

博士論文

光学活性な  $\alpha$ -アリールプロピオン酸骨格を有する  
グルコキナーゼ活性化薬の合成研究

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## 略語表

Ac (acetyl)  
 $\alpha$ -GI ( $\alpha$ -Glucosidase Inhibitor)  
aq. (aqueous)  
Ar (aryl)  
A.U. (arbitrary unit)  
Bn (benzyl)  
calcd (calculated)  
cat. (catalyst)  
de (diastereomeric excess)  
DMF (*N,N*-dimethylformamide)  
DMPU (*N,N'*-dimethylpropyleneurea)  
DPP-4 (dipeptidyl peptidase-IV)  
dr (diastereomeric ratio)  
er (enantiomeric ratio)  
equiv (equivalent)  
Et (ethyl)  
GK (glucokinase activator)  
HPLC (high performance liquid chromatography)  
*i*-Pr (isopropyl)  
IR (infrared)  
LiHMDS (lithium bis(trimethylsilyl)amide)  
Me (methyl)  
n (normal)  
NBD (Norbornadiene)  
NMM (*N*-methyldmorpholine)  
NMP (*N*-methylpyrrolidinone)  
NMR (nuclear magnetic resonance)  
PMP (1,2,2,6,6-Pentamethylpiperidine)  
Ph (Phenyl)  
QOL (quality of life)  
rt (room temperature)  
SGLT (sodium glucose co-transporter)  
SU (sulfonyleurea)  
t (tertiary)  
Temp. (temperature)  
TMP (2,2,6,6-Tetramethylpiperidine)  
THF (tetrahydrofuran)

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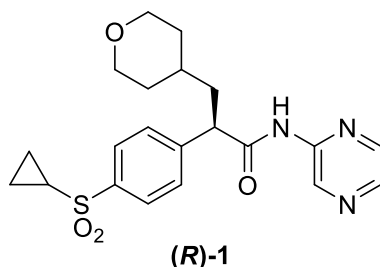
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## 第 1 章 緒言

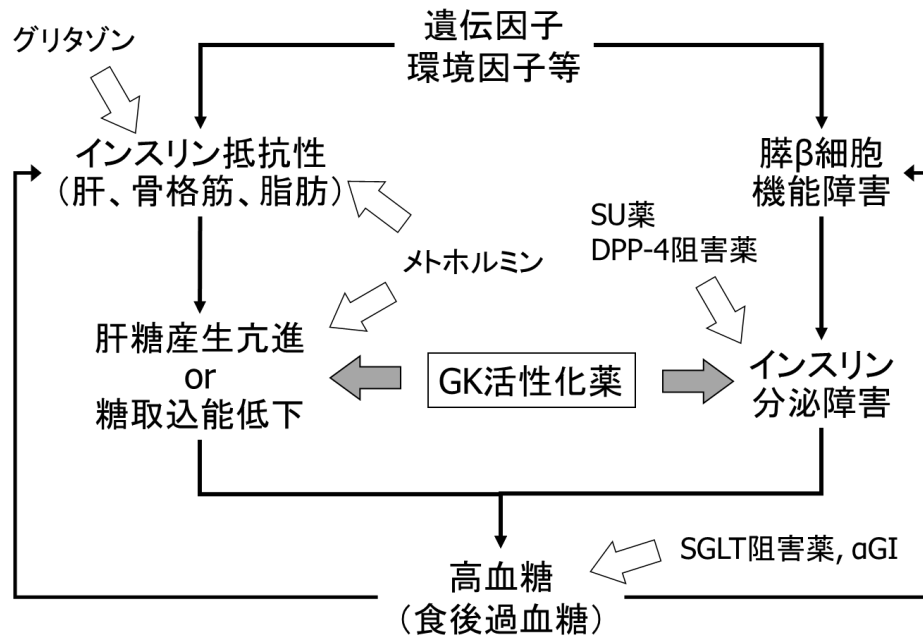
本論文ではⅡ型糖尿病治療薬として期待される GK 活性化薬 **(R)-1** の合成研究について取り上げる (図表 1-1) <sup>1</sup>.

【図表 1-1】 GK 活性化薬 **(R)-1**

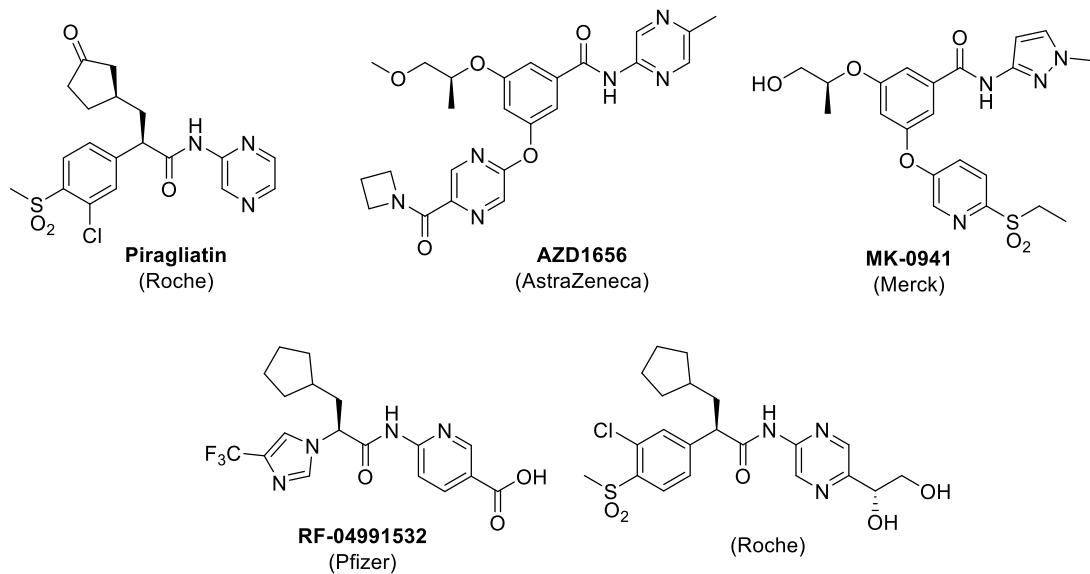


糖尿病患者数は、生活習慣と社会環境の変化に伴って、世界的に急速に増加しており、その中でも、Ⅱ型糖尿病の割合が多い<sup>2</sup>。薬物療法を行う患者の病態によっては、経口血糖降下薬の作用機序に起因する低血糖や体重増加などの副作用が課題となっており、患者の生活の質 (QOL) 向上に繋がる新たな治療薬の開発が期待されている。GK 活性化薬はグルコキナーゼのアロステリック部位と相互作用し、グルコキナーゼを活性化することで、膵 β 細胞でのインスリン分泌能の増強と肝での糖利用の亢進という 2 つの作用を同時に示し、他剤での治療が難しい血糖値をコントロールできる可能性がある (図表 1-2) <sup>3</sup>。そのため、多くの製薬会社が GK 活性化薬の開発に取り組んでおり、**(R)-1** 以外にもグルコキナーゼ活性化作用を持つ化合物がいくつか報告されている (図表 1-3) <sup>4</sup>。

【図表 1-2】 2 型糖尿病発症機序と GK 活性化薬



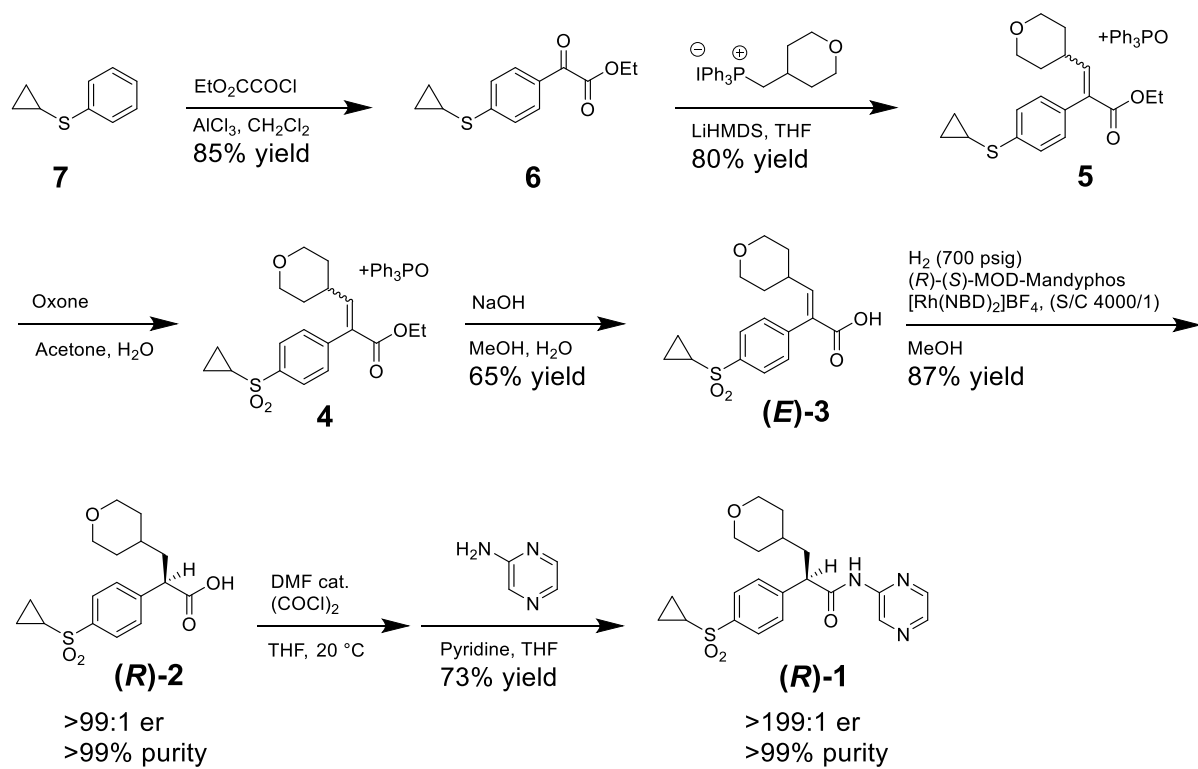
【図表 1-3】 GK 活性化作用を持つ化合物



これらの化合物が医薬品として承認されるためには、臨床試験での有効性・安全性の評価に加え、適切な品質の医薬品が恒常的に生産、供給できるようにされてなければならない。そのため、医薬品の製造プロセスにおいては品質を保証するためのプロセスを組み込むことが求められている<sup>5</sup>。また、医薬品製造過程においても危険性や有害性をもつ化学物質を取り扱うことは多く、製薬企業はヒトの健康や環境生態への影響リスクを把握した上で、レスポンス・ケア活動にも自主的に取り組んでいる。そのため、医薬品の製造プロセスは、Buttersらが提唱した「SELECT」で取り上げられる「Safety:安全」,「Environmental:環境」,「Legal:法規制」,「Economy:事業性」,「Control:品質」,「Throughput:生産性」などの複数の評価軸に沿って開発がなされている<sup>6</sup>。

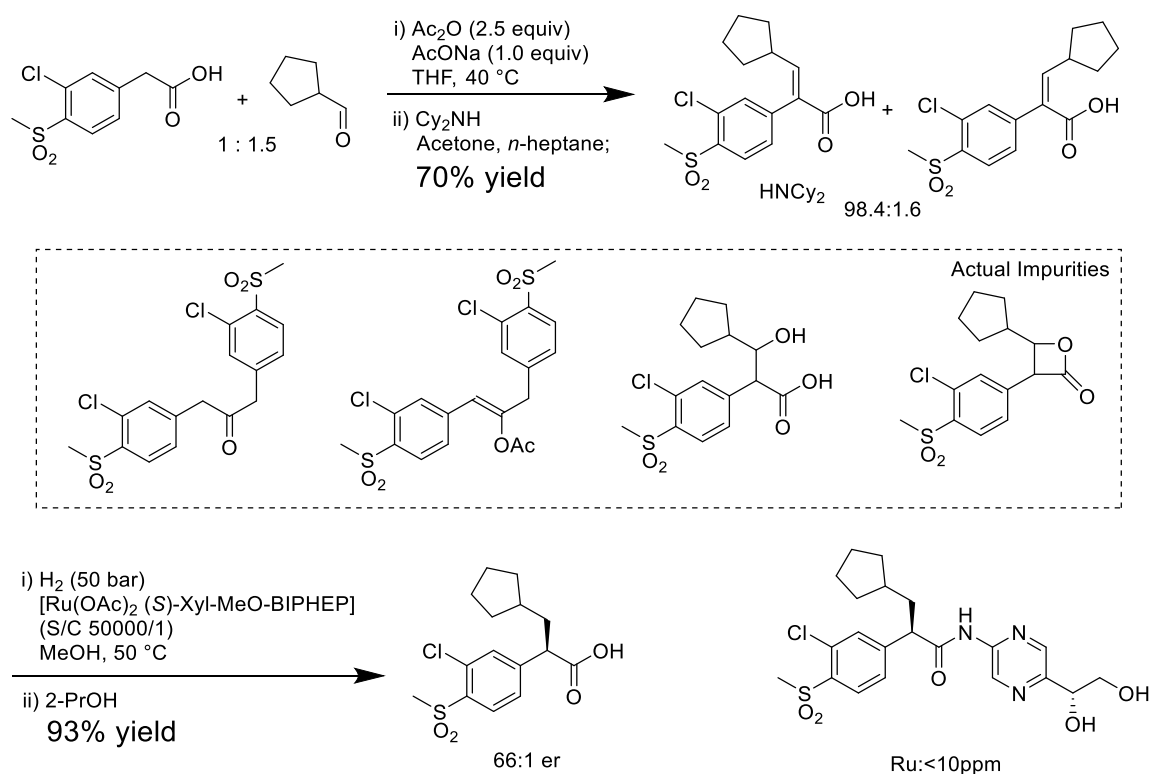
以下、既存の**(R)-1** 合成法について考察した。Magnus らが報告した GK 活性化薬**(R)-1** 合成法では、不斉水素化反応と Wittig 反応を経て合成されるアクリル酸誘導体**(E)-3** を鍵中間体としている（図表 1-4）<sup>7</sup>。不斉水素化反応で用いるロジウムは、元素不純物ガイドライン ICH Q3D で規定されるクラス 2B に該当し、経口製剤における許容一日暴露量 (PDE) は 100 µg/day と厳しい基準が設けられている<sup>8</sup>。Magnus らの方法では原薬中のロジウム濃度を許容量以下に下げる過程で収率低下を伴う活性炭吸着精製を用いる必要がある<sup>9</sup>。また、Wittig 反応では副生される Ph<sub>3</sub>PO を除去するために**(E)-3** の単離時に複数回の分液精製を行っており、購入原料 **7** から**(E)-3** までの 4 反応の total 収率が 44%となっている。これら 2 つの反応における過度な精製は、目的物の収率低下を招くだけでなく、溶媒の大量使用や作業時間の延長を招き、結果として「SELECT」の観点から好ましくない合成ルートとなっているのではないかと考えた。

【図表 1-4】 Magnus らの (R)-1 合成



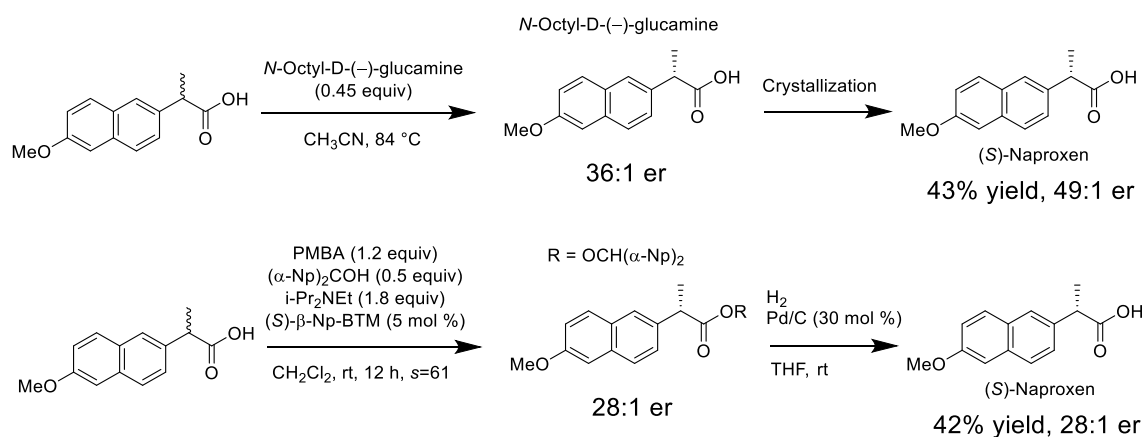
(*R*)-**1** と類似構造をもつ GK 活性化薬の合成においても、アクリル酸誘導体を鍵中間体とする合成法が報告されている。Bachmann らは不斉水素化反応に用いる遷移金属触媒をロジウムから被毒化され難いルテニウムに変更することで Magnus らの方法で課題となっていた触媒精製による収率低下を回避しているとともに、Wittig 反応に代え副生成物が水となる Perkin 反応を利用していることから工業化製法として問題は少ないと考えられる (図表 1-5)<sup>10</sup>。その一方で本合成法は製法特許として権利化されているため(*R*)-**1** の工業化製法に用いるには問題がある<sup>11</sup>。

【図表 1-5】 Perkin 反応と Ru 触媒を用いた不斉水素還元反応による GK 活性化薬の合成



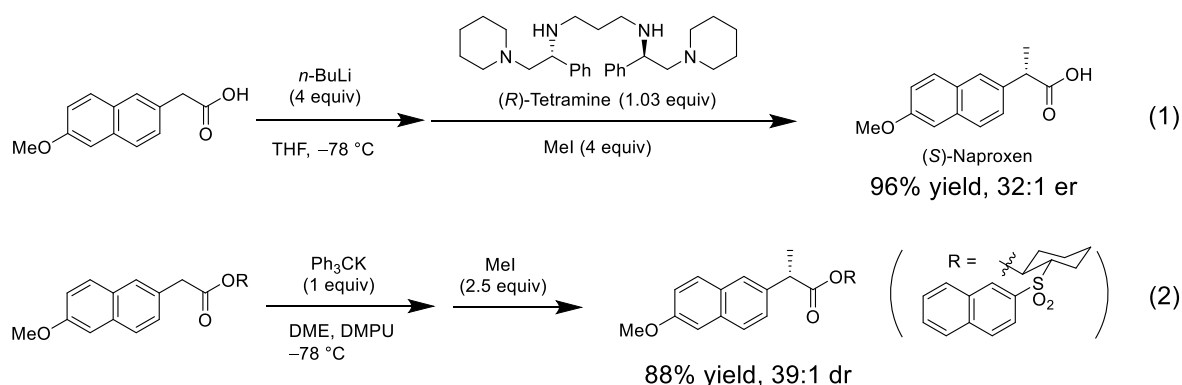
非ステロイド系抗炎症薬 (*S*)-Naproxen の合成ではアクリル酸誘導体の不斉水素化反応を用いない立体構築法がいくつか報告されている<sup>12</sup>。ラセミ体を原料としたジアステレオマー法による光学分割法は、(*S*)-Naproxen の工業化に利用されており、(*R*)-1 合成でも事業性面で有利な合成法となる可能性がある (図表 1-6)<sup>13</sup>。また、2010 年に Shina らによって開発された速度論的光学分割は (+)-ベンゾテトラミソールを不斉触媒とすることで、種々の  $\alpha$ -アリールプロピオン酸に対するビス( $\alpha$ -ナフチル)メタノールとの選択的なエステル化反応を見出しているが<sup>14</sup>、(*R*)-1 製造を考えた場合の収率は最大 50% であり、必要量の原薬を合成するために必要なラセミ体はその 2 倍量以上必要となるため非効率的な方法になる<sup>15</sup>。

【図表 1-6】 光学分割による (*S*)-Naproxen 合成



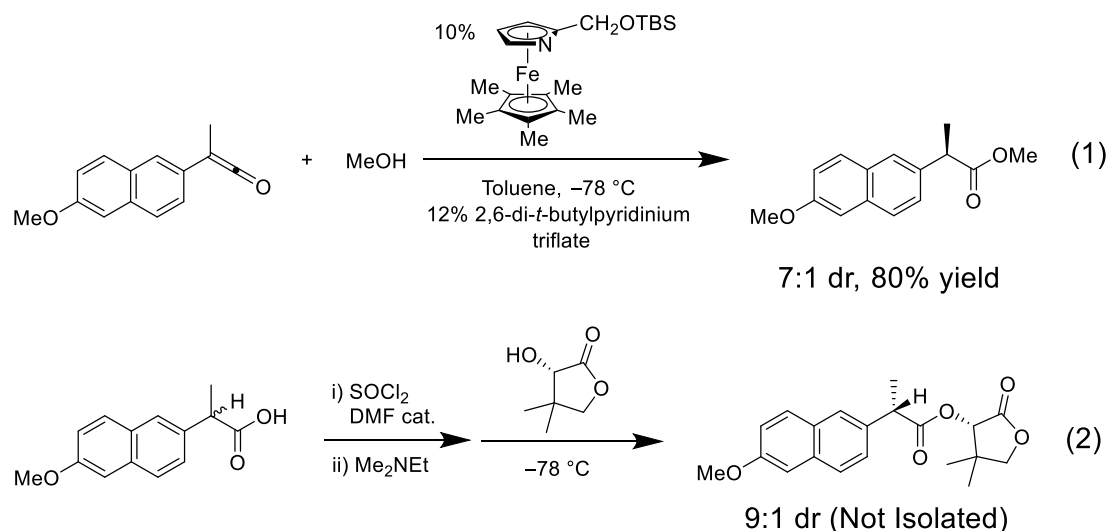
アリール酢酸誘導体に対する不斉アルキル化反応を用いた(*S*)-Naproxen の合成が 2 例報告されている (図表 1-7). 近年新たに開発された Zakarian らの光学活性テトラアミン配位子を用いたカルボン酸の不斉アルキル化反応や Corey らのスルホン不斉補助基を用いたエステルの不斉アルキル化反応は, エノラートの *E/Z* 選択性, エノラートの反応面の選択性が高く, 収率やジアステレオ選択性が優れている<sup>16,17</sup>. その一方で, これら 2 つの報告では  $\alpha$  水素の酸性度が高い基質での結果は含まれていない. 目的化合物(***R***)-1 はアリール基上に電子吸引性基があることで不斉炭素上の水素の酸性度が高まっており, (***R***)-1 合成にこれらの条件を用いた場合ラセミ化やジアルキル化などの副反応が進行することが懸念される.

【図表 1-7】アリール酢酸誘導体に対する不斉メチル化反応による(*S*)-Naproxen 合成



ケテンに対するアルコールの立体選択的付加反応を用いた(*S*)-Naproxen の合成が 2 例報告されている。1999 年に Fu らは面性キラルなアザフェロセン触媒を用いたケテンに対するメタノールの立体選択的付加反応を報告している<sup>18</sup>。強塩基を用いることなしに $\alpha$ 水素の立体を構築できるが、単離精製したケテンを用いる必要がある。一方、1989 年に Larsen らはケテンを経由する立体選択的なエステル化反応を In-Situ で発生させたケテンに対してキラルアルコールである(*R*)-パントラクトンを立体選択的に付加させることで、エステル $\alpha$ 炭素の立体を構築することに成功している(図表 1-8)<sup>19</sup>。強塩基を用いることなしに $\alpha$ 水素の立体を構築することができるため、(*R*)-1 など $\alpha$ 水素の酸性度が高い基質の立体構築においてもラセミ化の懸念がなく、ケテンを単離精製する必要がないことも SELECT の観点から有効な手段であると思われる。

【図表 1-8】ケテンに対するアルコールの立体選択的付加反応による(*S*)-Naproxen 合成





以上, (*S*)-Naproxen の既存合成法を考察した. これらの考察結果を基に, 第 2 章では, Larsen らのケテンに対するパントラクトンの立体選択的付加反応を応用し,  $\alpha$ -アリールプロピオン酸誘導体の高立体選択的合成法の開発について述べる. 第 3 章では, GK 活性化薬 (***R***)-1 の第 2 章で開発した合成法を利用した工業化製法の開発について述べる.



