139.4, 142.5, 151.6, 176.9 ; HRMS (ESI) calcd for $C_{31}H_{53}NNaO_8Si$ $[M+Na]^+$ 618.3433, found 618.3427.

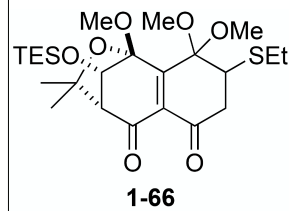
Minor isomer: 1H NMR (400 MHz, $CDCl_3$) δ -0.04 (3H, s, CH_3 of TBS), 0.02 (3H, s, CH_3 of TBS), 0.83 (9H, s, t -Bu of TBS), 1.02 (3H, t, $J = 7.3$ Hz, $-NCH_2CH_3$), 1.42 (1H, ddd, $J = 15.6, 4.1, 3.7$ Hz, H6a), 1.55 (1H, m, H3a), 1.72 (1H, br ddd, $J = 11.9, 6.4, 6.0$ Hz, H2a), 1.82 (1H, ddd, $J = 15.6, 11.0, 3.7$ Hz, H6b) 1.88-1.95 (2H, m, H3b and H17 or H19) 2.03-2.10 (2H, m, H5 and H17 or H19), 2.14-2.28 (1H, m, m, $-NCH_2CH_3$), 2.32 (1H, d, $J = 11.0$ Hz, H17 or H19), 2.79-2.90 (1H, m, H2b), 2.96 (1H, d, $J = 9.1$ Hz, H18), 3.30 (1H, d, $J = 9.1$ Hz, H18), 3.38 (3H, s, CH_3), 3.57 (3H, s, CH_3), 3.68 (3H, s, CH_3) 3.83 (3H, s, CH_3), 4.21-4.26 (2H, m, H1, and OH), 4.87 (1H, ddd, $J = 11.0, 3.7, 3.7$ Hz, H7), 5.11 (1H, d, $J = 5.5$ Hz, CH_3OCH_2O-), 5.13 (1H, d, $J = 5.5$ Hz, CH_3OCH_2O-), 6.82 (1H, d, $J = 8.2$ Hz, Ph), 6.99 (1H, d, $J = 8.2$ Hz, Ph), 7.06 (1H, dd, $J = 8.2, 8.2$ Hz, Ph).

Spectral data

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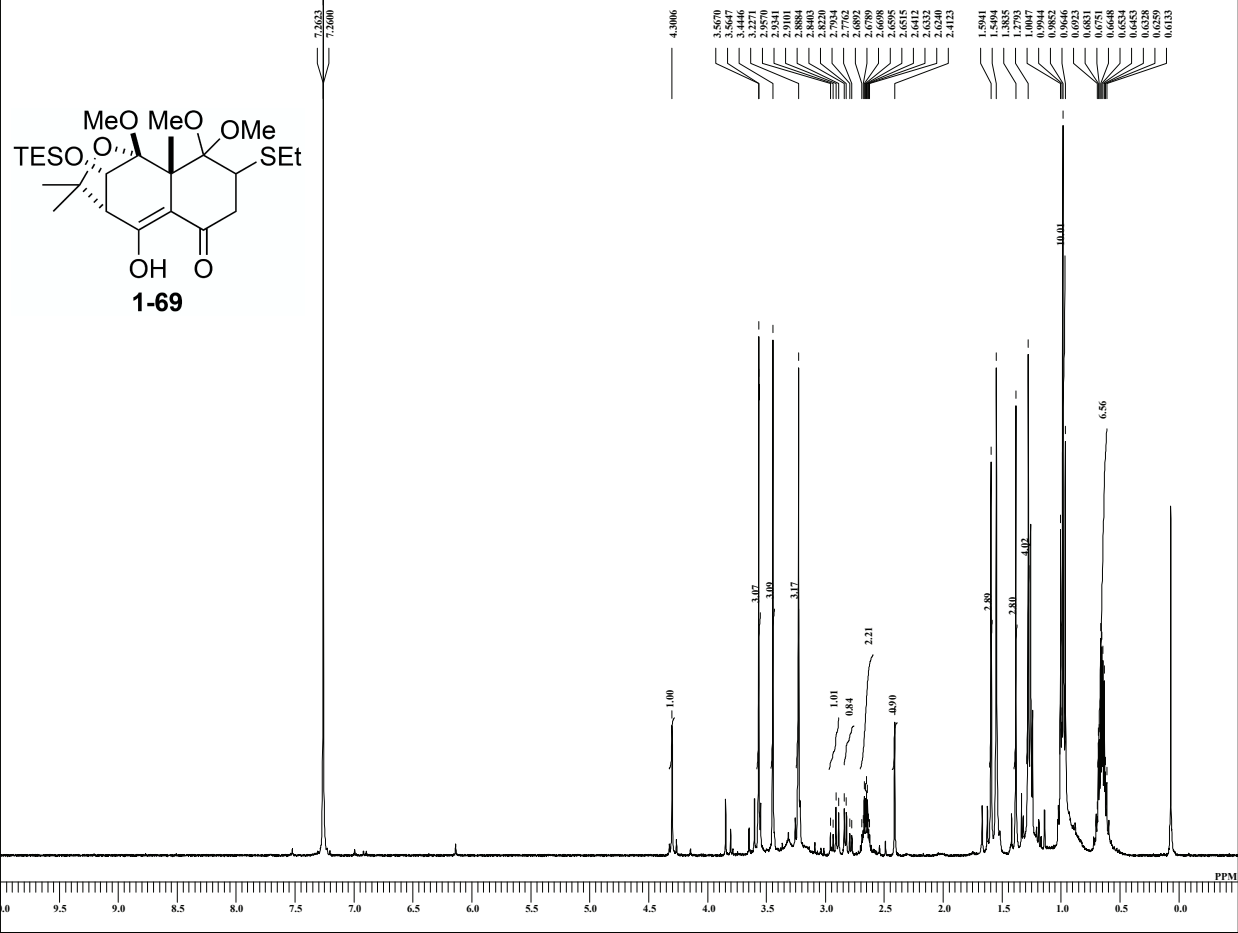


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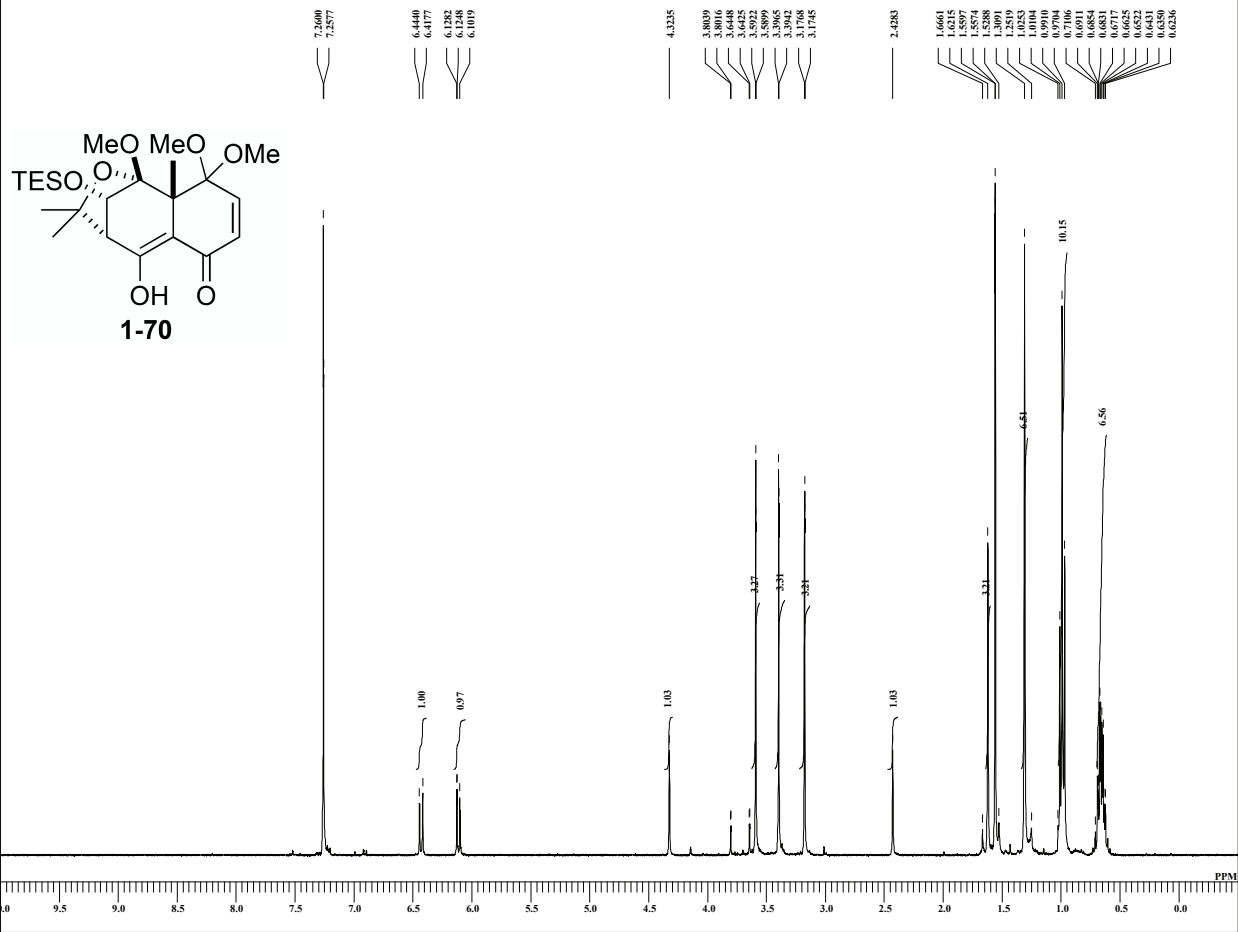
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XREF 7.26 ppm

HT-13-187-f2-3

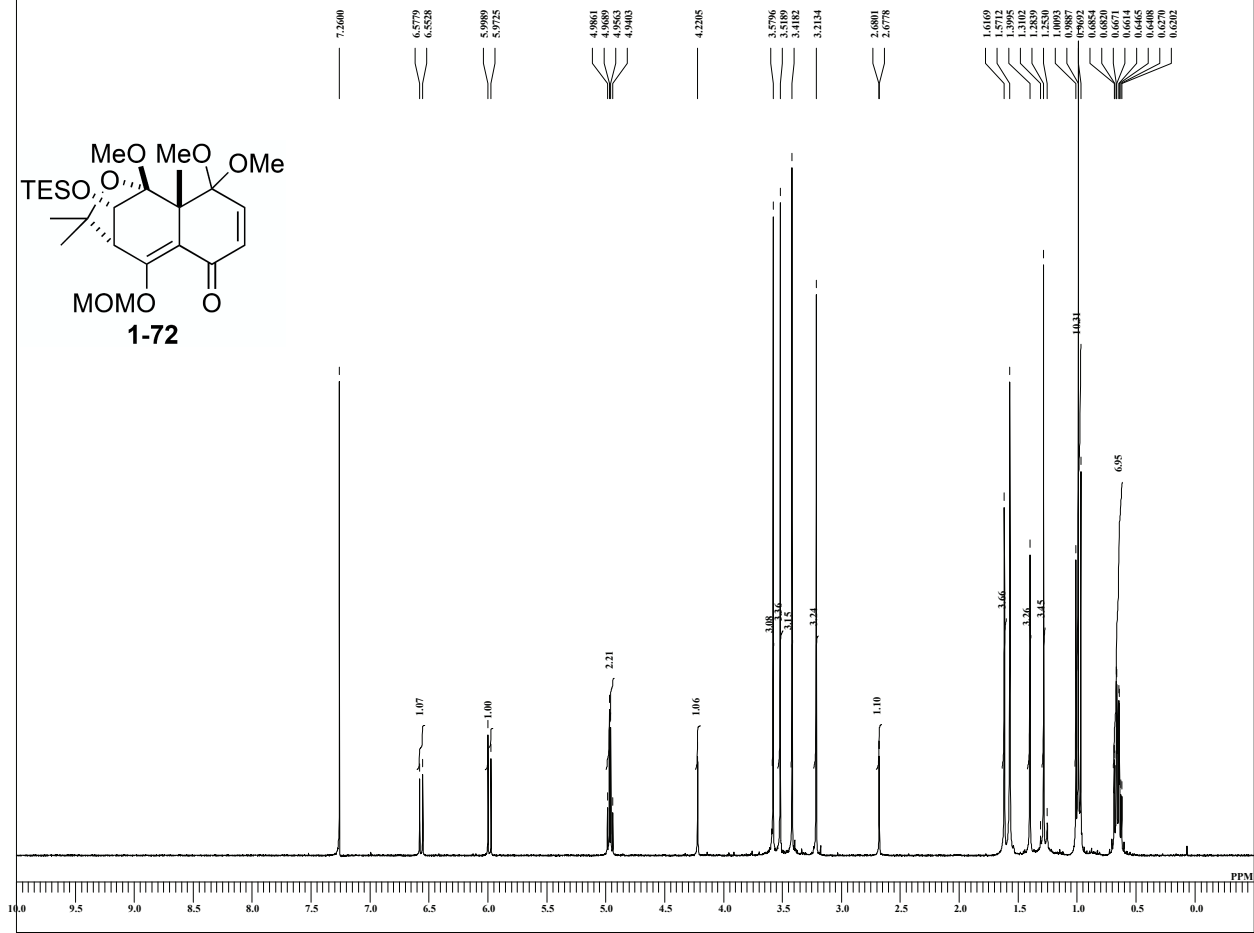
F:\201404\todoroki\HT-13\HT-13-187-f2-3-1.jdf



DFILE HT-13-187-f2-3-1.jdf
COMINT HT-13-187-f2-3-1.jdf
DATIM 23-06-2012 15:08:05
MENUF
OBNUC 1H
OFR 395.88 MHz
OFRFQ 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 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 1.5000 sec
SCANS 8
ADBIT 16
RGAIN 46
BF 0.05 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
EXPFCM
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 kHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE HT-13-187-f2-3-1.jdf
SF
LKSET 13.20 kHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.0 c
SLVNT CDCl3
XREF 7.26 ppm

HT-13-057-f6-10

F:\201404\todoroki\HT-13\HT-13-057-f6-10-1.jdf

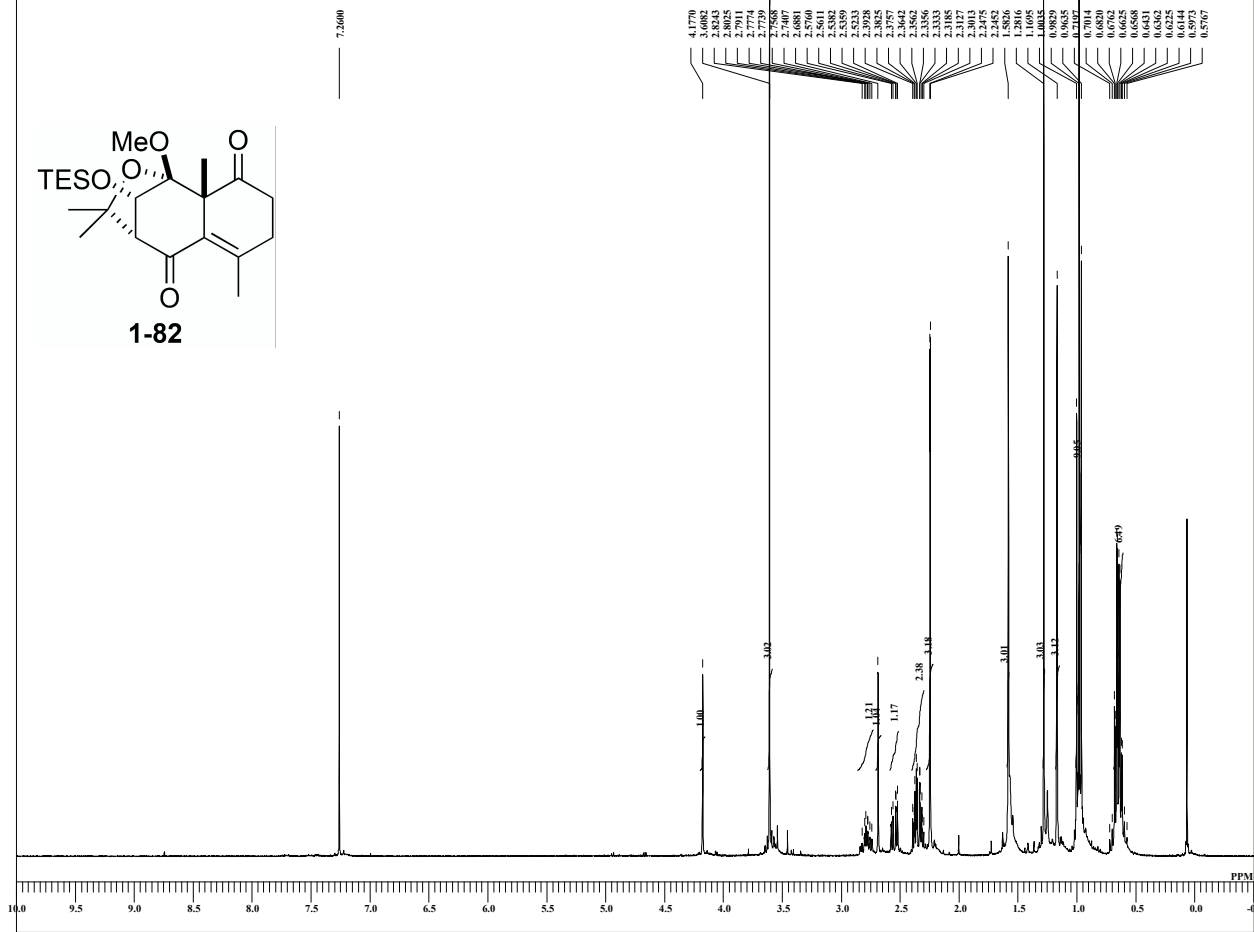


HT-13-057-f6-10-1.jdf
11-07-2012 18:37:46

DFILE	HT-13-057-f6-10-1.jdf
COMINT	HT-13-057-f6-10-1.jdf
DATIM	11-07-2012 18:37:46
MENUF	
OBNUC	1H
OR	395.88 MHz
ORFQ	395.88 MHz
ORSET	6.28 kHz
ORFIN	0.87 Hz
PW1	6.38 usec
DEADT	0.00 usec
PREDL	0.00000 msec
IWT	1.0000 sec
POINT	16384
SPO	16384
TIMES	7
DUMMY	1
FREQU	7422.80 Hz
FLT	30000 Hz
DELAY	16.68 usec
ACQTM	2.2073 sec
PD	1.5000 sec
SCANS	7
ADBIT	16
RGAIN	44
BF	0.05 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	HT-13-057-f6-10-1.jdf
SF	
LKSET	13.20 kHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	25.0 c
SLVNT	CDCl3
EXREF	7.26 ppm

HT-14-043

F:\201404\todoroki\HT-14\HT-14-043-1.jdf

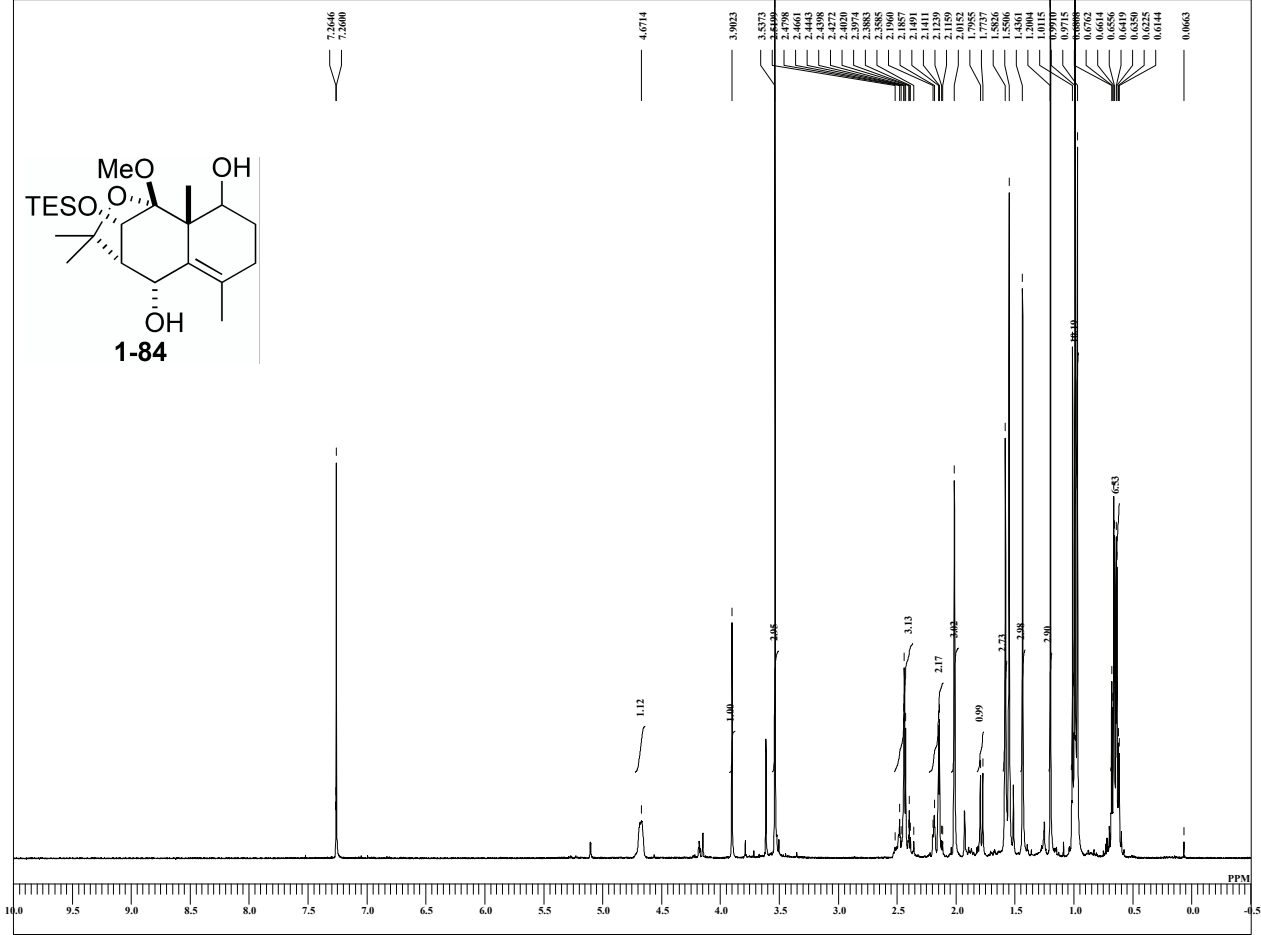


HT-14-043-1.jdf
08-09-2012 16:05:20

DFILE	HT-14-043-1.jdf
COMINT	HT-14-043-1.jdf
DATIM	08-09-2012 16:05:20
MENUF	
OBNUC	1H
OR	395.88 MHz
ORFQ	395.88 MHz
ORSET	6.28 kHz
ORFIN	0.87 Hz
PW1	6.38 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	1.5000 sec
SCANS	8
ADBIT	16
RGAIN	40
BF	0.05 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	HT-14-043-1.jdf
SF	
LKSET	13.20 kHz
LKFIN	75.7 Hz
LKLEV	0
LGAIN	0
LKPHS	0
LKSG	0
CSPED	0 Hz
FILDC	
FILDF	
CTEMP	24.5 c
SLVNT	CDCl3
EXREF	7.26 ppm

HT-14-097-f13-17

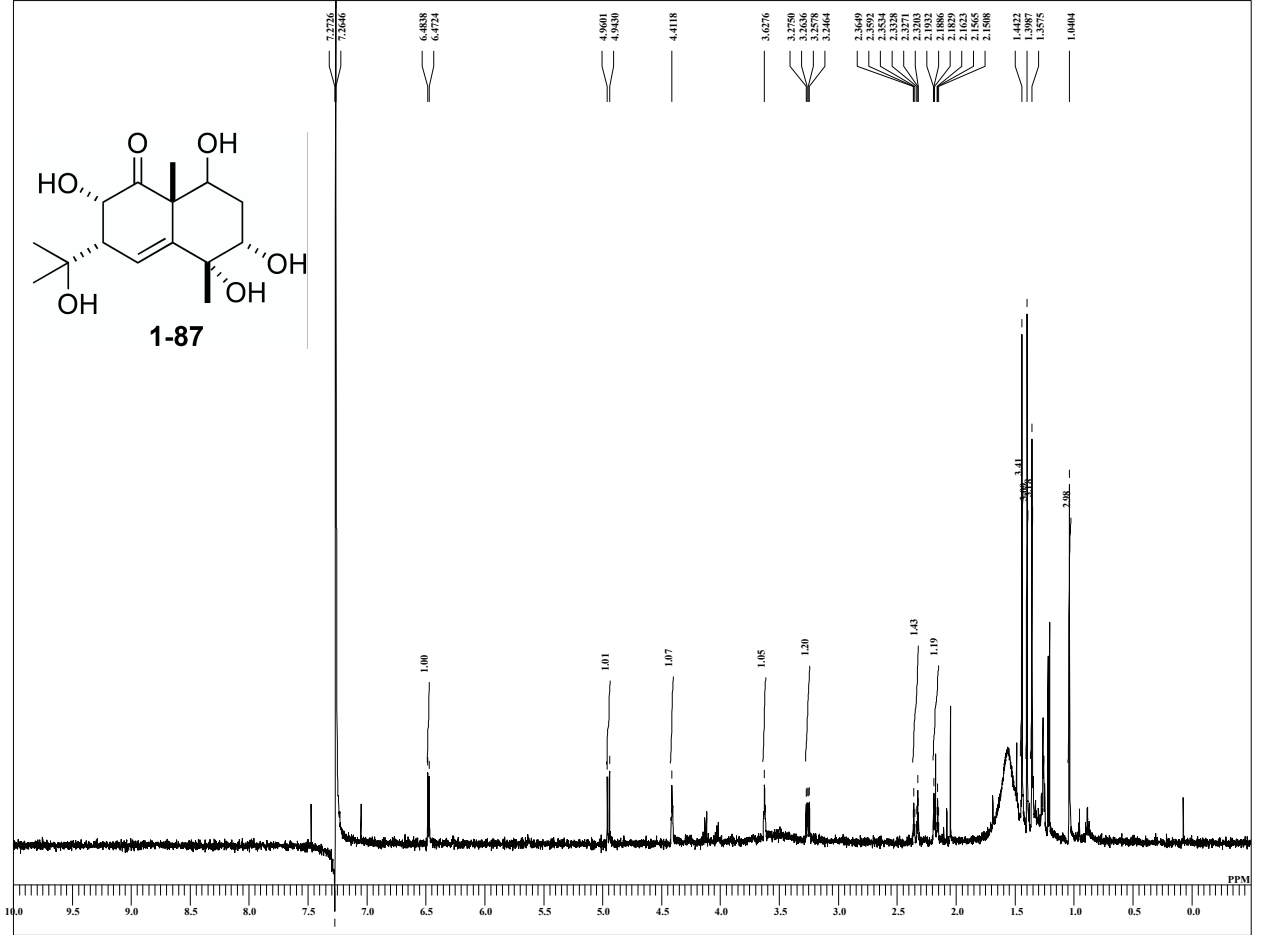
F:\201404\todoroki\HT-14\HT-14-097-f13-17-1.jdf



DFILE HT-14-097-f13-17-1.jdf
COMINT HT-14-097-f13-17
DATIM 29-09-2012 17:14:29
MENUF
OBNUC 1H
OFR 395.88 MHz
OFRFQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PWT 6.38 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 1.5000 sec
SCANS 8
ADBIT 16
RGAIN 40
BF 0.05 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 HT-14-097-f13-17-1.jdf
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.6 c
SLVNT CDCl3
EXREF 7.26 ppm

HT-14-193-prep2

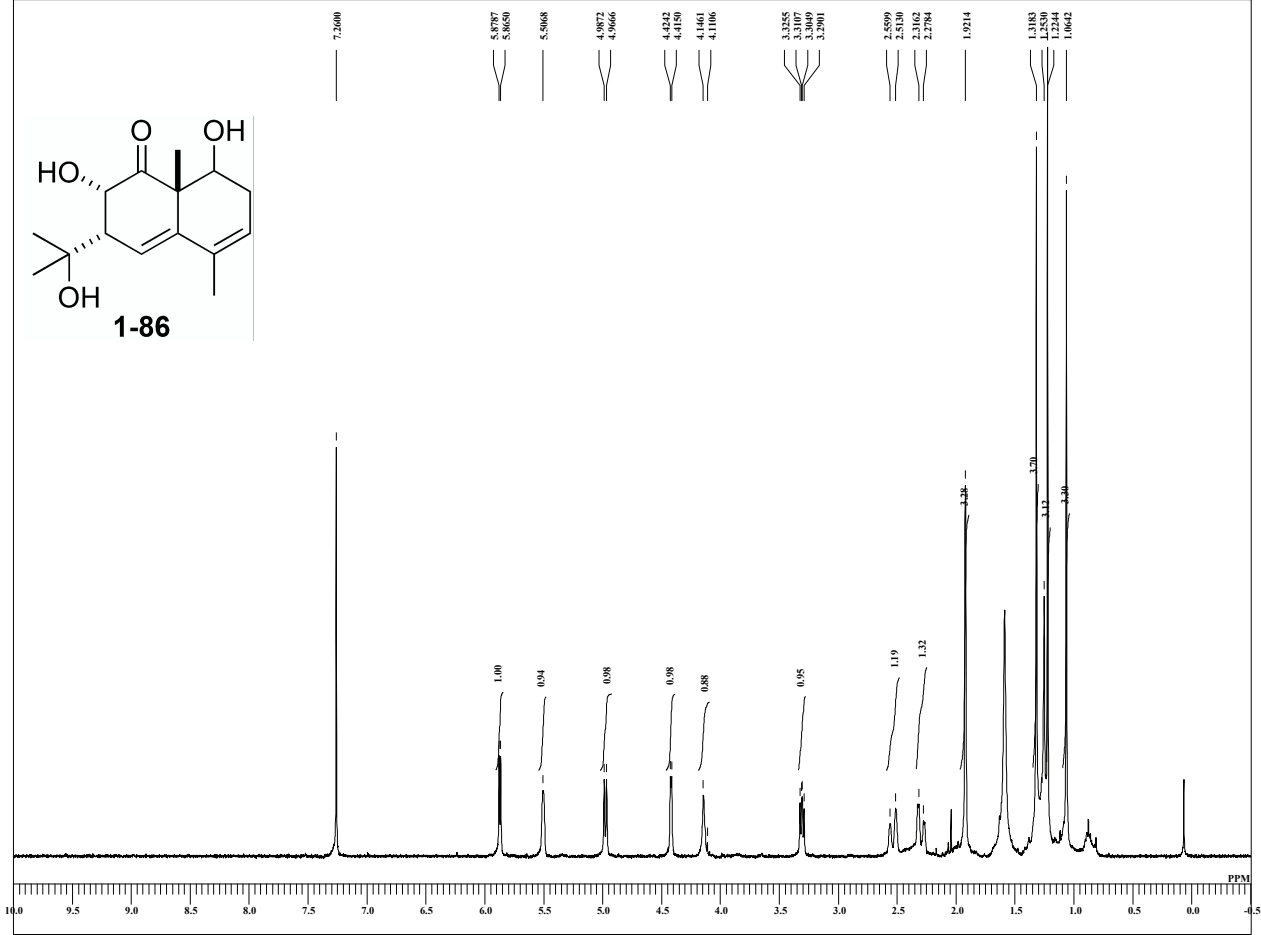
F:\201404\todoroki\HT-14\HT-14-193-prep2.1