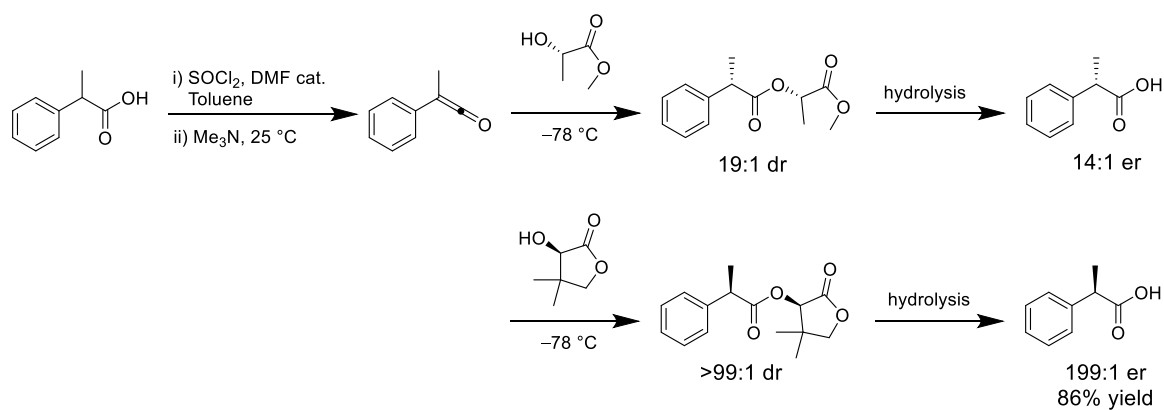
## 第 2 章 ケテンに対するキラルアルコールの立体選択的付加反応を利用した $\alpha$ -アリールプロピオン酸誘導体の高立体選択的合成法の開発

### 第 1 節 パントラクトンエステルを経由した GK 活性化薬 (*R*)-1 前駆体の合成

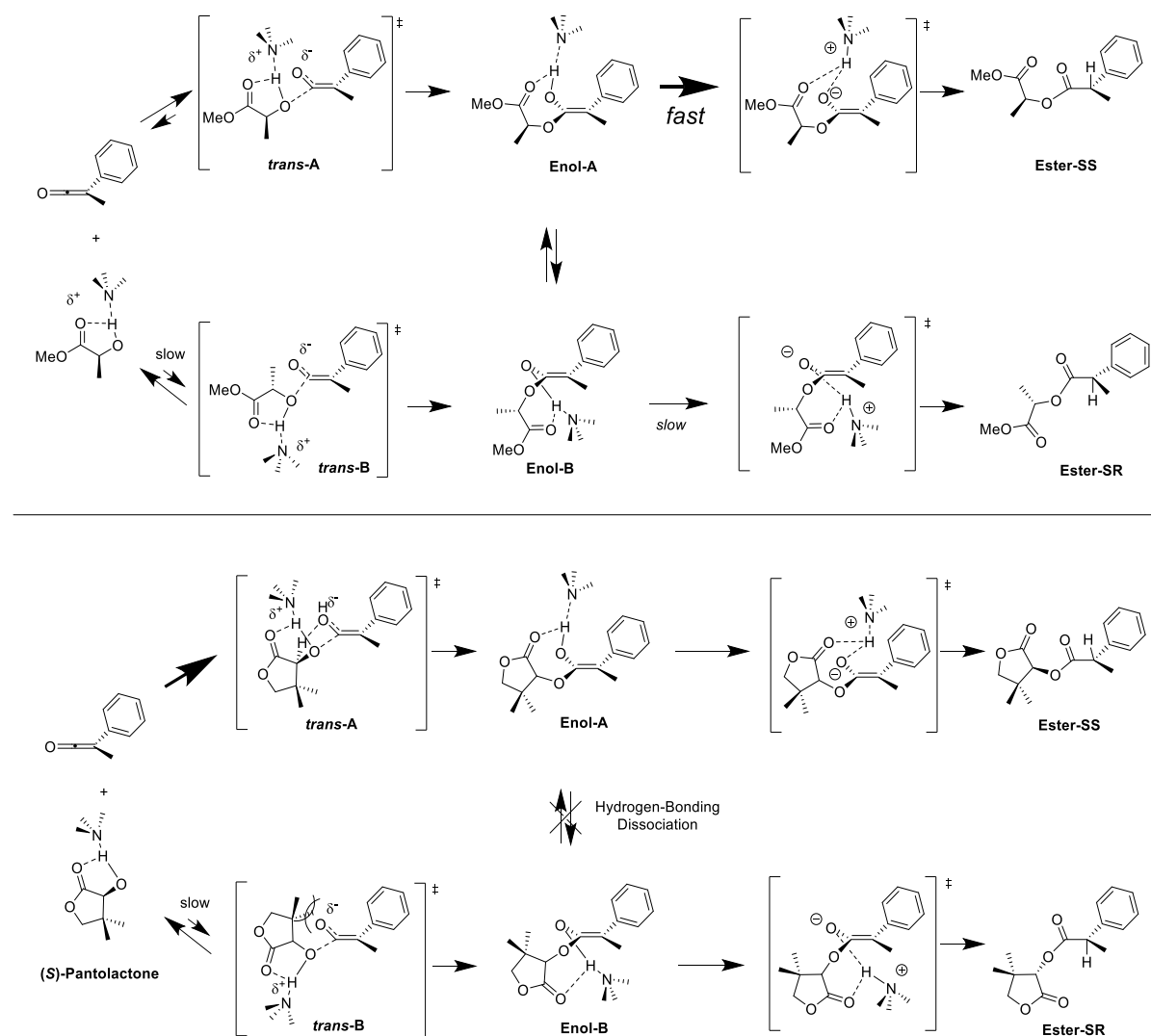
Larsen らはメチルフェニルケテンに対して、キラルアルコールである(*S*)-乳酸メチルと(*R*)-パントラクトンが付加させ、高立体選択的に対応するエステルへと導き、それらを加水分解することで、 $\alpha$ -フェニルプロピオン酸を合成できることを報告している (図表 2-1) <sup>19</sup>.

2004 年に Houk らは、(*S*)-乳酸メチルと(*S*)-パントラクトンを経由してメチルフェニルケテンに付加させた場合に立体選択性が発現する機構を B3LYP/6-31G\*を用いた密度関数理論計算に基づく定量モデルから推定しており、(*S*)-乳酸メチルと(*S*)-パントラクトンでは立体選択性発現のメカニズムが違ふことが述べられている (図表 2-2) <sup>20</sup>. それによると(*S*)-乳酸メチルと(*S*)-パントラクトンともメチルフェニルケテンのケテンと同一平面に位置するフェニル基の *trans* 方向から付加するが、(*S*)-乳酸メチルを用いた場合、生成されるエノール A とエノール B は平衡状態の関係にあるが、エノール A から(*S,S*)エステルへの互変異がエノール B から(*R,R*)エステルへの互変異よりも速いことによってジアステレオ選択性が発現すると述べられている (上段). 一方、(*S*)-パントラクトンを用いた際に生成されるエノール中間体ではアミンとパントラクトンの水素結合により安定なコンフォメーションを形成するためエノール A とエノール B との間の平衡移動が起こらないとされている (下段). またエノール A に至る遷移状態 *trans*-A は近接するケテンカルボニル基酸素と水酸基と同一炭素上の水素との水素結合による安定化を受けているがエノール B に至る遷移状態 *trans*-B は近接するケテンカルボニル基酸素とパントラクトンカルボニル基酸素電子的反発を受け不安定化されていることにより、エステル化反応は遷移状態 *trans*-A を経てエノール A が生成し、エノール B への平衡移動なしに(*S,S*) パントラクトンエステルが立体選択的に生成するとされている.

【図表 2-1】 メチルフェニルケテンに対するキラルアルコールの付加反応

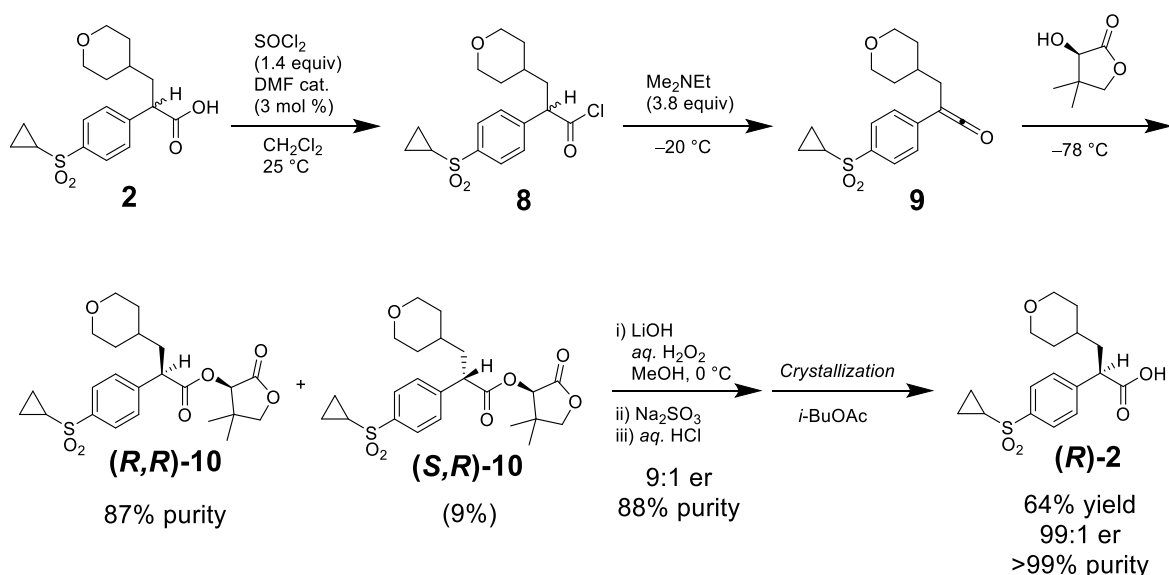


【図表 2-2】 メチルフェニルケテンに対するアルコールの立体選択的付加の推定機構



以上のことからケテン中間体 **9** に対し(*R*)-パントラク톤を付加させることによって、高立体選択的にパントラク톤エステル(*R,R*)-**10** へ変換できると考えた。そこで、Larsen らの報告と同様の条件下で(*R*)-パントラク톤を用い、酸クロライド **8** に対してパントラク톤エステル化を試みた。その結果、目的の (*R,R*)-**10** がジアステレオ選択的に生成することを確認した(図表 2-3) <sup>21</sup>。(*R,R*)-**10** は不斉炭素上に酸性度の高いプロトンを有しているため一般的なアルカリ加水分解ではエピメリ化とラセミ化が起こる可能性があることから、Evans らの水酸化リチウム、過酸化水素水の条件で加水分解したところ <sup>22</sup>、ラセミ化、エピメリ化をうけることなく鏡像体比 9:1 で目的物(*R*)-**2** を 88% の HPLC 純度で得ることができた。

【図表 2-3】 パントラク톤エステル混合物 **10** を経由した(*R*)-**2** の合成



以上、パントラク톤の立体選択的付加反応を利用することにより目的とする(*R*)-**2**を得た。しかし、(*R,R*)-**10** のジアステレオ選択性は 9:1、(*R*)-**2** の単離収率は 64%にとどまっていることから、高立体選択的にパントラク톤を付加させるための反応条件を検討した。

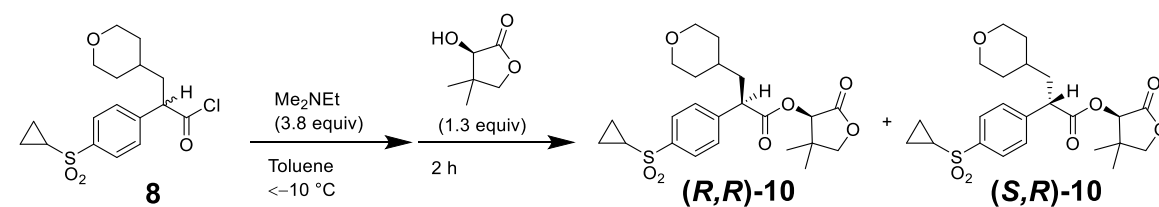


## 第 2 節 ケテンに対するパントラクトン付加のジアステレオ面選択性に関する考察

Houk らが推定しているメカニズムから我々の反応を考察すると、メチルフェニルケテンと同様に、遷移状態 *trans*-A, エノール A を経由しジアステレオ選択的に(*R,R*)-**10** が生成していると考えることができる。その一方で酸クロリド **8** から変換されるケテン **9** はアリール基上に電子吸引性スルホン基を有するため、メチルフェニルケテンに比べてケテンカルボニル基酸素の電子密度が低下していることが想定される。そのため、Houk らの反応機構で提唱されるエノール A や遷移状態 *trans*-A の水素結合による安定化効果や遷移状態 *trans*-B の電子的反発による不安定効果がメチルフェニルケテンに比べて小さいと思われる。その結果、エノール A からエノール B への平衡移動が起こりやすくなる、また遷移状態 *trans*-A と遷移状態 *trans*-B の活性化エネルギー差も小さくなり、生成されるエステル **10** のジアステレオ選択性がメチルフェニルケテンの場合よりも低くなっていると考えた。そこで、遷移状態のエネルギーに影響を及ぼすと考えられる反応温度と溶媒極性について検討した。

酸クロリド **8** を  $\text{Me}_2\text{NEt}$  存在下，トルエン中で  $-10^\circ\text{C}$ ， $-78^\circ\text{C}$  でそれぞれパントラクトンと反応させた際に生成されるパントラクトンエステル **(R,R)-10** の生成量及び **(S,R)-10** とのジアステレオ選択性を HPLC 面積値百分率から評価した（図表 2-4）．その結果， $-78^\circ\text{C}$  で反応させた場合 **(R,R)-10** のピーク面積値及びパントラクトンエステルのジアステレオ選択性が高くなっている．反応温度を下げることで，遷移状態や中間体分子の熱運動が抑えられ，選択性が高くなっているのではないかと考えた．

【図表 2-4】 **(R,R)-10** の生成量とジアステレオ選択性に及ぼす反応温度の効果



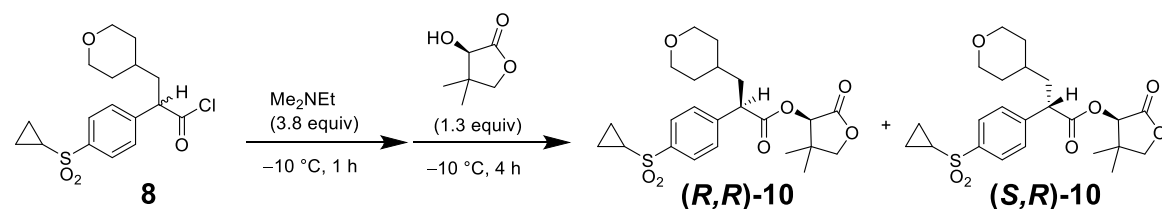
Entry	Temp.	HPLC Area% of <b>(R,R)-10</b>	<b>(R,R)-10</b> : <b>(S,R)-10</b> <sup>a</sup>
1	$-78^\circ\text{C}$	82.96	11:1
2	$-10^\circ\text{C}$	55.81	5:1

<sup>a</sup> Determined by HPLC.



次に、反応溶媒によるジアステレオ選択性への影響を確認するために、極性が異なる溶媒を用いた際に生成するパントラクトンエステル(*R,R*)-10 の生成量について検討した。比誘電率の異なる Toluene, THF, CH<sub>2</sub>Cl<sub>2</sub>, MeCN の 4 種類の溶媒を用い反応を行ったところ、溶媒の比誘電率が低くなるにつれて(*R,R*)-10 の生成量が増加し、パントラクトンエステルのジアステレオ選択性が高くなっていることが確認できた (図表 2-5)<sup>24</sup>。極性が低い溶媒を用いることにより中間体及び遷移状態における静電相互作用が強くなり、ジアステレオ選択性が高くなっているのではないかと考えた。

【図表 2-5】 (*R,R*)-10 の生成量とジアステレオ選択性に及ぼす溶媒比誘電率の効果



Entry	Solvent	$\epsilon$	HPLC Area% of ( <i>R,R</i> )-10	( <i>R,R</i> )-10:( <i>S,R</i> )-10 <sup>a</sup>
1	Toluene	2.43	69.09	5.1:1
2	THF	7.47	63.97	4.7:1
3	CH <sub>2</sub> Cl <sub>2</sub>	9.02	67.56	3.9:1
4	MeCN	36.00	35.42	1.9:1

<sup>a</sup> Determined by HPLC.

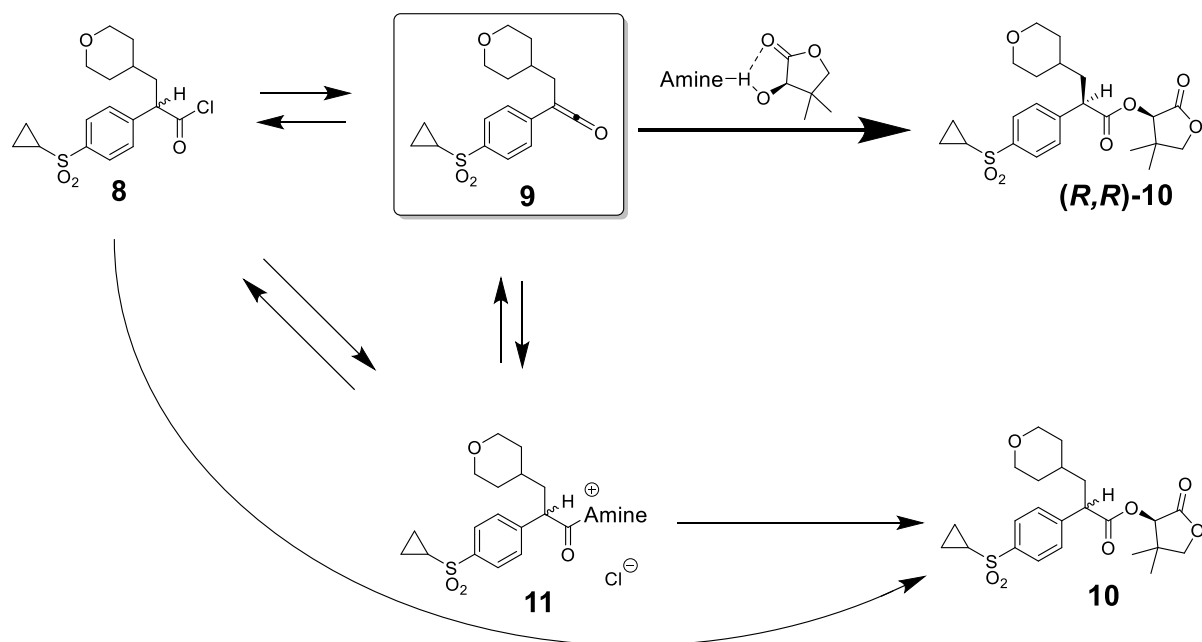
以上、反応温度を低下させる、反応溶媒の極性を下げることによってパントラクトンエステル(*R,R*)-10 のジアステレオ選択性が向上することを明らかにした。



### 第 3 節 脱塩化水素反応を利用したケテンの化学平衡状態に関する考察

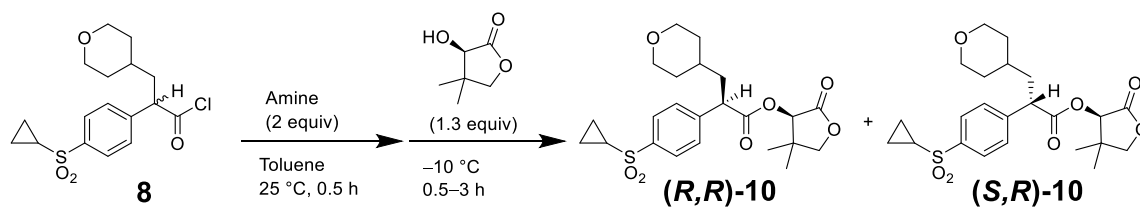
一般的に、酸クロリドからアミン存在下、ケテンを生成させる場合、用いるアミンの求核性によってアシルアンモニウムが副生し、酸クロリド、ケテン、アシルアンモニウムが平衡状態として存在し、それぞれに対してアルコールが付加反応したエステルが生成することが報告されている<sup>25,26</sup>。酸クロリド **8** からケテン **9** を合成する場合においても酸クロリド **8**、ケテン **9**、アシルアンモニウム **11** が化学平衡の状態にあり、それぞれに対してパントラクトンが付加することで(*R,R*)-**10** と(*S,R*)-**10** が生成していると考えられ、ケテン **9** からエステル化が進行した場合は立体選択的に(*R,R*)-**10** が生成するが、酸クロライド **8** やアシルアンモニウム **11** からエステル化が進行した場合は非立体選択的にエステル化が進行し、生成するエステルのジアステレオ選択性は低下すると思われる (図表 2-6)。即ち、酸クロライド **8**、ケテン **9**、アシルアンモニウム **11** の間の化学平衡の状態を制御することも立体選択的に(*R,R*)-**10** を合成するには重要である。そこで、これら 3 つの中間体の化学平衡に影響を及ぼすアミンと反応温度について検討した。

【図表 2-6】 パントラクトンエステル生成の推定経路



一般的に、酸クロリドの $\alpha$ 水素の  $pK_a$  とアミン共役酸の  $pK_a$  との差が大きくなる程、化学平衡は一方向へと偏ると考えられ、アミン共役酸の  $pK_a$  が高いアミンを用いることによって、アミン塩酸塩へ化学平衡が偏り、ケテンの生成量が高くなることが想定される。パントラクトンエステル(***R,R***-**10** と ***S,R***-**10** の生成比は(*R*)-パントラクトンが付加するケテンの生成量に影響を受けていると考え、塩基性が異なるアミンを用いた際に生成するパントラクトンエステルのジアステレオ選択性について検討した。アミン共役酸の  $pK_a$  が異なる 9 種類のアミン (*i*-Pr)<sub>2</sub>NEt, PMP, TMP, (*n*-Bu)<sub>3</sub>N, Et<sub>3</sub>N, (*n*-Pr)<sub>3</sub>N, Me<sub>2</sub>NEt, NMM, Pyridine を用い、トルエン中 25°C でケテンに変換し、−10°C でパントラクトンを付加させたところ、(*i*-Pr)<sub>2</sub>NEt, PMP, NMM の 3 つのアミンを除く 7 種類のアミン共役酸の  $pK_a$  が高くなるにつれてパントラクトンエステルのジアステレオ選択性が高くなる傾向が確認された (図表 2-7) <sup>27</sup>。  $pK_a$  とジアステレオマー過剰率(*de*)との間に決定係数 0.99 の相関性が確認され、塩基性が強いアミンを用いることにより酸クロリド **8** からケテン **9** へ酸解離平衡が偏り、ケテン **9** に対して(*R*)-パントラクトンが立体選択的に付加したパントラクトンエステルの生成量が増加していると考えた。塩基性が強い (*i*-Pr)<sub>2</sub>NEt や PMP を用いた場合、パントラクトンエステルのジアステレオ選択性が低い結果となった。生成物 **10** の収率が低いことから、アミンと酸クロリド **8** との間に立体障害が発生し、酸クロリド **8** からケテン **9** への変換量が少なくなっており、ケテン **9** に対して(*R*)-パントラクトンが立体選択的に付加したパントラクトンエステルの生成量が少なく、酸クロリド **8** に対して(*R*)-パントラクトンが非立体選択的に求核置換を起こしたパントラクトンエステル **10** の生成比率が高くなることによって、ジアステレオ選択性が低くなっているのではないかと推察した (Entries 1, 2) <sup>28</sup>。また、Entries 7, 8 を比較すると塩基性が弱い NMM を用いた際に生成物 **10** のジアステレオ選択性が高くなっていた。求核性が高いアミンを用いることによって、アシルアンモニウム **11** の副生量が多くなり、アシルアンモニウム **11** に対して(*R*)-パントラクトンが非立体選択的な求核置換を起こしたパントラクトンエステルの生成量が増加し、生成物 **10** のジアステレオ選択性が低くなったのではないかと推察した。

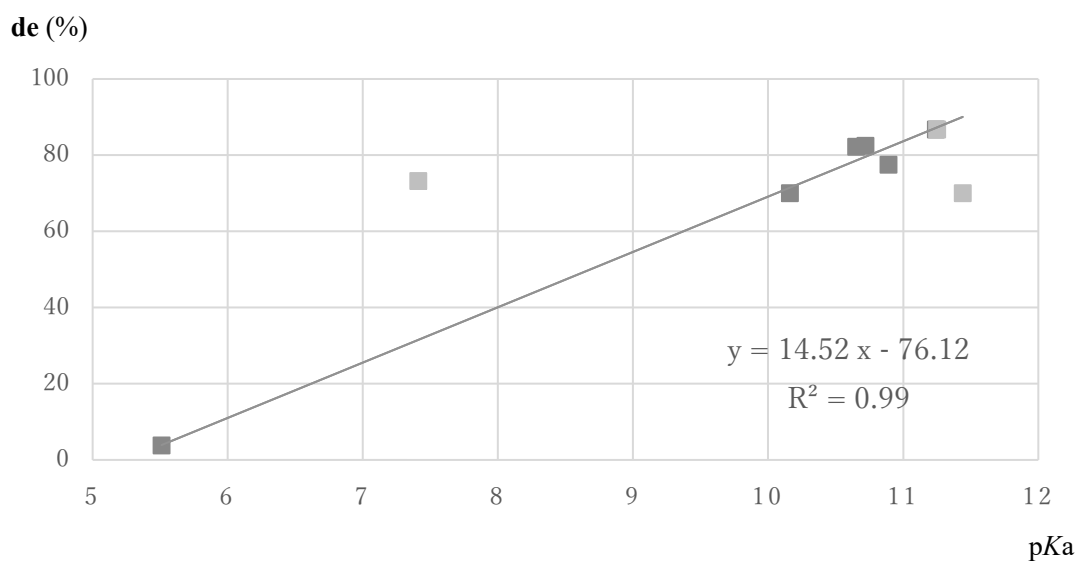
【図表 2-7】 パントラクトンエステルのジアステレオ選択性とアミン共役酸 pKa との相関性



Entry	Amine	pKa <sup>a</sup>	Yield <sup>b</sup>	<b>(R,R)-10</b> : <b>(S,R)-10</b> <sup>c</sup>
1	( <i>i</i> -Pr) <sub>2</sub> NEt	11.44	<12% <sup>d</sup>	87:13
2	PMP	11.25	<18% <sup>d</sup>	69:31
3	TMP	11.24	82%	93:7
4	( <i>n</i> -Bu) <sub>3</sub> N	10.89	73%	89:11
5	Et <sub>3</sub> N	10.72	81%	91:9
6	( <i>n</i> -Pr) <sub>3</sub> N	10.65	75%	91:9
7	Me <sub>2</sub> NEt	10.16	89%	85:15
8	NMM	7.41	86%	89:11
9	Pyridine	5.51	90%	52:48

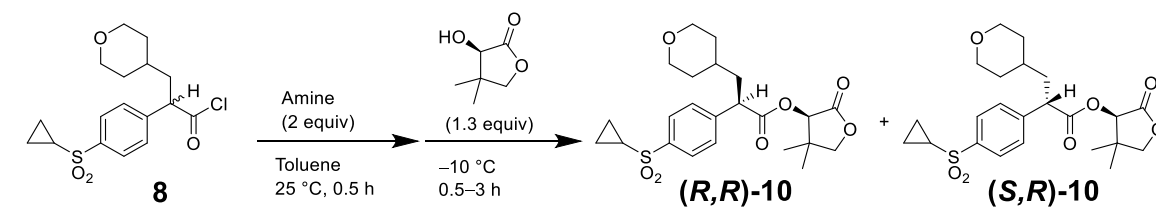
<sup>a</sup> pKa value of a conjugated acid of amine. <sup>b</sup> Isolated yield of the mixture of **(R,R)-10** and **(S,R)-10**

based on **2**. <sup>c</sup> Determined by HPLC. <sup>d</sup> **10** was not isolated.