DFILE HT-14-193-prep2.1
COMINT HT-14-193-prep2
DATIM 24-10-2012 22:53:19
MENUF
OBNUC 1H
OFR 495.13 MHz
OFRFQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 9.64 Hz
PWT 6.00 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 17
DUMMY 1
FREQU 9286.78 Hz
FLT 38000 Hz
DELAY 13.16 usec
ACQTM 1.7642 sec
PD 1.5000 sec
SCANS 17
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 92 usec
IRATN 79
DFILE HT-14-193-prep2.1
SF
LKSET 748.40 KHz
LKFIN 98.2 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.4 c
SLVNT CDCl3
EXREF 7.26 ppm

HT-14-095-prep

F:\201404\todoroki\HT-14\HT-14-095-prep-1.jdf



HT-14-095-prep-1.jdf

COMET HT-14-095-prep
DATIM 28-09-2012 21:29:38

MENUF
OBNUC 1H
OFR 395.88 MHz
OFRFQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PWI 6.58 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 1.5000 sec
SCANS 8
ADBIT 16
RGAIN 46
BF 0.05 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2

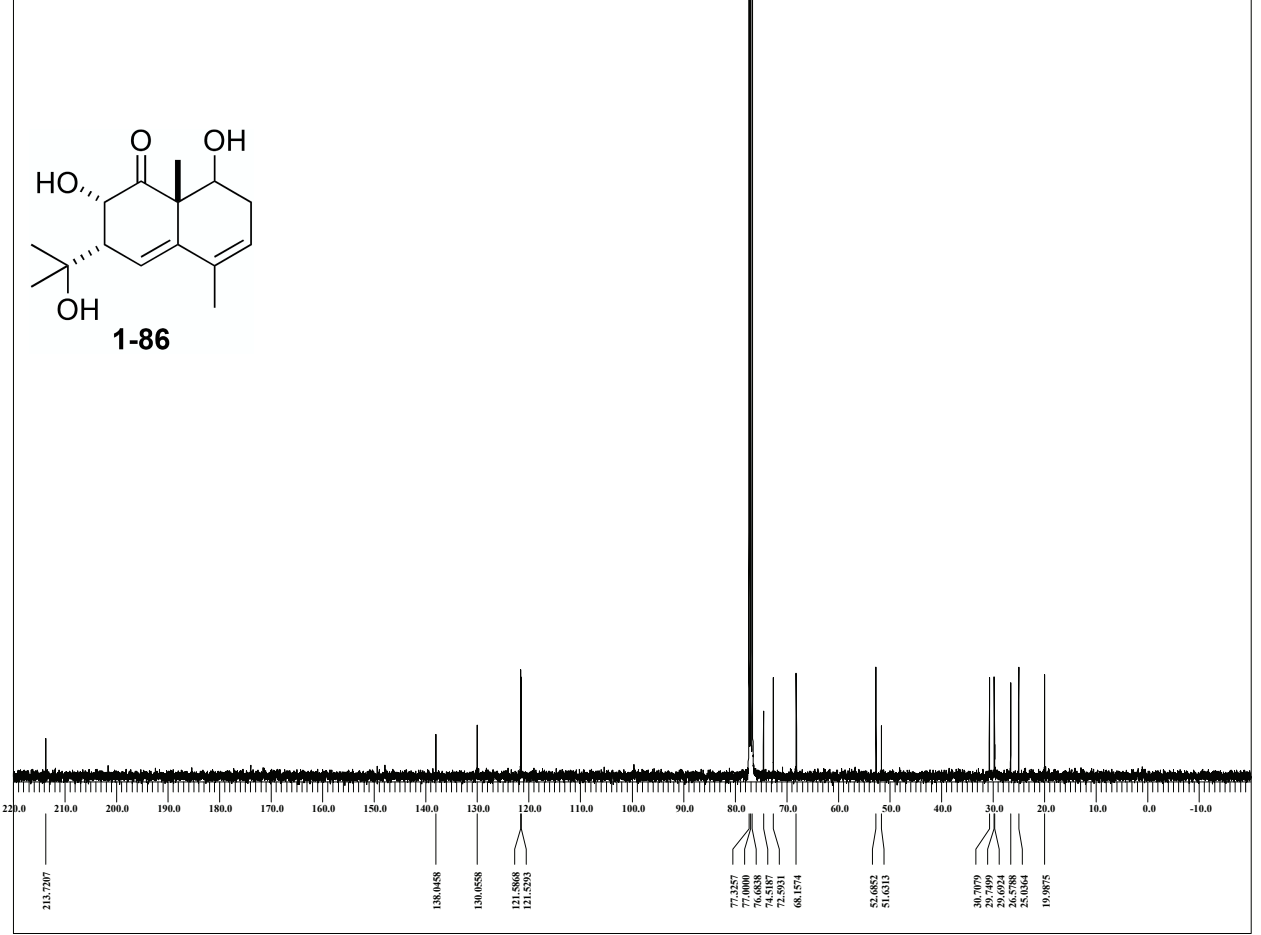
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79

HT-14-095-prep-1.jdf

SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.0 c
SLVNT CDCl₃
EXREF 7.26 ppm

HT-14-095-prep

F:\201404\todoroki\HT-14\HT-14-095-prep-C-1.jdf



HT-14-095-prep-C-1.jdf

COMET HT-14-095-prep
DATIM 29-09-2012 03:41:48

MENUF
OBNUC 13C
OFR 99.55 MHz
OFRFQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PWI 3.25 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 7200
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 7200
ADBIT 16
RGAIN 60
BF 1.00 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec

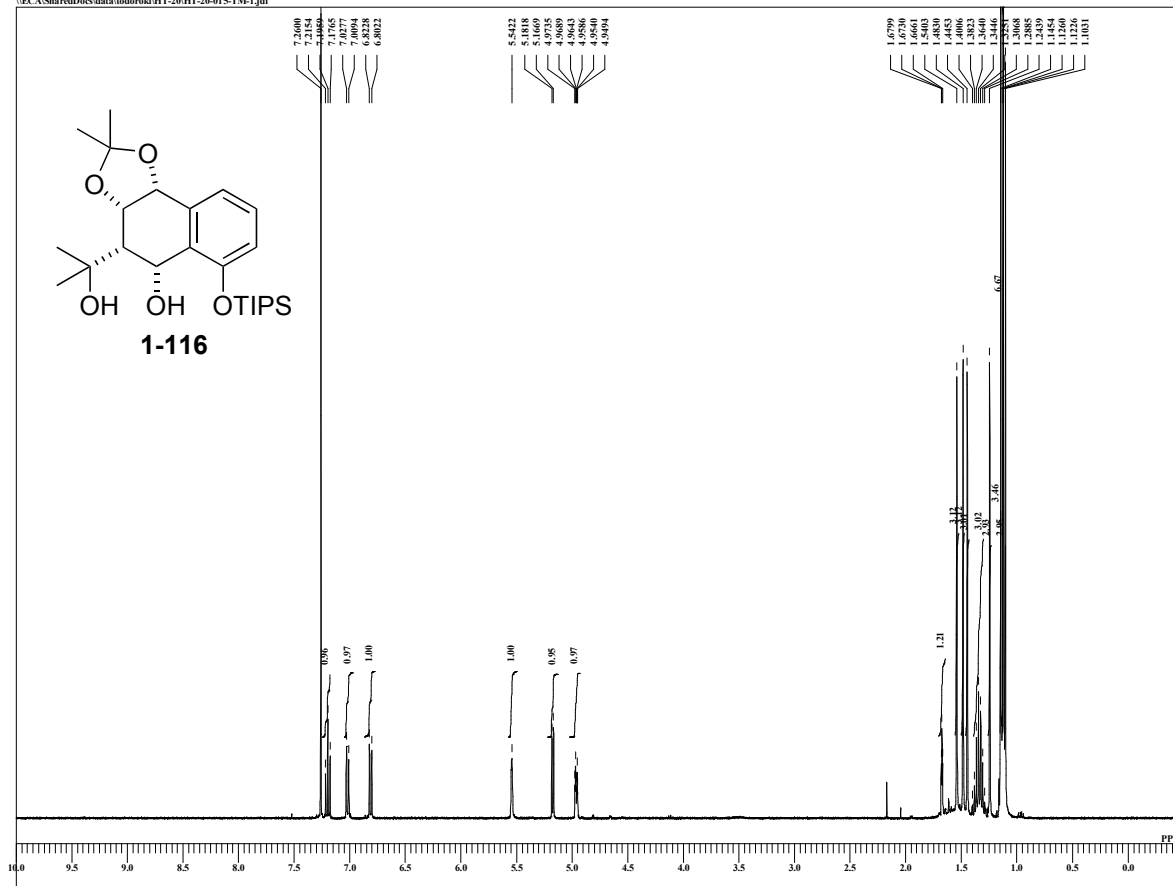
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79

HT-14-095-prep-C-1.jdf

SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 24.3 c
SLVNT CDCl₃
EXREF 77.00 ppm

HT-20-015-TM

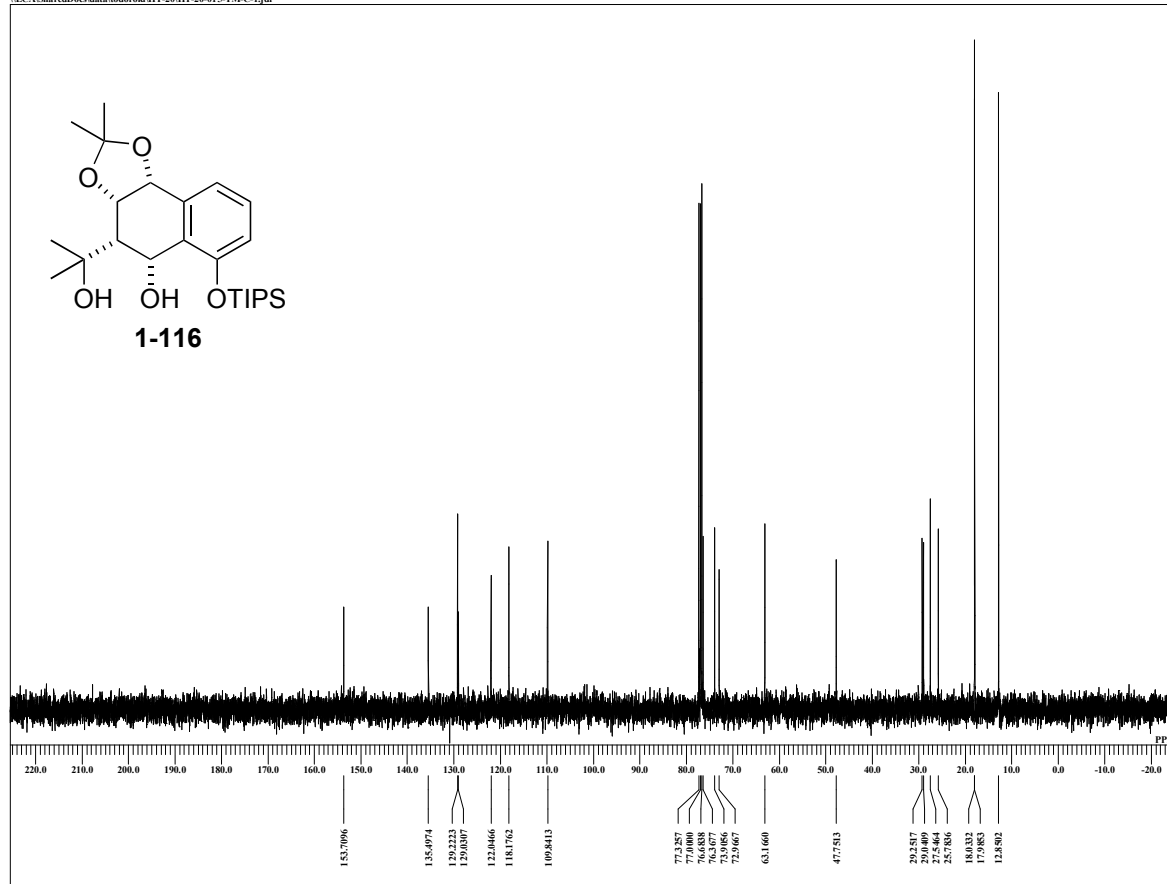
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DFILE HT-20-015-TM-1.jdf
 COMNT HT-20-015-TM
 DATIM 25-10-2013 13:14:42
 MENUF
 OBNUC 1H
 OFR 395.88 MHz
 OFRQ 395.88 MHz
 OBSET 6.28 KHz
 OFBIN 0.87 Hz
 PW1 6.44 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 16384
 SPO 16384
 TIMES 8
 DUMMY 1
 FREQU 7422.80 Hz
 FLT 30000 Hz
 DELAY 16.68 usec
 ACQTM 2.2073 sec
 PD 1.5000 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
 IBSET 6.28 KHz
 IBFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-015-TM-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPIB 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 25.9 e
 SLVNT CDCl3
 EXREF 7.26 ppm

HT-20-015-TM-C

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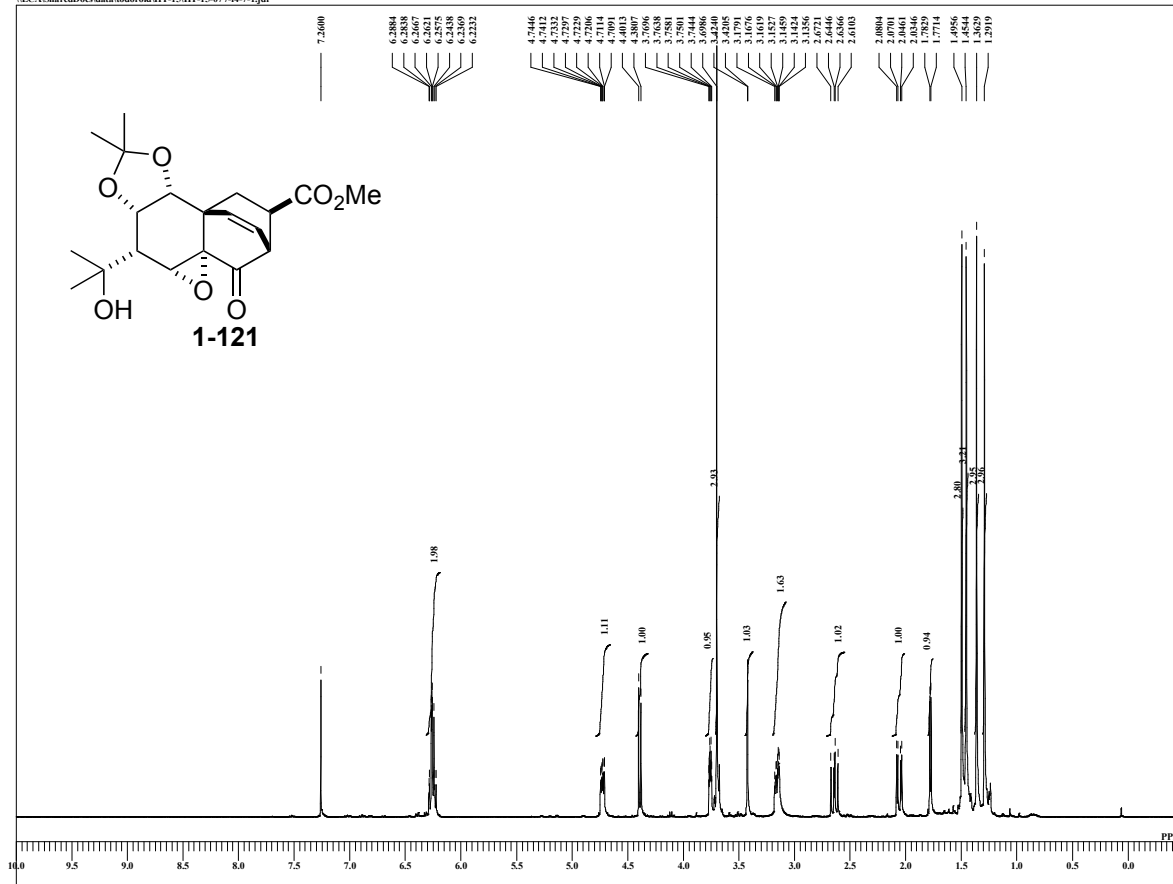
DFILE HT-20-015-TM-C-1.jdf
 COMNT HT-20-015-TM-C
 DATIM 25-10-2013 13:18:01
 MENUF
 OBNUC 13C
 OFR 99.55 MHz
 OFRQ 99.55 MHz
 OBSET 5.13 KHz
 OFBIN 0.98 Hz
 PW1 3.83 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 32768
 SPO 32768
 TIMES 22
 DUMMY 4
 FREQU 31250.00 Hz
 FLT 125000 Hz
 DELAY 20.50 usec
 ACQTM 1.0486 sec
 PD 2.0000 sec
 SCANS 22
 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
 IBSET 6.28 KHz
 IBFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-015-TM-C-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPIB 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 26.0 e
 SLVNT CDCl3
 EXREF 77.00 ppm

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\\ECA\SharedDocs\data\todoroki\HT-17\HT-17-015-C-1.jdf

HT-15-077-f4-7

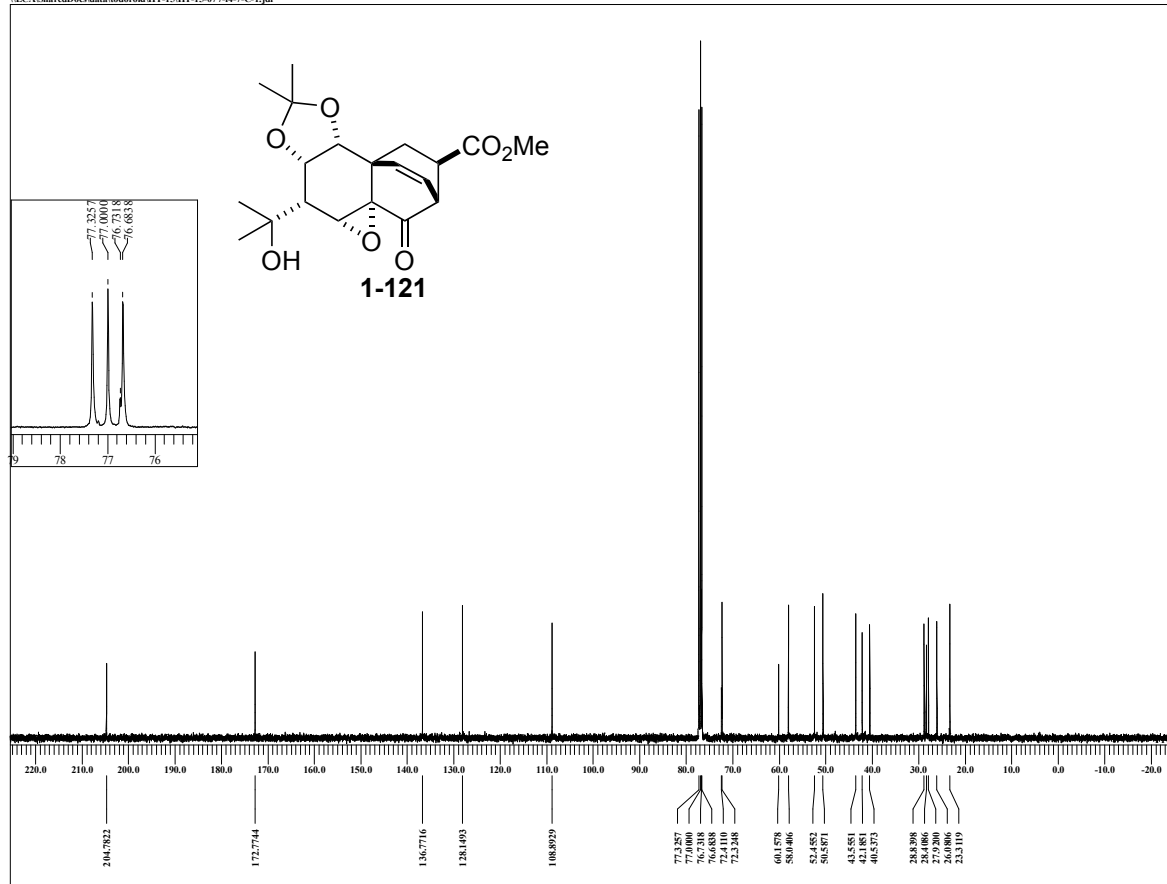
\\ECA\SharedDocs\data\todoroki\HT-15\HT-15-077-f4-7-1.jdf



DFILE HT-15-077-f4-7-1.jdf
 COMNT HT-15-077-f4-7
 DATIM 29-11-2012 11:30:18
 MENUF
 OBNUC ¹H
 OFR 395.88 MHz
 OFBQ 395.88 MHz
 OBSE 6.28 KHz
 OFIN 0.87 Hz
 PW1 6.38 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 1.5000 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
 IRNUC ¹H
 IFR 395.88 MHz
 IBSE 6.28 KHz
 IBF 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-15-077-f4-7-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDW
 CTMP 20.6 e
 SLVNT CDCl₃
 EXREF 7.26 ppm

HT-15-077-f4-7

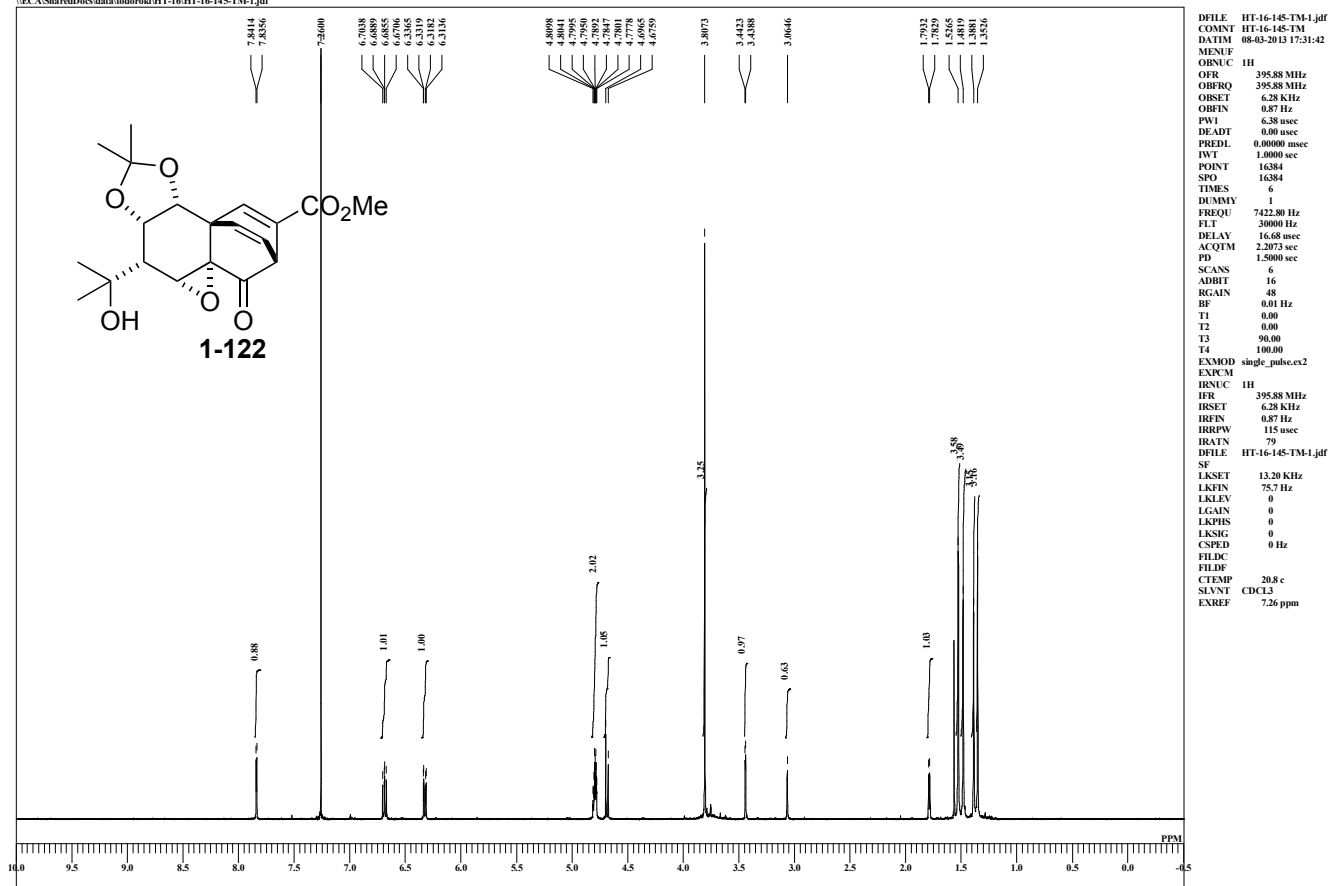
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DFILE HT-15-077-f4-7-C-1.jdf
 COMNT HT-15-077-f4-7
 DATIM 29-11-2012 13:00:50
 MENUF
 OBNUC ¹³C
 OFR 99.55 MHz
 OFBQ 99.55 MHz
 OBSE 5.13 KHz
 OFIN 0.98 Hz
 PW1 3.25 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 32768
 SPO 32768
 TIMES 1146
 DUMMY 4
 FREQU 31250.00 Hz
 FLT 125000 Hz
 DELAY 20.50 usec
 ACQTM 1.0486 sec
 PD 2.0000 sec
 SCANS 1146
 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 ¹³C
 IFR 99.55 MHz
 IBSE 5.13 KHz
 IBF 0.98 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-15-077-f4-7-C-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDW
 CTMP 20.8 e
 SLVNT CDCl₃
 EXREF 77.00 ppm

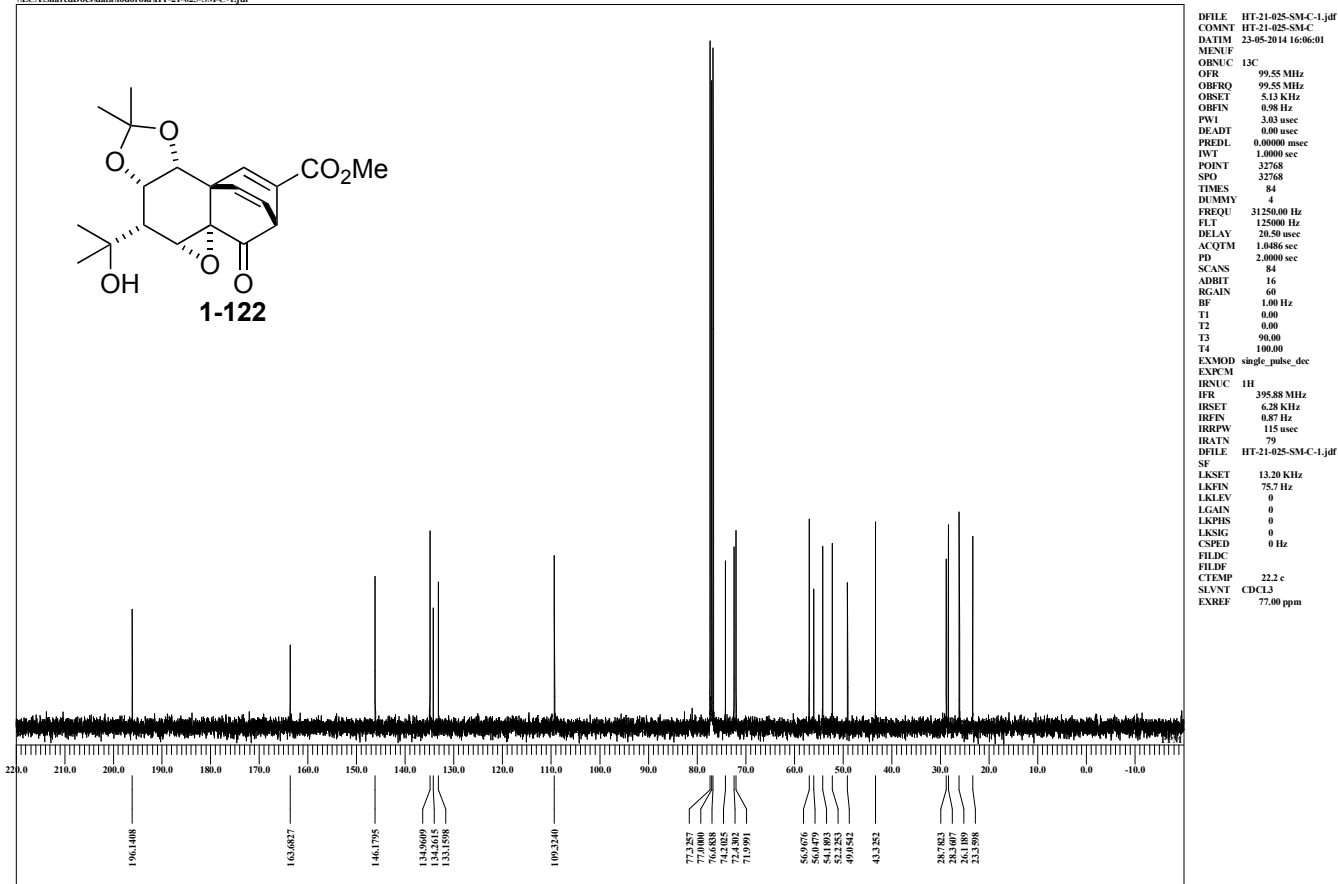
HT-16-145-TM

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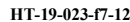