そこで、アミンの求核性による**(R,R)-10**の生成量への影響を確認した。トリアルキルアミンの求核性を示す指標の1つである Swain-Scott の  $n$  パラメーター値が異なる4つのアミン  $\text{Me}_2\text{NEt}$  ( $n:5.72$ ),  $(i\text{-Pr})_2\text{NEt}$  ( $n:5.42$ ),  $\text{Et}_3\text{N}$  ( $n:4.87$ ),  $\text{NMM}$  ( $n:4.56$ ) を用いた **(R,R)-10** の HPLC 面積百分率と Swain-Scott の  $n$  値との間に決定係数 0.98 の直線性が確認された (図表 2-8) <sup>27</sup>。アミンの求核性が低くなるにつれて、**(R,R)-10** の生成量が増加し、それに合わせてパントラクトンエステルのジアステレオ選択性も高くなっていることが確認できた。即ち、アミンの求核性も **(R,R)-10** の生成量に影響を及ぼしていると思われる。

【図表 2-8】 (R,R)-10 の生成量と Swain-Scott パラメーター(n)との相関性

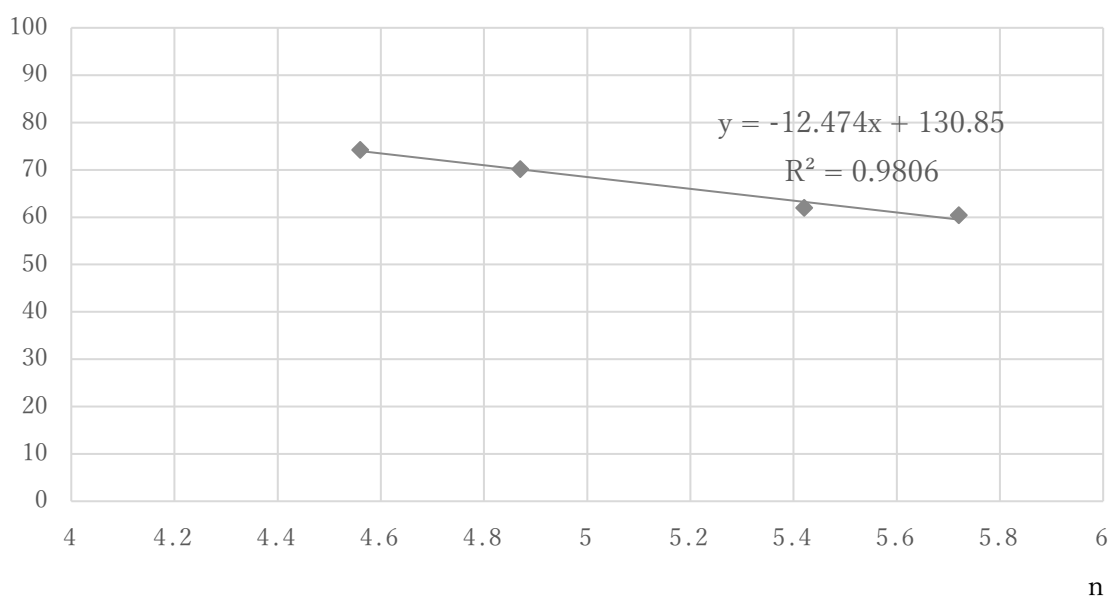


Entry	Amine	n	HPLC Area% of (R,R)-10	(R,R)-10:(S,R)-10 <sup>a</sup>
1	Me <sub>2</sub> NEt	5.72	60.43	6:1
2	Me <sub>2</sub> N( <i>i</i> -Pr)	5.42	61.98	8:1
3	Et <sub>3</sub> N	4.87	70.16	13:1
4	NMM	4.56	74.26	11:1

<sup>a</sup> Determined by HPLC.

HPLC Area% of (R,R)-10

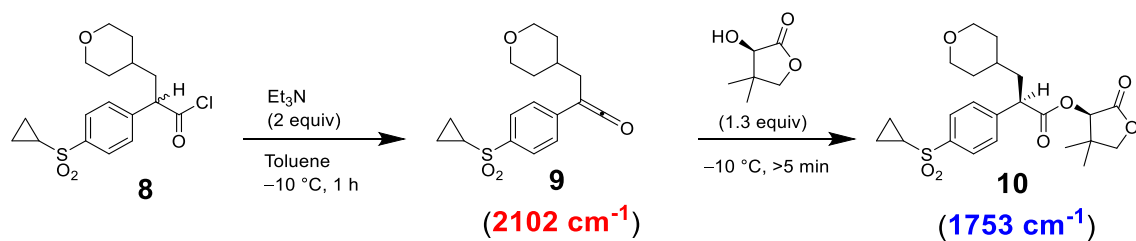
(%)





次に、異なる温度におけるケテンの生成量を ReactIR の  $2102\text{cm}^{-1}$  のピーク強度から評価した（図表 2-9）。反応温度が高くなる程、ピーク強度が平衡に到達するまでにかかる時間が短くなっており、 $25^{\circ}\text{C}$ 、 $-10^{\circ}\text{C}$ 、 $-40^{\circ}\text{C}$ 、 $-78^{\circ}\text{C}$ でのピーク強度を比較することにより、 $-10^{\circ}\text{C}$ で平衡状態に到達した時点におけるケテンの生成量が最も多くなっていると思われた。低温下では白色結晶の析出が見られており、アミン塩酸塩などが析出することによって、 $25^{\circ}\text{C}$ の時よりも溶液中のアミン塩酸塩の濃度が低くなり、平衡状態がケテンに偏ったのではないかと考えた。また、温度を更に低下させることでピーク強度は小さくなっており、 $-78^{\circ}\text{C}$ ではケテンが生成されていないと思われた。低温下でアシルアンモニウムが選択的に生成するという報告があることから<sup>29</sup>、低温下では酸クロリド **8** は直接アシルアンモニウム **11** に変換しているのではないかと考えた。

【図表 2-9】 反応溶液中の React-IR 測定結果

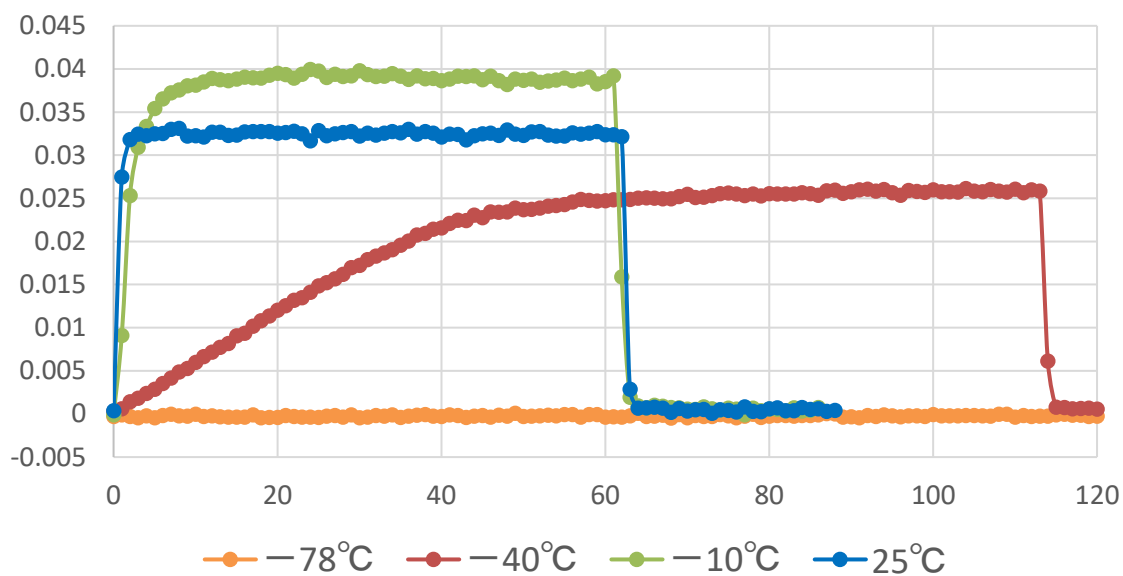
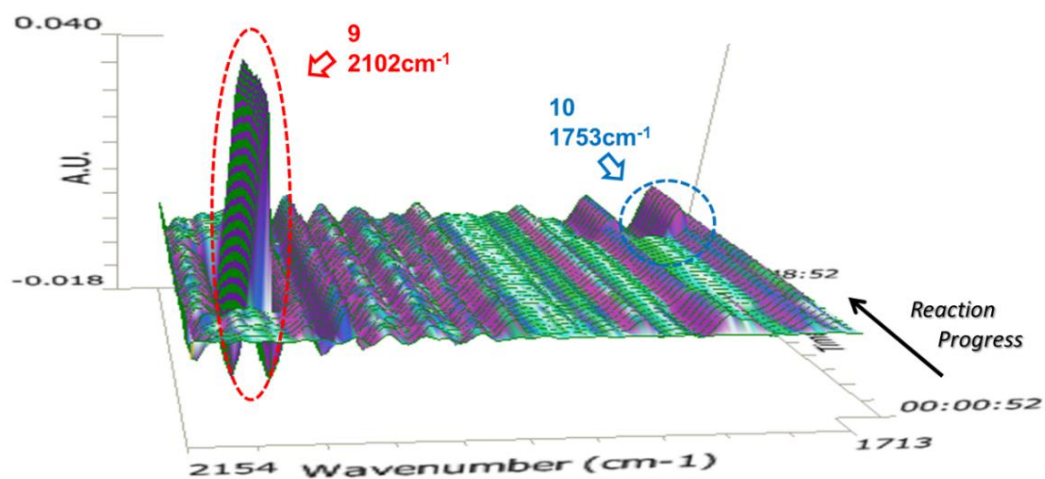


Equipment: ReactIR™ 45m (Mettler Toledo)

Hardware: DiComp probe connected to an MCT detector with AgX 6mm x 1.5m Fiber

Settings: Sampling wavenumbers 2800 to 650 at 8 wavenumber resolution

Data Treatment: 2nd derivative



ReactIR の結果より、酸クロリド **8** からケテン **9** に変換する温度によってケテン生成量が異なることが予想されるため、25℃と−10℃でケテンを生成させた際に生成される(*R,R*)-**10** と (*S,R*)-**10** とのジアステレオ選択性を HPLC 面積百分率から評価し、ケテン生成温度によるパントラクトンエステル(*R,R*)-**10** の生成量及びジアステレオ選択性への影響を確認した (図表 2-10)。その結果、−10℃で反応させた場合よりも 25℃で反応させた際に生成されるパントラクトンエステル(*R,R*)-**10** の生成量は少なく、ジアステレオ選択性は高くなっていることが確認された。酸クロリド **8** からケテン **9** に変換する温度を高くすることによって、アシルアンモニウム **11** と酸クロリド **8** からケテン **9** への平衡移動が起きることに加え、ケテン **9** の分解反応も進行するのではないかと考えた<sup>30</sup>。

【図表 2-10】 (*R,R*)-**10** の生成量とジアステレオ選択性に及ぼす反応温度の効果

Entry	Temp.	HPLC Area% of ( <i>R,R</i> )- <b>10</b>	( <i>R,R</i> )- <b>10</b> :( <i>S,R</i> )- <b>10</b> <sup>a</sup>
1	25 °C	74.15	44:1
2	−10 °C	86.97	38:1

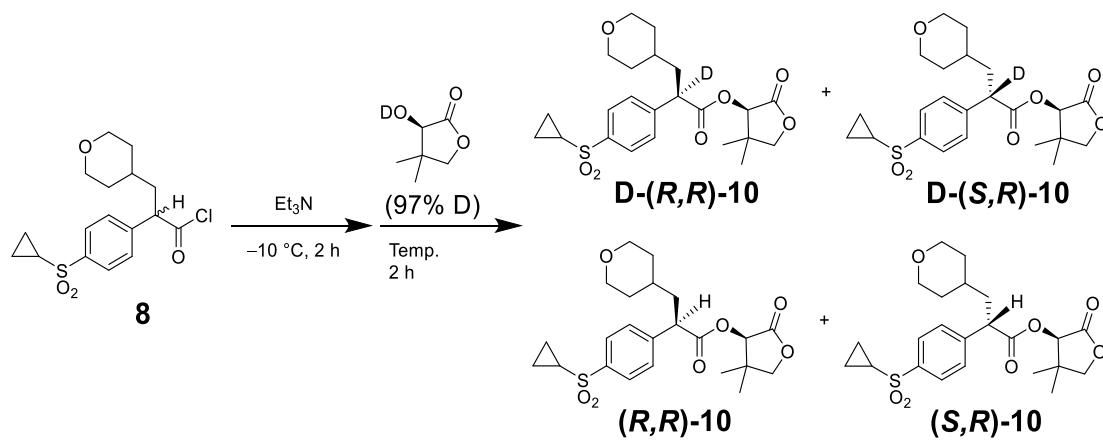
<sup>a</sup> Determined by HPLC.

以上、塩基性が強いアミンを用いることによって、パントラクトンエステルのジアステレオ選択性が向上される傾向が確認されたが、一部のアミンでは求核性や立体障害の影響によってジアステレオ選択性が低下していることを明らかにした。また、酸クロリドからケテンに変換させる反応温度がケテンの生成量とパントラクトンエステルのジアステレオ選択性に影響を及ぼしており、反応温度が高い場合にパントラクトンエステルの生成量が低下していることを明らかにした。

#### 第4節 非立体選択的なパントラクトンエステルの副生に関する考察

軽水素化パントラクトンの代わりに 97%重水素化パントラクトンを用いた際に生成される重水素化パントラクトンと軽水素化パントラクトンエステルの生成量とそれぞれのジアステレオ選択性を比較し、非立体選択的なパントラクトンエステルの副生について考察した (図表 2-11)。溶媒の種類、パントラクトンの付加温度に関わらず、ケテンに対して(*R*)-パントラクトンが立体選択的に付加した重水素化パントラクトンエステルが優先的に生成しており、軽水素化パントラクトンエステルのジアステレオ選択性が重水素化パントラクトンエステルのジアステレオ選択性よりも低くなっていた。軽水素化パントラクトンエステルは重水素化パントラクトン中の軽水素化パントラクトンが立体選択的に付加することによって生成されるだけでなく、アシルアンモニウム **11** 及び酸クロリド **8** に対して非立体選択的にパントラクトンが付加することによっても生成されるため、生成物のジアステレオ選択性が低下していると思われる。また、軽水素化パントラクトンエステルの副生量は溶媒の影響を受けており、極性が高い MeCN を用いた場合に重水素化率が低下していた。溶媒和によって分極構造であるアシルアンモニウム **11** が安定化を受け、アシルアンモニウム **11** の存在比が高くなったためではないかと思われる。*(R)*-パントラクトンの付加温度が $-78^{\circ}\text{C}$ と $-10^{\circ}\text{C}$ との間で生成されるエステルの重水素化率が変わっていないことから、ケテン生成後に $-10^{\circ}\text{C}$ から $-78^{\circ}\text{C}$ まで冷却する過程で、ケテン **9**, アシルアンモニウム **11**, 酸クロリド **8** の存在比が変わらず、それら 3 つの中間体の間で平衡移動が生じていないのではないかと考えた。

【図表 2-11】 97%重水素化パントラクトンを用いた重水素化パントラクトンエステルの立体選択的合成



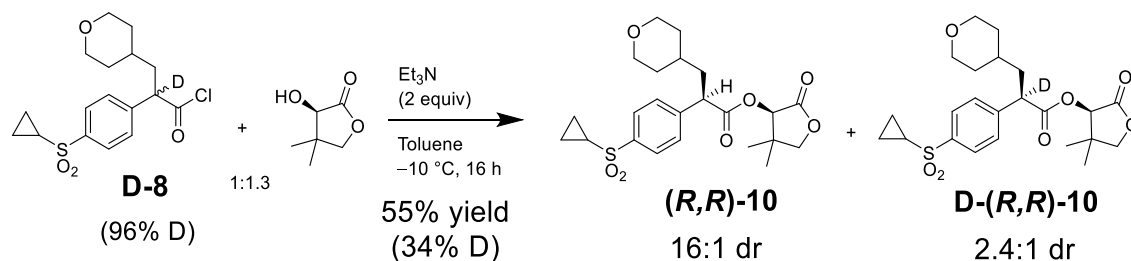
Entry	Solvent ( $\epsilon$ )	Temp.	Yield <sup>a</sup>	D content <sup>b</sup>	<b>D-(R,R)-10:</b>	<b>(R,R)-10:</b>
					<b>D-(S,R)-10 <sup>b</sup></b>	<b>(S,R)-10 <sup>b</sup></b>
1	$\text{CH}_3\text{CN}$	$-10\text{ }^\circ\text{C}$	91%	56%	4.6:1	3:1
2	THF	$-10\text{ }^\circ\text{C}$	94%	93%	11:1	6:1
3	Toluene	$-10\text{ }^\circ\text{C}$	90%	92%	17:1	3:1
4	Toluene	$-78\text{ }^\circ\text{C}$	85%	92%	>99:1	3:1

<sup>a</sup> Isolated yield of the mixture of **(R,R)-10**, **(S,R)-10**, **D-(R,R)-10**, and **D-(S,R)-10** based on **2**. <sup>b</sup>

Determined by  $^1\text{H}$  NMR.

また、軽水素化酸クロリド **8** の代わりに酸クロリドの  $\alpha$  水素が 96% 重水素化された **D-8** を用いた場合、ケテン **9** に対して (*R*)-パントラク톤のプロトンが立体選択的に  $\alpha$  炭素に付加したと思われる軽水素化パントラクトンエステルが優先的に生成されるものの、アシルアンモニウム **11** と酸クロリド **8** との求核置換反応によって副生された重水素化パントラクトンエステルの存在比が高くなっていることが確認された (図表 2-12)。 $-10^{\circ}\text{C}$  におけるケテン **9** の生成量は酸クロリドの  $\alpha$  水素の脱離速度に影響を受けていることが想定される。

【図表 2-12】 96% 重水素化酸クロリドを用いたパントラクトンエステルの立体選択的合成

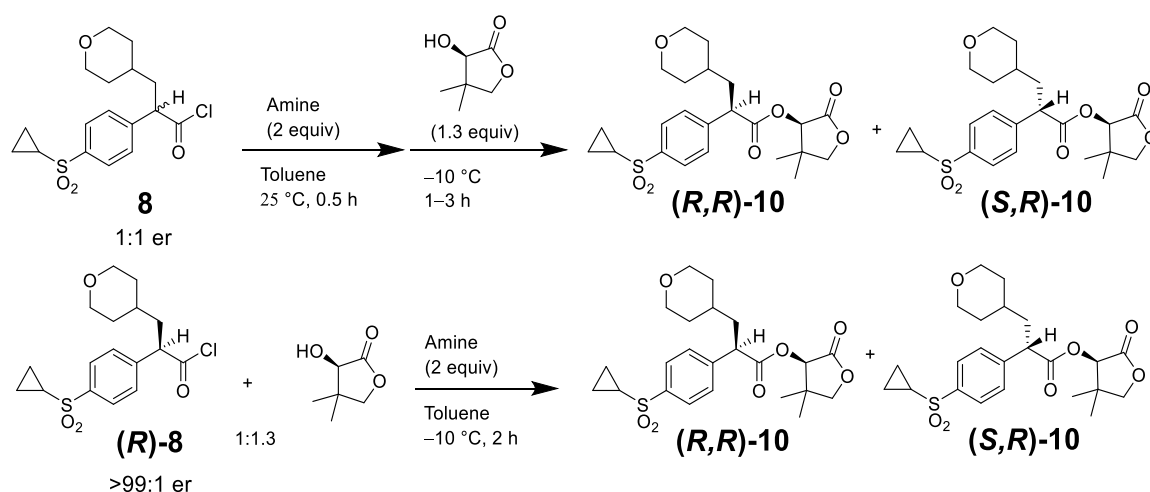


以上、重水素化実験の結果から、生成物パントラクトンエステル **10** 中にはケテンに対して立体選択的に(*R*)-パントラクトンが付加したエステルと非立体選択的に(*R*)-パントラクトンが付加したエステルの副生があり、非立体選択的なエステルを生成する中間体であるアシルアンモニウム **11** の副生量と酸クロリド **8** の残留量を低減することで、生成物のジアステレオ選択性を向上させることができるのではないかと考えた。そこで、アシルアンモニウムの副生に影響を及ぼすアミンの求核性と酸クロリドの残存に影響を及ぼすアミンの塩基性について検討した。



第3節から、アルキル鎖が長いアミンを用いることで酸クロリド **8** からケテン **9** への転換率が下がる傾向があることが確認されており、アルキル鎖が短いアミンを用いることで、酸クロリドの残留量を低減できると考えた。そこで、求核性が異なるアルキル鎖が短いトリアルキルアミンを用い、ラセミ体 **8** (1:1 er) と光学活性体(*R*)-**8** (>99:1 er) を用いた際にそれぞれから生成されるパントラクトンエステルのジアステレオ選択性を比較し、アシルアンモニウムもしくは酸クロリドに対してパントラクトンが非立体選択的に付加したパントラクトンエステルの副生の影響を確認した(図表 2-14)。求核性が高い Pyridine を用いた場合には、生成物 **10** の  $\alpha$  炭素の立体が酸クロリドの  $\alpha$  炭素の立体に影響を受けており、ケテン **9** を経由しないパントラクトンの求核置換反応が進行したと考えられる(図表 2-13)。一方、アミンとして Me<sub>2</sub>NEt を用いた場合、-10℃で光学活性体(*R*)-**8** から生成されるパントラクトンエステル **10** のジアステレオ選択性は 25℃でラセミ体 **8** から生成されるパントラクトンエステル **10** のジアステレオ選択性よりも高く、ケテン **9** を経由しないパントラクトンエステルの副生があると思われる。また、Me<sub>2</sub>NEt よりも更に求核性が低い Et<sub>3</sub>N を用いた場合には、ケテン **9** を経由しないパントラクトンの求核置換反応の影響が小さくなっており、求核性が低いアミンを用いることで、酸クロリド **8** から直接変換されたアシルアンモニウム **11** に対する非立体選択的パントラクトンエステルの生成が抑制される傾向があると考えた。

【図表 2-13】 光学活性体酸クロリド(*R*)-**8** を用いたパントラクトンエステル(*R,R*)-**10** の合成



Entry	Amine	<b>8</b>		<b>(R)-8</b>	
		Yield <sup>a</sup>	( <i>R,R</i> )- <b>10</b> : ( <i>S,R</i> )- <b>10</b> <sup>b</sup>	Yield <sup>a</sup>	( <i>R,R</i> )- <b>10</b> : ( <i>S,R</i> )- <b>10</b> <sup>b</sup>
1	Pyridine	90%	1:1	89%	73:1
2	Me <sub>2</sub> NEt	89%	6:1	87%	8:1
3	Et <sub>3</sub> N	81%	11:1	93%	12:1

<sup>a</sup> Isolated yield of the mixture of (*R,R*)-**10** and (*S,R*)-**10** based on **2** or (*R*)-**2**. <sup>b</sup> Determined by HPLC.

次に、単離したエチルフェニルケテン **12** をモデル化合物として用い、Et<sub>3</sub>N 塩酸塩、Me<sub>3</sub>N 塩酸塩、Pyridine 塩酸塩を 1 当量添加した際に生成されるパントラクトンエステル **13** の生成量とジアステレオ選択性を比較することにより、アミン塩酸塩存在下におけるケテンから酸クロリド及びアシルアンモニウムへの平衡移動の影響を確認した (図表 2-14) <sup>31</sup>. アミンなしではエチルフェニルケテン **12** と (*R*)-パントラクトンとは反応しないことから、アミン塩酸塩が反応を促進させていると思われる. 1 当量のトリアルキルアミン Et<sub>3</sub>N と Me<sub>2</sub>NEt 存在下ではケテン **12** に対する (*R*)-パントラクトンの付加反応が高収率で進行し、そのジアステレオ選択性が変わらないことから、アミン塩酸塩から遊離した Et<sub>3</sub>N と Me<sub>3</sub>N が触媒となって反応進行に関与した場合には、ジアステレオ選択性は変わらないと思われる. 一方、Pyridine を用いた場合には、アミンのアルキル鎖とパントラクトンとの間での水素結合による相互作用がないため、Houk らの反応機構で提唱される中間体及び遷移状態の安定化効果が弱いことが想定され、ケテンに対するパントラクトンが付加する面選択性が低下していると思われる. また、共役酸 p*K*<sub>a</sub> が高いアミン塩酸塩ほど、収率が低く、ジアステレオ選択性の低下が抑制されている傾向があることから、アミン塩酸塩からアミンと塩酸の乖離が抑制されることによって、酸クロリド及びアシルアンモニウムを経由する非立体選択的なパントラクトンエステルの副生量が少なくなっているのではないかと考えた. 即ち、塩基性が強いアミンを用いることにより、ケテンから酸クロリドとアシルアンモニウムへの平衡移動が抑制され、アミン塩酸塩共存下でのジアステレオ選択性の低下が抑制される.

【図表 2-14】 単離ケテンに対する(*R*)-パントラクトンの立体選択的付加反応

**12**                      **(*R,R*)-13**                      **(*S,R*)-13**

Entry	Amine	Yield <sup>a</sup>	( <i>R,R</i> )-13:( <i>S,R</i> )-13 <sup>b</sup>
1	None	<1% <sup>c</sup>	1.2:1
2	Et <sub>3</sub> N·HCl	8%	24:1
3	Me <sub>3</sub> N·HCl	24%	19:1
4	Pyridine·HCl	20%	2.4:1
5	Et <sub>3</sub> N	87%	49:1
6	Me <sub>2</sub> NEt	90%	49:1
7	Pyridine	51%	6:1

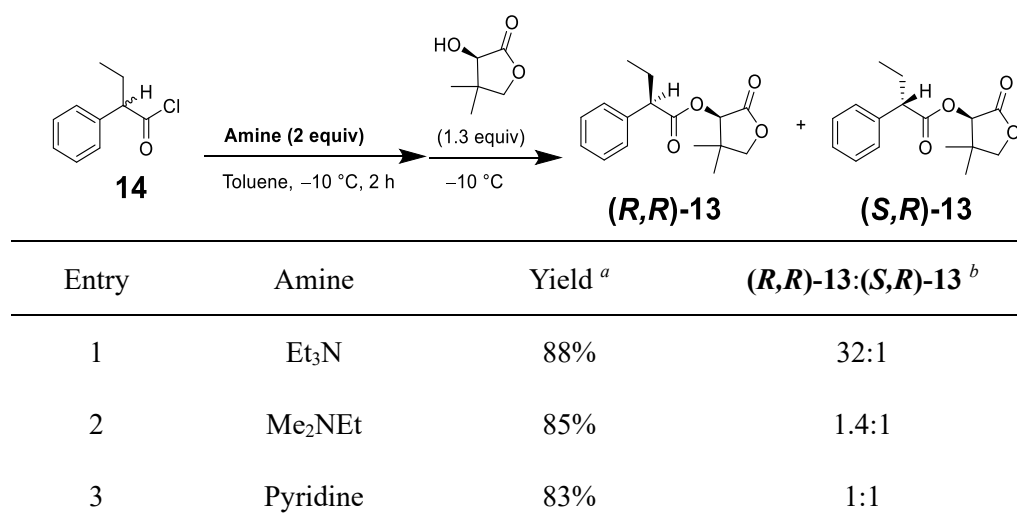
<sup>a</sup> Isolated yield of the mixture of (*R,R*)-13 and (*S,R*)-13 based on 12. <sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> 13 was not isolated.

以上, 低温下で求核性が低く, 塩基性が強いアルキル鎖の短いトリアルキルアミンを用い, 低温下で酸クロリドからケテンを変換させることによって, パントラクトンエステルのジアステレオ選択性を向上させることができることを明らかにした.

参考までに、モデル化合物の酸クロリドである 2-フェニル酪酸クロリド **14** に対し、Et<sub>3</sub>N, Me<sub>2</sub>NEt, Pyridine を用い、低温下で酸クロリドからケテンを生成させた際に生成されるパントラクトンエステルのジアステレオ選択性を比較したところ、Et<sub>3</sub>N を用いた際に生成されるパントラクトンエステルのジアステレオ選択性が最も高くなることが確認された (図表 2-15). 図表 2-14 に示す単離ケテンに対する (*R*)-パントラクトンが付加したパントラクトンエステルのジアステレオ選択性と比較し、求核性が低く、塩基性が強い Et<sub>3</sub>N を用いることでケテンに対する (*R*)-パントラクトンが付加したパントラクトンエステルの生成量が多くなっていると考えられる.

【図表 2-15】 2-フェニル酪酸クロリドの立体選択的パントラクトンエステル化反応

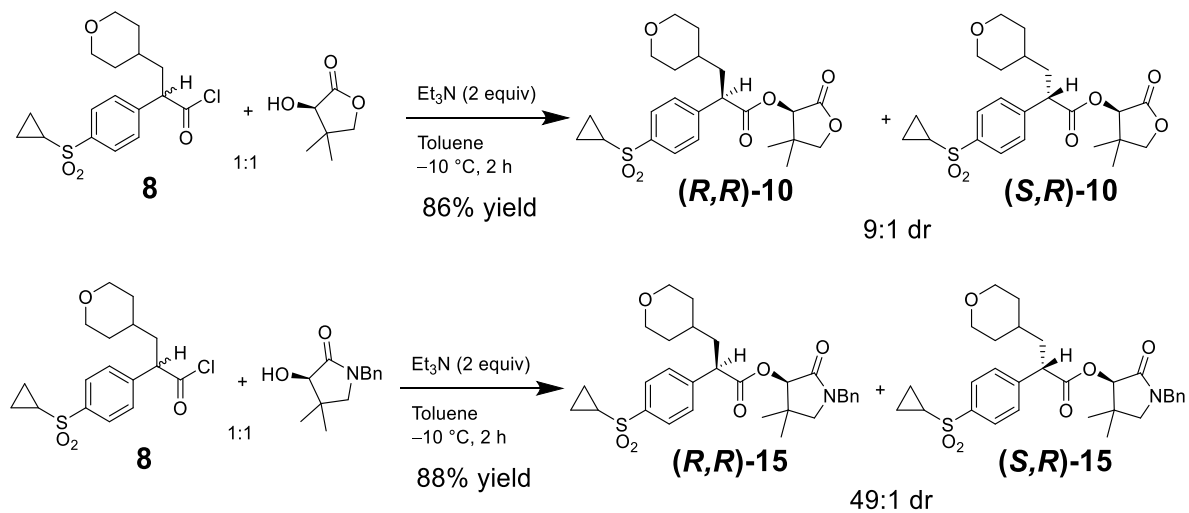


<sup>a</sup> Isolated yield of the mixture of (*R,R*)-13 and (*S,R*)-13 based on **14**. <sup>b</sup> Determined by <sup>1</sup>H NMR.

## 第 5 節 *N*-ベンジル-(*R*)-パントラクタムを用いた立体選択的エステル合成

ケテンに対するパントラクトン付加の面選択性は図表 2-2 に示す Houk らが提唱するエノール A や遷移状態 *trans*-A における水素結合による安定化効果と遷移状態 *trans*-B における立体障害による不安定化効果の影響を受けていると考えられ<sup>32</sup>, 面選択性を更に向上させるにはそれぞれの安定化効果と不安定化効果を高めることが重要である. そこで, パントラクトン上のエステルカルボニル基をアミドカルボニル基に変更した *N*-ベンジル-(*R*)-パントラクタムを用いることで<sup>33</sup>, エノール A や遷移状態 *trans*-A における水素結合力がより強くなり, ケテンに対するキラルアルコール付加の面選択性が向上されるのではないかと考えた. Et<sub>3</sub>N 存在下基質 **8** から生成させたケテンに対して, (*R*)-パントラクトンを用いた際に生成されるパントラクトンエステル **10** のジアステレオ選択性は -10°C で 9:1 dr であったが, 同一反応条件下で *N*-ベンジル-(*R*)-パントラクタムを用いた際に生成される *N*-ベンジル-(*R*)-パントラクタムエステル **15** のジアステレオ選択性は 49:1 dr であることが確認された (図表 2-16). キラルアルコールの水酸基炭素に隣接するカルボニル基の電子密度が高まることで遷移状態と中間体での静電相互作用が強くなり, 温和な条件下でもケテンに対するキラルアルコールの面選択性が高くなっていると考えた.

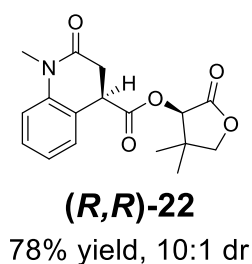
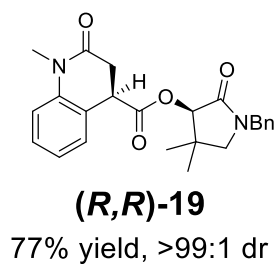
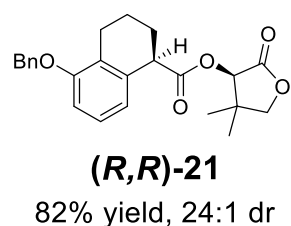
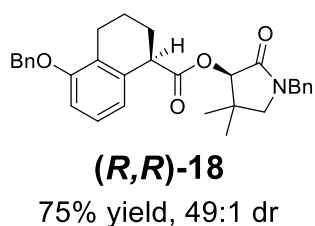
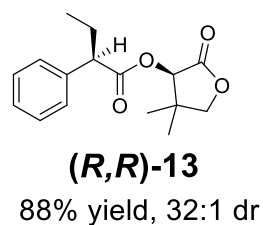
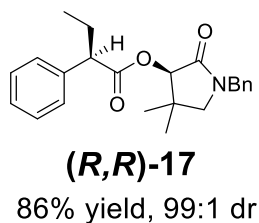
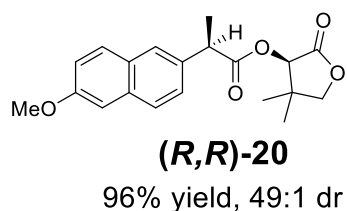
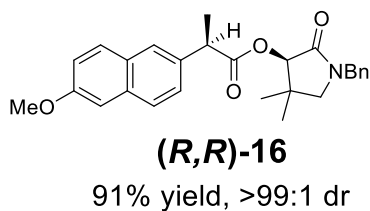
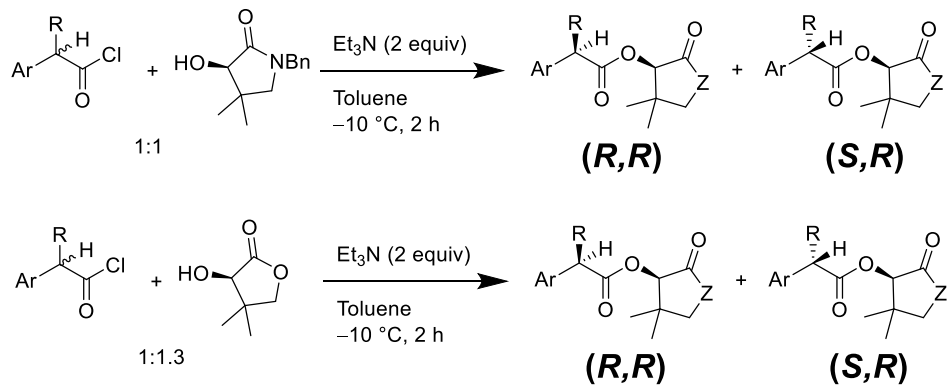
【図表 2-16】 (*R*)-パントラクタム及び *N*-ベンジル-(*R*)-パントラクタムを用いた立体選択的エステル合成





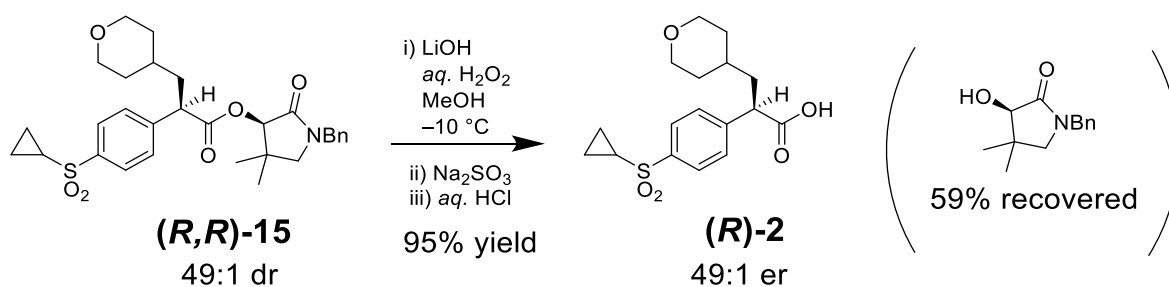
(*R*)-パントラクトンの代わりに *N*-ベンジル-(*R*)-パントラクタムを用いた立体選択的なエステル合成は基質 **8** に限定されることなく、種々の官能基を有する医薬品中間体に有効であると考えた。異なる官能基を有する 4 つの酸クロリドを用い、Et<sub>3</sub>N 存在下で(*R*)-パントラクトンと *N*-ベンジル-(*R*)-パントラクタムとのエステル化を試みた (図表 2-17) <sup>34</sup>。その結果、基質全てに対して *N*-ベンジル-(*R*)-パントラクタムが高立体選択的に付加したパントラクタムエステルが合成され、同一条件下でパントラクトンを用いた際に生成されるエステルのジアステレオ選択性よりも高い選択性を示した。

【図表 2-17】 (*R*)-パントラクタム及び *N*-ベンジル-(*R*)-パントラクタムを用いた立体選択的エステル合成



また、生成物 **(R,R)-15** は Evans らの条件で加水分解することによって、エピメリ化，ラセミ化を起こさずに高収率で加水分解できることを確認した（図表 2-18）<sup>20</sup>。そのため，パントラクトンエステルもパントラクトンエステルと同じように  $\alpha$ -アリーールプロピオン酸誘導体の立体構築に利用できる中間体になると考えた。

【図表 2-18】 *N*-ベンジル-**(R)**-パントラクトムエステルを用いた**(R)**-2 合成



以上，ケテンに対して立体選択的に付加させるキラルアルコールの水酸基炭素に隣接するカルボニル基の電子密度によって生成されるエステルのジアステレオ選択性が変わることを確認し，キラルアルコールを(*R*)-パントラクトンから *N*-ベンジル-(*R*)-パントラクタムに変更することにより，生成されるエステルのジアステレオ選択性が高くなることを明らかにした．

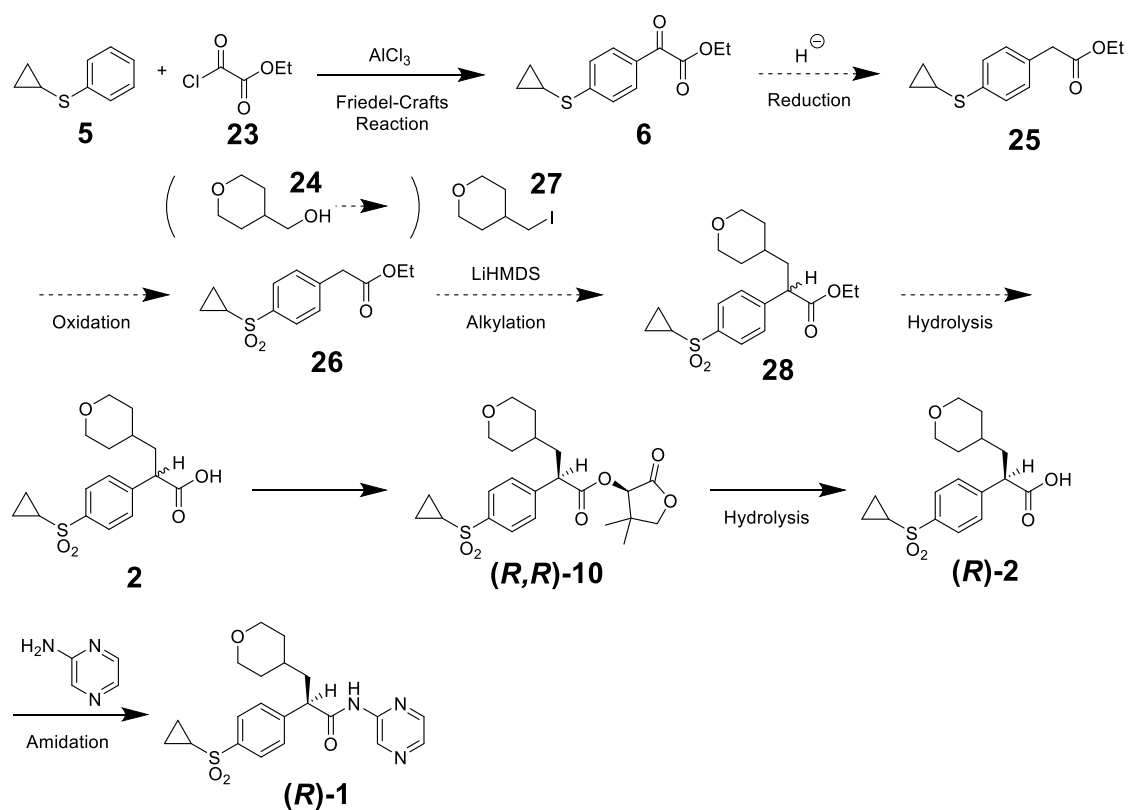
### 第3章 パントラクトンエステルを経由する GK 活性化薬 (*R*)-1 の合成に関する研究

#### 第1節 GK 活性化薬 (*R*)-1 の合成計画

医薬品の製造において高品質が求められることは大前提であり、市販用製品は安全性試験および臨床試験で安全性が確認されているものと同等以上の品質であることが求められ、一般的に 1 日最大投与量 2g 以下の医薬品の工業化製法では非臨床試験や臨床試験で安全性が確認されていない不純物が 0.15%または 1 日摂取量 1.0mg が原薬中に残留することは許されない<sup>35</sup>。そのため、GK 活性化薬(*R*)-1 に対する工業化製法でも、新たな不純物が副生しないような反応条件の設定と、それらの不純物を基準値以下まで除去できる精製条件を構築することが重要になると考えられる。

パントラクトンエステル(*R,R*)-10 を経由する新たな合成ルートの出発原料として、アクリル酸誘導体を経由する既存製法と同じ Cyclopropylphenylsulfide (**5**), Ethyl chloroglyoxylate (**23**), Tetrahydro-2*H*-pyran-4-ylmethanol (**24**)を選択した (図表 3-1)<sup>7</sup>。また、アリール酢酸エステルとヨウ素化体とのアルキル化反応を利用する合成ルートを選択することによって既存製法の収率低下を引き起こしている Wittig 反応を回避し、出発原料からの通算収率を向上させることを計画した。

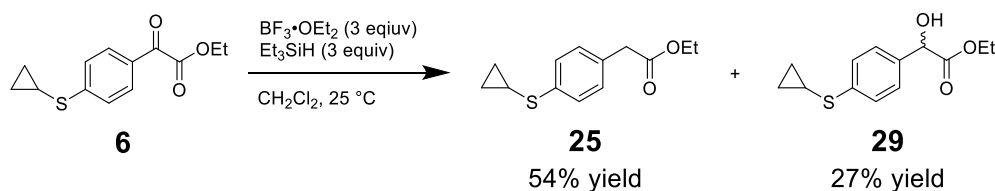
【図表 3-1】 パントラクトンエステル誘導体を経由した(R)-1 の合成計画



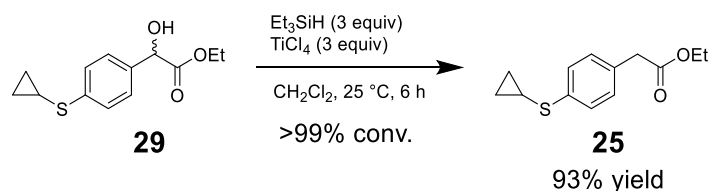
## 第2節 $\alpha$ -アリール酢酸エステルのアルキル化を利用した (*R*)-1 前駆体ラセミ体の合成

アリール酢酸エステル **25** は、図表 1-4 に示す Magnus らの(*R*)-1 合成法から得られる中間体 **6** のベンジル位の酸素を脱離させることで変換できると考え<sup>7</sup>、ベンジル位の還元反応に利用される  $\text{BF}_3/\text{OEt}_2$  と  $\text{Et}_3\text{SiH}$  を用い、**6** から **25** への変換を試みた<sup>36</sup>。その結果、目的物 **25** が生成されることを確認できた。しかし、収率は 54%にとどまっており、反応中間体のベンジルアルコール **29** が 27%残留した (図表 3-2)。Lewis 酸性の強い  $\text{TiCl}_4$  を用いた場合のみベンジルアルコール **29** が消失し<sup>37</sup>、目的物 **25** が収率 93%で得られたことからエステルの  $\alpha$  炭素に位置するためカチオン種が形成されにくいことが原因と推察した (図表 3-3)。  $\text{TiCl}_4$  の後処理時に激しい発熱と発ガスが伴うこと、  $\text{TiCl}_4$  の溶媒として用いられる  $\text{CH}_2\text{Cl}_2$  は作業者への健康被害が報告され法規制上で使用が制限されること<sup>38</sup>、  $\text{TiCl}_4$  を代替できる Lewis 酸が見出されなかったことの3点から Lewis 酸を用いない代替法に切り替えることを考えた<sup>39</sup>。

【図表 3-2】 ベンジルケトエステルの脱酸素化反応



【図表 3-3】  $\text{TiCl}_4$  と  $\text{Et}_3\text{SiH}$  を用いたベンジルケトエステルの脱酸素化反応

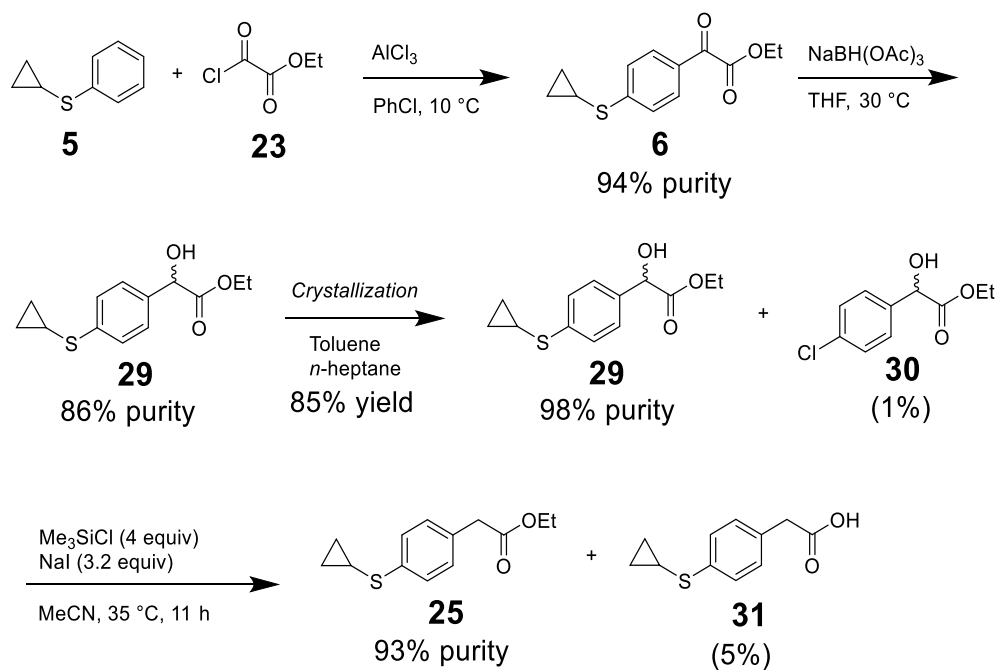






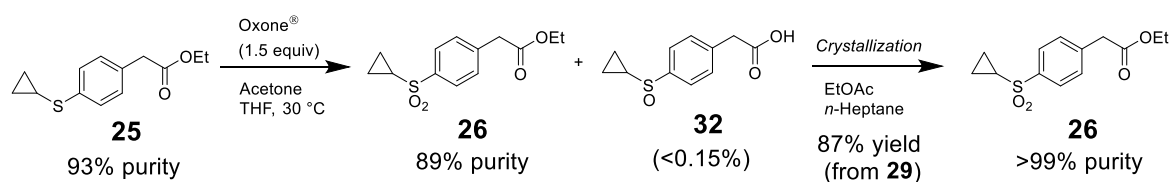
次に、ベンジルアルコール **29** の水酸基はエステルの  $\alpha$  炭素上に存在するため、エステルの  $\alpha$  位の脱酸素に用いられる  $\text{Me}_3\text{SiCl}$ - $\text{NaI}$ - $\text{MeCN}$  条件を用いて還元することを計画した<sup>40</sup>。中間体 **6** はエステル基を有しているが、温和な条件下で選択的に還元できる  $\text{NaBH}_4$  を用いてベンジルアルコール **29** に還元できると考えた<sup>41</sup>。しかし、目的とする **29** 以外の不純物が副生することが確認され、隣接するエステル部位も加水分解を受けているのではないかと考えた。そこで、 $\text{NaBH}_4$  よりも求核性が低い  $\text{NaBH}(\text{OAc})_3$  を用いたところ<sup>42</sup>、目的とする **29** が選択的に生成していることを HPLC 測定にて確認した。生成物 **29** は晶析精製によって HPLC 純度は 98%まで向上し、Friedel-Crafts 反応で副生されたクロロベンゼン付加体 **30** の残留が 12%から 1~2%まで低減された（図表 3-4）。続いて、**29** を  $\text{MeCN}$  中に溶解させた後、 $\text{Me}_3\text{SiCl}$  と  $\text{NaI}$  を用い、**25** への変換を試みた。 $\text{Me}_3\text{SiCl}$ ,  $\text{NaI}$  の当量を変更することによって、本反応条件で懸念される Ritter 反応等の副反応の進行は抑制され、反応転化率 99%以上で **29** が残存することなく目的物 **25** へ変換できることを確認した。また、本反応条件下ではエステルが加水分解されたカルボン酸 **31** が 5~10%程度副生されるが<sup>43</sup>、抽出洗浄で水層に除去できることを確認した。

【図表 3-4】  $\text{Me}_3\text{SiCl-NaI-CH}_3\text{CN}$  条件によるベンジルアルコール体 **35** の脱酸素反応



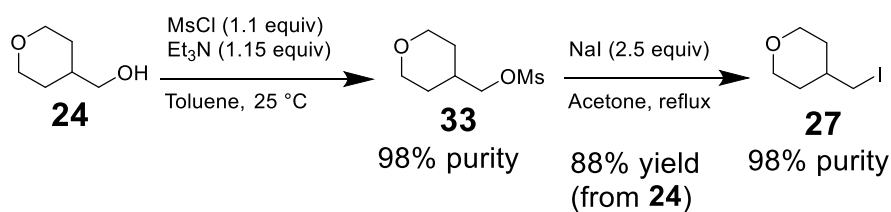
アリール酢酸エステル **25** は油状物質であるため、生産性の観点から単離せずに溶液のまま酸化させることを計画した。酸化剤として取り扱いが簡便である Oxone<sup>®</sup>とアセトンから調製したジメチルジオキシラン存在下でスルホン体 **26** へ変換させることを試した<sup>44</sup>。その結果、目的物 **26** が高収率で生成されたが、反応中間体であるスルホキシド体 **32** が 3~5%残留し、純度が低下することが確認された。スルホキシド体が反応中に析出し、スルホンへの変換速度が低下したことが原因ではないかと考え、溶媒の THF 比率を上げることでスルホンを溶解し、反応させた。その結果、スルホキシド体の残留が 0.15%未満となることを確認した。スルホン体 **26** を晶析することによって HPLC 化学純度が 99%以上まで向上し、ベンジルアルコール体 **6** から通算収率 87%で合成できることを確認した (図表 3-5)。