HT-21-025-SM-C

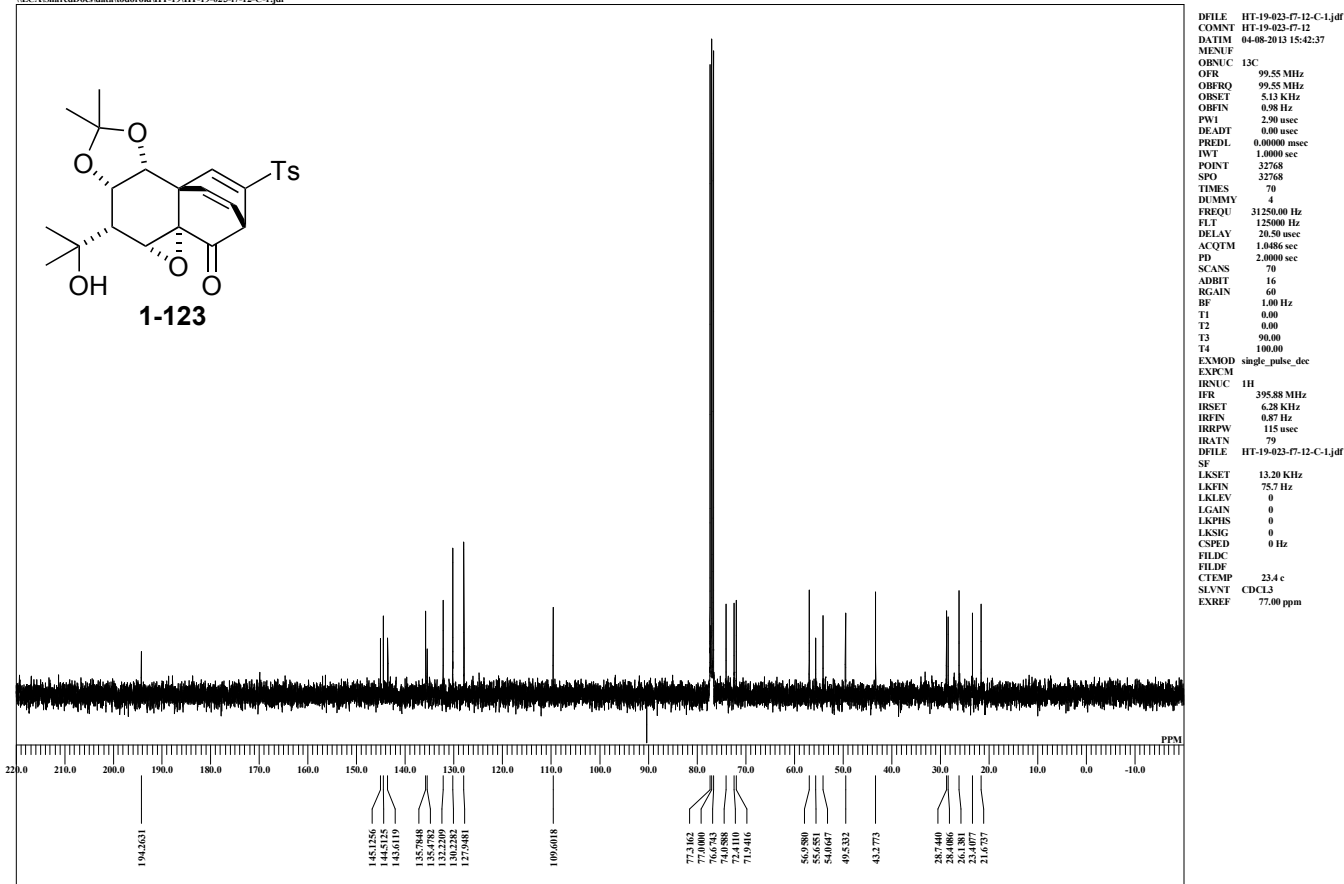
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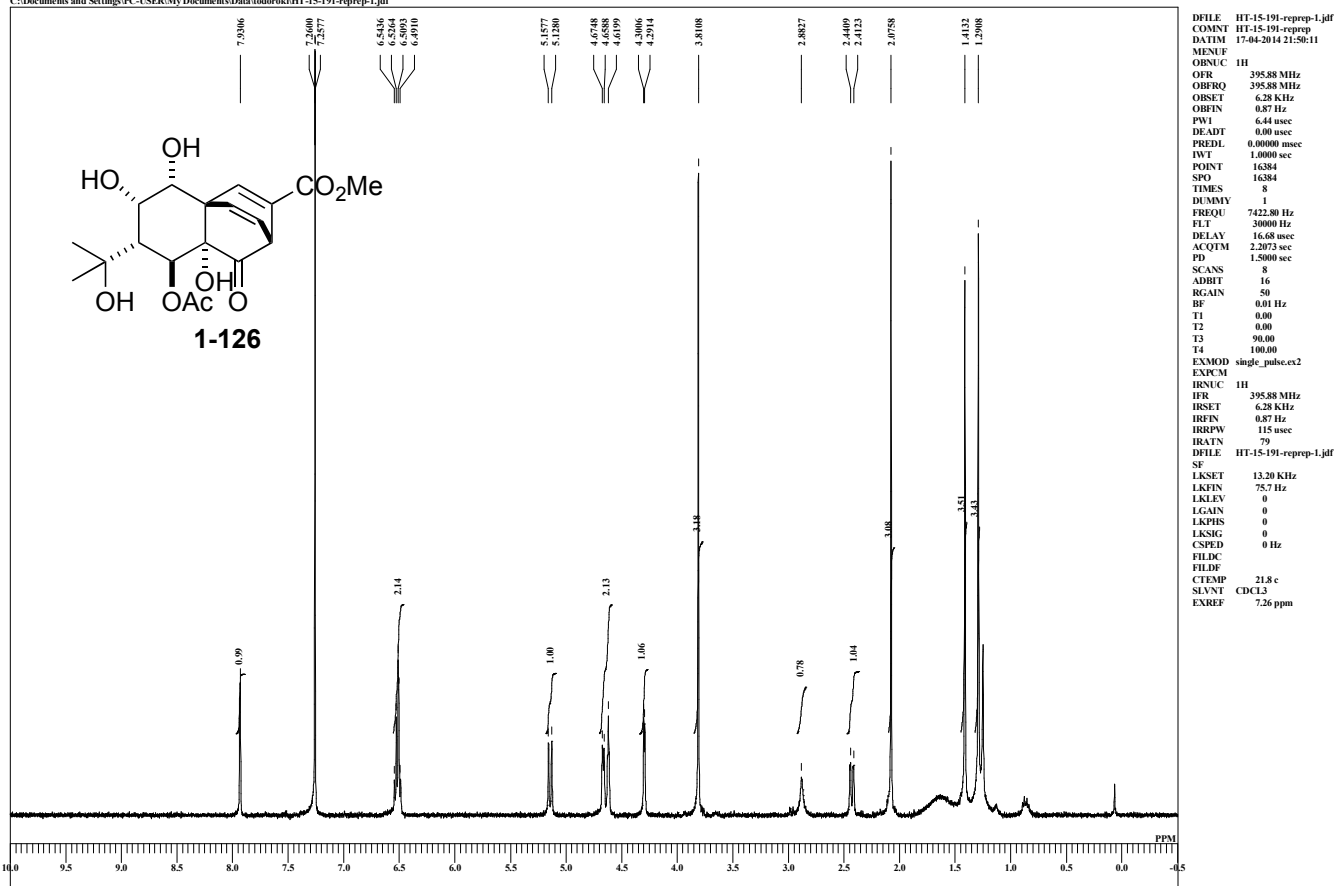


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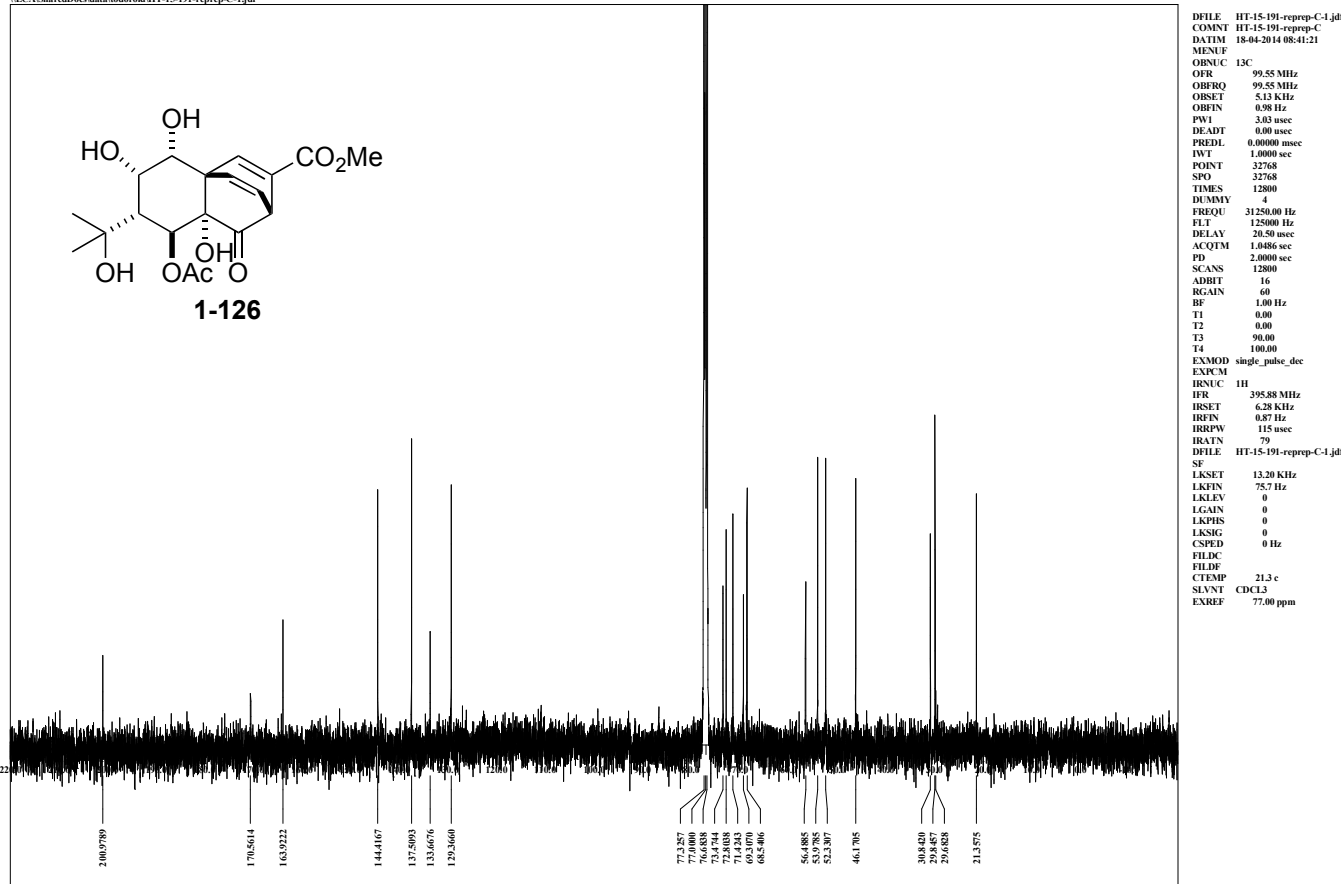
HT-15-191-reprep

C:\Documents and Settings\PC-USER\My Documents\data\todoroki\HT-15-191-reprep-1.jdf

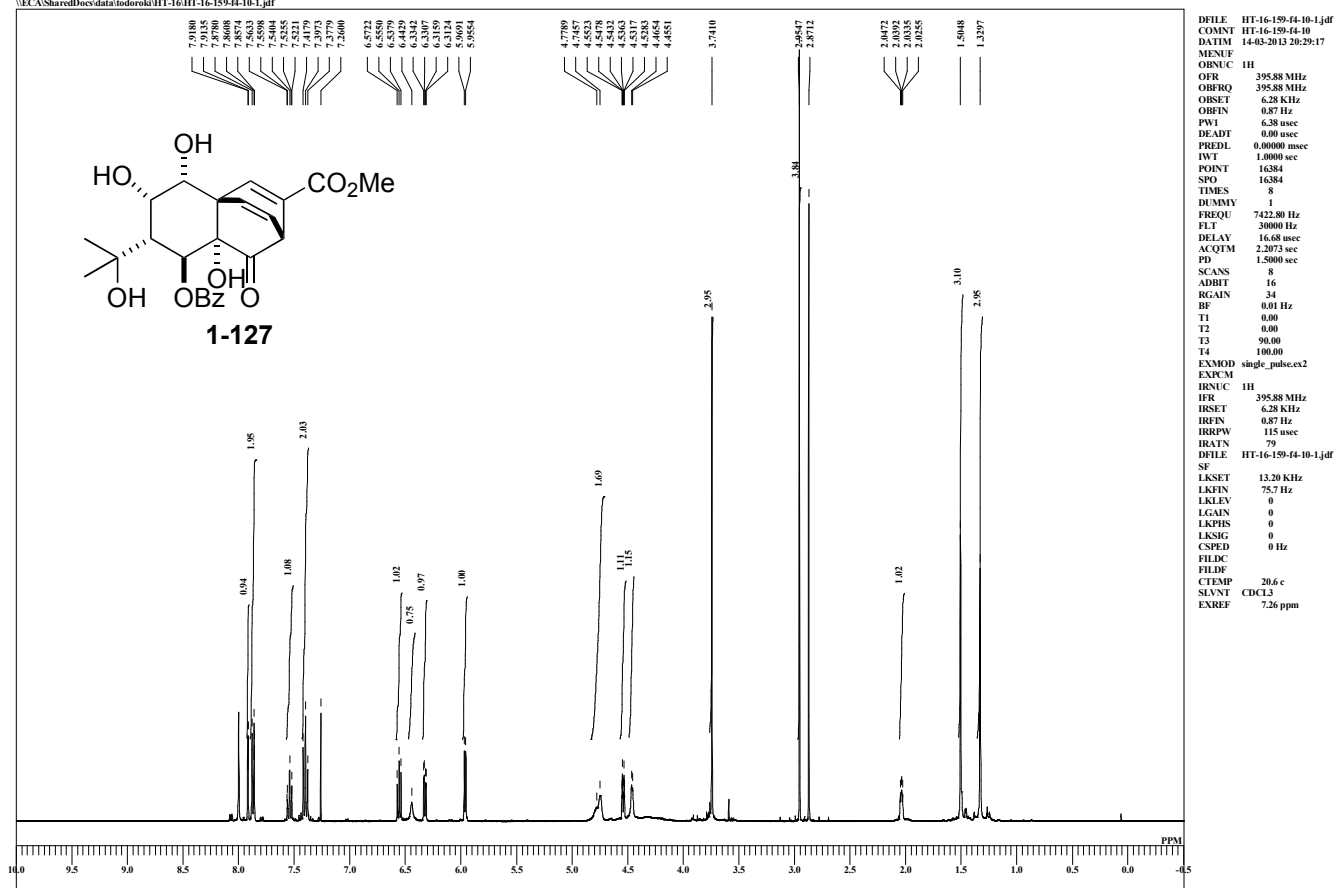


HT-15-191-reprep-C

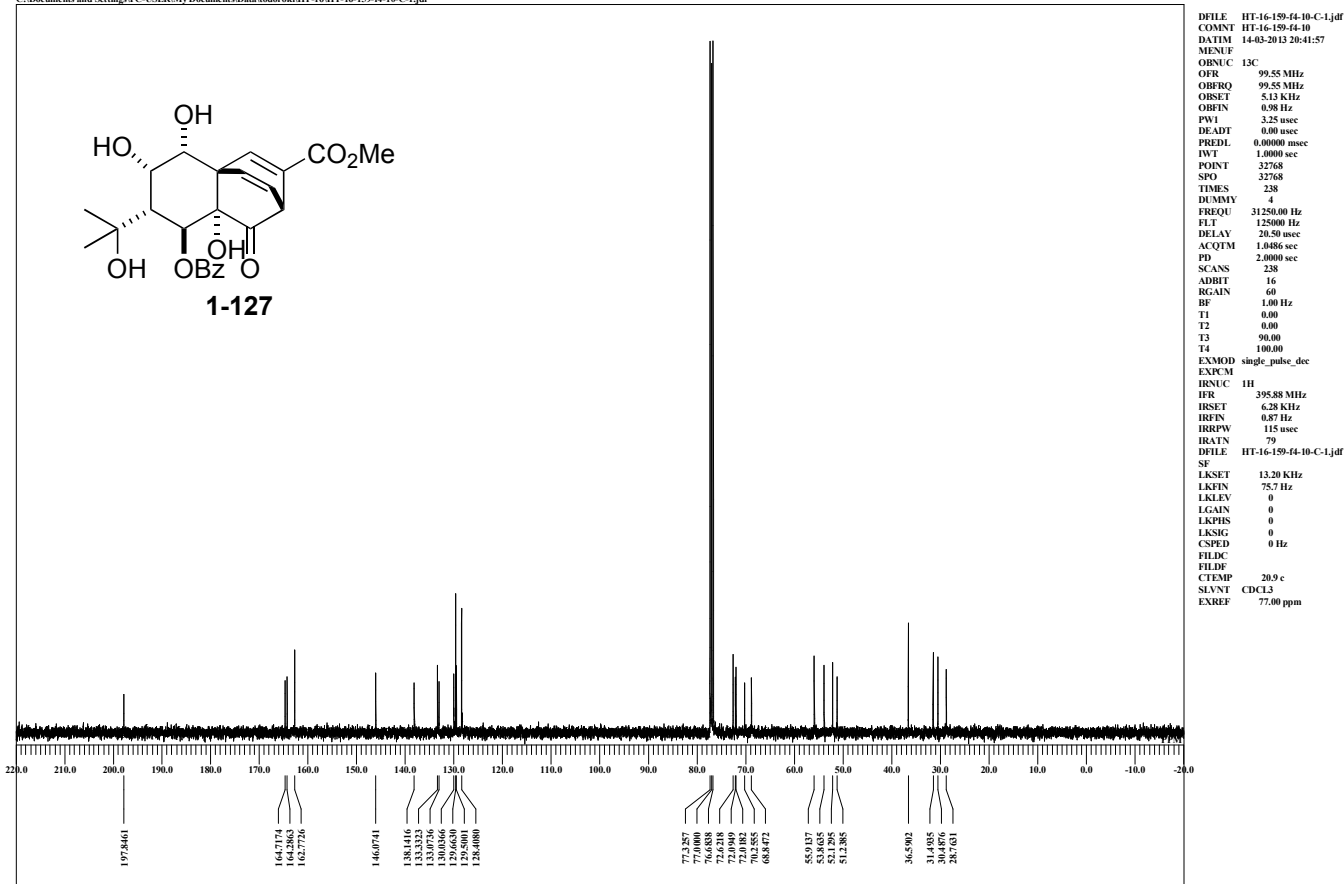
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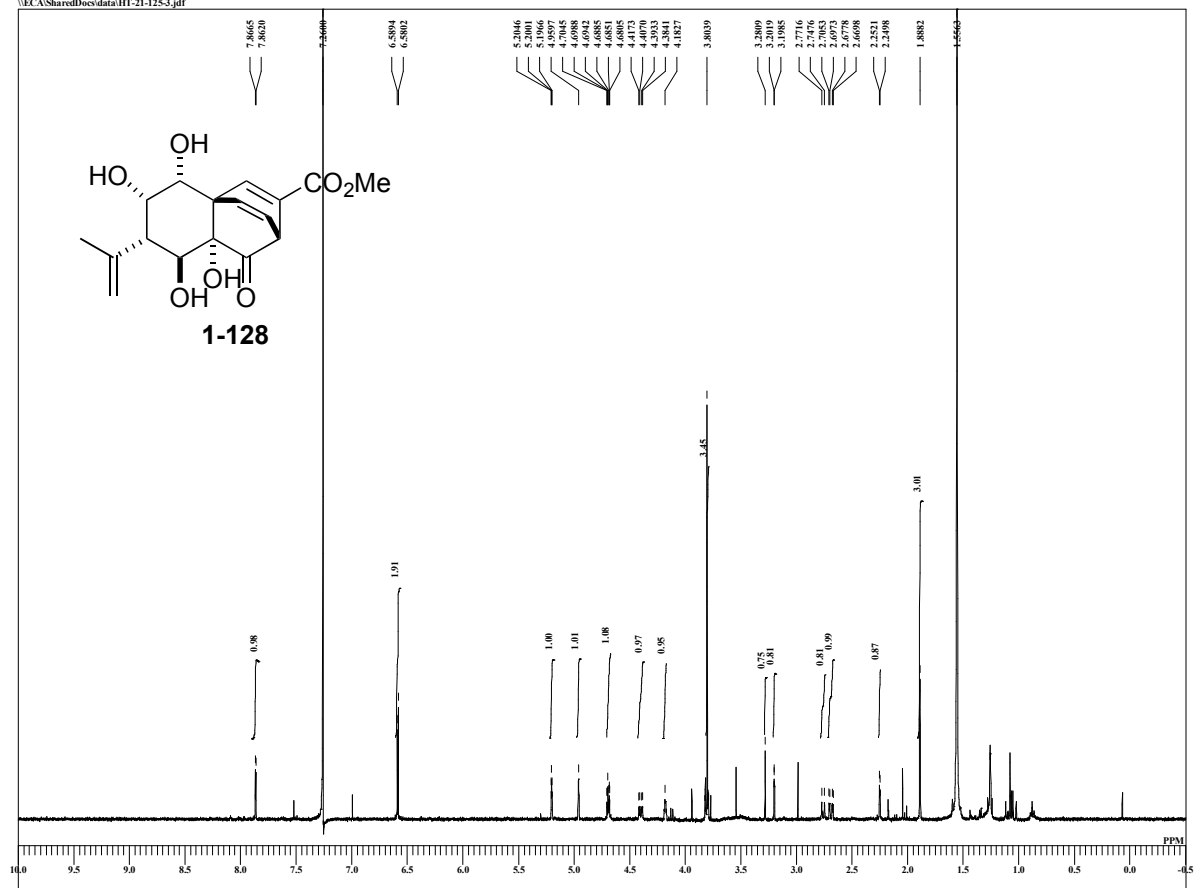


C:\Documents and Settings\PC-USER\My Documents\Data\todoroki\HT-16\HT-16-159-f4-10-C-1.jdf



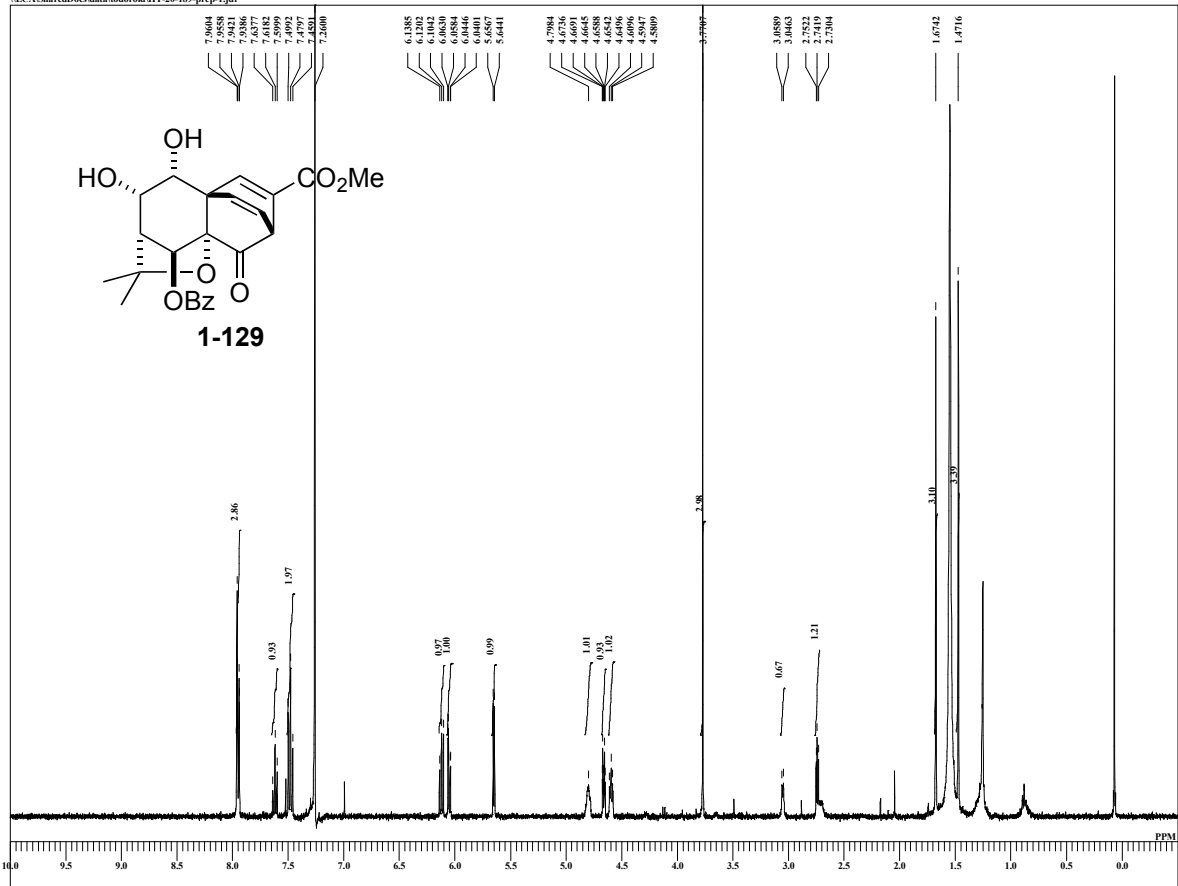
HT-21-125

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HT-20-189-prep

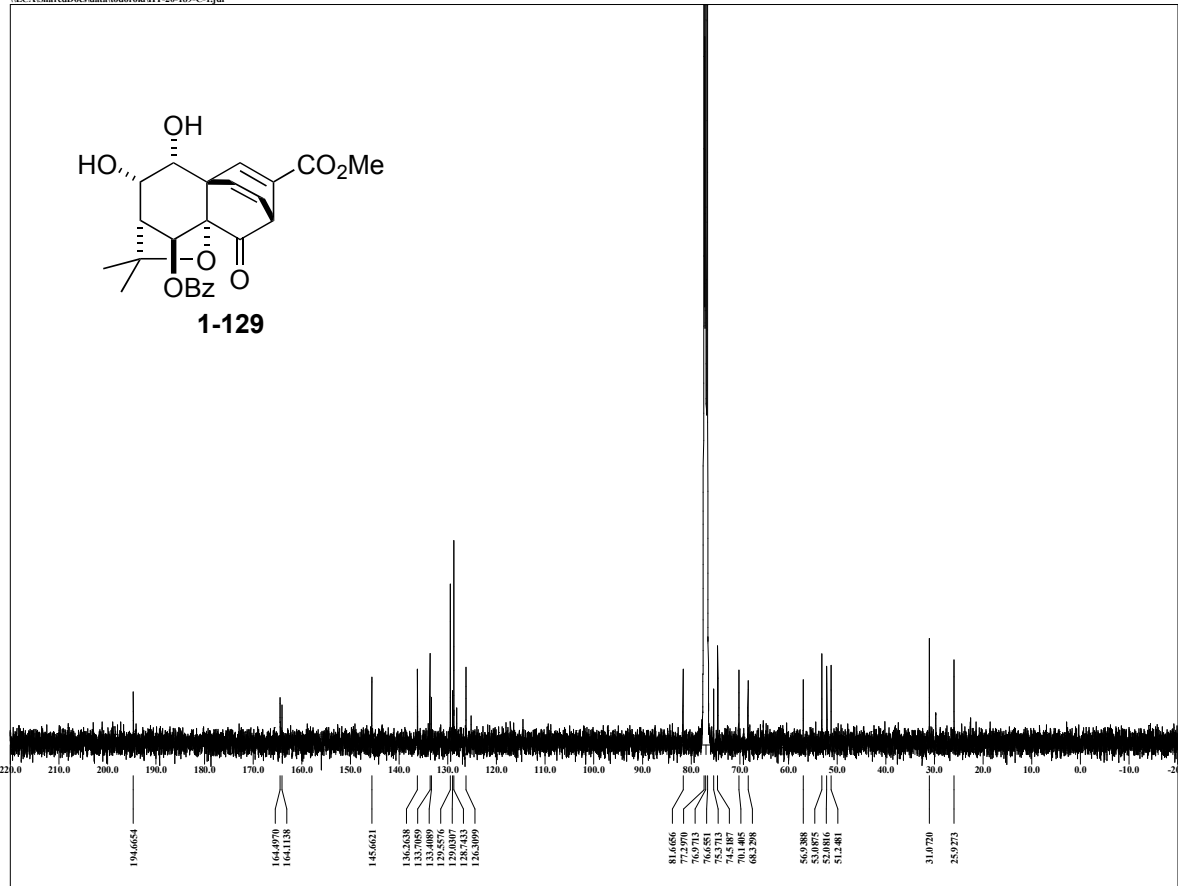
\\ECA\SharedDocs\data\ndoroki\HT-20-189-prep-1.jdf