【図表 3-5】 ジメチルジオキシランを用いたスルフィドからスルホンへの酸化反応



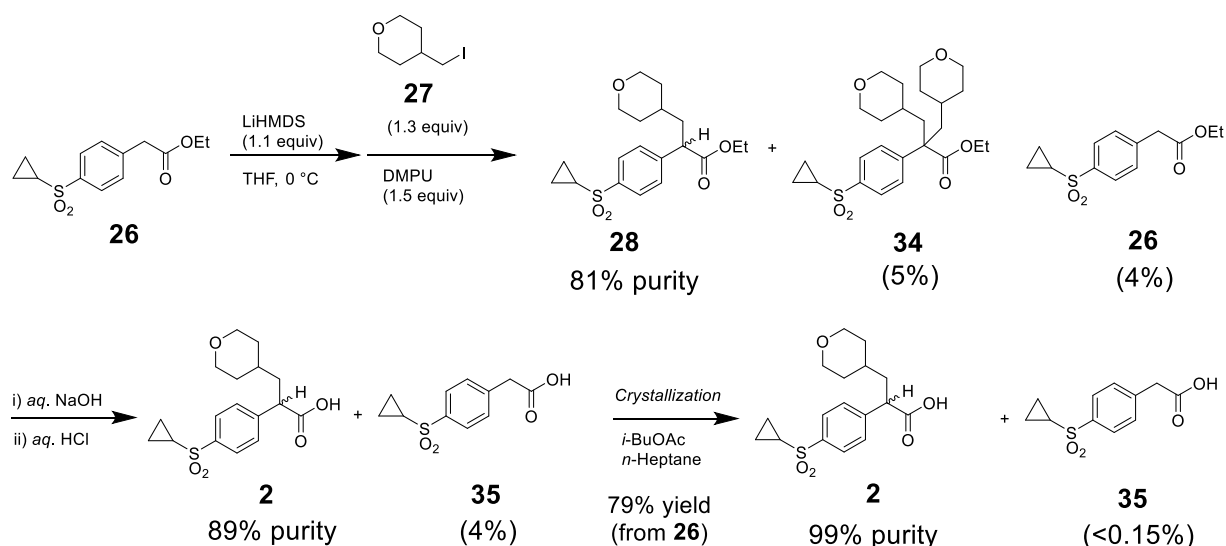
アリール酢酸エステル **26** のアルキル化剤としてはヨウ素体 **27** を用いることを計画した。  
 ヨウ素体 **27** は市販の Tetrahydro-2*H*-pyran-4-ylmethanol (**24**) をメシル酸体 **33** へと変換させる  
 ことで合成できると考えた。メシル酸体 **33** は変異原性物質であることが懸念されたため、単  
 離することなく NaI と反応させ、ヨウ素体 **27** を合成した (図表 3-6)。

【図表 3-6】メシル酸体 **33** を経由したヨウ素体 **27** の合成



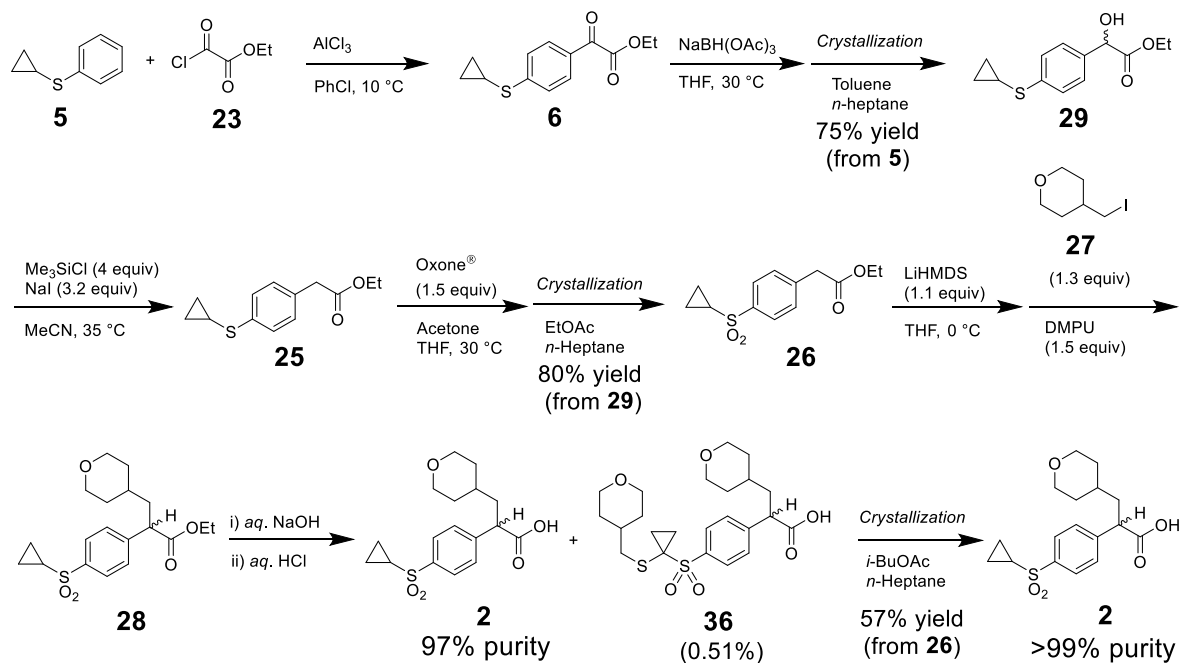
アリール酢酸エステル **26** のリチウムエノラート化にはアルキル化剤中にテトラヒドロピラン骨格を有することから、安価な有機リチウム試薬を用いた場合には  $\beta$  水素脱離が進行する可能性があると考え、温和な条件下で反応できる LiHMDS を試した<sup>45,46</sup>。期待通り、0℃付近の温度でも複雑な不純物の副生は抑制され、アルキル化体 **28** が主生成物として生成することを HPLC 分析によって確認した。また、生産効率の観点から **28** は単離せずに、水酸化ナトリウム水溶液を加えて、二層で加水分解した結果、期待通りラセミ体 **2** へと変換できることを確認した。反応条件上避けられないジアルキル化体 **34** が約 5% 副生されたが、アルキル鎖の立体障害によって水酸化ナトリウムによる加水分解がアルキル化体 **28** よりも受け難くなっており、温和な加水分解条件を設定することでジアルキル化体を加水分解させることなく、加水分解後の Toluene 分液で除去できることを確認した。また、未反応で残留した **26** が加水分解されたカルボン酸 **35** も約 4% 副生することが確認されたが、晶析精製することによって 0.15% 未満まで低減され、HPLC 化学純度が 99% 以上となるラセミ体カルボン酸 **2** を収率 79% で結晶として単離できる条件を構築した (図表 3-7)。

【図表 3-7】 アルキル化反応を利用したラセミ体 **2** の合成



以上で述べた合成法により出発原料 **5** から通算収率 58%でラセミ体カルボン酸 **2** を大量合成できると考えた。そこで、本合成法に基づいてラセミ体カルボン酸 **2** を 20.5 kg 合成したところ通算収率は 34%であり、想定よりも 24%低下した（図表 3-8）。Friedel-Crafts 反応と脱酸素反応では反応時間が小スケールよりも延長しており、生成物の分解が想定よりも進行したことが原因と考えられるため、小スケールと反応時間を同じにすることで収率低下を抑制できると思われる。一方、アルキル化反応では、小スケールでは想定されていなかった不純物 **36** を始めとする複数の不純物が副生しており、晶析後のラセミ体 **2** の結晶中に **36** が 0.51%残留していることが確認できた。GK 活性化薬(**R**)-**1** 中に **36** 由来の不純物が混入することを阻止するには、ラセミ体 **2** 中に残留する **36** を 0.05%未満まで低減する必要があり、Toluene, *i*-BuOAc, *n*-Heptane を用いた再結晶を 6 回繰り返すことで残留する **36** を 0.05%未満まで低減することで収率は約 20%低下した。

【図表 3-8】 アルキル化反応を利用したラセミ体 **2** の 20.5 kg 合成



アルキル化反応の収率が 57%まで低下した場合、原薬の生産に必要な原材料の使用量が増加するため、商業生産時の原薬原価が高くなることが想定される。そこで、不純物 **36** を副生させない合成条件を設定することで、収率を向上させることを考えた。不純物 **36** は、その推定構造から反応溶液中に混入した硫黄との副反応が原因と思われ、20.5 kg 合成での酸化反応で使用した Oxone® (2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) 中の酸性成分 KHSO<sub>4</sub> と還元剤 Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> との混合時間が延長することによって硫黄が大量に副生し、中間体 **26** に大量の硫黄が混入したためではないかと考えた (図表 3-9, Entries 1, 2)。そこで、**26** の合成条件で用いる還元剤を NaHSO<sub>3</sub> に変更することで酸性条件下における硫黄の副生を抑制し、**36** の副生が抑制できるのではないかと考えた<sup>47</sup>。KHSO<sub>4</sub> 存在下で、還元剤として Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> を用いた場合には攪拌時間を 24 時間まで延長された場合に不純物 **36** が 0.80%副生されたが、NaHSO<sub>3</sub> を用いた場合には不純物 **36** が副生されておらず、不純物 **36** を混入させることなくラセミ体 **2** を収率 78%で合成できることを確認した (Entries 3, 4)。

【図表 3-9】 硫黄混入による不純物 **36** の副生

Entry	Scale	Reductant	Operation		2	
			Time <sup>a</sup>	Yield (%) <sup>b</sup>	HPLC Purity (%) <sup>c</sup>	36 (%) <sup>c</sup>
1	>25 kg	Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	2 h	(65) <sup>d</sup>	97.0	0.51
2	5 g	Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	<15 min	79	98.6	<0.05
3 <sup>e</sup>	5 g	Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	24 h	74	95.4	0.80
4 <sup>e</sup>	5 g	NaHSO <sub>3</sub>	24 h	78	98.6	<0.05

<sup>a</sup> Total time for stirring and settling. <sup>b</sup> Crystallized yield based on **26**. <sup>c</sup> Relative HPLC area %. <sup>d</sup> Assay yield determined by HPLC. <sup>e</sup> KHSO<sub>4</sub> (0.87 w/w) was added to the filtrate before adding the reductant.

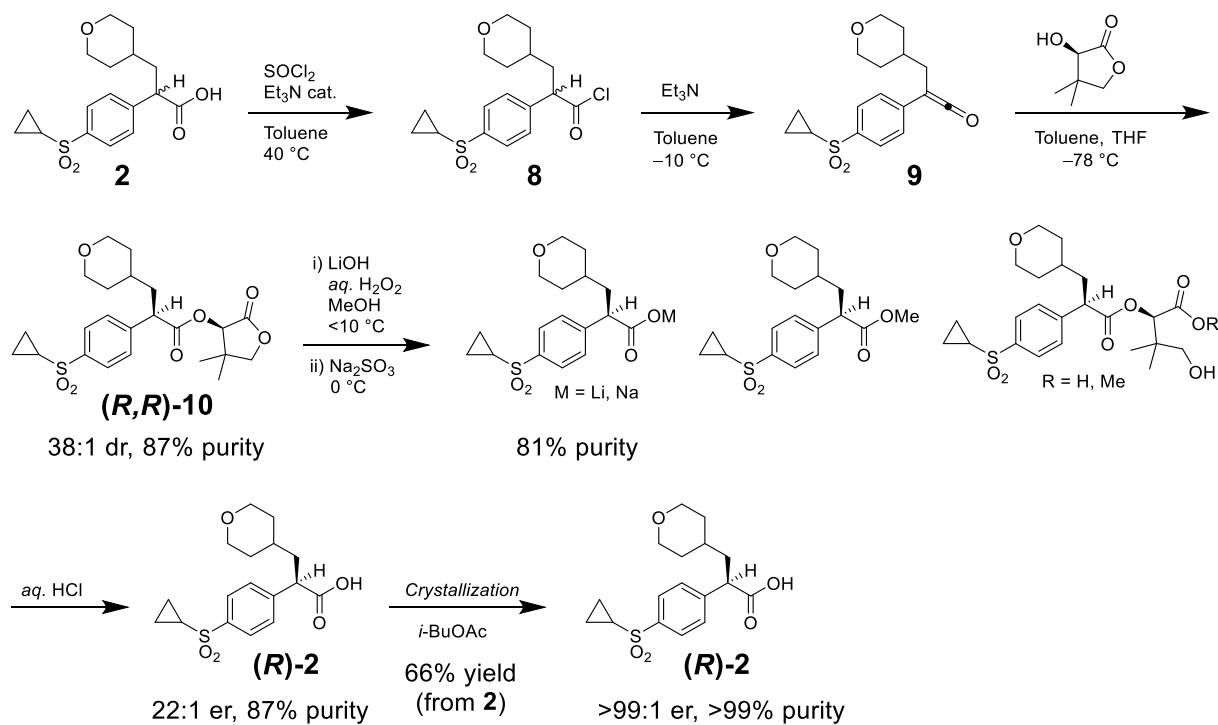
以上，既存製法と同じ出発原料から Wittig 反応を用いないアルキル化反応を経由した合成法を構築することに成功した．また，本合成法を用いることによってラセミ体 **2** を大量合成できることを明らかにした．



### 第3節 パントラクトンエステルを経由した GK 活性化薬(*R*)-1 の立体選択的合成

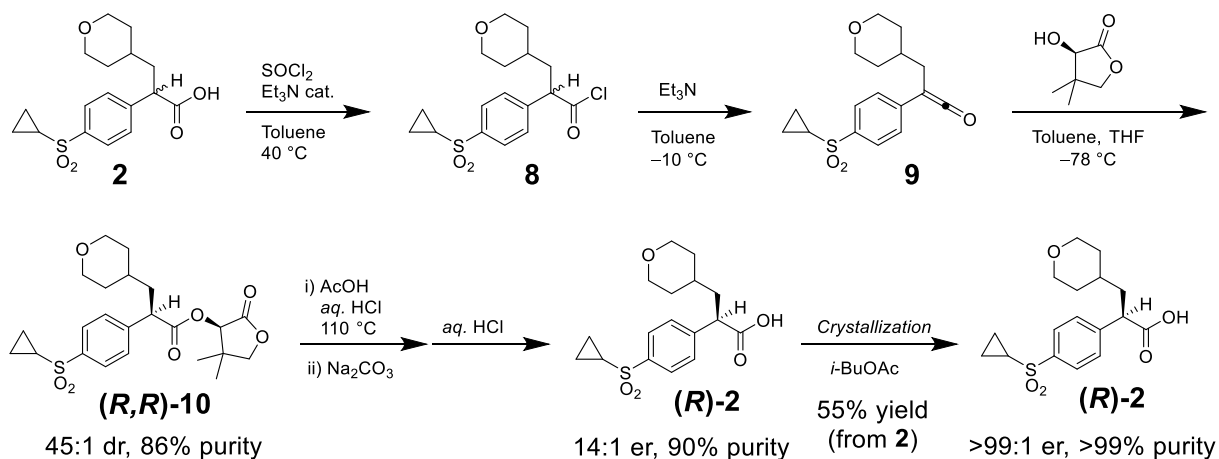
第2章で開発した合成法に基づき, Toluene, Et<sub>3</sub>N を用い, 酸クロリドからケテンに−10℃で変換させた後, (*R*)-パントラクトンの THF 溶液を−78℃付近で滴下することによってジアステレオ選択性 38:1 dr, HPLC 純度 87%のパントラクトンエステル **10** を合成できることを確認した. 続いて Evans らの条件を用いて加水分解し, 晶析精製することによって化学純度>99%, 光学純度>99%ee の(*R*)-**2** を結晶として単離できることを確認した (図表 3-10). しかし, (*R*)-**2** の単離収率は 66%にとどまっており, 更なる収率向上に向けて加水分解条件を検討した.

【図表 3-10】 LiOH, H<sub>2</sub>O<sub>2</sub> を用いた(*R,R*)-**10** の加水分解による(*R*)-**2** の合成



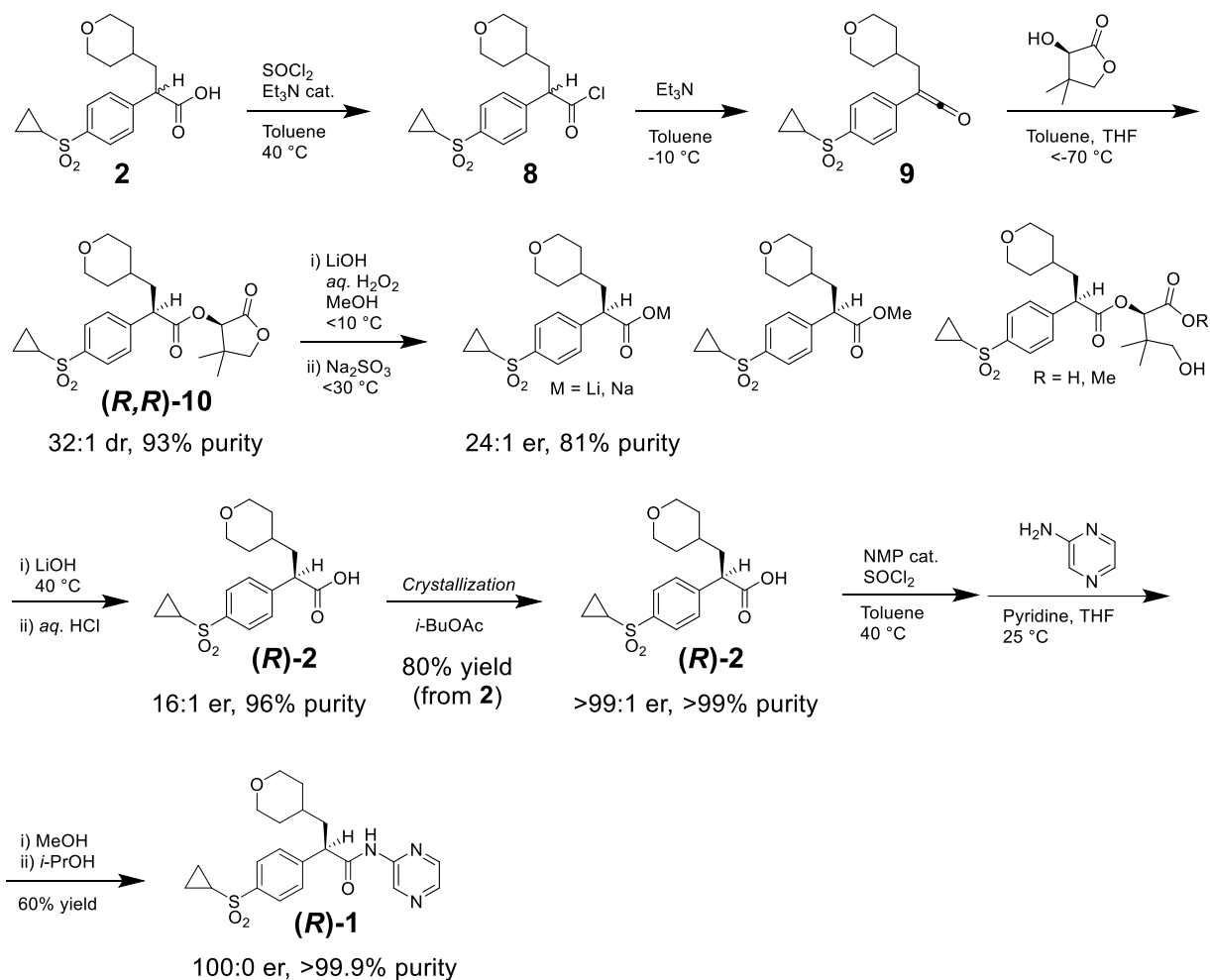
Evans らの条件では、加水分解時にパントラクトンが開環したエステル誘導体やメチルエステル体を始めとする副生物があり、それらの副生物が加水分解されない。そのため、分液精製によってそれらの副生物を除去しており、収率が低くなっている。そこで、加水分解条件としてエピメリ化、ラセミ化が起こり難い塩酸／酢酸の条件を用いることで、それらの副生成物を抑制できないかを確認した（図表 3-11）。その結果、エピメリ化、ラセミ化が抑制されることに加え、期待通り、パントラクトンが開環したエステル誘導体が残留することなしに目的物のカルボン酸へと変換できることを確認した。しかし、本条件で単離される**(R)-2**の収率は 55%であり、反応完結に用いた大量の酢酸によって水層中の**(R)-2**を十分に抽出できなかったこと、テトラヒドロピラン環が開環する等の副反応が生じ、Evans らの条件よりも収率が低下することが明らかになった。

【図表 3-11】 HCl, AcOH を用いた(*R,R*)-10 の加水分解による(*R*)-2 の合成



そこで, Evans らの条件で得られた反応溶液に高温下で水酸化リチウムを追加し, 副生されるパントラクトンが開環したエステル誘導体やメチルエステル体を(**R**)-**2** に強制的に加水分解することで, カルボン酸への転換率を向上させることを考えた. 期待通り, Evans らの条件で副生されていた 15%程度 of エステルが加水分解され, 反応溶液中の(**R**)-**2** の HPLC 面積百分率が 81%から 96%まで向上することを確認した. その一方で, 水酸化リチウムで処理する際にベンジル位の立体反転が一部生じ, 生成比が 16:1 er まで低下したが, 晶析精製することによりエナンチオ選択性 >99:1 er, HPLC 純度 >99% of (**R**)-**2** を収率 80%で合成できることを明らかにした (図表 3-12). また, 本合成法から合成される(**R**)-**2** は Magnus らの条件下 2-Aminopyrazine とアミド化させることで<sup>7</sup>, 0.15%を超える非臨床試験や臨床試験で安全性が確認されていない不純物や光学異性体が混入することなく GK 活性化薬(**R**)-**1** へと変換できることを確認した.

【図表 3-12】 GK 活性化薬(*R*)-1 の 11.8 kg 合成

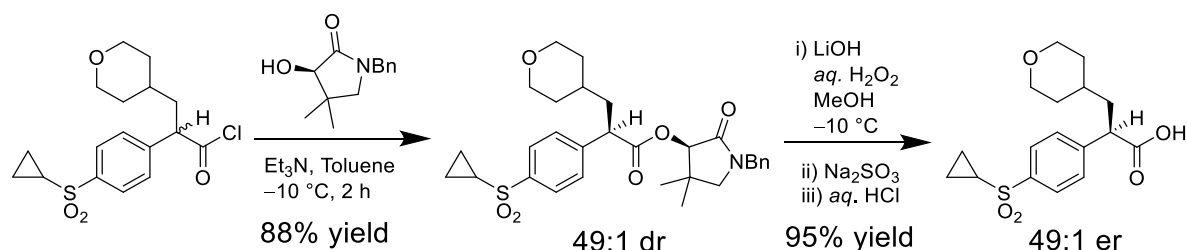


以上、パントラクトンエステル(*R,R*)-10 を中間体とする工業化製法を構築し、品質に問題のない GK 活性化薬 (*R*)-1 を大量合成できることを明らかにした。

## 第4章 結言

著者は、パントラクトンエステル中間体及びパントラクタムエステル中間体の立体選択的合成法を開発し、 $\alpha$ -アリールプロピオン酸骨格を有する種々の医薬品中間体の立体選択的合成に成功した。更にその合成法を利用し、GK 活性化薬(**R**)-**1** の工業化製法を開発することに成功した。

第2章では、Larsen らの反応を詳細に解析し、酸クロリドからパントラクトンエステルを高収率かつ高ジアステレオ選択的に合成するには、ケテンの生成量を増加させることとケテンに対するパントラクトンの付加面選択性を向上させることが重要であることを明らかにした。塩基性が強く、求核性が低いアルキル鎖の短いアミンを用いることによって、低温下で酸クロリドからケテンに変換することで、非立体選択的なパントラクトンエステルの副生とケテンの分解を抑制し、生成されるパントラクトンエステルのジアステレオ選択性と生成量が向上することを明らかにした。また、Houk らの反応機構における水素結合を介した中間体及び遷移状態の安定化効果に注目し、(*R*)-パントラクトンの代わりに *N*-ベンジル-(*R*)-パントラクタムを用いることによって、ケテンに対してキラルアルコールが付加する面選択性を向上できることを明らかにした。



さらに、*N*-ベンジル-(*R*)-パントラクタムを用いた立体構築法は、GK 活性化薬(**R**)-**1** だけでなく、(*S*)-Naproxen を始めとする  $\alpha$ -アリールプロピオン酸骨格を有する種々の医薬品中間体に利用できることを明らかにした。

[illegible]

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## 実験の部

### I. General

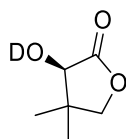
All air- and moisture-sensitive manipulations were carried out under nitrogen atmosphere. Toluene (Wako Pure Chemical Industries, Ltd.),  $\text{MgSO}_4$  (Wako Pure Chemical Industries, Ltd.), *n*-heptane (Wako Pure Chemical Industries, Ltd.), EtOAc (Wako Pure Chemical Industries, Ltd.), THF (Wako Pure Chemical Industries, Ltd.),  $\text{Et}_3\text{N}$  (Wako Pure Chemical Industries, Ltd.), methanesulfonyl chloride (Wako Pure Chemical Industries, Ltd.), 20.5% LHMDs (Chemetall GmbH), 35% *aq.* HCl (Wako Pure Chemical Industries, Ltd.), activated coal (Seracheme Co., Ltd., Japan EnviroChemicals),  $\text{SOCl}_2$  (Tokyo Chemical Industry Co., Ltd.), (*R*)-pantolactone (Daiichi Fine Chemical Co., Ltd.), citric acid (Sigma Aldrich Japan), lithium hydroxide monohydrate (The Honjo Chemical Corporation), 30%  $\text{H}_2\text{O}_2$  (Wako Pure Chemical Industries, Ltd.), MeOH (Wako Pure Chemical Industries, Ltd.),  $\text{Na}_2\text{SO}_3$  (Kamisu Chemical Co., Ltd.), pyridine (Wako Pure Chemical Industries, Ltd.), *N,N*-dimethylethylamine (Wako Pure Chemical Industries, Ltd.), benzylamine (Wako Pure Chemical Industries, Ltd.), *n*-hexane (Wako Pure Chemical Industries, Ltd.),  $\text{D}_2\text{O}$  (Euriso Top<sup>®</sup>), 2-phenylbutyryl chloride (Tokyo Chemical Industry Co., Ltd.), (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (Naproxen<sup>®</sup>; Tokyo Chemical Industry Co., Ltd.), triethylamine hydrochloride (Tokyo Chemical Industry Co., Ltd.), trimethylamine hydrochloride (Tokyo Chemical Industry Co., Ltd.), pyridine hydrochloride (Tokyo Chemical Industry Co., Ltd.), 1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (Enamine, net),  $\text{NH}_4\text{Cl}$  (Sigma Aldrich Japan),  $\text{AlCl}_3$  (Nippon Soda Co., Ltd.), PhCl (Wako Pure Chemical Industries, Ltd.), ethyl chloroglyoxylate (Haimen Best Fine Chem.), cyclopropylphenylsulfide (Asahi Kagaku Kogyo Co., Ltd.)  $\text{NaHSO}_3$  (Wako Pure Chemical Industries, Ltd.), NaI (Wako Pure Chemical Industries, Ltd.),  $\text{CH}_3\text{CN}$  (Wako Pure Chemical Industries, Ltd.), TMSCl (Wako Pure Chemical Industries, Ltd.), NaCl (Diasalt Co., Ltd.), acetone (Mitsubishi Chemical Corporation), oxone<sup>®</sup> (Wako Pure Chemical Industries, Ltd.), tetrahydro-2*H*-pyran-4-ylmethanol (BASF), methanesulfonyl chloride (Wako Pure Chemical Industries, Ltd.),  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  (Daito Chemical Co., Ltd.), 20.5% LiHMDS (Chemetall GmbH),

DMPU (Wako Pure Chemical Industries, Ltd.), NaOH (Tosoh Corporation), 35% *aq.* HCl (Wako Pure Chemical Industries, Ltd.), activated coal (Seracheme Co., Ltd., Japan EnviroChemicals), *i*-BuOAc (Wako Pure Chemical Industries, Ltd., KH Neochem Co., Ltd.), NMP (Mitsubishi Chemical Corporation), 2-aminopyridine (Koei Chemical Company, Limited), pyridine (Daicel Corporation), 2-propanol (Mitsui Chemicals, INC.), *N*-methyldmorpholine (Wako Pure Chemical Industries, Ltd.), *N,N*-diisopropylethylamine (Wako Pure Chemical Industries, Ltd.), *N,N*-dimethylethylamine (Wako Pure Chemical Industries, Ltd.), 1,2,2,6,6-pentamethylpiperidine (Wako Pure Chemical Industries, Ltd.), and 2,2,6,6-tetramethylpiperidine (Wako Pure Chemical Industries, Ltd.) were used as received.

## II. Preparation of Substrate

### Deuterium-Labeling (*R*)-Pantolactone (97%-D) (Cas No. 1522365-16-7)

Deuterium-labeling (*R*)-pantolactone (97% D) was prepared by the combination of dissolution of (*R*)-pantolactone in D<sub>2</sub>O and concentration under vacuum at room temperature four times. The deuteration was determined by peak area % of <sup>1</sup>H NMR spectroscopy at 5.95 ppm (d, <sup>3</sup>*J*<sub>HH</sub> = 6.0 Hz, 1H) in anhydrous DMSO-d<sub>6</sub>.

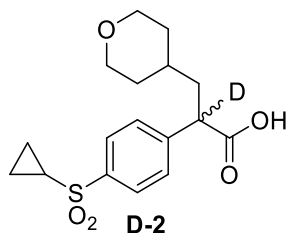


<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 4.08 (s, <sup>1</sup>H), 3.92 (s, 1H), 1.07 (s, 3H), 0.89 (s, 3H). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 176.9, 75.0, 74.4, 40.2, 22.3, 19.0. Anal. Calcd for C<sub>6</sub>H<sub>8</sub>O<sub>3</sub>D: C, 54.95; H, 6.92; D, 1.54. Found : C, 55.01; H, 7.68. [ $\alpha$ ]<sub>D</sub><sup>20</sup> -31.3 (c 1.09, MeOD).



**2-[4-(Cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)-2-deuteriopropioic acid (D-2)**  
**(Cas No. 1522365-20-3)**

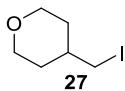
To a solution of **2** (10.00 g, 2.955 mmol) and Et<sub>3</sub>N (0.12 mL, 0.89 mmol) in toluene (50 mL) was added SOCl<sub>2</sub> (2.80 mL, 38.4 mmol) at 40 °C. After stirring at 40 °C overnight, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (100 mL) and Et<sub>3</sub>N (8.20 mL, 58.8 mmol) was added to the solution at −10 °C. After stirring for 1 h, the reaction mixture was quenched with D<sub>2</sub>O (1.0 mL). After warming to 20 °C, the resulting solution was concentrated under vacuum. The residue was dissolved in EtOAc (100 mL), washed with H<sub>2</sub>O (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was dissolved in toluene (40 mL), and Et<sub>3</sub>N (0.093 mL, 0.67 mmol) and SOCl<sub>2</sub> (2.24 mL, 30.7 mmol) was added to the solution. After stirring at 40 °C overnight, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (100 mL) and Et<sub>3</sub>N (6.10 mL, 43.7 mmol) was added to the solution at −10 °C. After stirring for 1 h, the reaction mixture was quenched with D<sub>2</sub>O (1.0 mL). After warming to 20 °C, the resulting solution was concentrated under vacuum. The residue was dissolved in EtOAc (100 mL), washed with H<sub>2</sub>O (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (31/69 → 90/10) to give a crude oil. The crude was crystallized from the mixture of *i*-BuOAc (5.5 mL) and *n*-heptane (1.0 mL) to give the compound **D-2** as a colorless crystal (1.00 g; 10.0% yield). The deuteration was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub>.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.87 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.51 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 3.96-3.91 (m, 2H), 3.30 (tdd,  $^3J_{\text{HH}} = 11.8$  Hz, 5.4 Hz, 2.0 Hz, 2H), 2.46 (tt,  $^3J_{\text{HH}} = 8.0$  Hz, 4.8 Hz, 1H), 2.12-2.04 (m, 1H), 1.80-1.73 (m, 1H), 1.62-1.57 (m, 2H), 1.48-1.26 (m, 5H), 1.08-1.01 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  174.1, 145.4, 139.1, 128.9, 127.4, 66.7, 47.1(t,  $^1J_{\text{CD}} = 20.7$  Hz), 32.5, 32.3, 32.1, 31.9, 5.3. Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{O}_5\text{SD}$ : C, 60.16; H, 6.24; D, 0.59; S, 9.45. Found : C, 60.34; H, 6.48; S, 9.41.

#### **4-(Iodomethyl)tetrahydro-2H-pyran (4-THPCH<sub>2</sub>I, **27**)** (CAS No.101691-94-5)

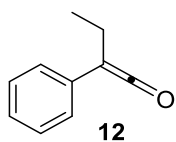
To a solution of tetrahydro-2H-pyran-4-ylmethanol **24** (35.00 g, 0.301 mol) and  $\text{Et}_3\text{N}$  (35.1 g, 0.347 mol) in toluene (245 mL) was added a solution of methanesulfonyl chloride (38.0 g, 0.332 mol) in toluene (105 mL) at 5 °C dropwise over 1 h. After stirring at 25 °C for 1.5 h, the reaction mixture was quenched with  $\text{H}_2\text{O}$  (175 mL). The resulting solution was separated and the aqueous layer was extracted with toluene (105 mL). The organic layers were collected and concentrated under vacuum. The residue **33** was dissolved in acetone (280 mL) and NaI (112.9 g, 0.753 mol) was added to a solution, which was warmed to 60 °C. After stirring for 4 h, the suspension was dissolved in  $\text{H}_2\text{O}$  (280 mL) and concentrated under vacuum. The residue was extracted with EtOAc (280 mL), washed with 20% aq.  $\text{Na}_2\text{S}_2\text{O}_3$  (140 mL), dried over  $\text{MgSO}_4$  (3.5 g), filtered, and dried under vacuum to give **27** as a pale yellow oil (59.73 g; 87.7% yield).



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.00-3.94 (m, 2H), 3.37 (td,  $^3J_{\text{HH}} = 11.8$  Hz, 2.0 Hz, 2H), 3.10 (d,  $^3J_{\text{HH}} = 6.7$  Hz, 2H), 1.82-1.75 (m, 2H), 1.75-1.66 (m, 1H), 1.36-1.25 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  67.6, 37.7, 33.6, 13.9. Anal. Calcd for  $\text{C}_6\text{H}_{11}\text{IO}$ : C, 31.88; H, 4.90. Found : C, 31.76; H, 4.72.

### 2-Phenyl-1-buten-1-one (**12**) (Cas No. 20452-67-9)

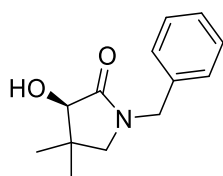
$\text{Me}_2\text{NEt}$  (11.8 mL, 438 mmol) was added to the solution of **14** (20.00 g, 109.5 mmol) in THF (200 mL) and stirred at  $-10$  °C for 14 h. The yellow suspension was filtered and concentrated under vacuum. The residue was purified by distillation (75-78 °C, 5.9 hPa) to give **12** as a yellow oil (6.50 g, 40.6% yield).



$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  7.34-7.27 (m, 2H), 7.10-7.02 (m, 3H), 2.43 (q,  $^3J_{\text{HH}} = 7.4$  Hz, 2H), 1.23 (t,  $^3J_{\text{HH}} = 7.4$  Hz, 3H).

**(*R*)-1-Benzyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one (*N*-Benzyl-(*R*)-pantolactam) (Cas No. 1227380-63-3)**

Benzylamine (17 mL, 156 mmol) was added to a solution of (*R*)-pantolactone (20.00 g, 154 mmol) in toluene (50 mL). The reaction mixture was stirred at 65 °C for 15 h and was concentrated under vacuum at 50 °C. The residue was dissolved in *n*-hexane (100 mL). After stirring at −10 °C overnight, the resulting precipitate was collected by filtration, washed with cold *n*-hexane (50 mL), and dried at 50 °C under vacuum to give (*R*)-*N*-benzyl-2,4-dihydroxy-3,3-dimethylbutanamide (26.01 g) as a white solid. A solution of (*R*)-*N*-benzyl-2,4-dihydroxy-3,3-dimethylbutanamide (26.00 g) in THF (260 mL) and Et<sub>3</sub>N (16.9 mL, 122 mmol) was stirred at −10 °C, and then a solution of methanesulfonyl chloride (8.6 mL, 110 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred for 0.5 h, and was added to 20.5% LHMDS in THF (320 mL) at −5 °C, and then the reaction mixture was stirred for 12 h. The reaction mixture was quenched by 10% *aq.* NH<sub>4</sub>Cl (100 mL) and warmed to 20 °C. The resulting solution was concentrated at 50 °C under vacuum, and the residue was extracted with toluene (300 mL), washed with 10% *aq.* citric acid (100 mL), dried over MgSO<sub>4</sub>, filtered on activated coal and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 6/4) to give a crude solid. The crude was diluted in the mixture of toluene (21 mL) and *n*-hexane (35 mL) to give (*R*)-1-benzyl-3-hydroxy-4,4 -dimethylpyrrolidin-2-one as a white solid (6.00 g; 17.8% yield).



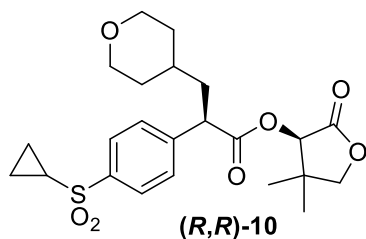
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.36-7.27 (m, 3H), 7.24-7.20 (m, 2H), 4.52 (d, <sup>2</sup>J<sub>HH</sub> = 14.6 Hz, 1H), 4.38 (d, <sup>2</sup>J<sub>HH</sub> = 14.6 Hz, 1H), 4.01 (d, <sup>3</sup>J<sub>HH</sub> = 3.1 Hz, 1H), 3.36 (d, <sup>3</sup>J<sub>HH</sub> = 3.4 Hz, 1H), 2.97 (d, <sup>2</sup>J<sub>HH</sub> = 9.8 Hz, 1H), 2.83 (d, <sup>2</sup>J<sub>HH</sub> = 9.7 Hz, 1H), 1.18 (s, 3H), 0.95 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 174.8, 135.8, 128.7, 128.3, 127.8, 77.9, 56.4, 46.9, 38.6, 24.8, 20.1. Anal. Calcd for C<sub>30</sub>H<sub>37</sub>NO<sub>6</sub>S: C, 66.77; H, 6.91; N, 2.60; S, 5.94. Anal. Calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>: C, 71.21; H, 7.81; D, 6.39. Found : C, 71.45; H, 7.87; S, 6.26. [α]<sub>D</sub><sup>20</sup> +55.0 (c 1.02, MeOH).

### III. Experimental Procedure

#### [Figure 2-3]

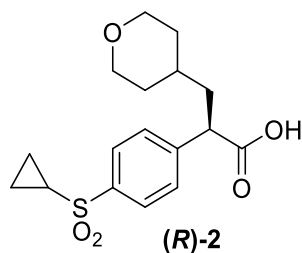
To a solution of **2** (5.00 g, 14.8 mmol), and DMF (0.03 mL) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added SOCl<sub>2</sub> (1.51 mL) at 25 °C. After stirring at 25 °C overnight, the reaction mixture was cooled to -20 °C. Me<sub>2</sub>NEt (6.09 mL) was added to the solution at -20 °C. After stirring for 0.5 h, the reaction mixture was cooled to -78 °C. The solution of (*R*)-pantolactone (2.50 g) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added to it dropwise over 20 min. After stirring to -78 °C for 2 h, the mixture was warmed to -40 °C. After stirring to -40 °C overnight, the resulting solution was warmed to 0 °C. The resulting mixture was washed with H<sub>2</sub>O (50 mL) and 20% *aq.* NaCl (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was dissolved in MeOH (40 mL), and 30% *aq.* H<sub>2</sub>O<sub>2</sub> (4.5 mL) and 4N *aq.* LiOH (4.5 mL) were added it at 0-3 °C. After stirring for 1 h, the reaction mixture was quenched with 10% *aq.* Na<sub>2</sub>SO<sub>3</sub> (50 mL). After warming to 20 °C and adding toluene (50 mL) and H<sub>2</sub>O (90 mL), the resulting solution was separated. After warming to 50 °C and adding toluene (50 mL), 5N *aq.* HCl (25 mL) and CHCl<sub>3</sub> (50 mL x 3) were added to it. The resulting mixture was washed with 20% *aq.* NaCl (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was dissolved in *i*-BuOAc (25 mL) at 110 °C. The solution was cooled to 20 °C over 15 min. After stirring at 20 °C for 30 min, a crystal was filtered, and dried at 50 °C for 2 h under vacuum to give (*R*)-**2** as a colorless crystal (64.4 % yield from **2**, 99:1 er).

**(3R)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2R)-2-[4-(cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2H-pyran-4-yl)propanoate ((R,R)-10) (Cas No.: 1397795-12-8)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.88 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.55 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 5.33 (s, 1H), 4.06-3.99 (m, 2H), 3.98-3.92 (m, 3H), 3.31 (td,  $^2J_{\text{HH}} = 11.8$  Hz,  $^3J_{\text{HH}} = 2.0$  Hz, 2H), 2.47 (tt,  $^3J_{\text{HH}} = 7.9$  Hz, 4.8 Hz, 1H), 2.14 (ddd,  $^2J_{\text{HH}} = 13.8$  Hz,  $^3J_{\text{HH}} = 8.3$  Hz, 6.7 Hz, 1H), 1.83 (dt,  $^2J_{\text{HH}} = 13.8$  Hz,  $^3J_{\text{HH}} = 7.0$  Hz, 1H), 1.67-1.58 (m, 2H), 1.54-1.42 (m, 1H), 1.41-1.28 (m, 4H), 1.17 (s, 3H), 1.08-1.02 (m, 2H), 1.03 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  171.9, 171.6, 143.7, 140.0, 129.0, 128.0, 76.0, 75.6, 67.7, 67.7, 48.2, 40.2, 40.2, 32.9, 32.8, 32.7, 23.1, 19.9, 6.0. Anal. Calcd for  $\text{C}_{23}\text{H}_{30}\text{O}_7\text{S}$ : C, 61.31; H, 6.71; S, 7.12. Found : C, 61.29; H, 6.79; S, 7.00.  $[\alpha]^{20}_{\text{D}} +1.3$  (c 1.03, MeOH).

**(R)-2-[4-(Cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2H-pyran-4-yl)propanoic acid ((R)-2) (Cas No. 745053-49-0)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.87 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.51 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 2H), 3.97-3.90 (m, 2H), 3.80 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H), 3.30 (tdd,  $^2J_{\text{HH}} = 11.8$  Hz,  $^3J_{\text{HH}} = 5.1$  Hz, 2.0 Hz, 2H), 2.46 (tt,  $^3J_{\text{HH}} = 7.9$  Hz, 4.9 Hz, 1H), 2.12-2.04 (m, 1H), 1.81-1.72 (m, 1H), 1.64-1.55 (m, 2H), 1.46-1.25 (m, 5H), 1.08-1.01 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  174.1, 145.5, 139.1, 128.9, 127.4, 66.8, 47.5, 39.7, 32.5, 32.3, 32.1, 31.9, 5.3. Anal. Calcd for  $\text{C}_{17}\text{H}_{22}\text{O}_5\text{S}$ : C, 60.33; H, 6.55; S, 9.47. Found: C, 60.08; H, 6.50; S, 9.49.  $[\alpha]^{20}_{\text{D}} -53.4$  (c 1.06, MeOH).

**[Figure 2-4]**

**(Entry 1)**

To a solution of **2** (5.00 g, 14.8 mmol), and DMF (0.03 mL) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added SOCl<sub>2</sub> (1.51 mL) at 25 °C. After stirring at 25 °C overnight, the reaction mixture was cooled to –20 °C. Me<sub>2</sub>NEt (6.09 mL) was added to the solution at –20 °C. After stirring for 0.5 h, the reaction mixture was cooled to –78 °C. The solution of (*R*)-pantolactone (2.50 g) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added to it dropwise over 20 min, and the mixture was stirred at –10 °C for 2 h.

**(Entry 2)**

To a solution of **2** (0.50 g, 1.48 mmol), and DMF (0.003 mL) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added SOCl<sub>2</sub> (0.15 mL) at 25 °C. After stirring at 25 °C overnight, the reaction mixture was cooled to –10 °C. Me<sub>2</sub>NEt (0.61 mL) was added to the solution at –10 °C. After stirring for 0.5 h, the solution of (*R*)-pantolactone (0.25 g) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added to it dropwise over 20 min, and the mixture was stirred at –10 °C for 2 h.

**[Figure 2-5]**

To a solution of **2** (0.50 g, 1.48 mmol), and DMF (0.003 mL) in solvent (5.0 mL) was added SOCl<sub>2</sub> (0.15 mL) at 25 °C. After stirring at 25 °C overnight, the reaction mixture was cooled to –10 °C. Me<sub>2</sub>NEt (0.61 mL) was added to the solution at –10 °C. After stirring for 0.5 h, the solution of (*R*)-pantolactone (0.25 g) in solvent (5.0 mL) was added to it dropwise over 20 min. After stirring to –10 °C for 4 h, the resulting solution was warmed to 0 °C. The resulting mixture was washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (5 mL) and 20% *aq.* NaCl (5 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum.

**[Figure 2-7]**

An amine was added to a solution of **8** at 25 °C. After stirring for 0.5 h, a solution of (*R*)-pantolactone was added at −10 °C to the reaction mixture dropwise. After stirring for 2–3 h, the resulting mixture was purified by extraction and column chromatography to give (*R,R*)-**10**.

**[Figure 2-8]**

An amine was added to a solution of **8** at 25 °C. After stirring for 0.5 h, a solution of (*R*)-pantolactone was added at −10 °C to the reaction mixture dropwise and the mixture was stirred for 0.5–3 h.

**[Figure 2-10]**

**(Entry 1)**

Et<sub>3</sub>N (4.13 mL) was added to a solution of **8** (14.8 mmol) in toluene (100 mL) at 25 °C. After stirring for 1 h, (*R*)-pantolactone (2.50 g) in THF (20 mL) was added to it dropwise over 20 min at −78 °C and the reaction mixture was stirred for 2 h.

**(Entry 2)**

Et<sub>3</sub>N (12.4 mL) was added to a solution of **8** (44.3 mmol) in toluene (45 mL) at −10 °C. After stirring for 1 h, (*R*)-pantolactone (6.92 g) in THF (60 mL) was added to it dropwise over 20 min at −78 °C and the reaction mixture was stirred for 2 h.



**[Figure 2-11]****(Entry 1)**

Et<sub>3</sub>N (0.82 mL, 5.9 mmol) was added to the solution of **8** (2.95 mmol) in CH<sub>3</sub>CN (10 mL) at −10 °C. After stirring at −10 °C for 0.5 h, to the yellow solution was added dropwise a solution of deuterium-labeling (*R*)-pantolactone (97% D) (0.38 g, 2.9 mmol) in CH<sub>3</sub>CN (10 mL). After stirring for 2 h, citric acid (1.0 g, 4.8 mmol) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene (20 mL), washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the mixture of deuterated **D-10** and non-deuterated **10** as a white solid (1.22 g, **D-10:10** = 56:44). The deuteration and the dr were determined by peak area % of <sup>1</sup>H NMR spectroscopy in toluene-d<sub>8</sub> (**D-(*R,R*)-10** + (*R,R*)-**10**: peak (s, 1H) in 4.94 ppm, (*R,R*)-**10**: peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 6.4 Hz, 1H) in 3.83 ppm, **D-(*S,R*)-10** + (*S,R*)-**10**: peak (s, 1H) in 5.01 ppm, (*S,R*)-**10** peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.9, 6.7 Hz, 1H) in 3.70 ppm).

	<b>D-10</b>	<b>10</b>	<b>D-10 + 10</b>
<b>(<i>R,R</i>)</b>	0.46	0.32	0.78
<b>(<i>S,R</i>)</b>	0.10	0.12	0.22
<b>(<i>R,R</i>) + (<i>S,R</i>)</b>	0.56	0.44	1.00

**(Entry 2)**

Et<sub>3</sub>N (0.82 mL, 5.9 mmol) was added to the solution of **8** (2.95 mmol) in THF (10 mL) at −10 °C. After stirring at −10 °C for 0.5 h, to the yellow solution was added dropwise a solution of deuterium-labeling (*R*)-pantolactone (97% D) (0.38 g, 2.9 mmol) in THF (10 mL). After stirring for 2 h, citric acid (1.0 g, 4.8 mmol) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene (20 mL), washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the mixture of deuterated **D-10** and non-deuterated **10** as a white solid (1.25 g, **D-10:10** = 93:7). The deuteration and the dr were determined by peak area % of <sup>1</sup>H NMR spectroscopy in toluene-d<sub>8</sub> (**D-(*R,R*)-10** + (*R,R*)-**10**: peak (s, 1H) in 4.94 ppm, (*R,R*)-**10**: peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 6.4 Hz, 1H) in 3.83 ppm, **D-(*S,R*)-10** + (*S,R*)-**10**: peak (s, 1H) in 5.01 ppm, (*S,R*)-**10** peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.9, 6.7 Hz, 1H) in 3.70 ppm).

	<b>D-10</b>	<b>10</b>	<b>D-10 + 10</b>
<b>(<i>R,R</i>)</b>	0.85	0.06	0.91
<b>(<i>S,R</i>)</b>	0.08	0.01	0.09
<b>(<i>R,R</i>) + (<i>S,R</i>)</b>	0.93	0.07	1.00

**(Entry 3)**

Et<sub>3</sub>N (0.82 mL, 5.9 mmol) was added to the solution of **8** (2.95 mmol) in toluene (10 mL) at −10 °C. After stirring at −10 °C for 0.5 h, to the yellow solution was added dropwise a solution of deuterium-labeling (*R*)-pantolactone (97% D) (0.38 g, 2.9 mmol) in toluene (10 mL). After stirring for 2 h, citric acid (1.0 g, 4.8 mmol) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was separated. The organic layer was washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the mixture of deuterated **D-10** and non-deuterated **10** as a white solid (1.20 g, **D-10**:**10** = 12:1). The deuteration and the dr were determined by peak area % of <sup>1</sup>H NMR spectroscopy in toluene-d<sub>8</sub> (**D-(*R,R*)-10** + (*R,R*)-**10**: peak (s, 1H) in 4.94 ppm, (*R,R*)-**10**: peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 6.4 Hz, 1H) in 3.83 ppm, **D-(*S,R*)-10** + (*S,R*)-**10**: peak (s, 1H) in 5.01 ppm, (*S,R*)-**10** peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.9, 6.7 Hz, 1H) in 3.70 ppm).