DFILE HT-20-189-prep-1.jdf
 COMNT HT-20-189-prep
 DATIM 14-04-2014 20:22:07
 MENUF
 OBNUC 1H
 OFR 395.88 MHz
 OFBQ 395.88 MHz
 OBSE 6.28 KHz
 OFBN 0.87 Hz
 PW1 6.44 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 16384
 SPO 16384
 TIMES 40
 DUMMY 1
 FREQU 7422.80 Hz
 FLT 30000 Hz
 DELAY 16.68 usec
 ACQTM 2.2073 sec
 PD 1.5000 sec
 SCANS 40
 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 395.88 MHz
 IBSE 6.28 KHz
 IBFN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-189-prep-1.jdf
 SF
 LKSET 13.20 KHz
 LKFN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDW
 CTEMP 21.6 c
 SLVNT CDCl3
 EXREF 7.26 ppm

HT-20-189-C

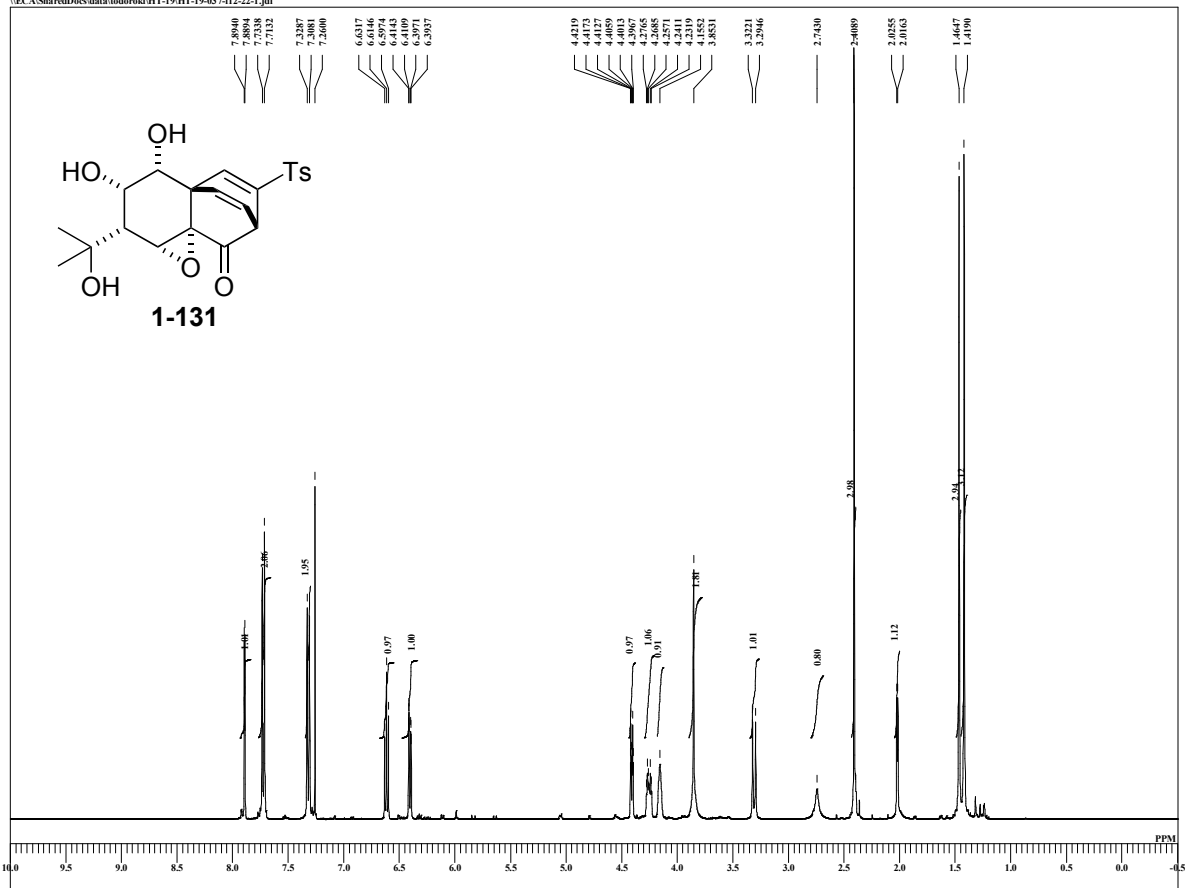
\\ECA\SharedDocs\data\ndoroki\HT-20-189-C-1.jdf



DFILE HT-20-189-C-1.jdf
 COMNT HT-20-189-C
 DATIM 26-05-2014 06:37:02
 MENUF
 OBNUC 13C
 OFR 99.55 MHz
 OFBQ 99.55 MHz
 OBSE 5.13 KHz
 OFBN 0.98 Hz
 PW1 3.83 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 32768
 SPO 32768
 TIMES 4200
 DUMMY 4
 FREQU 31250.00 Hz
 FLT 125000 Hz
 DELAY 20.50 usec
 ACQTM 1.0486 sec
 PD 2.0000 sec
 SCANS 4200
 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
 IBSE 6.28 KHz
 IBFN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-189-C-1.jdf
 SF
 LKSET 13.20 KHz
 LKFN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDW
 CTEMP 21.6 c
 SLVNT CDCl3
 EXREF 77.00 ppm

HT-19-037-f12-22

\\ECA\SharedDocs\data\ndoroki\HT-19\HT-19-037-f12-22-1.jdt



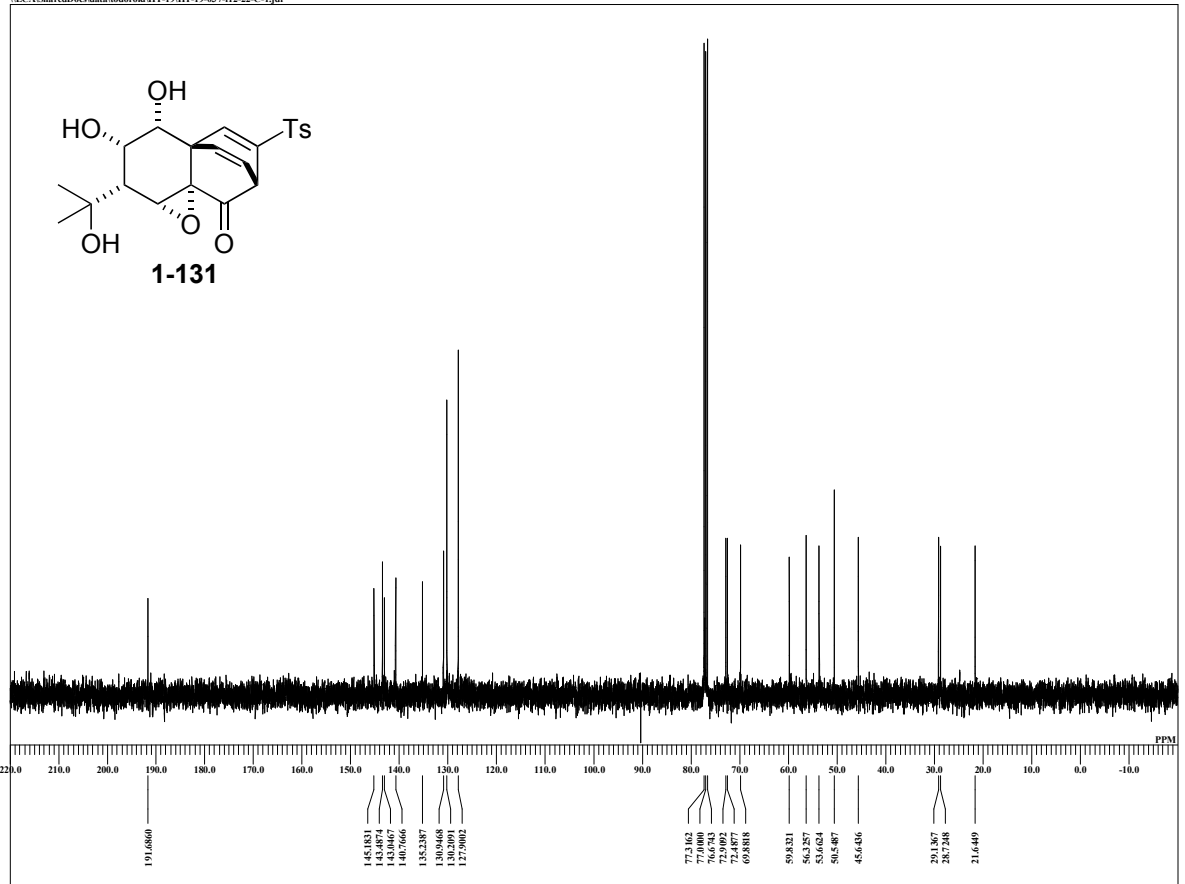
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D1FILE HT-19-037-f12-22-1.jdt
COMNT HT-19-037-f12-22
DATIM 10-08-2013 21:06:18
MENUF
OBNUC 1H
OFR 395.88 MHz
OFRQ 395.88 MHz
OBSET 6.28 KHz
OBFN 0.87 Hz
PW1 6.50 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 1.5000 usec
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
IRNUC 1H
IFR 395.88 MHz
IRFQ 395.88 MHz
IRSET 6.28 KHz
IRFN 0.87 Hz
IRRPW 115 usec
IRATN 79
D1FILE HT-19-037-f12-22-1.jdt
SF
LKSET 13.20 KHz
LKFN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.3 c
SLVNT CDCl3
EXREF 7.26 ppm

```

HT-19-037-f12-22

\\ECA\SharedDocs\data\ndoroki\HT-19\HT-19-037-f12-22-C-1.jdt

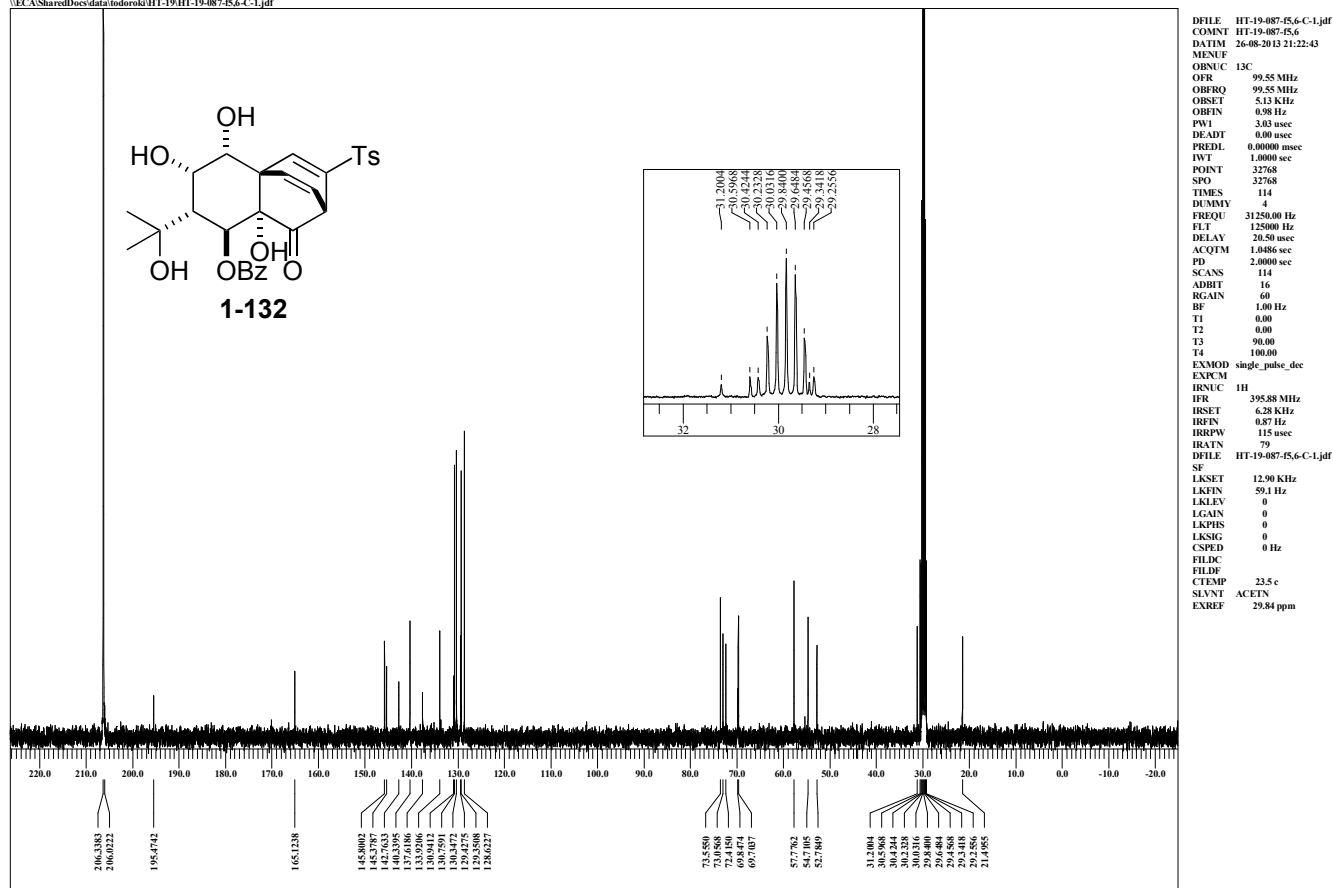
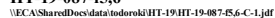


```

D1FILE HT-19-037-f12-22-C-1.jdt
COMNT HT-19-037-f12-22
DATIM 10-08-2013 21:08:33
MENUF
OBNUC 13C
OFR 99.55 MHz
OFRQ 99.55 MHz
OBSET 5.13 KHz
OBFN 0.98 Hz
PW1 2.90 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 29
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 29
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
IRFQ 395.88 MHz
IRSET 6.28 KHz
IRFN 0.87 Hz
IRRPW 115 usec
IRATN 79
D1FILE HT-19-037-f12-22-C-1.jdt
SF
LKSET 13.20 KHz
LKFN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.5 c
SLVNT CDCl3
EXREF 77.00 ppm

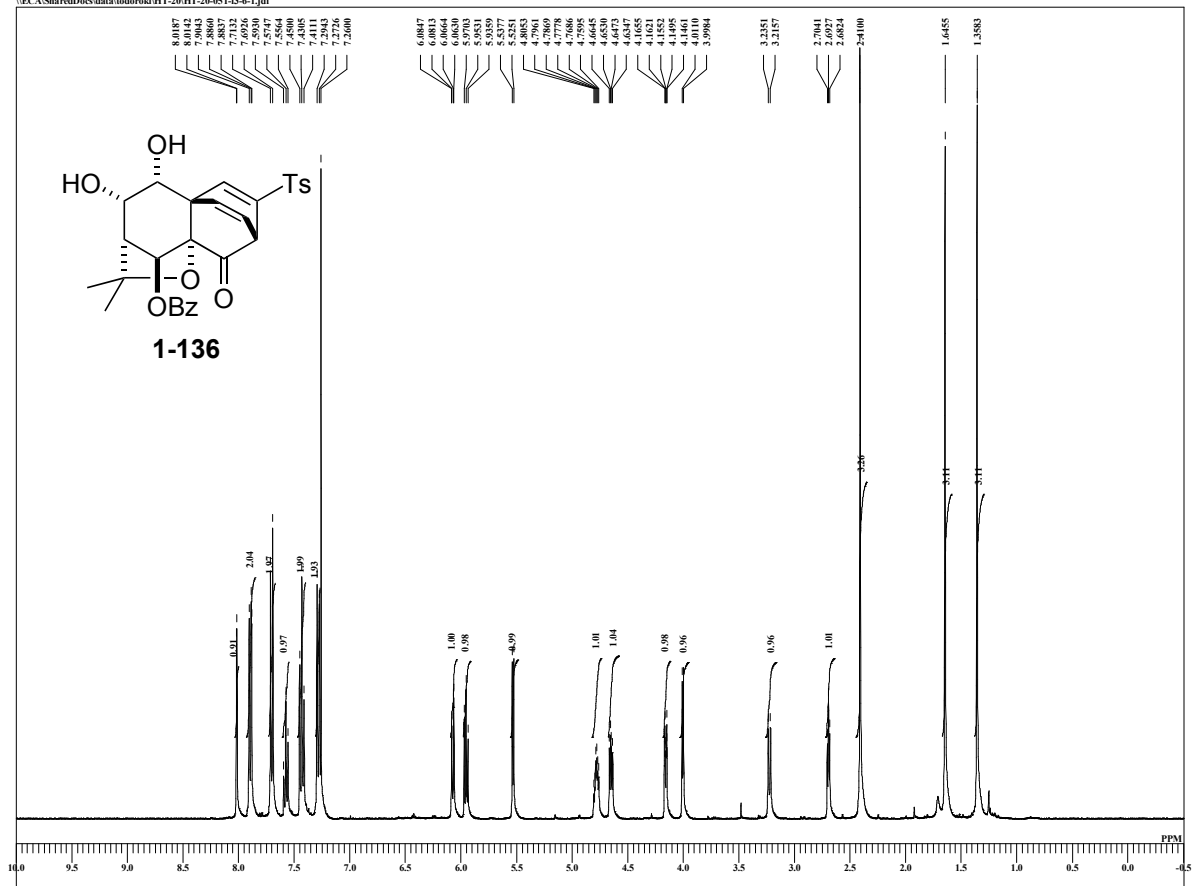
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HT-20-051-f3-6

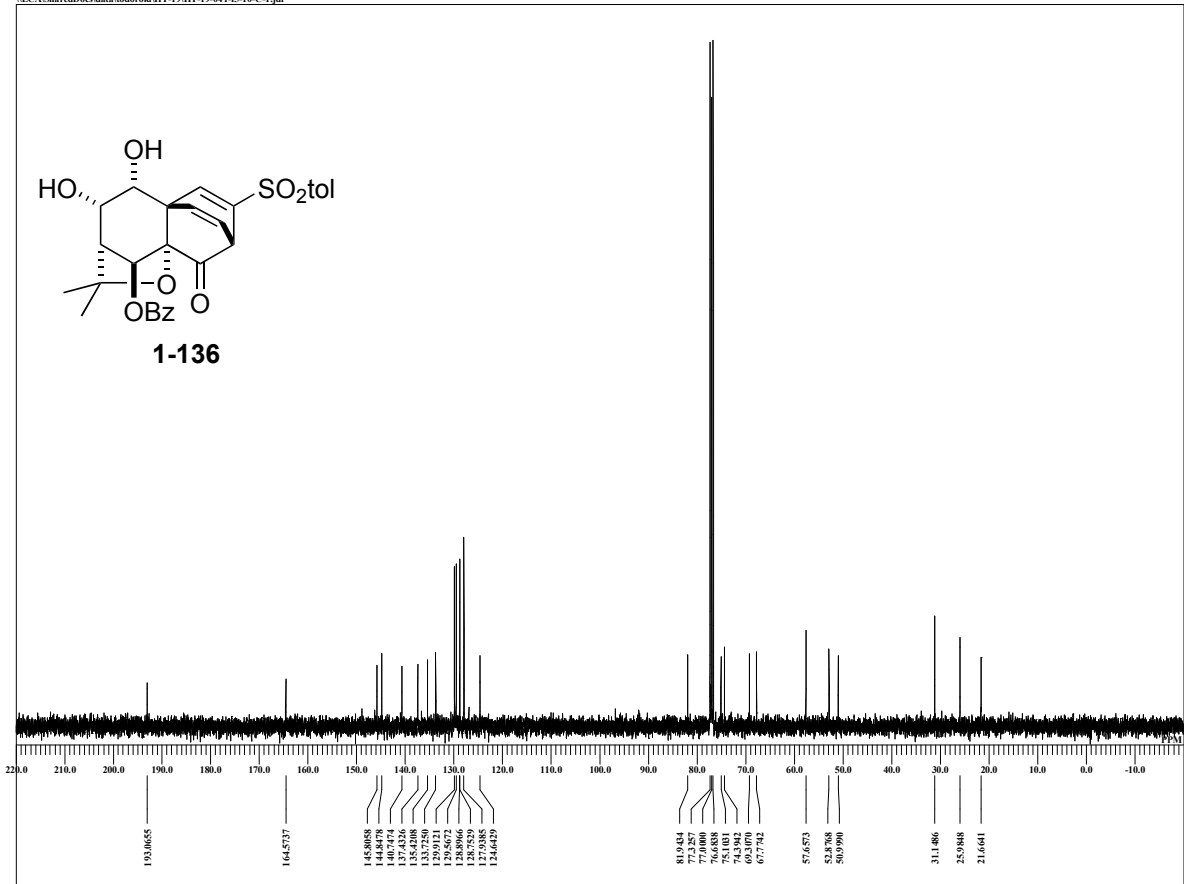
\\ECA\SharedDocs\data\todoroki\HT-20\HT-20-051-f3-6-1.jdf



DFILE HT-20-051-f3-6-1.jdf
 COMNT HT-20-051-f3-6
 DATIM 11-11-2013 16:55:57
 MENUF
 MENUC
 OBNUC 1H
 OFR 395.88 MHz
 OFBRQ 395.88 MHz
 OBSET 6.28 KHz
 OFBIN 0.87 Hz
 PW1 6.44 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 1.5000 usec
 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 395.88 MHz
 IBSET 6.28 KHz
 IBFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-051-f3-6-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 23.0 e
 SLVNT CDCl3
 EXREF 7.26 ppm

HT-19-041-f5-10

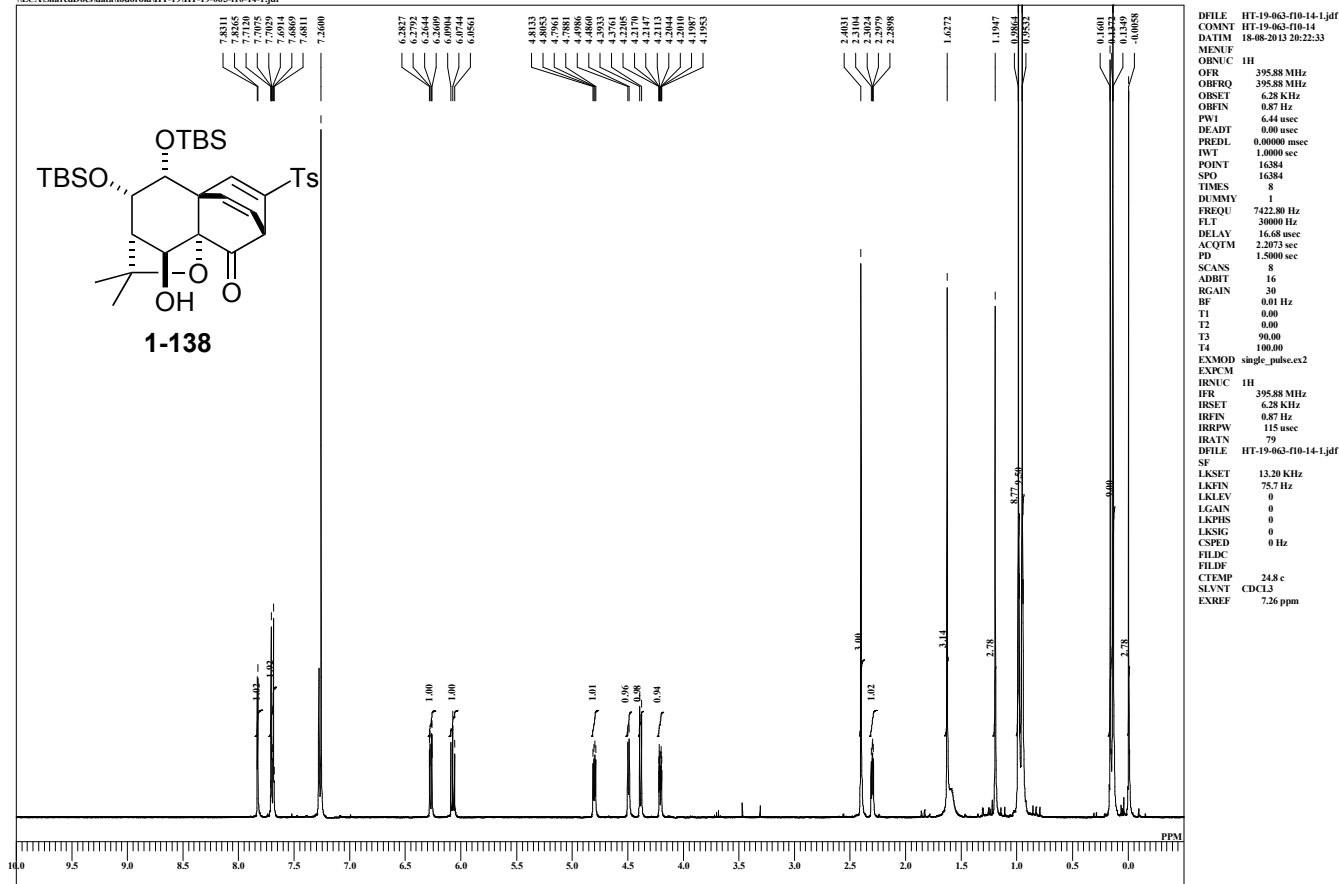
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DFILE HT-19-041-f5-10-C-1.jdf
 COMNT HT-19-041-f5-10
 DATIM 07-08-2013 22:17:26
 MENUF
 MENUC
 OBNUC 13C
 OFR 99.55 MHz
 OFBRQ 99.55 MHz
 OBSET 5.13 KHz
 OFBIN 0.98 Hz
 PW1 2.90 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 32768
 SPO 32768
 TIMES 103
 DUMMY 4
 FREQU 31250.00 Hz
 FLT 125000 Hz
 DELAY 20.50 usec
 ACQTM 1.0486 sec
 PD 2.0000 sec
 SCANS 103
 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
 IBSET 6.28 KHz
 IBFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-19-041-f5-10-C-1.jdf
 SF
 LKSET 13.20 KHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 25.0 e
 SLVNT CDCl3
 EXREF 77.00 ppm