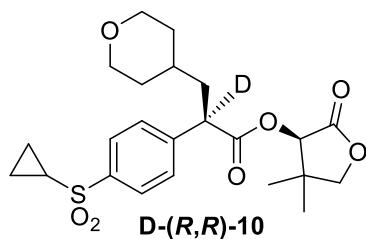
	<b>D-10</b>	<b>10</b>	<b>D-10 + 10</b>
<b>(<i>R,R</i>)</b>	0.87	0.06	0.93
<b>(<i>S,R</i>)</b>	0.05	0.02	0.07
<b>(<i>R,R</i>) + (<i>S,R</i>)</b>	0.92	0.08	1.00

**(Entry 4)**

Et<sub>3</sub>N (0.82 mL, 5.9 mmol) was added to the solution of **8** (2.95 mmol) in toluene (10 mL), and stirred at −10 °C for 0.5 h. After cooling down to −78 °C, to the yellow solution was added dropwise a solution of deuterium-labeling (*R*)-pantolactone (97% D) (0.38 g, 2.9 mmol) in THF (10 mL) over 20 minutes. After stirring at −78 °C for 2 h, citric acid (1.0 g, 4.8 mmol) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was separated, and the organic layer was washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the mixture of deuterated **D-10** and non-deuterated **10** as a white solid (1.13 g, **D-10:10** = 92:8). The deuteration and the dr were determined by peak area % of <sup>1</sup>H NMR spectroscopy in toluene-d<sub>8</sub> (**D-(*R,R*)-10** + (*R,R*)-**10**: peak (s, 1H) in 4.94 ppm, (*R,R*)-**10**: peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 6.4 Hz, 1H) in 3.83 ppm, **D-(*S,R*)-10** + (*S,R*)-**10**: peak (s, 1H) in 5.01 ppm, (*S,R*)-**10** peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.9, 6.7 Hz, 1H) in 3.70 ppm).

	<b>D-10</b>	<b>10</b>	<b>D-10 + 10</b>
<b>(<i>R,R</i>)</b>	0.92	0.06	0.98
<b>(<i>S,R</i>)</b>	<0.01	0.02	0.02
<b>(<i>R,R</i>) + (<i>S,R</i>)</b>	0.92	0.08	1.00

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2*R*)-2-[4-(cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)-2-deuteriopropanoate (D-(*R,R*)-10) (Cas No. 1522365-27-0)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.89 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.55 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 5.33 (s, 1H), 4.03 (dd,  $^2J_{\text{HH}} = 13.6$  Hz,  $^3J_{\text{HH}} = 9.0$  Hz, 2H), 3.95 (dd,  $^2J_{\text{HH}} = 12.0$  Hz,  $^3J_{\text{HH}} = 3.6$  Hz, 2H), 3.31 (td,  $^2J_{\text{HH}} = 11.8$  Hz,  $^3J_{\text{HH}} = 2.0$  Hz, 2H), 2.47 (tt,  $^3J_{\text{HH}} = 8.0$  Hz, 4.8 Hz, 1H), 2.14 (dd,  $^2J_{\text{HH}} = 13.6$  Hz,  $^3J_{\text{HH}} = 6.8$  Hz, 1H), 1.82 (dt,  $^2J_{\text{HH}} = 13.6$  Hz,  $^3J_{\text{HH}} = 6.8$  Hz, 1H), 1.67-1.58 (m, 2H), 1.54-1.42 (m, 1H), 1.41-1.28 (m, 4H), 1.17 (s, 3H), 1.08-1.02 (m, 2H), 1.04 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  171.9, 171.7, 143.6, 140.0, 129.0, 128.0, 76.0, 75.5, 67.7, 67.7, 47.8 (t,  $^1J_{\text{CD}} = 19.1$  Hz), 40.2, 32.9, 32.8, 32.7, 32.7, 23.0, 19.9, 6.0. Anal. Calcd for  $\text{C}_{23}\text{H}_{29}\text{O}_7\text{SD}$ : C, 61.18; H, 6.47; D, 0.45; S, 7.10. Found : C, 61.32; H, 6.74; S, 6.99.  $[\alpha]^{20}_{\text{D}} +1.5$  (c 1.02, MeOH).

**[Figure 2-12]**

**D-2** (0.20 g, 0.59 mmol) was dissolved in MeOD, and concentrated under vacuum. The residue was dissolved in toluene (2.0 mL), and to the solution were added Et<sub>3</sub>N (0.01 mL, 0.08 mmol) and SOCl<sub>2</sub> (0.06 mL, 0.8 mmol) at 40 °C. After stirring for 4 h, the reaction mixture was concentrated under vacuum. The residue **D-8** and (*R*)-pantolactone (0.070 g) were dissolved in toluene (2.0 mL), and cooled down to −10 °C. To the solution was added Et<sub>3</sub>N (0.16 mL, 1.2 mmol), and the resulting mixture was stirred for 16 h. Citric acid (1.0 g, 4.8 mmol) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution, which was warmed to 25 °C. The resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the ester (***R,R***-**10**) as a white solid (0.145 g, **10:D-10** = 2.4:1). The deuteration and the dr were determined by peak area % of <sup>1</sup>H NMR spectroscopy in toluene-d<sub>8</sub> (**D-(*R,R*)-10** + (***R,R***-**10**): peak (s, 1H) in 4.94 ppm, (***R,R***-**10**: peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 6.4 Hz, 1H) in 3.83 ppm, **D-(*S,R*)-10** + (***S,R***-**10**): peak (s, 1H) in 5.01 ppm, (***S,R***-**10** peak (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.9, 6.7 Hz, 1H) in 3.70 ppm).

	<b>10</b>	<b>D-10</b>	<b>10 + D-10</b>
<b>(<i>R,R</i>)</b>	0.62	0.24	0.86
<b>(<i>S,R</i>)</b>	0.04	0.10	0.14
<b>(<i>R,R</i>) + (<i>S,R</i>)</b>	0.66	0.34	1.00

**[Figure 2-13]**

**(Entry 1)**

To a solution of **(R)**-**2** (1.00 g, 2.96 mmol), and NMP (0.01 mL) in toluene (5 mL) was added SOCl<sub>2</sub> (0.28 mL) at 40 °C. After stirring at 40 °C for 7 h, the reaction mixture was concentrated under vacuum to give the residue **(R)**-**8**. The residue **(R)**-**8** dissolved in toluene (10 mL), and cooled down to −10 °C. To the solution was added pyridine (0.48 mL). After stirring for 30 min, a solution of (*R*)-pantolactone (0.50 g) in THF (4.0 mL) was added to the resulting mixture. After stirring for 14 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the corresponding ester **(R,R)**-**10** as a colorless solid (1.18 g, 88.6% yield, 73:1 dr). The dr was determined by HPLC.

**(Entry 2)**

To a solution of **(R)**-**2** (1.00 g, 2.96 mmol), and NMP (0.01 mL) in toluene (5 mL) was added SOCl<sub>2</sub> (0.28 mL) at 40 °C. After stirring at 40 °C for 5 h, the reaction mixture was concentrated under vacuum to give the residue **(R)**-**8**. The residue **(R)**-**8** and (*R*)-pantolactone (0.50 g) were dissolved in toluene (20 mL), and cooled down to −10 °C. To the solution was added Me<sub>2</sub>NEt (0.62 mL), and the resulting mixture was stirred for 3 h. Citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the corresponding ester **(R,R)**-**10** as a colorless solid (1.16 g, 87.1% yield, 88:12 dr). The dr was determined by HPLC.

**(Entry 3)**

To a solution of **(R)-2** (1.00 g, 2.96 mmol), and NMP (0.01 mL) in toluene (5 mL) was added SOCl<sub>2</sub> (0.28 mL) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum to give the residue **(R)-8**. The residue **(R)-8** and (*R*)-pantolactone (0.50 g) were dissolved in toluene (20 mL), and cooled down to −10 °C. To the solution was added Et<sub>3</sub>N (0.82 mL), and the resulting mixture was stirred for 40 min. Citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the corresponding ester **(R,R)-10** as a colorless solid (1.24 g, 93.1% yield, 92:8 dr). The dr was determined by HPLC.

**[Figure 2-14]**

**(Entry 1)**

To the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) was added −10 °C dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester **(R,R)-13** as a colorless oil (<1% NMR yield, 54:46 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.54 of peak (s, 1H) in 5.33 ppm and 0.46 of peak (s, 1H) in 5.36 ppm).



### (Entry 2)

Et<sub>3</sub>N·HCl (0.470 g, 3.42 mmol) was added to the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) and stirred at −10 °C for 40 min. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R***-**13**) as a colorless oil (8% NMR yield, 96:4 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.96 of peak (s, 1H) in 5.33 ppm and 0.04 of peak (s, 1H) in 5.36 ppm).

### (Entry 3)

Me<sub>3</sub>N·HCl (0.330 g, 3.42 mmol) was added to the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) and stirred at −10 °C for 40 min. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R***-**13**) as a colorless oil (24% NMR yield, 95:5 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.95 of peak (s, 1H) in 5.33 ppm and 0.05 of peak (s, 1H) in 5.36 ppm).

#### (Entry 4)

Pyridine·HCl (0.400 g, 3.42 mmol) was added to the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) and stirred at  $-10\text{ }^{\circ}\text{C}$  for 40 min. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to  $25\text{ }^{\circ}\text{C}$ , the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9  $\rightarrow$  2/3) to give the corresponding ester (***R,R*-13**) as a colorless oil (20% NMR yield, 71:29 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.71 of peak (s, 1H) in 5.33 ppm and 0.29 of peak (s, 1H) in 5.36 ppm).

#### (Entry 5)

Et<sub>3</sub>N (0.48 mL, 3.42 mmol) was added to the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) and stirred at  $-10\text{ }^{\circ}\text{C}$  for 0.5 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to  $25\text{ }^{\circ}\text{C}$ , the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9  $\rightarrow$  2/3) to give the corresponding ester (***R,R*-13**) as a colorless oil (0.82 g, 86.8% yield, 98:2 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.98 of peak (s, 1H) in 5.33 ppm and 0.02 of peak (s, 1H) in 5.36 ppm).

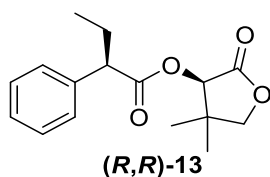
**(Entry 6)**

Me<sub>2</sub>NEt (0.37 mL, 3.42 mmol) was added to the solution of **12** (0.510 g, 3.49 mmol) in toluene (5.0 mL) and stirred at -10 °C for 0.5 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R***-**13**) as a colorless oil (0.85 g, 89.9% yield, 98:2 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.98 of peak (s, 1H) in 5.33 ppm and 0.02 of peak (s, 1H) in 5.36 ppm).

**(Entry 7)**

Pyridine (0.28 mL, 3.42 mmol) was added to the solution of **12** (0.500 g, 3.42 mmol) in toluene (5.0 mL) and stirred at -10 °C for 0.5 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.590 g, 4.45 mmol) in toluene (10 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R***-**13**) as a pale yellow oil (0.48 g, 50.8% yield, 85:15 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.85 of peak (s, 1H) in 5.33 ppm and 0.15 of peak (s, 1H) in 5.36 ppm).

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2*R*)-2-phenylbutanoate ((*R,R*)-13) (Cas No. 136011-03-5)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.38-7.23 (m, 5H), 5.33 (s, 1H), 4.02 (d,  $^2J_{\text{HH}} = 9.2$  Hz, 1H), 3.98 (d,  $^2J_{\text{HH}} = 9.2$  Hz, 1H), 3.63 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H), 2.25-2.13 (m, 1H), 1.97-1.85 (m, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.97 (t,  $^3J_{\text{HH}} = 7.4$  Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  172.8, 172.0, 138.0, 128.6, 128.1, 127.4, 76.1, 75.0, 53.4, 40.2, 26.4, 23.0, 19.8, 12.2. Anal. Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_4$ : C, 69.54; H, 7.30. Found : C, 69.18; H, 7.31.  $[\alpha]^{20}_{\text{D}} -0.4$  (c 1.04, MeOH).

**[Figure 2-15]**

**(Entry 1)**

$\text{Et}_3\text{N}$  (1.53 mL, 10.9 mmol) was added to the solution of **14** (1.00 g, 5.47 mmol) in toluene (5.0 mL) and stirred at  $-10$   $^\circ\text{C}$  for 1 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.930 g, 7.15 mmol) in toluene (12 mL) over 15 min. After stirring for 2 h, citric acid (1.0 g) and  $\text{H}_2\text{O}$  (4.0 mL) were added to the reaction solution. After warming to  $25$   $^\circ\text{C}$ , the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with  $\text{EtOAc}/n$ -hexane (1/9  $\rightarrow$  2/3) to give the corresponding ester (**(*R,R*)-13**) as a colorless oil (1.33 g, 87.9% yield, 97:3 dr). The dr was determined by peak area % of  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$  (0.97 of peak (s, 1H) in 5.33 ppm and 0.03 of peak (s, 1H) in 5.36 ppm).

**(Entry 2)**

Me<sub>2</sub>NEt (1.18 mL, 10.9 mmol) was added to the solution of **14** (1.00 g, 5.47 mmol) in toluene (5.0 mL) and stirred at −10 °C for 1.5 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.930 g, 7.15 mmol) in toluene (12 mL) over 30 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R*-13**) as a colorless oil (1.29 g, 85.3% yield, 58:42 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.58 of peak (s, 1H) in 5.33 ppm and 0.42 of peak (s, 1H) in 5.36 ppm).

**(Entry 3)**

Pyridine (0.88 mL, 10.9 mmol) was added to the solution of **14** (1.00 g, 5.47 mmol) in toluene (5.0 mL) and stirred at −10 °C for 1.5 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.930 g, 7.15 mmol) in toluene (12 mL) over 20 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (***R,R*-13**) as a colorless oil (0.63 g, 83.3% yield, 50:50 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.50 of peak (s, 1H) in 5.33 ppm and 0.50 of peak (s, 1H) in 5.36 ppm).

**[Figure 2-16]**

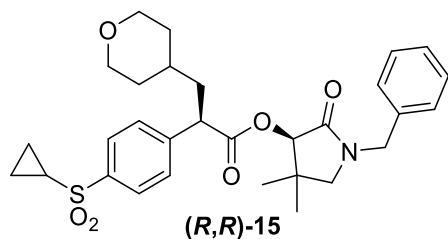
**(*R,R*)-10**

To a solution of **2** (0.50 g, 1.48 mmol), and Et<sub>3</sub>N (0.01 mL) in toluene (2.5 mL) was added SOCl<sub>2</sub> (0.14 mL) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum to give the residue **8**. The residue **8** and (*R*)-pantolactone (0.25 g) were dissolved in toluene (5 mL), and cooled down to −10 °C. To the solution was added Et<sub>3</sub>N (0.41 mL), and the resulting mixture was stirred at −10 °C for 2 h. Citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the corresponding ester (**(*R,R*)-10**) as a white solid (0.573 g, 85.9% yield, 90:10 dr). The dr was determined by peak area% of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.90 of peak (s, 1H) in 5.33 ppm and 0.10 of peak (s, 1H) in 5.36 ppm).

**(*R,R*)-15**

Et<sub>3</sub>N (0.82 mL, 5.9 mmol) was added to a solution of **8** (2.95 mmol) and *N*-Benzyl-(*R*)-pantolactam (0.65 g, 2.96 mmol) in toluene (20 mL) at −10 °C. After stirring for 2 h, citric acid (2.0 g) and H<sub>2</sub>O (9.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/3 → 3/2) to give the corresponding ester (**(*R,R*)-15**) as a white solid (1.41 g, 88.4% yield, 98:2 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.98 of peak(s, 1H) in 5.27 ppm and 0.02 of peak (s, 1H) in 5.25 ppm). The absolute configuration was determined by comparison of the ester obtained in the reaction of (***R***)-**8** and *N*-Benzyl-(*R*)-pantolactam with pyridine as a base.

**(3*R*)-1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl(2*R*)-2-[4-(cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)propanoate ((*R,R*)-15) (Cas No. 1522365-44-1)**

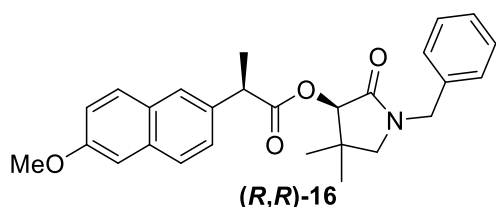


$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.88 (d,  $^3J_{\text{HH}} = 8.3$  Hz, 2H), 7.57 (d,  $^3J_{\text{HH}} = 8.3$  Hz, 2H), 7.37-7.28 (m, 3H), 7.23-7.18 (m, 2H), 5.25 (s, 1H), 4.46 (d,  $^2J_{\text{HH}} = 14.4$  Hz, 1H), 4.40 (d,  $^2J_{\text{HH}} = 14.3$  Hz, 1H), 4.12 (dd,  $^2J_{\text{HH}} = 14.4$  Hz,  $^3J_{\text{HH}} = 7.1$  Hz, 2H), 3.98-3.92 (m, 3H), 3.31 (t,  $^3J_{\text{HH}} = 11.7$  Hz, 2H), 3.00 (d,  $^2J_{\text{HH}} = 9.8$  Hz, 1H), 2.88 (d,  $^2J_{\text{HH}} = 9.6$  Hz, 1H), 2.46 (tt,  $^3J_{\text{HH}} = 7.9$  Hz, 4.8 Hz, 1H), 2.21-2.11 (m, 1H), 2.53 (s, 3H), 1.87-1.78 (m, 1H), 1.68-1.62 (m, 2H), 1.53-1.43 (m, 1H), 1.40-1.30 (m, 4H), 1.26 (t,  $^3J_{\text{HH}} = 7.0$  Hz, 3H), 1.11 (s, 3H), 1.06-1.02 (m, 2H), 0.89 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  172.1, 169.1, 144.1, 139.8, 135.5, 129.1, 128.8, 128.3, 128.0, 78.5, 67.7, 67.7, 56.3, 48.4, 46.9, 40.5, 37.6, 32.9, 32.8, 32.7, 25.1, 21.1, 6.0. Anal. Calcd for  $\text{C}_{30}\text{H}_{37}\text{NO}_6\text{S}$ : C, 66.77; H, 6.91; N, 2.60; S, 5.94. Found: C, 66.39; H, 6.89; N, 2.49; S, 5.71.  $[\alpha]_D^{20} +49.8$  (c 1.03, MeOH).

[Figure 2-17]

**(3*R*)-1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl-(2*R*)-2-(6-methoxynaphthalen-2-yl)propanoate**  
**((*R,R*)-16) (Cas No. 1522365-48-5)**

To a solution of (*S*)-Naproxen (0.50 g, 2.2 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (2.5 mL) was added SOCl<sub>2</sub> (0.21 mL, 2.9 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (5.0 mL). Et<sub>3</sub>N (0.61 mL, 4.3 mmol) was added to it and stirred at −10 °C for 1 h. To the yellow solution was added dropwise a solution of *N*-benzyl-(*R*)-pantolactam (0.48 g, 2.2 mmol) in toluene (6.0 mL) over 15 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% NaCl aq. (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (**(*R,R*)-16**) as a white solid (0.85 g, 90.7% yield, >99:1 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (1.00 of peak (s, 1H) in 5.26 ppm and <0.01 of peak (s, 1H) in 5.29 ppm).

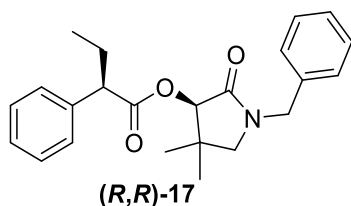


<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.74-7.68 (m, 3H), 7.48 (dd, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 1H), 7.33-7.27 (m, 3H), 7.22-7.16 (m, 2 H), 7.15-7.10 (m, 2 H), 5.26 (s, 1H), 4.47 (d, <sup>2</sup>J<sub>HH</sub> = 14.4 Hz, 1H), 4.39 (d, <sup>2</sup>J<sub>HH</sub> = 14.4 Hz, 1H), 4.06-4.00 (m, 1H), 3.92 (s, 3 H), 2.95 (d, <sup>2</sup>J<sub>HH</sub> = 9.6 Hz, 1H), 2.86 (d, <sup>2</sup>J<sub>HH</sub> = 9.6 Hz, 1H), 1.69 (d, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3H), 1.09 (s, 3H), 0.87 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 174.0, 169.6, 157.6, 135.7, 135.0, 133.7, 129.3, 128.7, 128.3, 127.8, 127.0, 126.5, 126.2, 118.8, 105.5, 78.0, 77.3, 56.4, 55.3, 46.8, 45.5, 37.5, 25.1, 21.0, 18.6. Anal. Calcd for C<sub>27</sub>H<sub>29</sub>NO<sub>4</sub>: C, 75.17; H, 6.77; N, 3.25. Found : C, 75.24; H, 6.67; N, 3.22. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +86.1 (c 1.01, MeOH).



**(3*R*)-1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl-(2*R*)-2-phenylbutanoate ((*R,R*)-17) (Cas No. 1522365-46-3)**

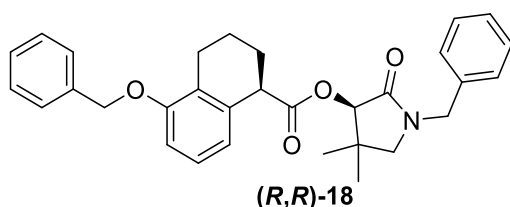
Et<sub>3</sub>N (1.53 mL, 10.9 mmol) was added to the solution of 2-phenylbutyryl chloride (1.00 g, 5.47 mmol) in toluene (5.0 mL) and stirred at −10 °C for 1 h. To the yellow solution was added dropwise a solution of *N*-benzyl-(*R*)-pantolactam (1.20 g, 5.47 mmol) in toluene (12 mL) over 15 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 5% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (**(*R,R*)-17**) as a white solid (1.71 g, 85.5% yield, 99:1 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.99 of peak (s, 1H) in 5.28 ppm and 0.01 of peak (s, 1H) in 5.28 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.38-71.8 (m, 10H), 5.25 (s, 1H), 4.47 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.6 Hz, 1H), 4.40 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.6 Hz, 1H), 3.63 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.8 Hz, 1H), 2.96 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.6 Hz, 1H), 2.87 (d, <sup>3</sup>*J*<sub>HH</sub> = 9.6 Hz, 1H), 2.26-2.15 (m, 1H), 1.96-1.85 (mt, 1H), 1.08 (s, 3H), 0.98 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.4 Hz, 3H), 0.89 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 173.3, 170.0, 138.4, 135.7, 128.7, 128.5, 128.3, 128.1, 127.8, 127.2, 77.9, 77.3, 56.3, 53.6, 46.9, 37.6, 26.5, 25.1, 21.1, 12.2. Anal. Calcd for C<sub>23</sub>H<sub>27</sub>NO<sub>3</sub>: C, 75.59; H, 7.45; N, 3.83. Found : C, 75.20; H, 7.39; N, 3.84. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +68.6 (c 0.98, MeOH).

**(3*R*)-1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl-(1*R*)-5-(benzyloxy)-1,2,3,4-tetrahydronaphthalene-1-carboxylate ((*R,R*)-18) (Cas No. 1522365-50-9)**

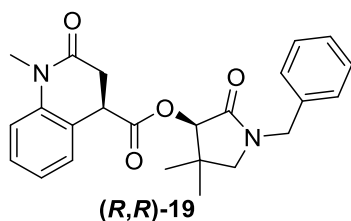
To a solution of the corresponding carboxylic acid (0.30 g, 1.1 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (1.5 mL) was added SOCl<sub>2</sub> (0.10 mL, 1.4 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (3.0 mL). Et<sub>3</sub>N (0.30 mL, 2.2 mmol) was added to it and stirred at -10 °C for 1 h. To the yellow solution was added dropwise a solution of *N*-benzyl-(*R*)-pantolactam (0.23 g, 1.1 mmol) in toluene (3.0 mL) over 15 minutes. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (*R,R*)-18 as a colorless oil (0.388 g, 75.4% yield, 98:2 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.98 of peak (s, 1H) in 5.32 ppm and 0.02 of peak (s, 1H) in 5.30 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.47-7.21 (m, 8H), 7.12 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.2 Hz, 1H), 6.91 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 1H), 6.78 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.4 Hz, 1H), 5.32 (s, 1H), 5.07 (s, 2H), 4.50 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.8 Hz, 1H), 4.41 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.4 Hz, 1H), 4.01 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.0 Hz, 1H), 2.99 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.8 Hz, 1H), 2.87 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.8 Hz, 1H), 2.87-2.69 (m, 2H), 2.27-2.27 (m, 1H), 2.13-2.05 (m, 1H), 2.02-1.90 (m, 1H), 1.87-1.75 (m, 1H), 1.11 (s, 3H), 0.86 (s, 3H).  
<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 174.4, 169.8, 156.4, 137.5, 135.7, 134.3, 128.8, 128.5, 128.3, 127.8, 127.7, 127.1, 126.6, 126.0, 122.0, 109.5, 77.9, 69.7, 56.4, 46.9, 45.1, 37.8, 26.7, 25.1, 23.0, 21.0, 20.0. Anal. Calcd for C<sub>31</sub>H<sub>33</sub>NO<sub>4</sub>: C, 76.99; H, 6.88; N, 2.90. Found : C, 76.86; H, 6.79; N, 2.83. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +102.3 (c 1.10, MeOH).