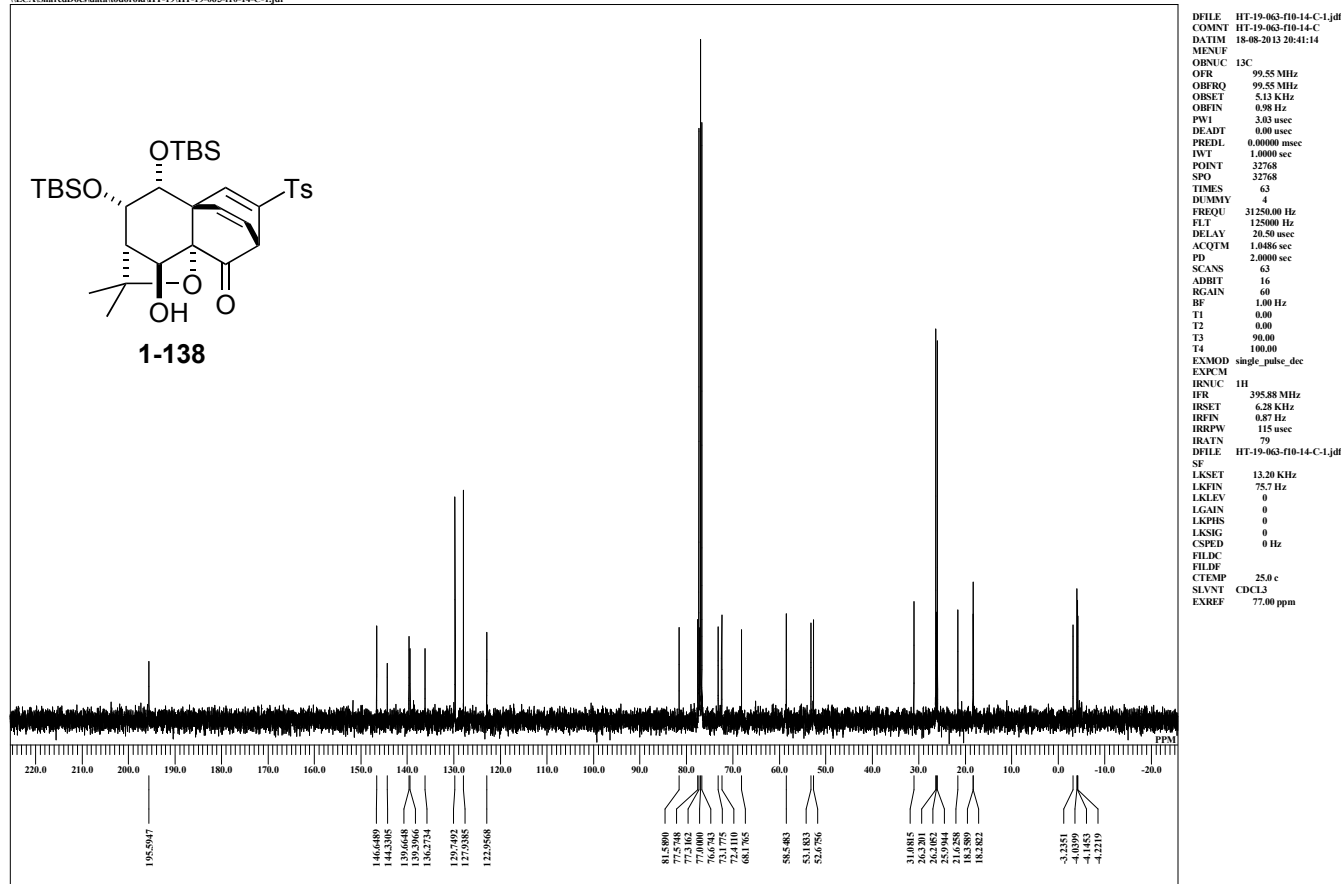
HT-19-063-f10-14

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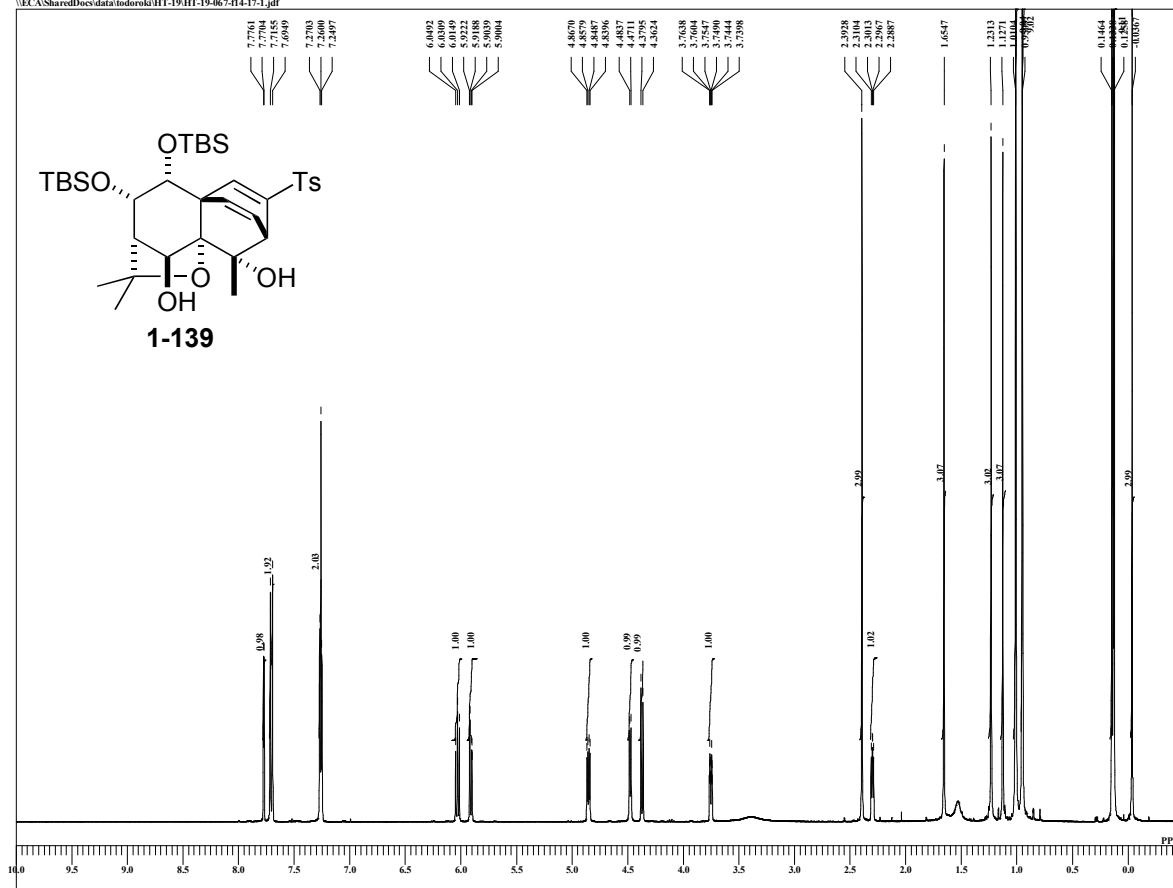
HT-19-063-f10-14-C

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HT-19-067-f14-17

\\ECA\SharedDocs\data\todoroki\HT-19\HT-19-067-f14-17-1.jdt



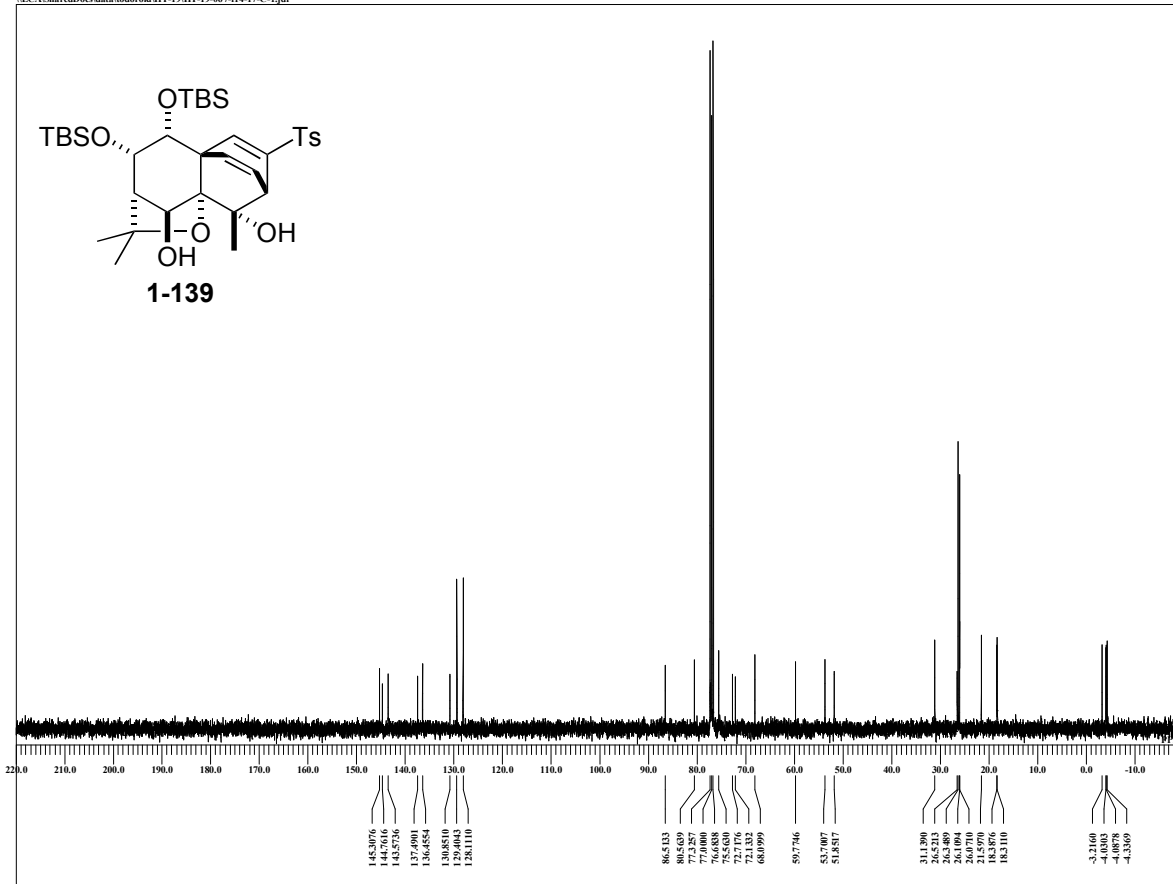
```

DFILE HT-19-067-f14-17-1.jdt
COMNT HT-19-067-f14-17
DATIM 19-08-20 13 14:07:38
MENUF
MENUC
OBNUC 1H
OFR 395.88 MHz
OFRQ 395.88 MHz
OBSET 6.28 KHz
OBFN 0.87 Hz
PW1 6.44 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 1.5000 usec
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
IRFN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE HT-19-067-f14-17-1.jdt
SF
LKSET 13.20 KHz
LKFN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.2 c
SLVNT CDCl3
EXREF 7.26 ppm

```

HT-19-067-f14-17-C

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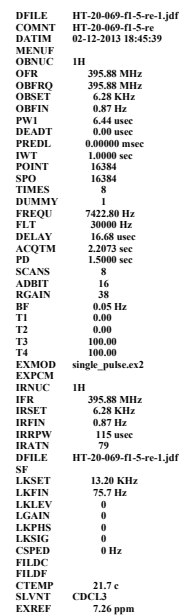


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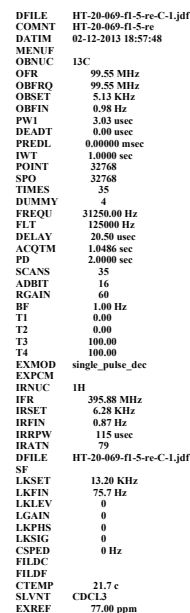
DFILE HT-19-067-f14-17-C-1.jdt
COMNT HT-19-067-f14-17-C
DATIM 19-08-20 13 14:13:40
MENUF
MENUC
OBNUC 13C
OFR 99.55 MHz
OFRQ 99.55 MHz
OBSET 5.13 KHz
OBFN 0.98 Hz
PW1 3.85 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 104
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.50 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 104
ADBIT 16
RGAIN 60
BF 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
IRFN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE HT-19-067-f14-17-C-1.jdt
SF
LKSET 13.20 KHz
LKFN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 25.4 c
SLVNT CDCl3
EXREF 77.00 ppm

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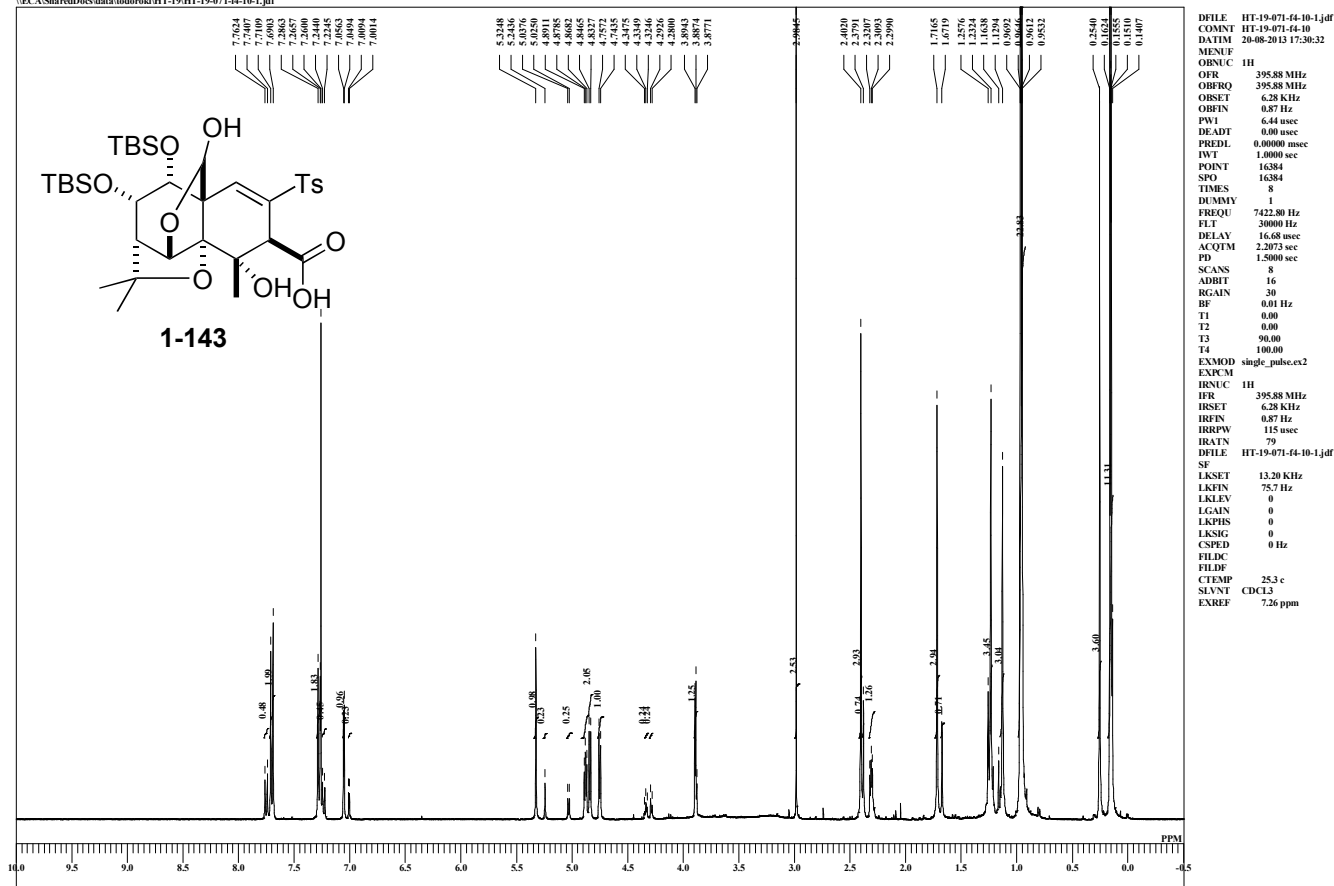


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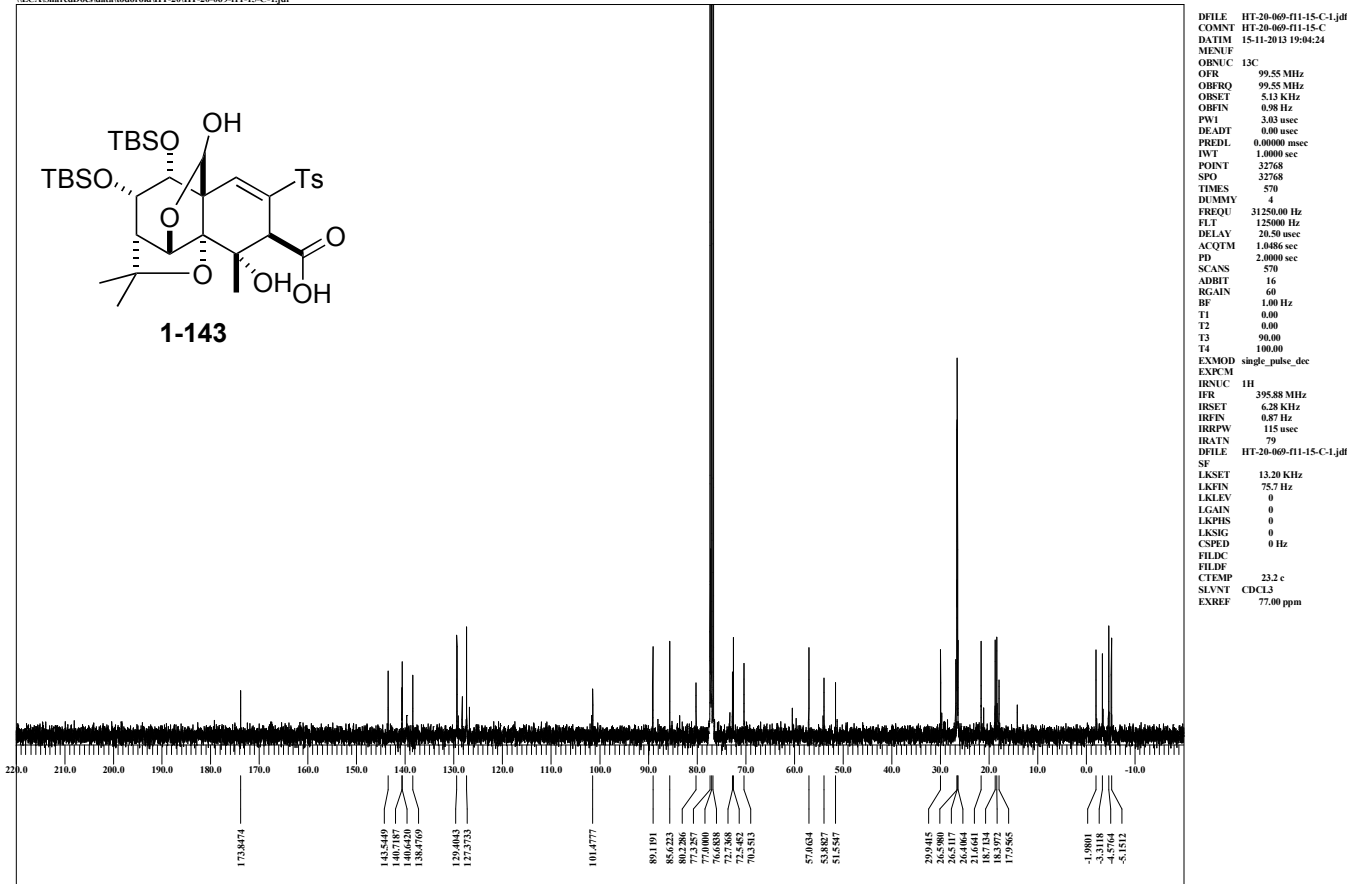
HT-19-071-f4-10

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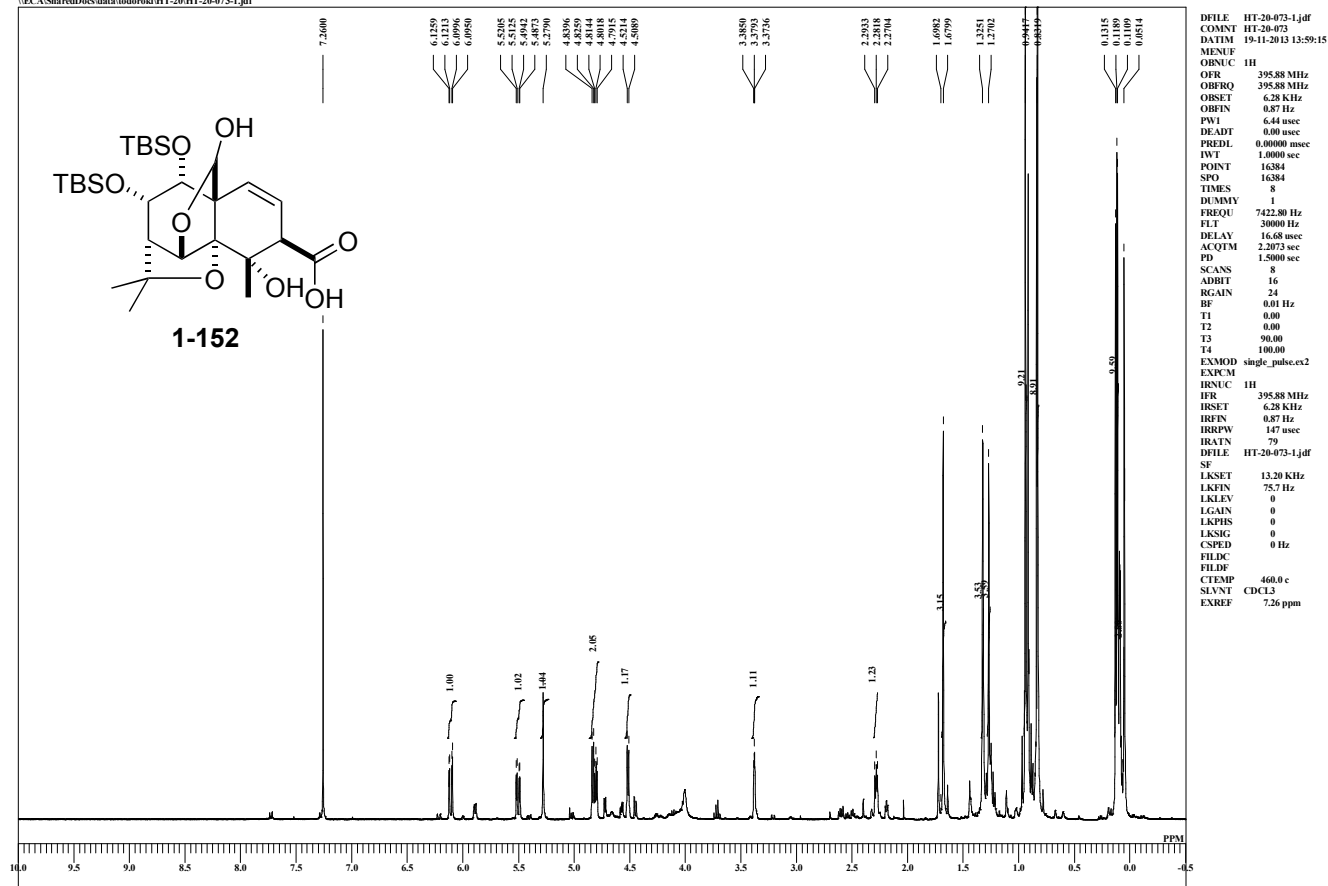
HT-20-069-f11-15-C

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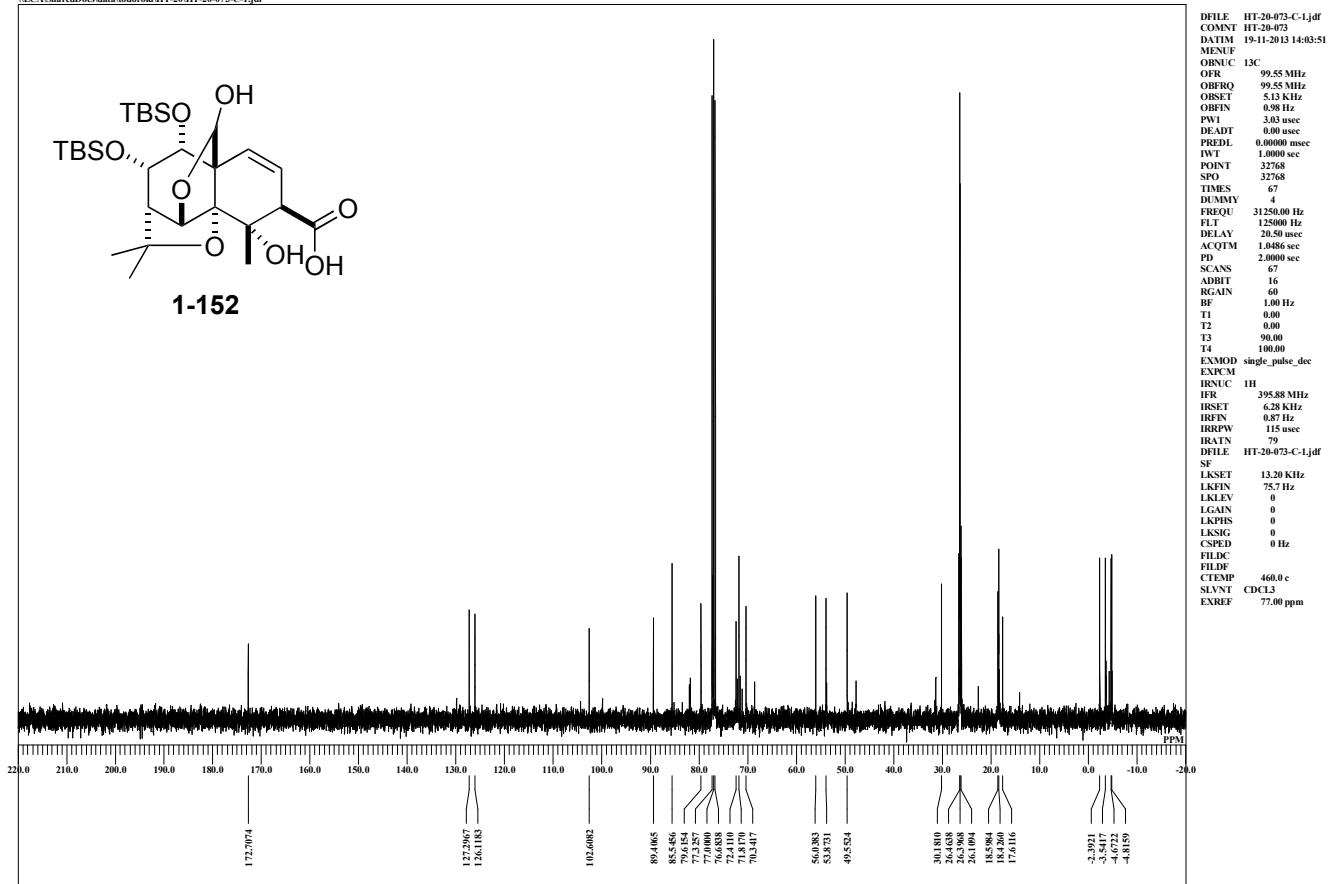
HT-20-073

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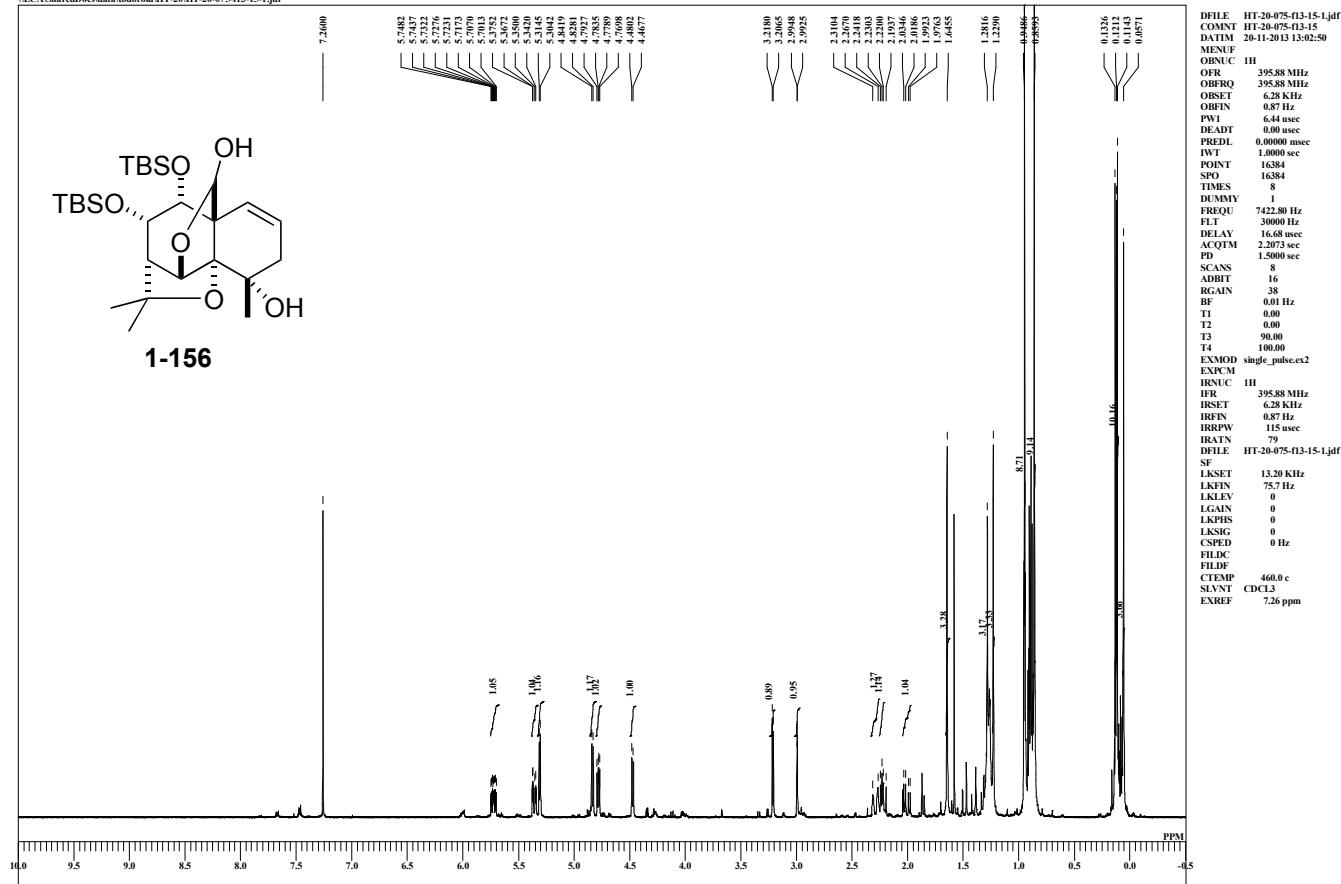
HT-20-073

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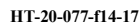


HT-20-075-f13-15

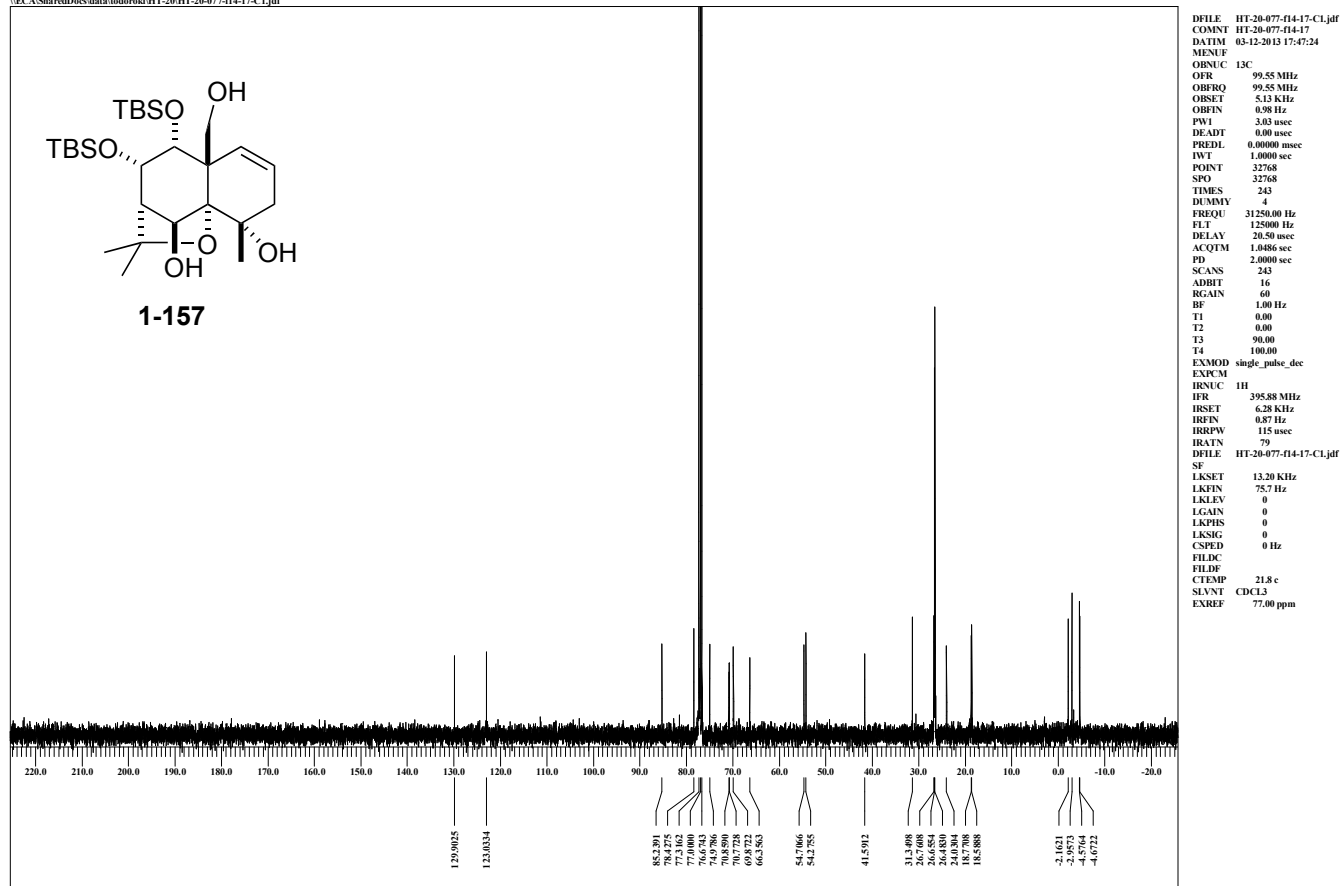
\\ECA\SharedDocs\data\todoroki\HT-20\HT-20-075-f13-15-1.jdt



\\FCA\SharedDocs\data\todoroki\HT-20\HT-20-079-1.idf

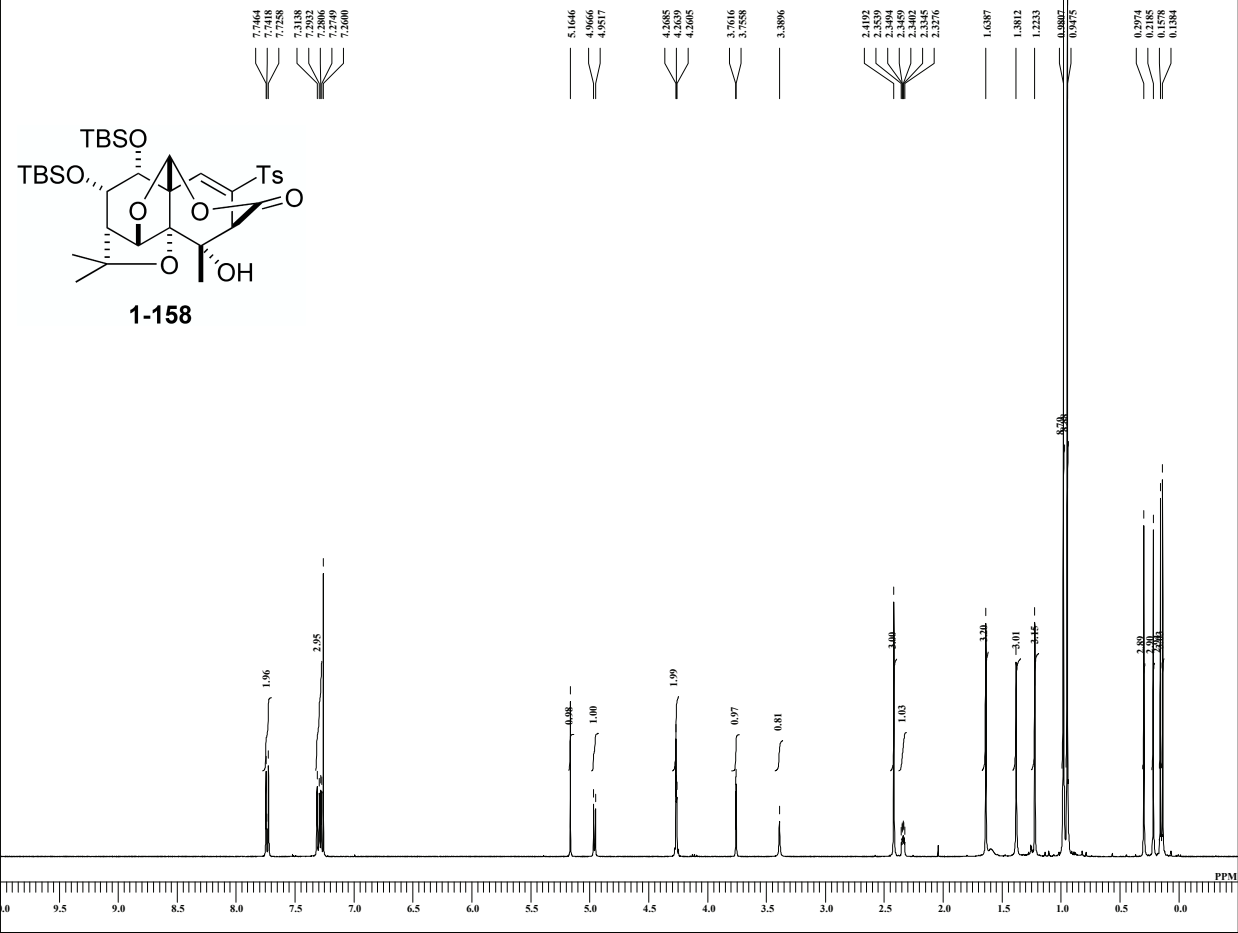


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HT-20-081

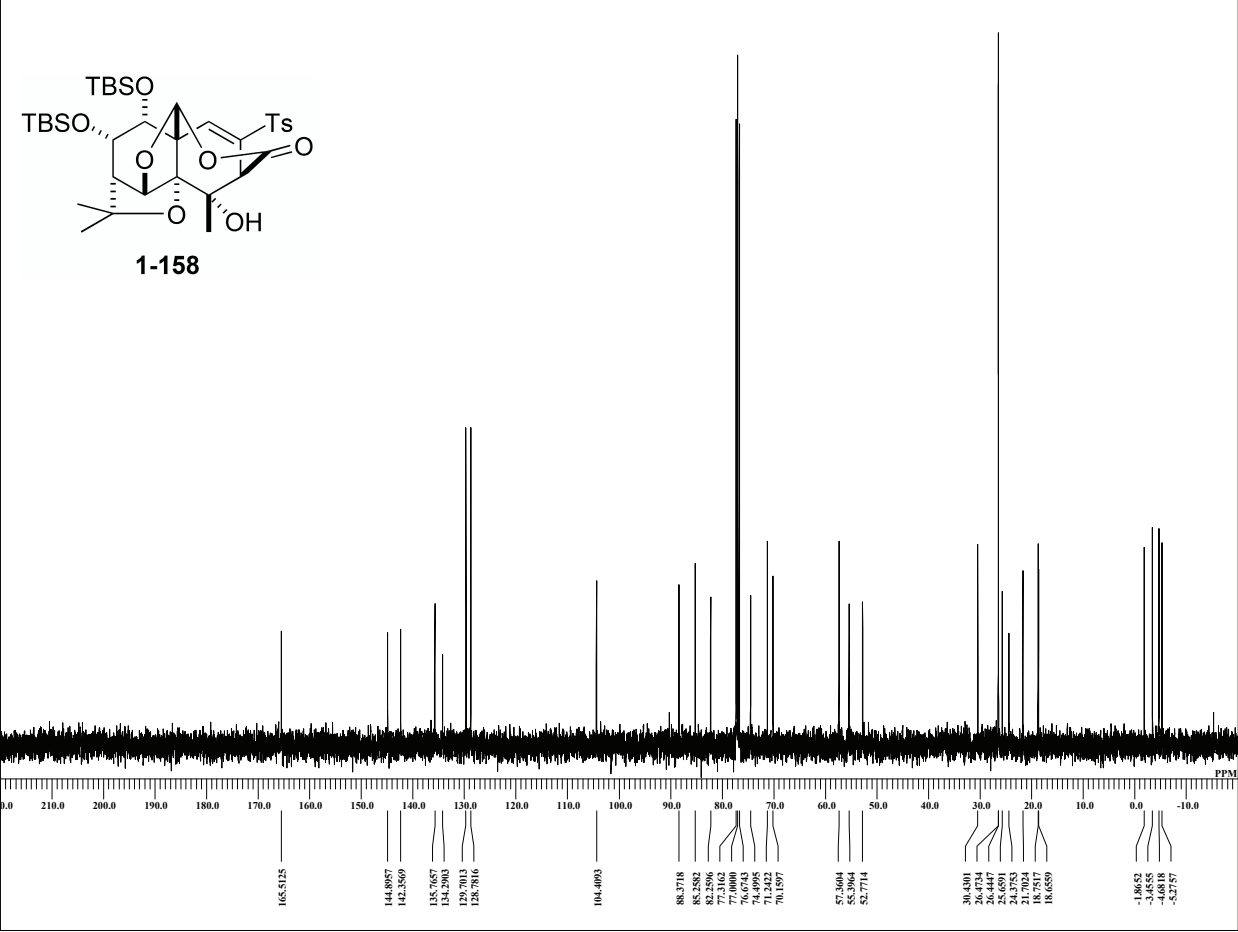
\\ECA\SharedDoc\data\todoroki\HT-20\HT-20-081-1.jdf



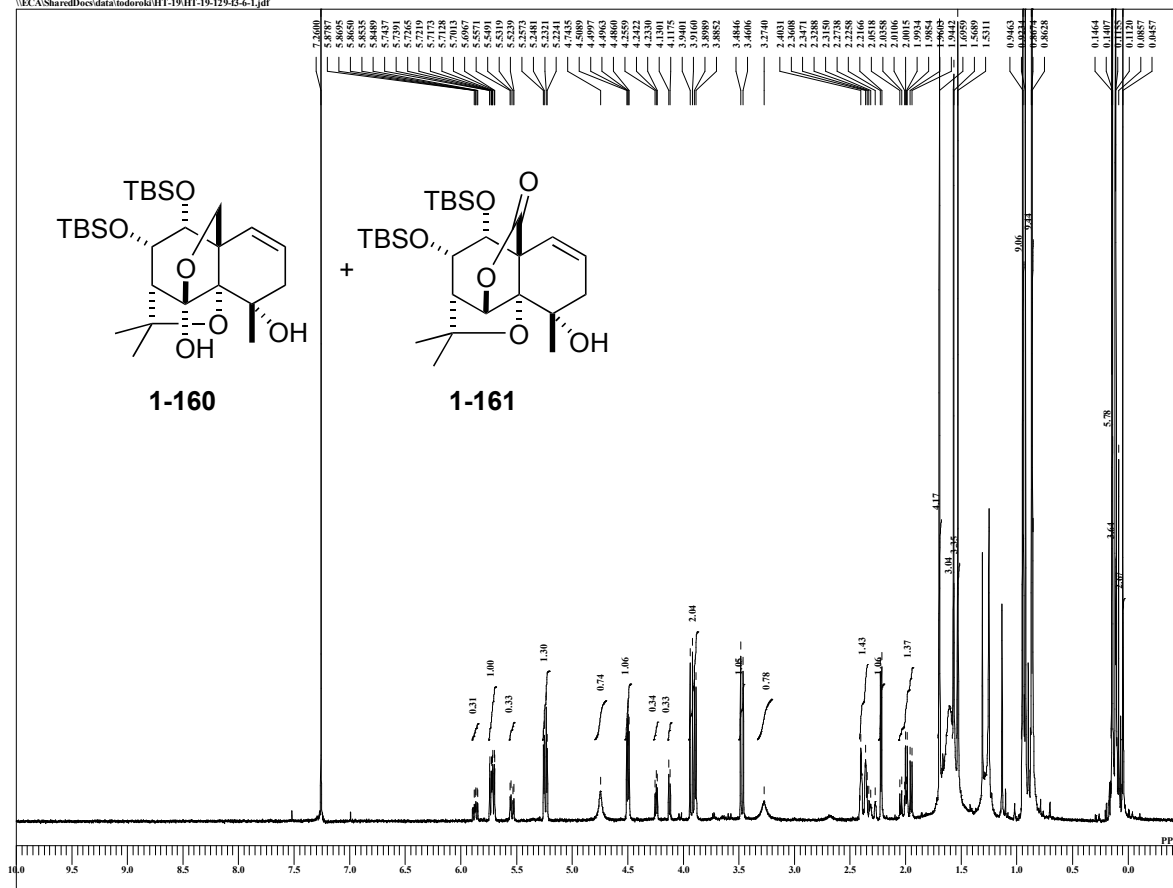
DFILE HT-20-081-1.jdf
COMINT HT-20-081
DATIM 04-12-2013 14:56:58
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFREQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PWI 6.44 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 16384
SPO 16384
TIMES 8
DUMMY 1
FREQU 7422.80 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 1.5000 sec
SCANS 8
ADBIT 16
RGAIN 36
BF 0.10 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse.ex2
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 147 usec
IRATN 79
DFILE HT-20-081-1.jdf
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 21.4 c
SLVNT CDCl3
XREF 7.26 ppm

HT-20-081-C

\\ECA\SharedDoc\data\todoroki\HT-20\HT-20-081-C-1.jdf

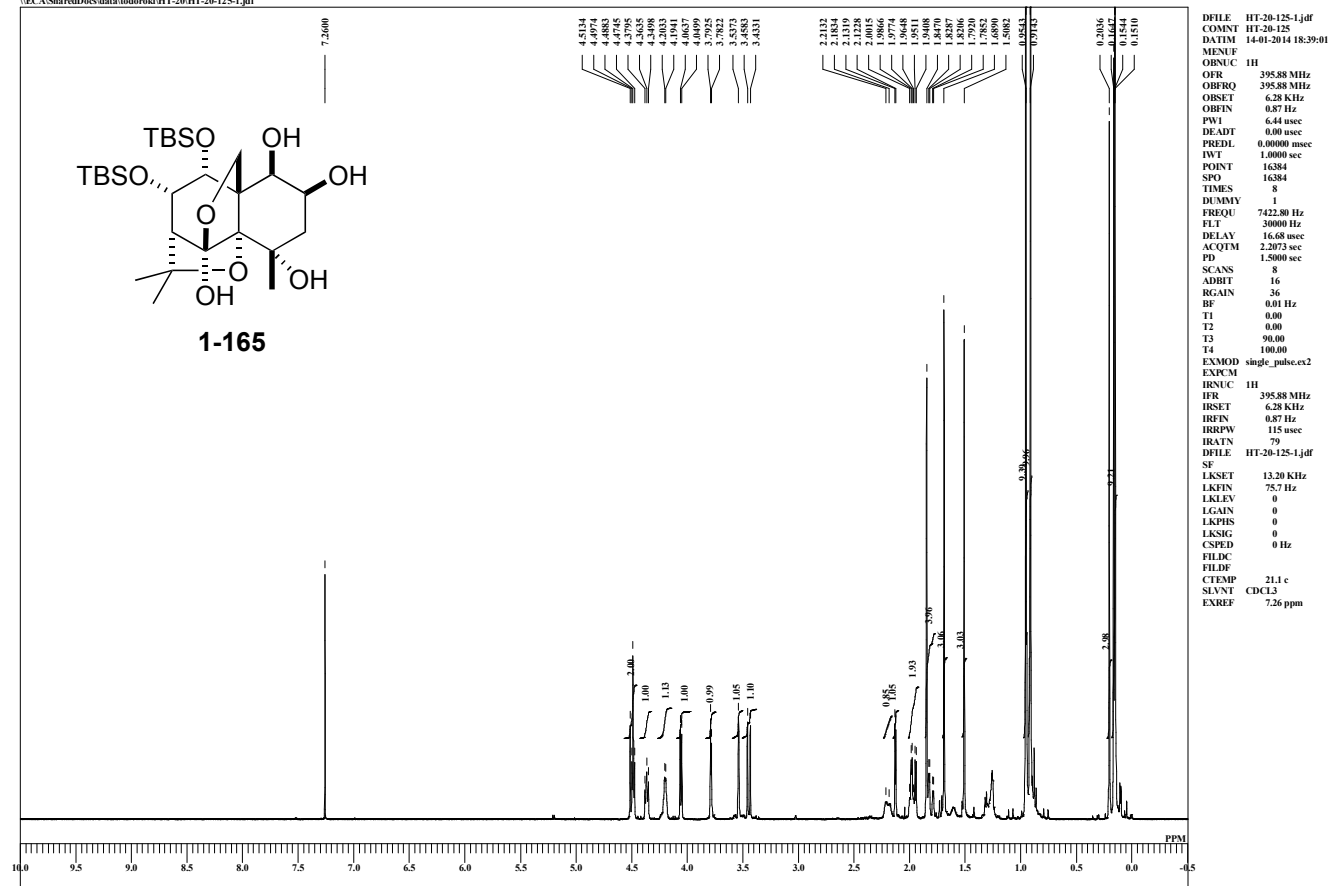


DFILE HT-20-081-C-1.jdf
COMINT HT-20-081-C
DATIM 04-12-2013 15:01:13
MENUF
OBNUC 13C
OFR 99.55 MHz
OBFREQ 99.55 MHz
OBSET 5.13 KHz
OBFIN 0.98 Hz
PWI 3.03 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 32768
SPO 32768
TIMES 33
DUMMY 4
FREQU 31250.00 Hz
FLT 125000 Hz
DELAY 20.20 usec
ACQTM 1.0486 sec
PD 2.0000 sec
SCANS 33
ADBIT 16
RGAIN 60
BF 1.00 Hz
T1 0.00
T2 0.00
T3 100.00
T4 100.00
EXMOD single_pulse_dec
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 115 usec
IRATN 79
DFILE HT-20-081-C-1.jdf
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSG 0
CSPED 0 Hz
FILDC
FILDF
CTEMP 21.5 c
SLVNT CDCl3
XREF 77.00 ppm

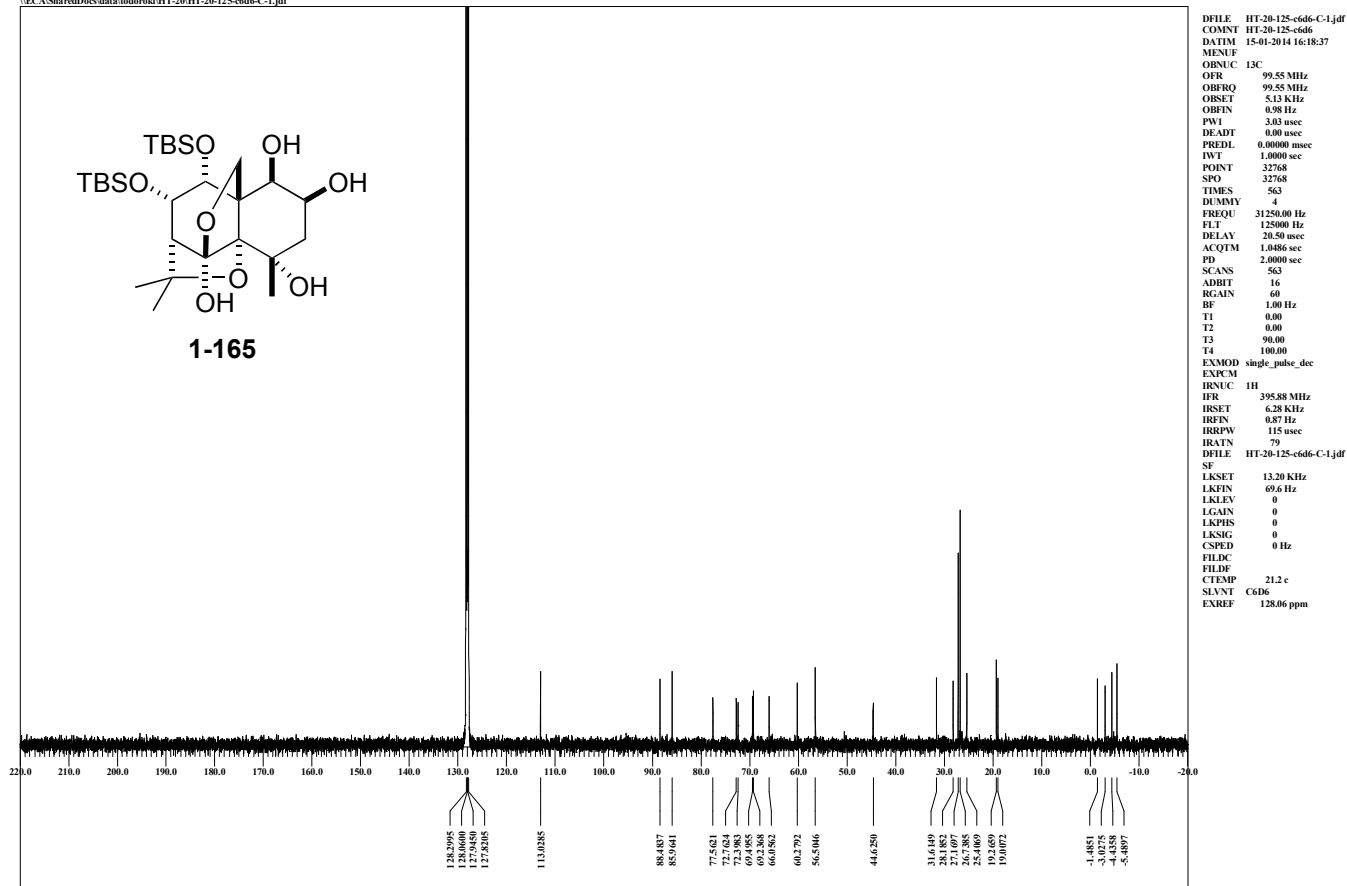


DFILE HT-19-129-f3-6-1.jdf
 COMNT HT-19-129-f3-6
 DATIM 08-09-2013 18:26:55
 MENEF
 OBNUC 1H
 OFR 395.88 MHz
 OFRQ 395.88 MHz
 OSSET 6.28 kHz
 OFIN 0.87 Hz
 PW1 6.44 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 16384
 SPO 16384
 TIMES 16
 DUMMY 1
 FREQU 7422.80 Hz
 FLT 30000 Hz
 DELAY 16.68 usec
 ACQIM 2.2073 sec
 PD 1.5000 sec
 SCANS 16
 ADBIT 16
 RGAIN 46
 BF 0.05 Hz
 T1 0.00
 T2 0.00
 T3 100.00
 T4 100.00
 EXMOD single_pulse.ex2
 EXPCM
 IRNUC 1H
 IFR 395.88 MHz
 ISSET 6.28 kHz
 IRFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-19-129-f3-6-1.jdf
 SF
 LKSET 13.20 kHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSFED 0 Hz
 FILDC
 FILDF
 CTEMP 21.5 c
 SLVNT CDCl3
 EXREF 7.26 ppm

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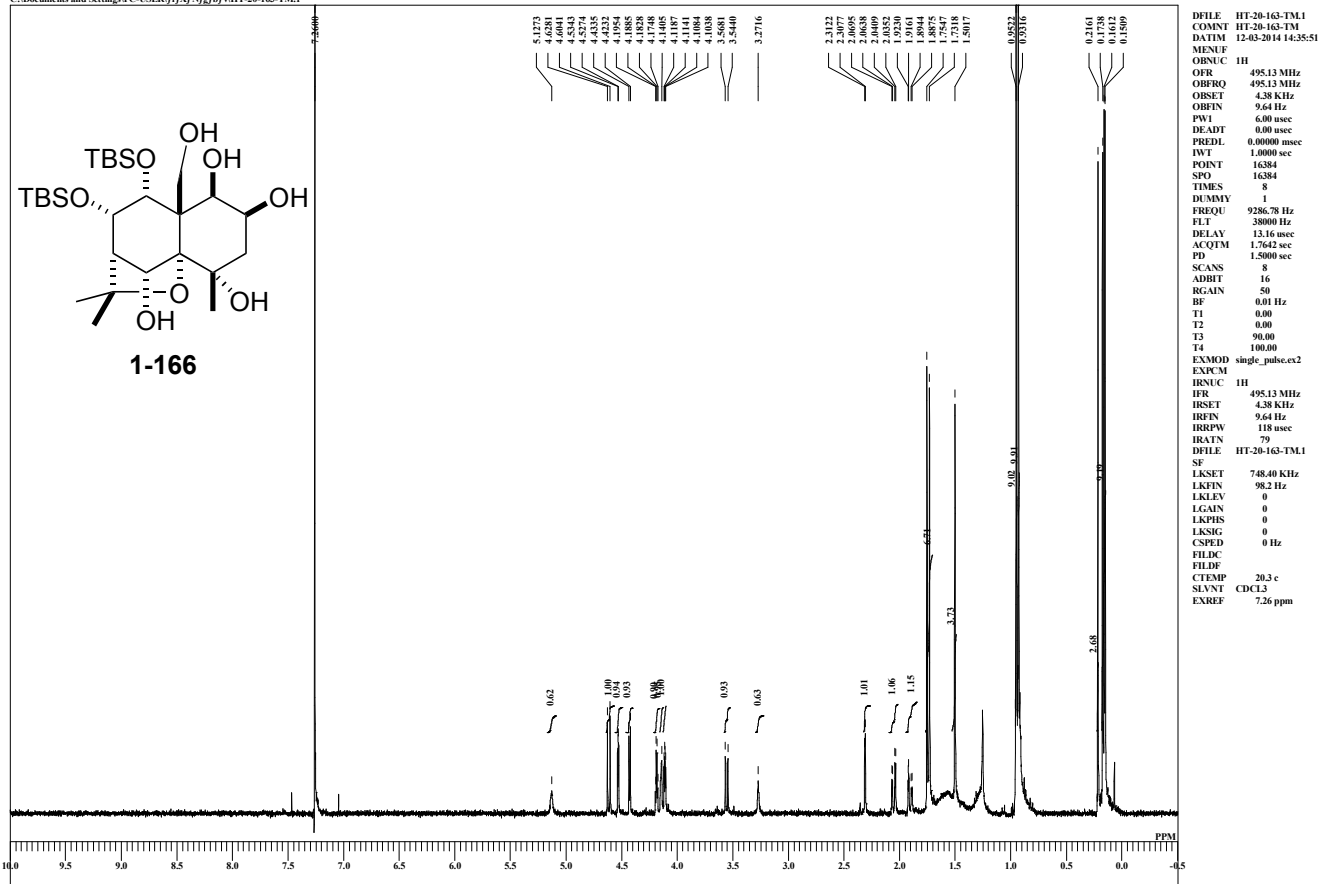


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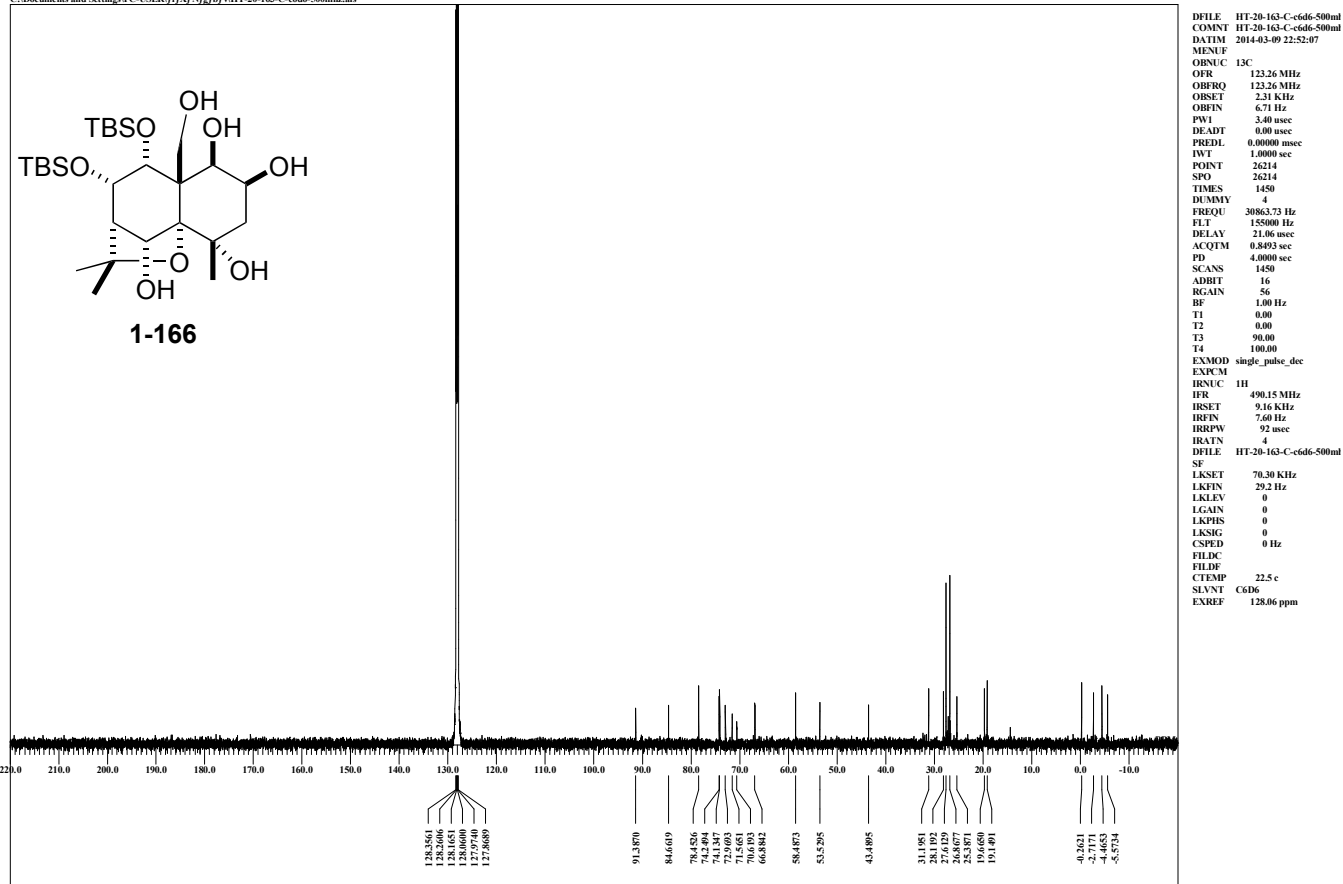
HT-20-163-TM

C:\Documents and Settings\PC-USER\ft\X\N\fg\h\HT-20-163-TM.1



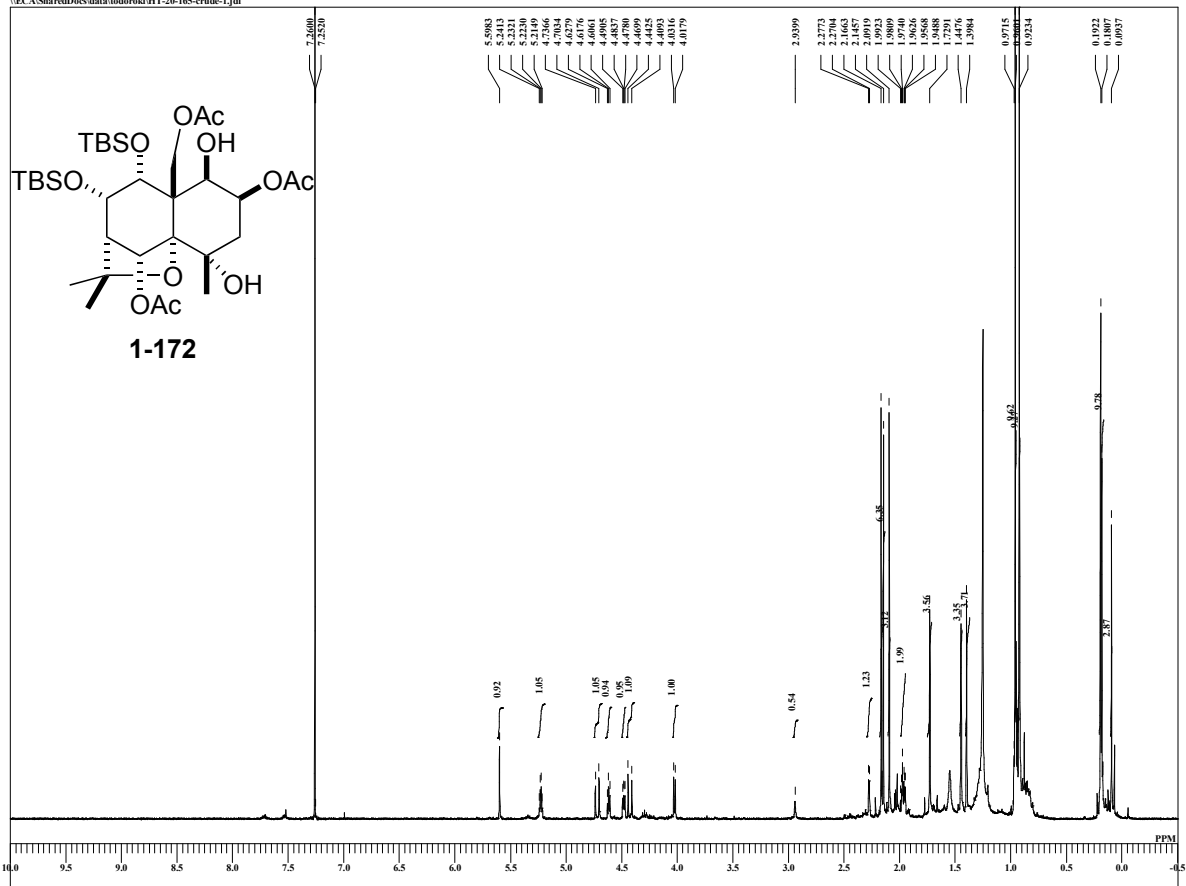
HT-20-163-C-c6d6-500mhz

C:\Documents and Settings\PC-USER\ft\X\N\fg\h\HT-20-163-C-c6d6-500mhz.als



HT-20-165-crude

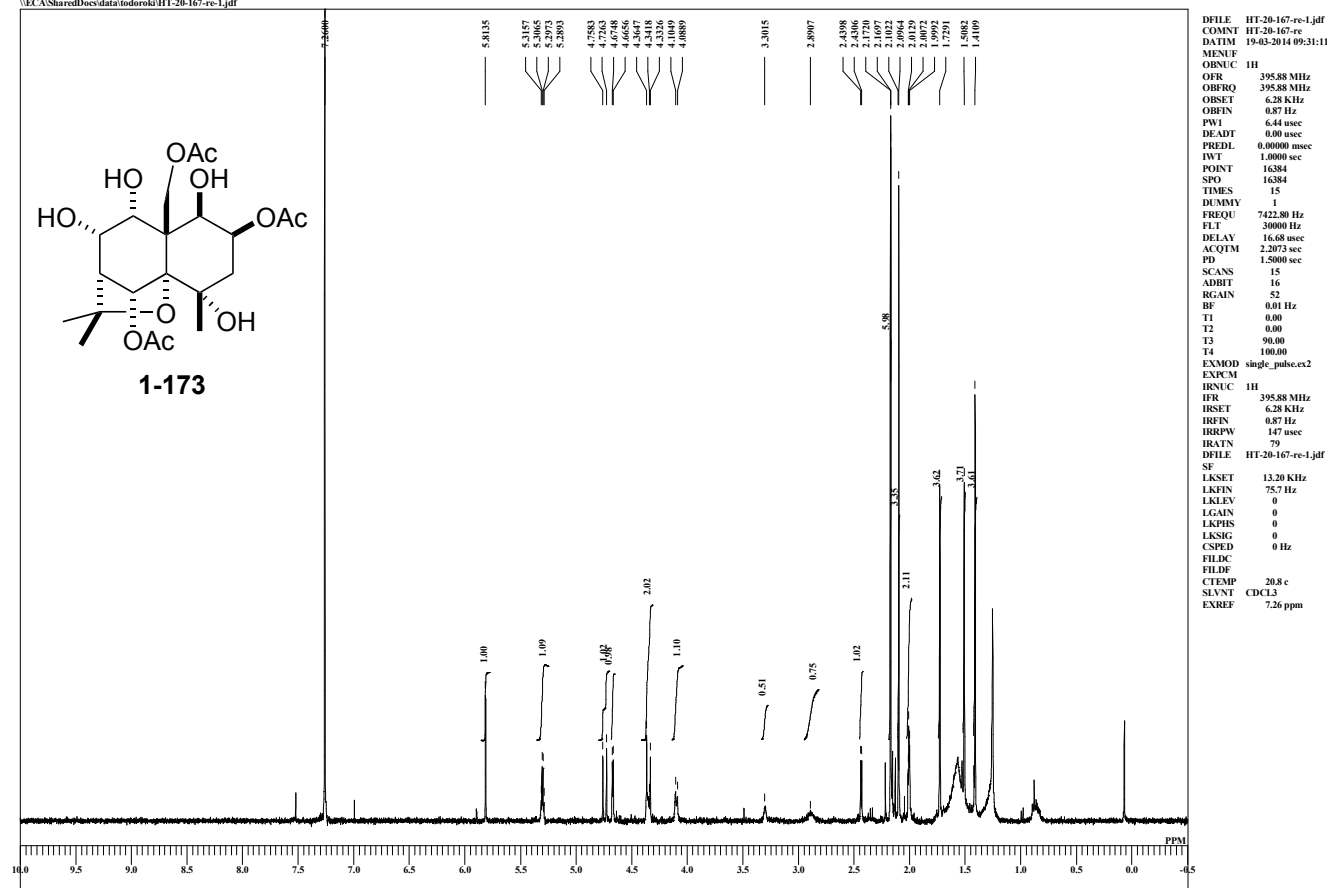
\\ECA\SharedDocs\data\mdroki\HT-20-165-crude-1.jdf



DFILE HT-20-165-crude-1.jdf
 COMNT HT-20-165-crude
 DATIM 15-03-2014 11:56:05
 MENT
 OBNUC 1H
 OFR 395.88 MHz
 OFRQ 395.88 MHz
 OSSET 6.28 kHz
 OFIN 0.87 Hz
 PW1 6.44 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 1.5000 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
 ISSET 6.28 kHz
 IRFIN 0.87 Hz
 IRRPW 115 usec
 IRATN 79
 DFILE HT-20-165-crude-1.jdf
 SF
 LKSET 13.20 kHz
 LKFIN 75.7 Hz
 LKLEV 0
 LGAIN 0
 LKPHS 0
 LKSG 0
 CSFED 0 Hz
 FILDC
 FILDE
 CTEMP 21.1 c
 SLVNT CDCl3
 EXREF 7.26 ppm

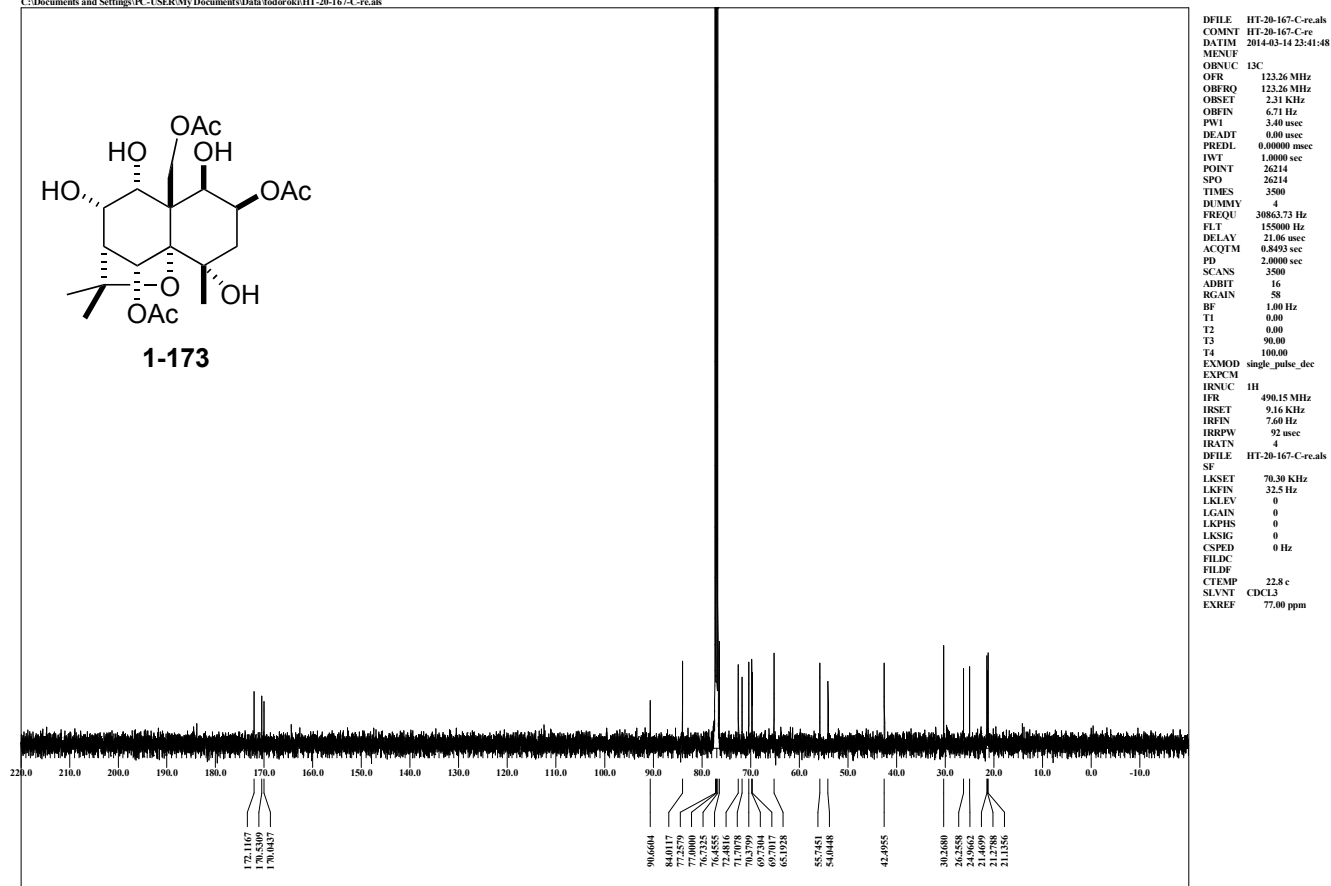
HT-20-167-re

\\ECA\SharedDocs\data\todoroki\HT-20-167-re-1.jdf



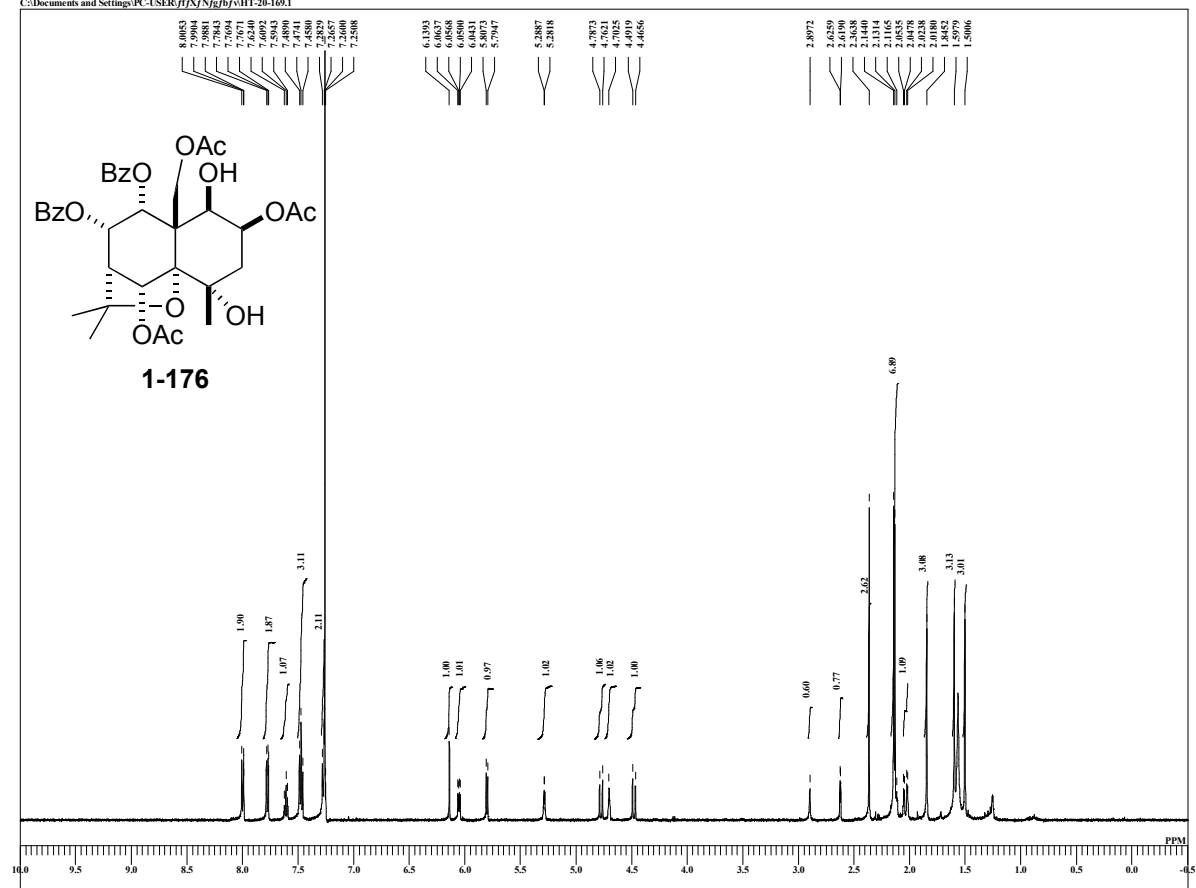
HT-20-167-C-re

C:\Documents and Settings\PC-USER\My Documents\Data\todoroki\HT-20-167-C-re.als



HT-20-169

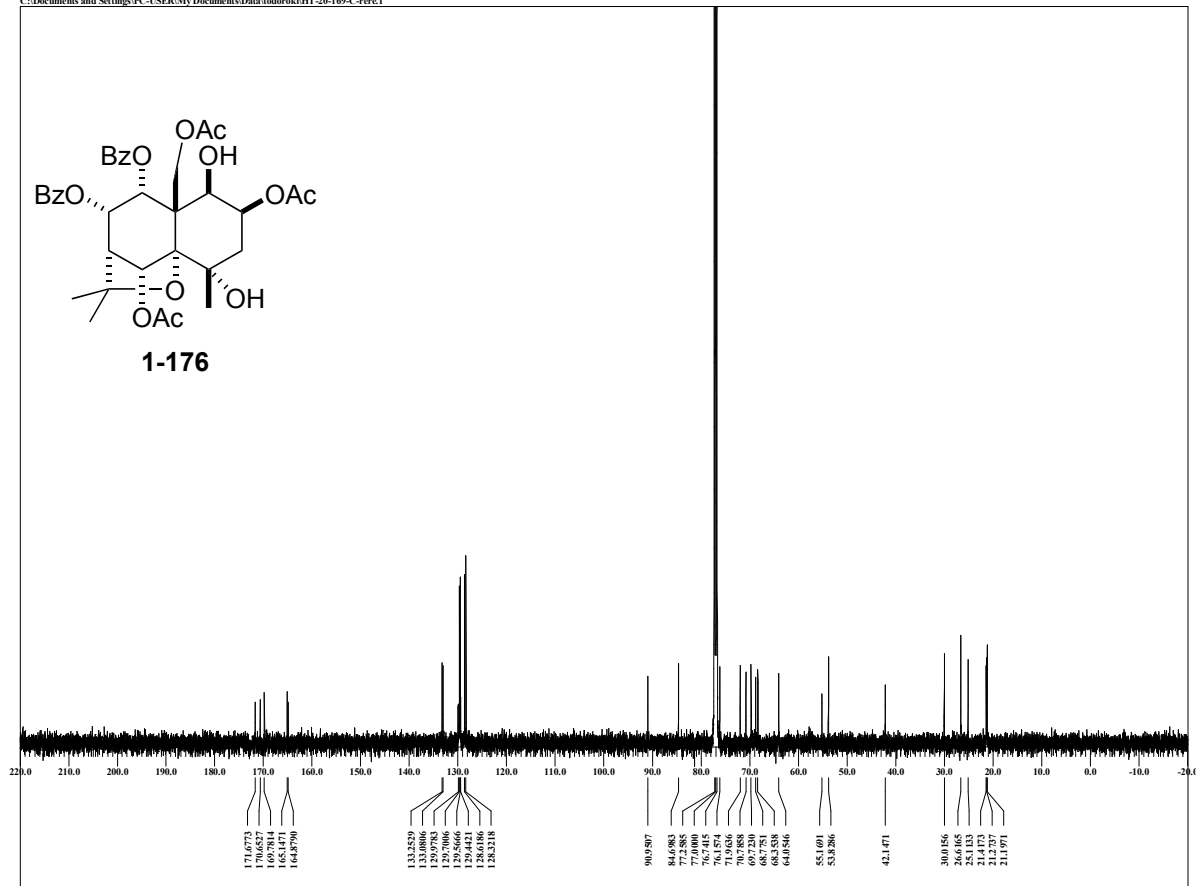
C:\Documents and Settings\PC-USER\ft\X\N\fg\h\HT-20-169.1



DFILE HT-20-169.1
 COMNT HT-20-169
 DATIM 26-03-2014 15:19:06
 MENUF
 OBNUC 1H
 OFR 495.13 MHz
 OFBRO 495.13 MHz
 OBSET 4.38 kHz
 OFBIN 9.64 Hz
 PW1 6.00 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
 ACQIM 1.7642 sec
 PD 1.5000 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 495.13 MHz
 IBSET 4.38 kHz
 IBFIN 9.64 Hz
 IRRPW 92 usec
 IRATN 79
 DFILE HT-20-169.1
 SF
 LKSET 748.40 kHz
 LKFIN 98.2 Hz
 LKLEV 0
 LGAIN 0
 LKPIN 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 20.4 c
 SLVNT CDCl3
 EXREF 7.26 ppm

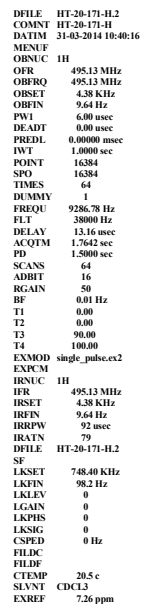
HT-20-169-C-rere

C:\Documents and Settings\PC-USER\My Documents\Data\todoroki\HT-20-169-C-rere.1

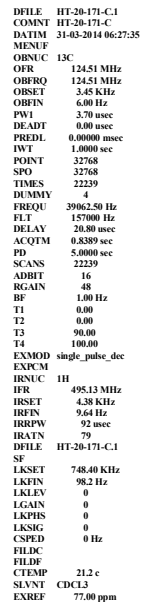


DFILE HT-20-169-C-rere.1
 COMNT HT-20-169-C-rere
 DATIM 26-03-2014 08:58:48
 MENUF
 OBNUC 13C
 OFR 124.51 MHz
 OFBRO 124.51 MHz
 OBSET 3.45 kHz
 OFBIN 9.64 Hz
 PW1 3.70 usec
 DEADT 0.00 usec
 PREDL 0.00000 msec
 IWT 1.0000 sec
 POINT 32768
 SPO 32768
 TIMES 14000
 DUMMY 4
 FREQU 39062.50 Hz
 FLT 157000 Hz
 DELAY 20.80 usec
 ACQIM 0.8389 sec
 PD 2.0000 sec
 SCANS 14000
 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 13C
 IFR 124.51 MHz
 IBSET 3.45 kHz
 IBFIN 9.64 Hz
 IRRPW 92 usec
 IRATN 79
 DFILE HT-20-169-C-rere.1
 SF
 LKSET 748.40 kHz
 LKFIN 98.2 Hz
 LKLEV 0
 LGAIN 0
 LKPIN 0
 LKSG 0
 CSPED 0 Hz
 FILDC
 FILDF
 CTEMP 20.9 c
 SLVNT CDCl3
 EXREF 77.00 ppm

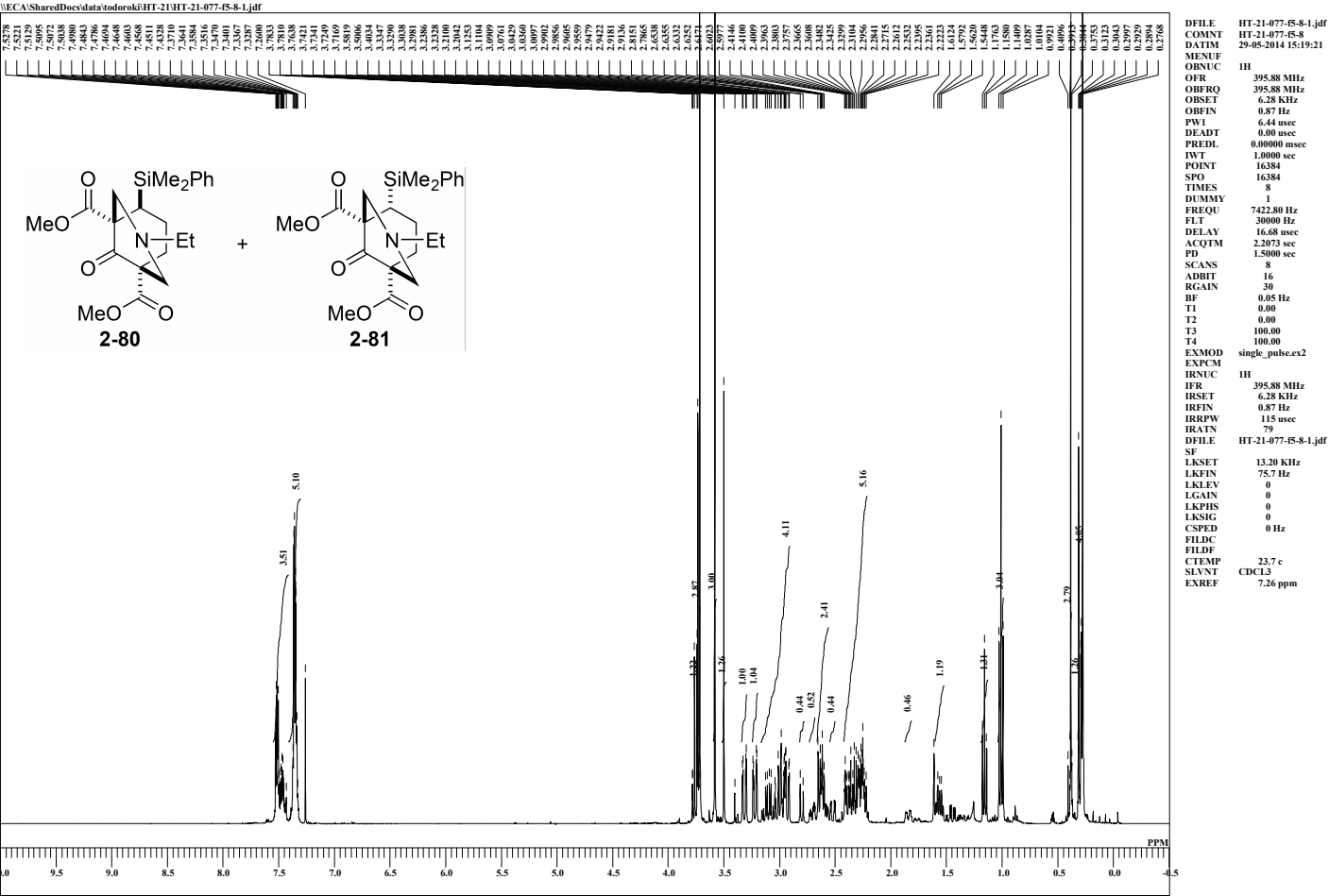
\\ECA\SharedDocs\data\todoroki\HT-20-171-H.2



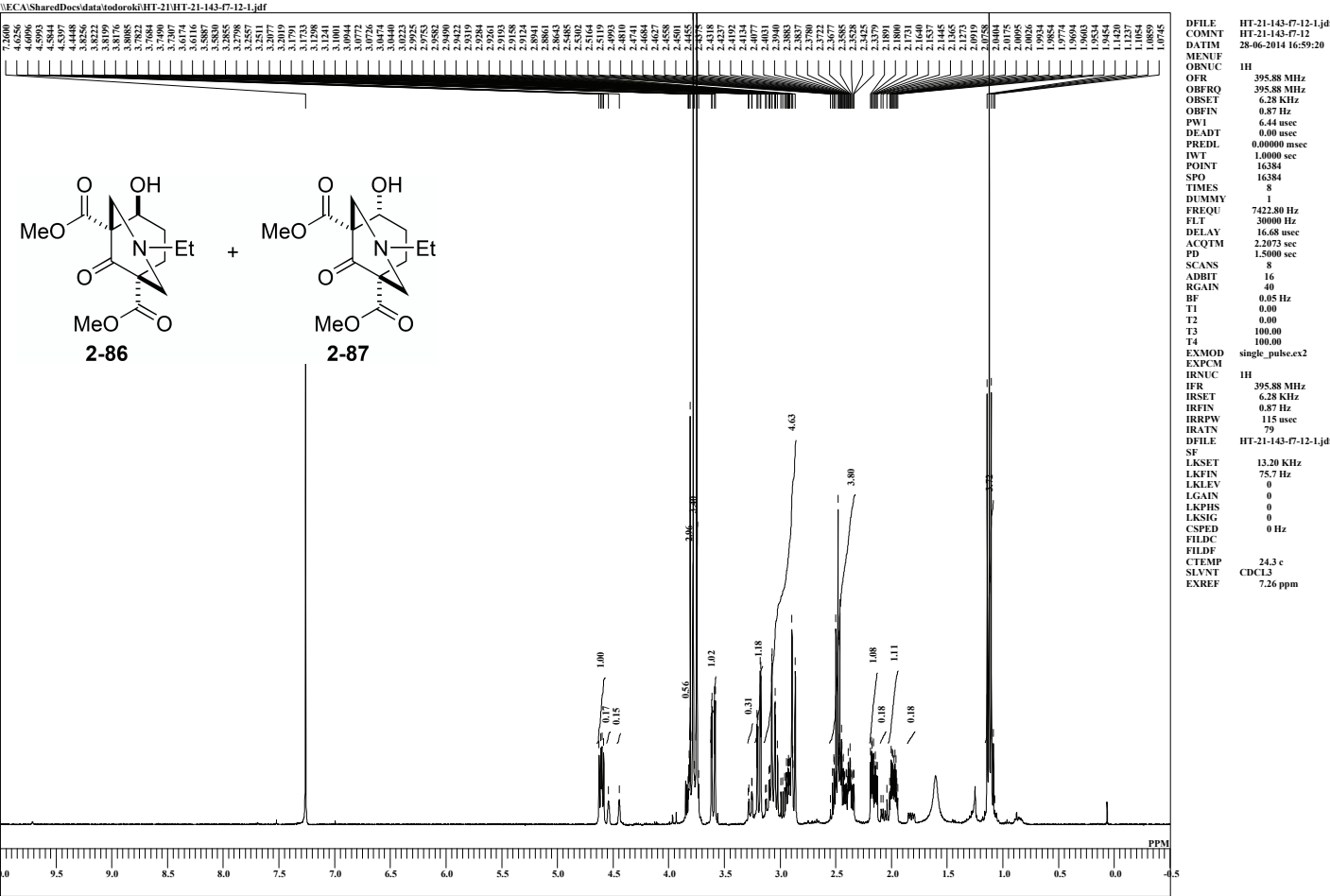
C:\Documents and Settings\PC-USER\My Documents\Data\todorok\HT-20-171-C.1



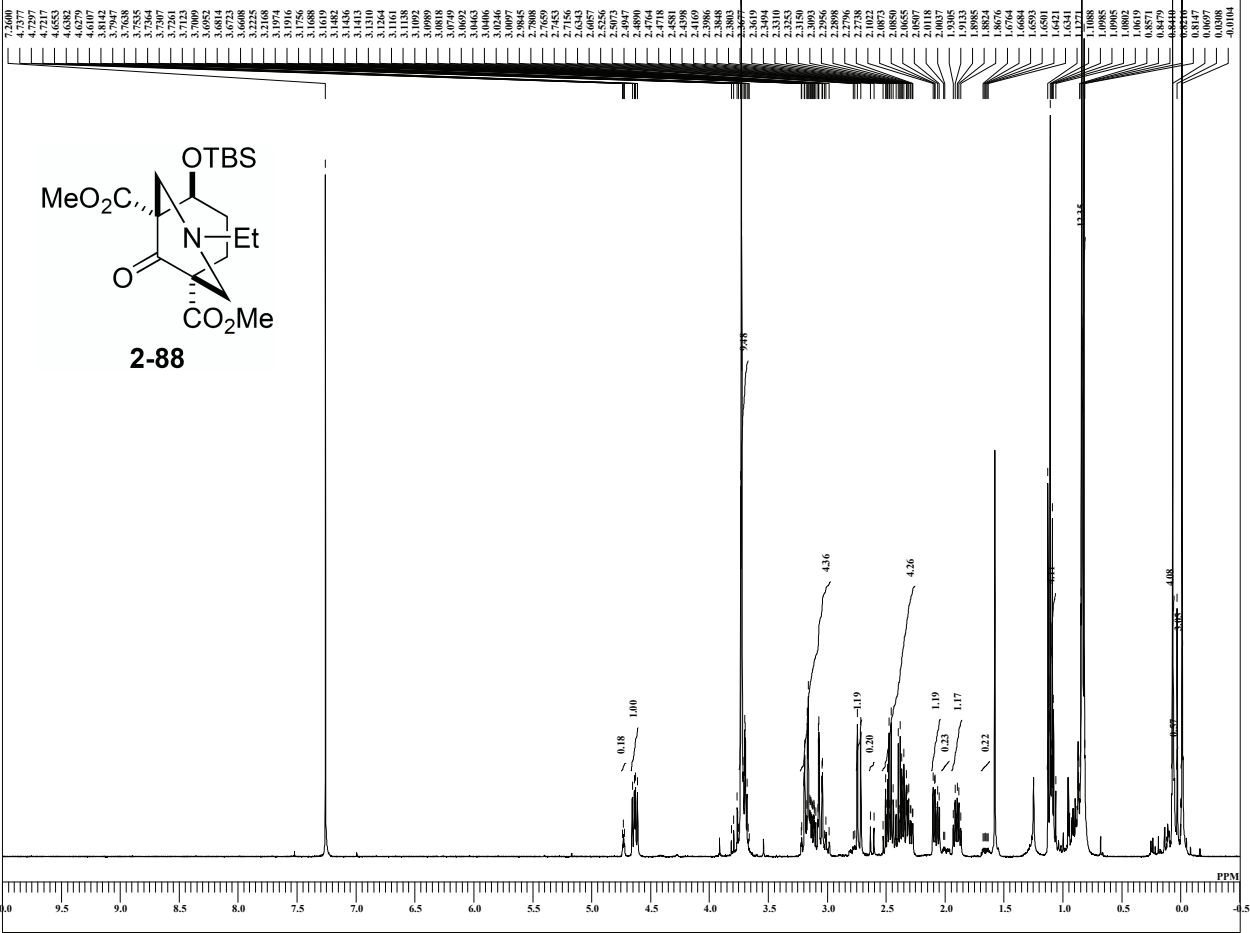
HT-21-077-f5-8



HT-21-143-f7-12



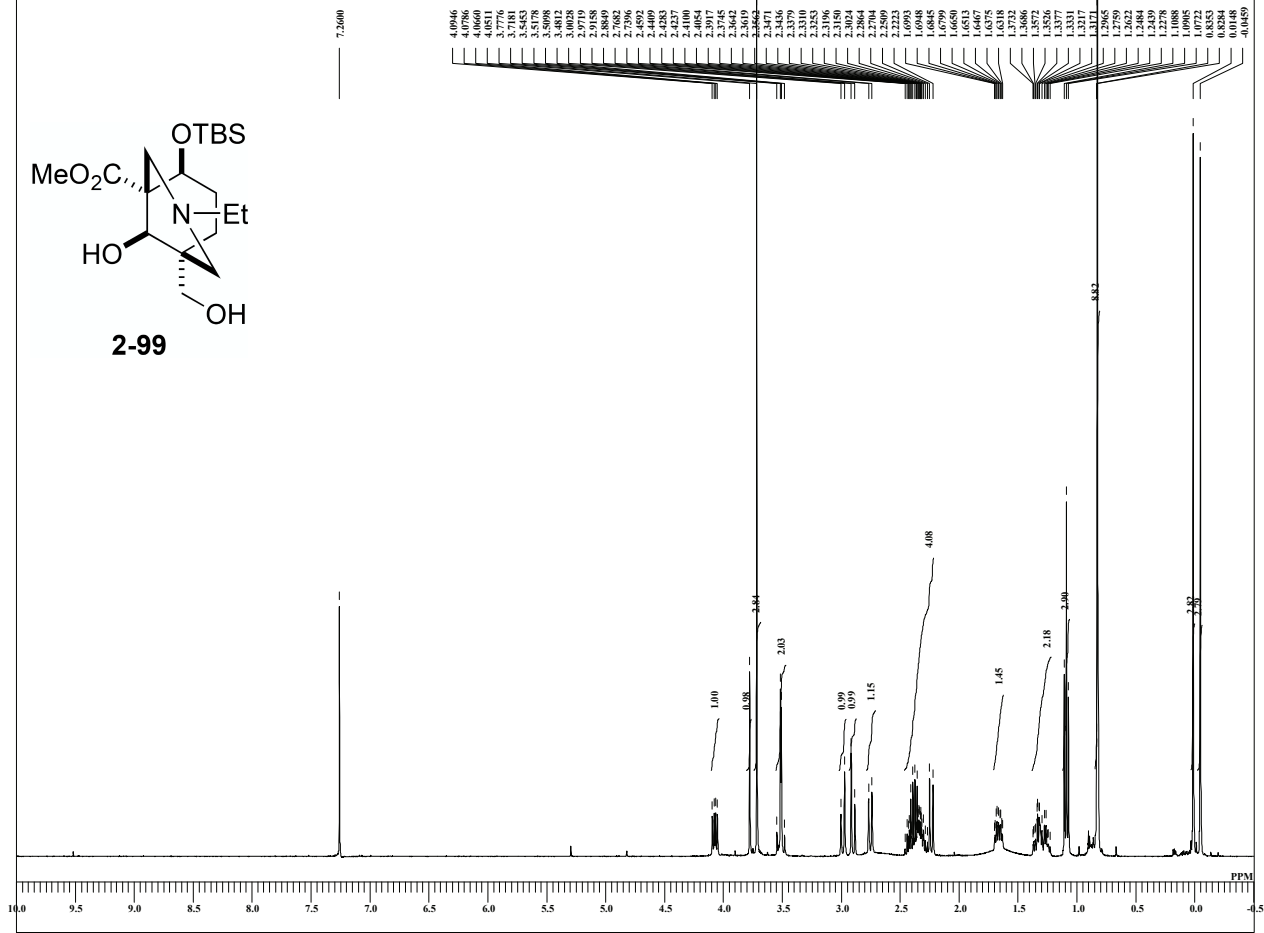
\\ECSA\SharedDocs\data\todoroki\HT-21\HT-21-161-1.jdf



DFILE HT-21-161-1.jdf
COMINT HT-21-161
DATIM 04-07-2014 09:25:34
MENUF
OBNUC 1H
OFR 395.88 MHz
OBFQ 395.88 MHz
OBSET 6.28 KHz
OBFIN 0.87 Hz
PW1 6.44 usec
DEADT 0.00 usec
PREDL 0.000000 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 1.5000 sec
SCANS 8
ADBIT 16
RGAIN 36
BF 0.05 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 HT-21-161-1.jdf
SF
LKSET 13.20 KHz
LKFIN 75.7 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPD 0 Hz
FILDF
CTEMP 24.2 c
SLVNT CDCl3
XREF 7.26 ppm

HT-109-f13-16

\\ECA\SharedDocs\data\todoroki\HT-22\HT-22-109-f13-16-1.jdf



HT-22-109-f13-16-1.jdf

1H

395.88 MHz

6.28 KHz

0.87 Hz

6.44 usec

0.00 usec

0.000000 msec

1.0000 sec

16384

16384

8

1

7422.80 Hz

30000 Hz

16.68 usec

2.2073 sec

1.5000 sec

8

16

38

0.05 Hz

0.00

0.00

100.00

100.00

single_pulse.ex2

1H

395.88 MHz

6.28 KHz

0.87 Hz

115 usec

79

HT-22-109-f13-16-1.jdf

13.20 KHz

75.7 Hz

0

0

0

0 Hz

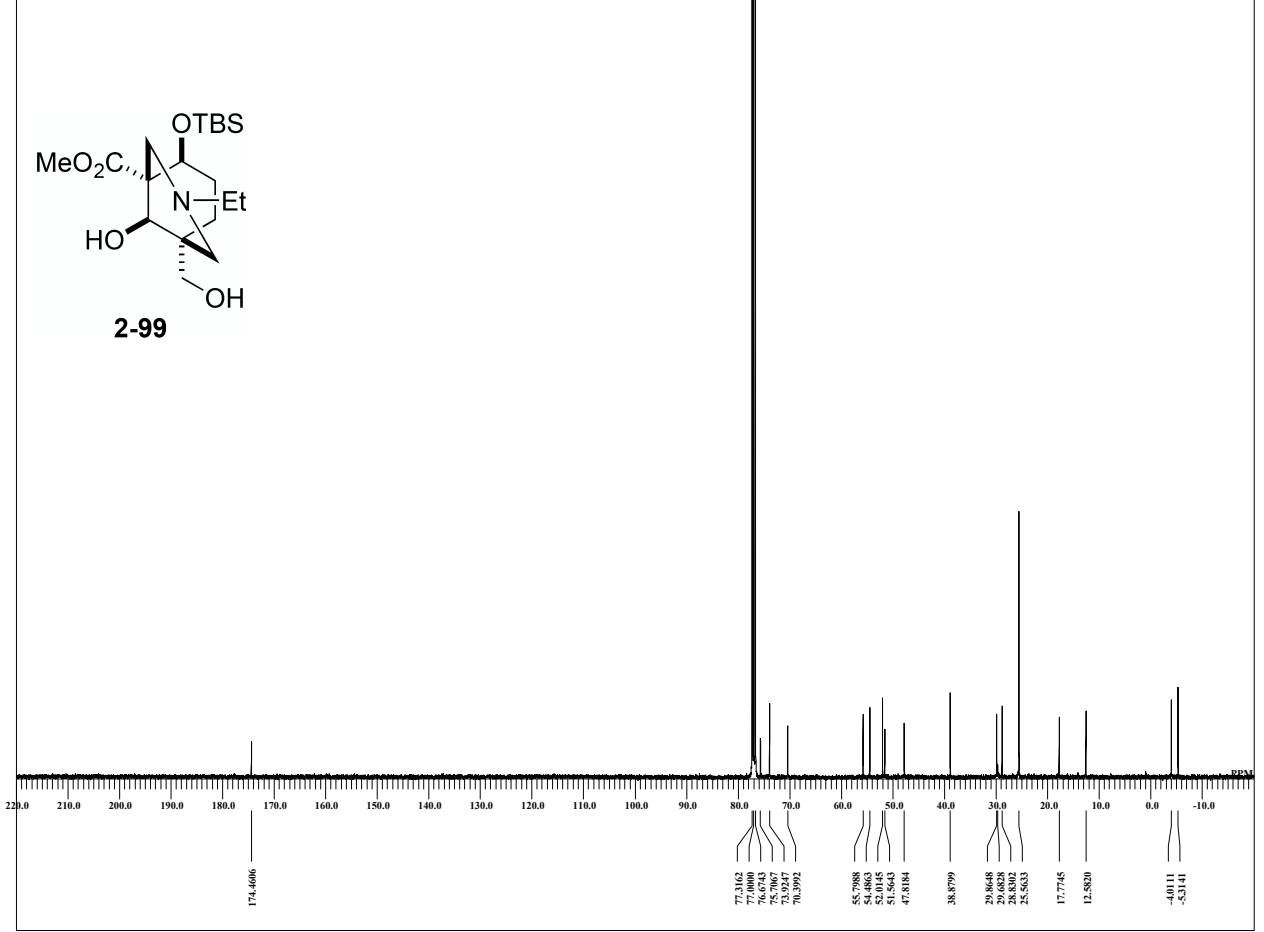
23.7 c

CDCl3

7.26 ppm

HT-22-003-f7-10

\\ECA\SharedDocs\data\todoroki\HT-22\HT-22-003-f7-10-C-1.jdf



HT-22-003-f7-10-C-1.jdf

13C

99.55 MHz

99.55 MHz

5.13 KHz

0.98 Hz

3.03 usec

0.00 usec

0.000000 msec

1.0000 sec

32768

32768

9000

4

31250.00 Hz

125000 Hz

20.50 usec

1.0486 sec

2.0000 sec

9000

16

60

1.00 Hz

0.00

0.00

90.00

100.00

single_pulse_dec

1H

395.88 MHz

6.28 KHz

0.87 Hz

115 usec

79

HT-22-003-f7-10-C-1.jdf

13.20 KHz

75.7 Hz

0

0

0

0 Hz

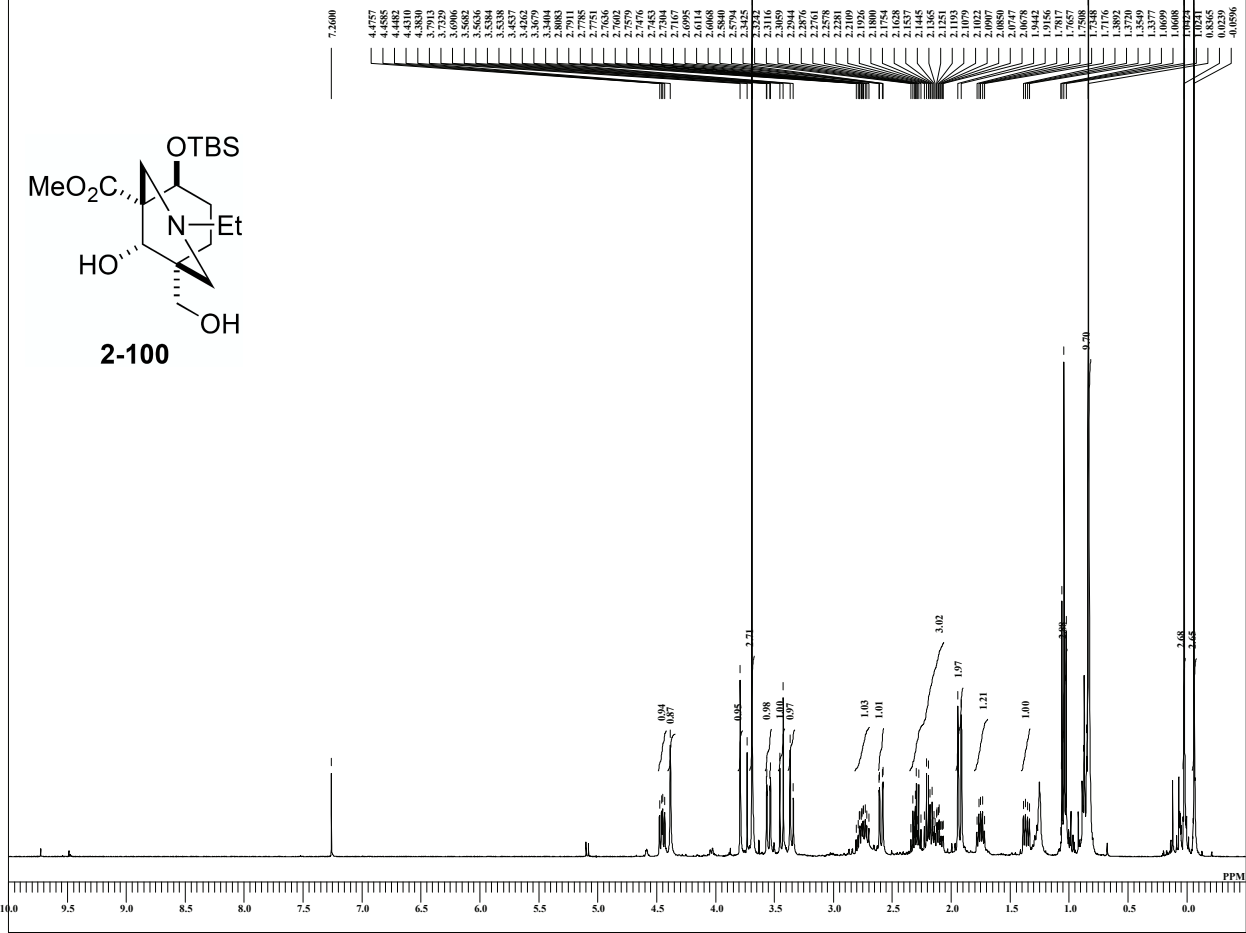
24.0 c

CDCl3

77.00 ppm

HT-22-109-f6-10

\\ECA\SharedDocs\data\todoroki\HT-22\HT-22-109-f6-10-1.jdf



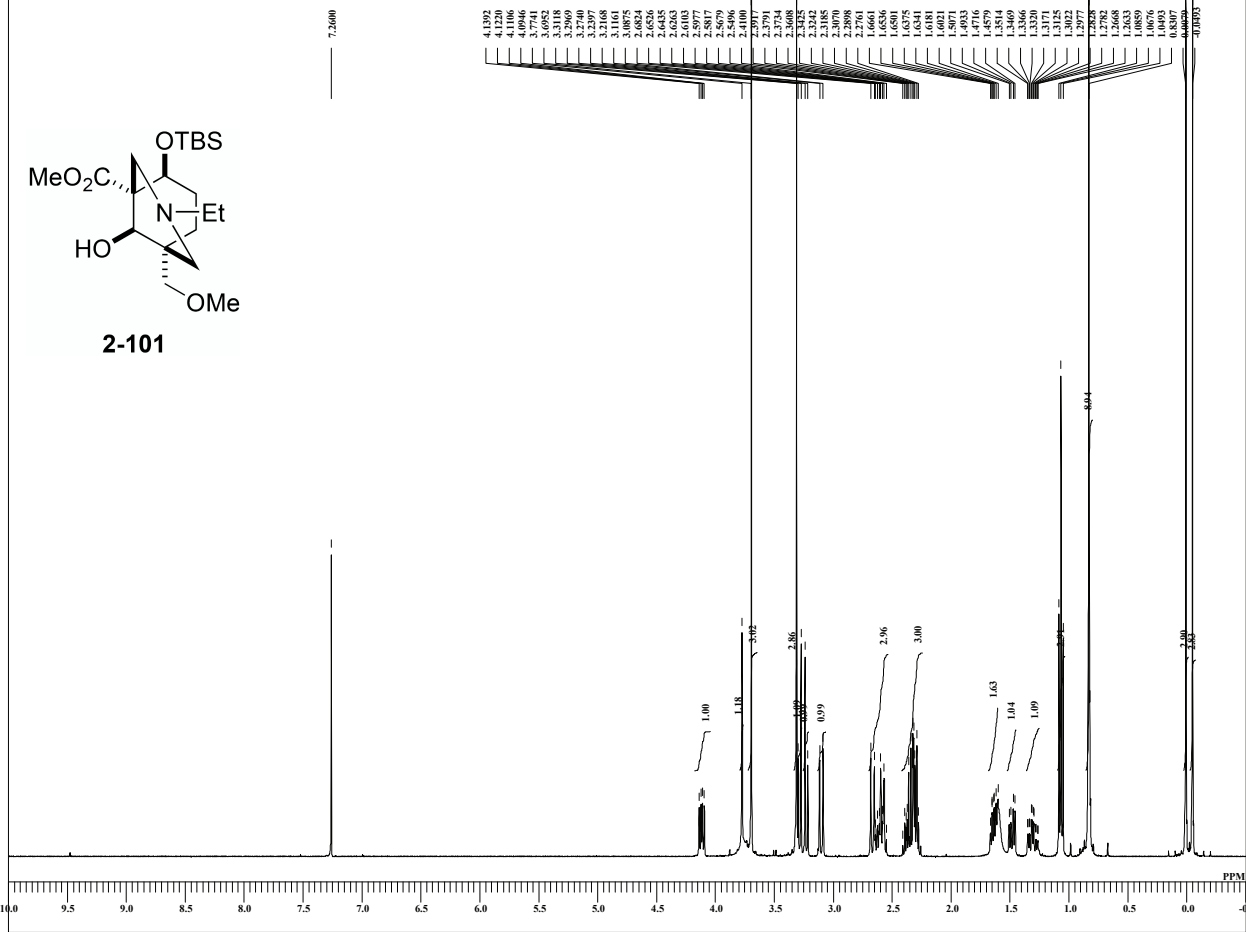
HT-22-109-f6-10-1.jdf

1H NMR parameters:

- 1H: 395.88 MHz
- OBNUC: 6.28 kHz
- OBFIN: 0.87 Hz
- PW1: 6.44 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: 1.5000 sec
- SCANS: 8
- ADBIT: 16
- RGAIN: 26
- BF: 0.05 Hz
- T1: 0.00
- T2: 0.00
- T3: 100.00
- T4: 100.00
- EXMOD: single_pulse.ex2
- EXPCH: 1H
- IRNUC: 395.88 MHz
- IFR: 6.28 kHz
- IRSET: 0.87 Hz
- IRFIN: 115 usec
- IRRPW: 115 usec
- IRATN: 79
- DFILE: HT-22-109-f6-10-1.jdf
- SF: 13.20 KHz
- LKSET: 13.20 KHz
- LKFIN: 75.7 Hz
- LKLEV: 0
- LGAIN: 0
- LKPHS: 0
- LKSG: 0
- CSPED: 0 Hz
- FILDC: 23.6 c
- FILDF: 23.6 c
- CTEMP: 23.6 c
- SLVNT: CDCl3
- EXREF: 7.26 ppm

HT-22-115

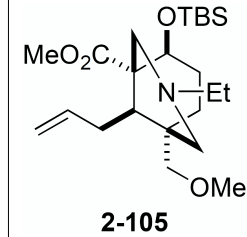
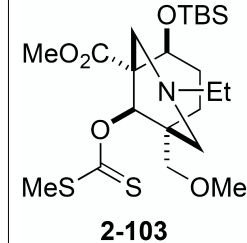
\\ECA\SharedDocs\data\todoroki\HT-22\HT-22-115-1.jdf



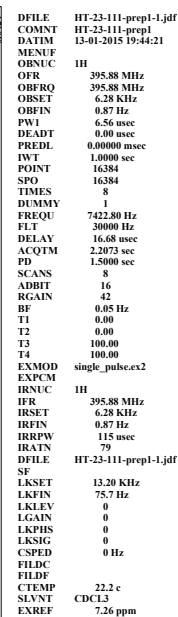
HT-22-115-1.jdf

1H NMR parameters:

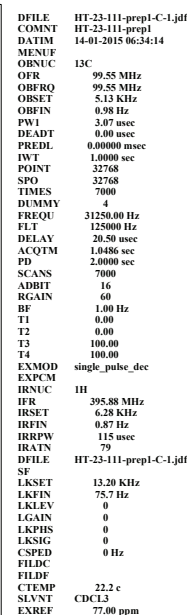
- 1H: 395.88 MHz
- OBNUC: 6.28 kHz
- OBFIN: 0.87 Hz
- PW1: 6.44 usec
- DEADT: 0.00 usec
- PREDL: 0.00000 msec
- IWT: 1.0000 sec
- POINT: 16384
- SPO: 16384
- TIMES: 11
- DUMMY: 1
- FREQU: 7422.80 Hz
- FLT: 30000 Hz
- DELAY: 16.68 usec
- ACQTM: 2.2073 sec
- PD: 1.5000 sec
- SCANS: 11
- ADBIT: 16
- RGAIN: 36
- BF: 0.05 Hz
- T1: 0.00
- T2: 0.00
- T3: 90.00
- T4: 100.00
- EXMOD: single_pulse.ex2
- EXPCH: 1H
- IRNUC: 395.88 MHz
- IFR: 6.28 kHz
- IRSET: 0.87 Hz
- IRFIN: 147 usec
- IRRPW: 147 usec
- IRATN: 79
- DFILE: HT-22-115-1.jdf
- SF: 13.20 KHz
- LKSET: 13.20 KHz
- LKFIN: 75.7 Hz
- LKLEV: 0
- LGAIN: 0
- LKPHS: 0
- LKSG: 0
- CSPED: 0 Hz
- FILDC: 23.9 c
- FILDF: 23.9 c
- CTEMP: 23.9 c
- SLVNT: CDCl3
- EXREF: 7.26 ppm



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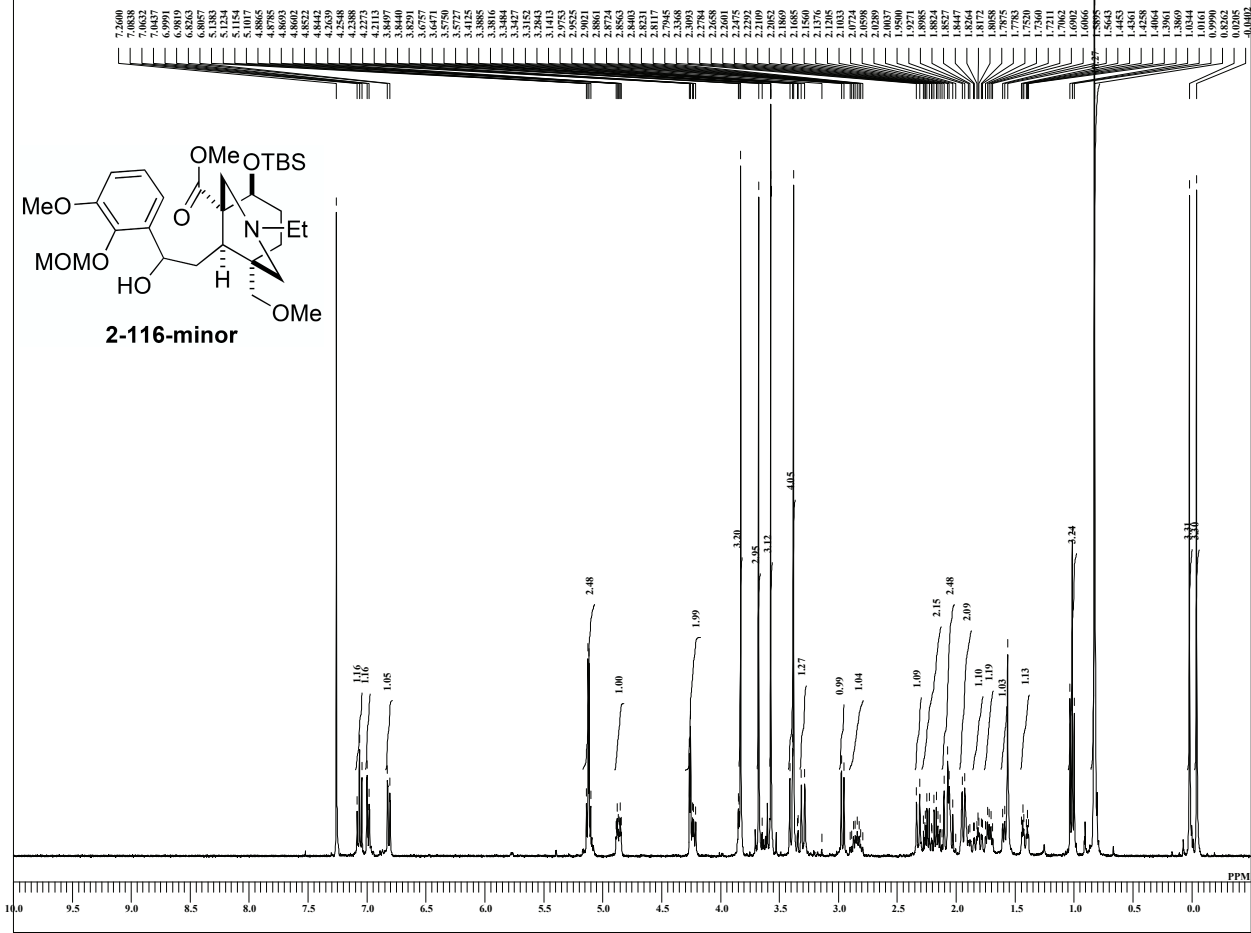


\\ECA\SharedDocs\data\todoroki\HT-23\HT-23-111-prep1-C-1.idf



HT-23-111-prep2

\\ECA\SharedDocs\data\todoroki\HT-23\HT-23-111-prep2-1.jdf



HT-23-111-prep2-1.jdf

HT-23-111-prep2
14-01-2015 09:06:12

1H

395.88 MHz

6.28 KHz

0.87 Hz

6.56 usec

0.00 usec

0.000000 msec

1.00000 sec

16384

16384

8

1

7422.80 Hz

30000 Hz

16.68 usec

2.2073 sec

1.5000 sec

8

16

44

0.05 Hz

0.00

0.00

100.00

100.00

EXMOD single_pulse.ex2

1H

395.88 MHz

6.28 KHz

0.87 Hz

115 usec

79

HT-23-111-prep2-1.jdf

13.20 KHz

75.7 Hz

0

0

0

0 Hz

22.2 c

CD13

7.26 ppm