**(3*R*)-1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl-(4*R*)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylate ((*R,R*)-19) (Cas No. 1522365-53-2)**

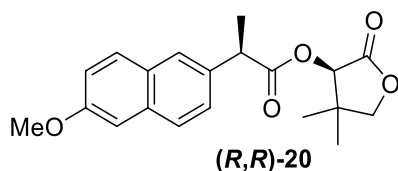
To a solution of the corresponding carboxylic acid (0.200 g, 0.975 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (1.5 mL) was added SOCl<sub>2</sub> (0.09 mL, 1.2 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in THF (2.0 mL) at −10 °C. To the mixture were added dropwise a solution of *N*-benzyl-(*R*)-pantolactam (0.214 g, 0.976 mmol) in THF (2.0 mL) and Et<sub>3</sub>N (0.28 mL, 2.0 mmol). After stirring for 2 h, H<sub>2</sub>O (4.0 mL) and toluene (8 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was separated. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/4 → 3/2) to give the corresponding ester (**(*R,R*)-19**) as a white solid (0.304 g, 76.7% yield, >99:1 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (1.00 of peak (s, 1H) in 5.27 ppm and <0.01 of peak (s, 1H) in 5.22 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.45 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 1H), 7.37-7.27 (m, 4H), 7.25-7.21 (m, 2H), 7.11 (td, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, <sup>4</sup>*J*<sub>HH</sub> = 0.8 Hz, 1H), 7.02 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.4 Hz, 1H), 5.27 (s, 1H), 4.49 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.8 Hz, 1H), 4.42 (d, <sup>2</sup>*J*<sub>HH</sub> = 14.8 Hz, 1H), 4.06 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.0 Hz, 1H), 3.36 (s, 1H), 3.13 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.0 Hz, <sup>3</sup>*J*<sub>HH</sub> = 5.6 Hz, 1H), 2.99 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.6 Hz, 1H), 2.90 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.6 Hz, 1H), 1.10 (s, 3H), 0.95 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 171.1, 169.1, 167.9, 140.1, 135.6, 128.9, 128.8, 128.6, 128.3, 127.9, 123.3, 122.6, 115.1, 78.8, 56.4, 46.9, 42.0, 37.6, 34.0, 29.5, 25.0, 21.0. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.92; H, 6.45; N, 6.89. Found : C, 70.75; H, 6.38; N, 6.90. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +49.5 (c 0.59, MeOH).

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2*R*)-2-(6-methoxynaphthalen-2-yl)propanoate**  
**((*R,R*)-20)**

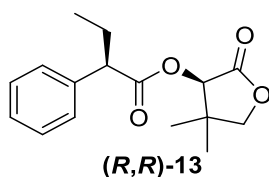
To a solution of Naproxen<sup>®</sup> (0.500 g, 2.17 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (2.5 mL) was added SOCl<sub>2</sub> (0.21 mL, 2.9 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (5.0 mL). Et<sub>3</sub>N (0.61 mL, 4.3 mmol) was added to it, and the mixture was stirred at −10 °C for 1 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.370 g, 2.84 mmol) in toluene (6.0 mL) over 15 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (**(*R,R*)-20**) as a white solid (0.71 g, 95.5% yield, 98:2 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.98 of peak (s, 1H) in 5.34 ppm and 0.02 of peak (s, 1H) in 5.38 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.73-7.68 (m, 3H), 7.44 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8 Hz, <sup>4</sup>*J*<sub>HH</sub> = 1.8 Hz, 1H), 7.17-7.10 (m, 2H), 5.26 (s, 1H), 4.06-3.96 (m, 3H), 3.92 (s, 3H), 1.68 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.2 Hz, 3H), 1.14 (s, 3H), 0.99 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 173.5, 172.0, 157.7, 134.5, 133.8, 129.3, 126.2, 119.0, 105.6, 76.1, 75.1, 55.3, 45.3, 40.2, 23.0, 19.8, 18.4. Anal. Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>5</sub>: C, 70.16; H, 6.48. Found : C, 70.34; H, 6.39. [α]<sup>20</sup><sub>D</sub> +20.0 (c 0.97, MeOH).

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2*R*)-2-phenylbutanoate ((*R,R*)-13)**

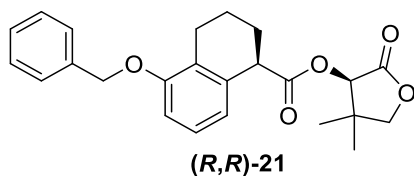
Et<sub>3</sub>N (1.53 mL, 10.9 mmol) was added to the solution of **14** (1.00 g, 5.47 mmol) in toluene (5.0 mL) and stirred at −10 °C for 1 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.930 g, 7.15 mmol) in toluene (12 mL) over 15 min. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (**(*R,R*)-13**) as a colorless oil (1.33 g, 87.9% yield, 97:3 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.96 of peak (s, 1H) in 5.33 ppm and 0.04 of peak (s, 1H) in 5.36 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.38-7.23 (m, 5H), 5.33 (s, 1H), 4.02 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.2 Hz, 1H), 3.98 (d, <sup>2</sup>*J*<sub>HH</sub> = 9.2 Hz, 1H), 3.63 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.8 Hz, 1H), 2.25-2.13 (m, 1H), 1.97-1.85 (m, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.97 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.4 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 172.8, 172.0, 138.0, 128.6, 128.1, 127.4, 76.1, 75.0, 53.4, 40.2, 26.4, 23.0, 19.8, 12.2. Anal. Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub>: C, 69.54; H, 7.30. Found : C, 69.18; H, 7.31. [α]<sub>D</sub><sup>20</sup> −0.4 (c 1.04, MeOH).

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(1*R*)-5-(benzyloxy)-1,2,3,4-tetrahydronaphthalene-1-carboxylate ((*R,R*)-21)**

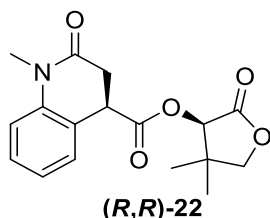
To a solution of the corresponding carboxylic acid (0.500 g, 1.78 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (2.5 mL) was added SOCl<sub>2</sub> (0.17 mL, 2.4 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in toluene (5.0 mL). Et<sub>3</sub>N (0.49 mL, 3.5 mmol) was added to it, and the mixture was stirred at -10 °C for 1 h. To the yellow solution was added dropwise a solution of (*R*)-pantolactone (0.30 g, 2.3 mmol) in toluene (5.0 mL) over 10 minutes. After stirring for 2 h, citric acid (1.0 g) and H<sub>2</sub>O (4.0 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was extracted with toluene, washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/9 → 2/3) to give the corresponding ester (*R,R*)-**21** as a white solid (0.570 g, 81.5% yield, 96:4 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.96 of peak (s, 1H) in 5.41 ppm and 0.04 of peak (s, 1H) in 5.39 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.47-7.42 (m, 2H), 7.42-7.36 (m, 2H), 7.34-7.28 (m, 1H), 7.12 (t, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 1H), 6.79 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 1H), 6.78 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.4 Hz, 1H), 5.41 (s, 1H), 5.07 (s, 2H), 4.04-3.98 (m, 3H), 2.88-2.80 (m, 1H), 2.79-2.69 (m, 1H), 2.23-2.15 (m, 1H), 2.13-2.04 (m, 1H), 2.01-1.91 (m, 1H), 1.88-1.77 (m, 1H), 1.17 (s, 3H), 0.98 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 173.9, 172.3, 156.4, 137.4, 133.8, 128.5, 127.8, 127.1, 126.6, 126.1, 121.7, 109.6, 76.1, 75.0, 69.7, 44.9, 40.3, 26.6, 23.0, 22.9, 19.9, 19.8. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>O<sub>5</sub>: C, 76.99; H, 6.88; N, 2.90. Found : C, 76.86; H, 6.79; N, 2.83. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +50.6 (c 1.11, MeOH).

**(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(4*R*)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylate ((*R,R*)-22)**

To a solution of the corresponding carboxylic acid (0.200 g, 0.975 mmol) and Et<sub>3</sub>N (0.01 mL, 0.08 mmol) in toluene (1.5 mL) was added SOCl<sub>2</sub> (0.09 mL, 1.2 mmol) at 40 °C. After stirring at 40 °C for 4 h, the reaction mixture was concentrated under vacuum. The residue was dissolved in THF (2.0 mL) at −10 °C. To the mixture were added dropwise a solution of (*R*)-pantolactone (0.16 g, 1.2 mmol) in THF (2.0 mL) and Et<sub>3</sub>N (0.28 mL, 2.0 mmol). After stirring for 2 h, H<sub>2</sub>O (4.0 mL) and toluene (8 mL) were added to the reaction solution. After warming to 25 °C, the resulting solution was separated. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/4 → 3/2) to give the corresponding ester (*R,R*)-**22** as a white solid (0.240 g, 77.6% yield, 91:9 dr). The dr was determined by peak area % of <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> (0.91 of peak (s, 1H) in 5.27 ppm and 0.09 of peak (s, 1H) in 5.22 ppm).



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.40-7.31 (m, 2H), 7.13-7.07 (m, 1H), 7.05-7.01 (m, 1H), 5.33 (s, 1H), 5.33 (s, 1H), 4.06-4.02 (m, 1H), 4.05 (d, <sup>2</sup>*J*<sub>HH</sub> = 8.8 Hz, 1H), 4.01 (d, <sup>2</sup>*J*<sub>HH</sub> = 8.8 Hz, 1H), 3.37 (s, 3H), 3.11 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.0 Hz, <sup>4</sup>*J*<sub>HH</sub> = 5.0 Hz, 1H), 2.87 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.0 Hz, <sup>4</sup>*J*<sub>HH</sub> = 6.2 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H).  
<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 171.6, 170.6, 167.7, 140.2, 129.1, 128.6, 123.3, 122.1, 115.2, 76.2, 75.8, 41.9, 40.2, 33.9, 29.5, 22.9, 19.8. Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>: C, 64.34; H, 6.03; N, 4.41. Found : C, 64.34; H, 6.01; N, 4.32. [ $\alpha$ ]<sub>D</sub><sup>20</sup> +15.7 (c 0.45, MeOH).

**[Figure 2-18]**

Lithium hydroxide monohydrate (0.10 g, 2.4 mmol) was added to a solution of 35% *aq.* H<sub>2</sub>O<sub>2</sub> (0.27 g, 3.1 mmol) and purified water (1.4 mL) at 0 °C. The resulting lithium peroxide solution was added dropwise to the solution of residue **(*R,R*)-15** (49:1 dr; 0.500 g, 0.926 mmol) in MeOH (2.5 mL) at −10 °C. After stirring at −10 °C for 1 h, a solution of Na<sub>2</sub>SO<sub>3</sub> (1.00 g) in water (10 mL) was added to a resulting solution. After warming to 20 °C, the resulting solution was washed with toluene (5.0 mL) four times. (The toluene layers were collected and concentrated under vacuum to recover *N*-benzyl-(*R*)-pantolactam as a colorless crystal (0.120 g, 58.9% yield). The aqueous layer was acidified by 35% *aq.* HCl (2.0 mL), was extracted with EtOAc (5.0 mL) three times, and collected organic layers were washed with 10% *aq.* NaCl (5.0 mL), dried over MgSO<sub>4</sub>, filtered. The filtrate was concentrated under vacuum to give **(*R*)-2** as a colorless crystal (0.297 g; 94.8% yield, 98:2 er).

The er was determined by HPLC system. Set up the HPLC system as follows: Wavelength: 230 nm, Column: Chiralcel® OJ-RH, 4.6 mm × 150 mm, 5 μm particle size, Column heater temperature: 30 °C, Mobile phase: H<sub>2</sub>O/CH<sub>3</sub>CN/H<sub>3</sub>PO<sub>4</sub> (800:200:0.8), Flow rate: 0.5 mL/minute, Injection volume: 10 μL, Integration time: For 50 minutes after injection.



**[Figure 3-2]**

To a solution of **6** (0.99 g, 3.96 mmol) and Et<sub>3</sub>SiH (1.38 g, 11.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added BF<sub>3</sub>·OEt<sub>2</sub> (1.69 g, 11.9 mmol) at 0 °C. After stirring at 25 °C for 4 h, the reaction mixture was washed with 10% *aq.* NaHCO<sub>3</sub> (15 mL) and H<sub>2</sub>O (15 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane (1/4 → 1/1) to give **25** as an oil (0.511 g, 54.4% yield) and **29** as a white solid (0.264 g, 27.0% yield).

**[Figure 3-3]**

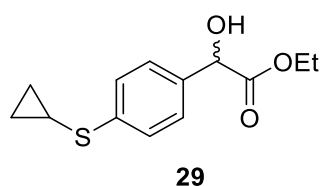
A 1.0 M solution of TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (12 mL, 12 mmol) was added to a solution of **29** (1.00 g, 3.96 mmol) and Et<sub>3</sub>SiH (1.9 mL, 12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> over 5 min at 25 °C. After stirring for 6 h, the reaction mixture was quenched with 10% *aq.* K<sub>2</sub>CO<sub>3</sub> (20 mL), and the mixture was separated. The organic layer was extracted with EtOAc, washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (10 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel with EtOAc/*n*-hexane to give **25** as an oil (0.87 g, 92.7% yield).

**[Figure 3-4]**

A reactor was charged with PhCl (9.6 L) and AlCl<sub>3</sub> (1.60 kg) and cooled to -12 °C. The temperature was maintained between -12 °C and 0 °C, and ethyl chloroglyoxylate **23** (1.64 kg) was added to the mixture dropwise over a period of 23 min. After the addition, the mixture was stirred for 40 min. A solution of cyclopropylphenylsulfide **5** (1.20 kg) in PhCl (2.4 L) was added to it dropwise over a period of 42 min at -4--3 °C. After addition, the mixture was warmed to 10-20 °C and stirred for 157 min. The resulting mixture was transferred to a second reactor that contained the purified water (14.4 L) over a period of 38 min at 14-25 °C. After quenching the reaction mixture, the aqueous layer was separated and extracted with EtOAc (6.0 L), while the first organic layer was concentrated under vacuum at 60 °C until no further distillate could be collected, and dissolved in EtOAc (8.4 L). The organic layers were collected, washed with 24.6% *aq.* NaCl (7.03 kg), 5.1% *aq.* NaHCO<sub>3</sub> (6.15 kg), and 24.6% *aq.* NaCl (7.03 kg) and concentrated under vacuum at 55 °C until no further distillate could be collected. The residue was dissolved in THF (3.0 L) and concentrated under vacuum at 55 °C until no further distillate could be collected. The residue **6** was dissolved in THF (6.0 L) and a suspension of NaBH(OAc)<sub>3</sub> in THF, which was prepared in another reactor with NaBH<sub>4</sub> (0.60 kg) and AcOH (3.84 kg) in THF (6.0 L), was added to it dropwise over a period of 23 min at 20-30 °C. The mixture was heated to 45-50 °C and stirred for 144 min. After cooling below 25 °C, the resulting mixture was washed with a 15% *aq.* NaCl (6.0 kg) and concentrated under vacuum at 55 °C until no further distillate could be collected. The residue was dissolved in EtOAc (12.0 L), washed with a mixture of NaCl (0.30 kg) and NaHCO<sub>3</sub> (0.60 kg) in purified water (5.1 kg) twice and a 15% *aq.* NaCl (6.0 kg), and concentrated under vacuum at 60 °C until no further distillate could be collected. The residue was dissolved in toluene (2.4 L) and concentrated under vacuum at 60 °C until no further distillate could be collected. The residue was diluted in toluene (3.6 L) and heated to 50-60 °C. After dissolution, *n*-heptane (6.0 L) was added to the solution and the resulting solution was cooled to 30 °C slowly over a period of 30 min. After crystallization, the resulting slurry was aged for 60 min at 29-32 °C, and cooled to 5-15 °C slowly over a period of 66 min.

*n*-Heptane (6.0 L) was added to the slurry dropwise over a period of 63 min. After aging for 15 h at 5–15 °C, the resulting slurry was filtered by centrifuge. The filter cake was washed with a cold mixture of toluene (0.60 L) and *n*-heptane (1.8 L). The cake was dried under vacuum at 50 °C to give **29** as a pale yellow crystal (1.71 kg; 84.9% yield).

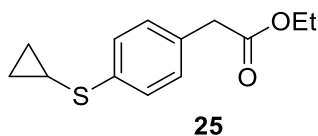
**Ethyl [4-(cyclopropylthio)phenyl](hydroxy)acetate (**29**)** (Cas No.1196118-13-4)



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.36 (d, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, 2H), 7.33 (d, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, 2H), 5.11 (d, <sup>3</sup>J<sub>HH</sub> = 4.6 Hz, 1H), 4.32–4.13 (m, 2H), 3.43 (t, <sup>3</sup>J<sub>HH</sub> = 5.1 Hz, 1H), 2.21–2.14 (m, 1H), 1.24 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3H), 1.11–1.04 (m, 2H), 0.72–0.66 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 172.4, 137.9, 136.4, 127.1, 125.8, 72.0, 60.3, 13.9, 11.3, 8.2, 8.1. Anal. Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>S: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.87; H, 6.29; S, 12.53.

To a suspension of **29** (50.00 g, 0.198 mol) and NaI (95.0 g, 0.634 mol) in CH<sub>3</sub>CN (150 mL) was added dropwise (CH<sub>3</sub>)<sub>3</sub>SiCl (86.1 g, 0.793 mol) at 35 °C. After stirring at 35 °C for 8 h, the reaction mixture was quenched with 20% *aq.* NaHSO<sub>3</sub> (600 mL) at 10 °C. The resulting solution was extracted with EtOAc (200 mL x 2) twice. The organic layers were collected, washed with 10% *aq.* NaCl (250 mL), 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (250 mL), and 10% *aq.* NaCl (250 mL), and dried under vacuum to give the compound **25** as a pale yellow oil (47.40 g).

**Ethyl [4-(cyclopropylthio)phenyl]acetate (**25**)** (Cas No.1058167-39-7)

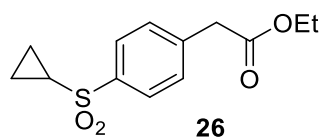


$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.32 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 2H), 7.20 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 4.15 (quartet,  $^3J_{\text{HH}} = 7.1$  Hz, 2H), 3.57 (s, 2H), 2.20-2.14 (m, 1H), 1.25 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 3H), 1.08-1.03 (m, 2H), 0.71-0.66 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  171.6, 137.5, 130.9, 129.6, 126.7, 77.4, 77.1, 76.7, 60.9, 40.9, 14.2, 12.1, 8.5. Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$ : C, 66.07; H, 6.82; S, 13.57. Found : C, 65.63; H, 6.78; S, 13.50.

**[Figure 3-5]**

The residue **25** (47.40 g) was dissolved in acetone (100 mL) and THF (250 mL). To a resulting solution was added a solution of oxone<sup>®</sup> (182.7 g, 0.297 mol) in  $\text{H}_2\text{O}$  (600 mL) dropwise over 1.5 h at 20 °C. After stirring at 30 °C for 2 h, the resulting suspension was diluted with EtOAc (400 mL) and filtered, and washed with EtOAc (100 mL). The filtrate was quenched with 10% *aq.*  $\text{Na}_2\text{S}_2\text{O}_3$  (200 mL) at 25 °C. The resulting solution was separated and the aqueous layer was extracted with EtOAc (200 mL). The organic layers were collected, washed with 10% *aq.*  $\text{Na}_2\text{CO}_3$  (200 mL) and 10% *aq.*  $\text{NaCl}$  (200 mL), and concentrated under vacuum. The residue was dissolved in EtOAc (125 mL) at 60 °C. The solution was cooled down to 10 °C slowly for crystallization. After crystallization, *n*-heptane was added dropwise at 10 °C, the resulting slurry was stirred at 10 °C for 1 h, filtered, washed with the mixture of EtOAc (35 mL) and *n*-heptane (70 mL), and dried under vacuum to give the compound **26** as a colorless crystal (46.23 g; 86.9% yield from **29**).

**Ethyl [4-(cyclopropylsulfonyl)phenyl]acetate (**26**)** (Cas No. 1058167-40-0)



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.86 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.48 (d,  $^3J_{\text{HH}} = 8.7$  Hz, 2H), 4.18 (quartet,  $^3J_{\text{HH}} = 7.2$  Hz, 2H), 3.71 (s, 2H), 2.49–2.42 (m, 1H), 1.38–1.33 (m, 2H), 1.27 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 3H), 1.06–1.00 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  170.4, 140.4, 139.1, 130.4, 127.2, 60.5, 39.8, 32.0, 14.0, 5.3. Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_4\text{S}$ : C, 58.19; H, 6.01; S, 11.95. Found: C, 58.11; H, 5.92; S, 11.89.

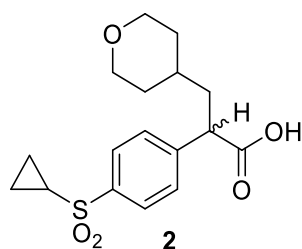
**[Figure 3-6]**

To a solution of tetrahydro-2*H*-pyran-4-ylmethanol **24** (35.00 g, 0.301 mol) and  $\text{Et}_3\text{N}$  (35.1 g, 0.347 mol) in toluene (245 mL) was added a solution of methanesulfonyl chloride (38.0 g, 0.332 mol) in toluene (105 mL) at 5 °C dropwise over 1 h. After stirring at 25 °C for 1.5 h, the reaction mixture was quenched with  $\text{H}_2\text{O}$  (175 mL). The resulting solution was separated and the aqueous layer was extracted with toluene (105 mL). The organic layers were collected and concentrated under vacuum. The residue **33** was dissolved in acetone (280 mL).  $\text{NaI}$  (112.9 g, 0.753 mol) was added to the solution, and the mixture was warmed to 60 °C. After stirring for 4 h, the suspension was dissolved in  $\text{H}_2\text{O}$  (280 mL) and concentrated under vacuum. The residue was extracted with  $\text{EtOAc}$  (280 mL), washed with 20% *aq.*  $\text{Na}_2\text{S}_2\text{O}_3$  (140 mL), dried over  $\text{MgSO}_4$  (3.5 g), filtered, and dried under vacuum to give the compound **27** as a pale yellow oil (59.73 g; 87.7% yield).

**[Figure 3-7]**

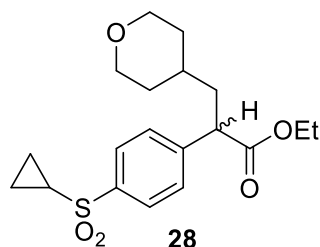
To a solution of **26** (40.00 g, 0.149 mol) in THF (200 mL) was added a 20.5% solution of LiHMDS in THF (133.9 g, 0.164 mol) at  $-5\text{ }^{\circ}\text{C}$  dropwise over 30 min. After stirring at  $-5\text{ }^{\circ}\text{C}$  for 1 h, a solution of **27** (43.81 g, 0.194 mol) and DMPU (28.7 g, 0.224 mol) in THF (80 mL) was added dropwise to the solution over 15 min at  $-5\text{ }^{\circ}\text{C}$ . After stirring at  $20\text{ }^{\circ}\text{C}$  for 3 h, 2 mol/L *aq.* NaOH (140 mL) was added, and the reaction mixture was warmed to  $50\text{ }^{\circ}\text{C}$ . After stirring at  $50\text{ }^{\circ}\text{C}$  for 3 h, the resulting solution was separated, and the organic layer was extracted with 10% *aq.* NaCl (200 mL). The aqueous layers were collected, washed with toluene (200 mL), and acidified by 35% *aq.* HCl (40 mL). The aqueous layer was extracted with EtOAc (200 mL) twice, and organic layers were washed with 10% *aq.* NaHSO<sub>3</sub> (200 mL), dried over MgSO<sub>4</sub> (40.0 g), filtered on activated coal (2.0 g), and washed with EtOAc (80 mL). After the filtrate was concentrated under vacuum, the residue was dissolved in *i*-BuOAc (160 mL) and the solution was concentrated under vacuum again. The residue was dissolved in *i*-BuOAc (160 mL) at  $90\text{ }^{\circ}\text{C}$ . The solution was cooled down slowly to  $40\text{ }^{\circ}\text{C}$  for crystallization. After crystallization, the slurry was stirred at  $75\text{ }^{\circ}\text{C}$  for 1 h, and cooled down to  $10\text{ }^{\circ}\text{C}$ . After cooling, *n*-heptane was added to the slurry, which was stirred at  $10\text{ }^{\circ}\text{C}$  for 3 h. A crystal was filtered, washed with *i*-BuOAc/*n*-heptane (40 mL/40 mL), and dried under vacuum to give the compound **2** as a colorless crystal (40.02 g; 79.3% yield).

**2-[4-(Cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2H-pyran-4-yl)propanoic acid (2)** (Cas No. 745052-93-1)



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.87 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.51 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 3.96–3.90 (m, 2H), 3.80 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H), 3.30 (tdd,  $^3J_{\text{HH}} = 11.8$  Hz, 5.1 Hz, 2.0 Hz, 2H), 2.46 (tt,  $^3J_{\text{HH}} = 7.9$  Hz, 4.9 Hz, 1H), 2.12–2.04 (m, 1H), 1.81–1.72 (m, 1H), 1.64–1.55 (m, 2H), 1.46–1.25 (m, 5H), 1.08–1.01 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  174.1, 145.5, 139.1, 128.9, 127.4, 66.8, 47.5, 39.7, 32.5, 32.3, 32.1, 31.9, 5.3. Anal. Calcd for  $\text{C}_{17}\text{H}_{22}\text{O}_5\text{S}$ : C, 60.33; H, 6.55; S, 9.47. Found: C, 60.26; H, 6.52; S, 9.45.

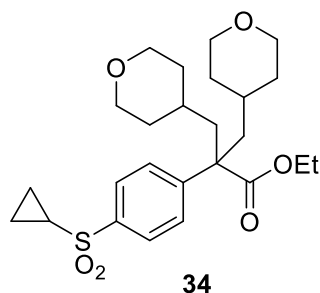
**Ethyl 2-[4-(cyclopropanesulfonyl)phenyl]-3-(oxan-4-yl)propanoate (28)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.86 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.50 (d,  $^3J_{\text{HH}} = 8.0$  Hz, 2H), 4.22–4.06 (m, 2H), 3.97–3.90 (m, 2H), 3.77 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H), 3.36–3.26 (m, 2H), 2.51–2.43 (m, 1H), 2.12–2.03 (m, 1H), 1.77–1.69 (m, 1H), 1.64–1.54 (m, 3H), 1.45–1.25 (m, 5H), 1.23 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 3H), 1.08–1.01 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  172.8, 144.8, 139.5, 128.7, 127.8, 67.6, 67.5, 61.1, 48.3, 40.3, 32.7, 32.7, 32.6, 32.5, 14.0, 5.8. Anal. Calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_5\text{S}$ : C, 62.27; H, 7.15; S, 8.75. Found: C, 62.10; H, 7.13; S, 8.84.

**Ethyl 2-[4-(cyclopropanesulfonyl)phenyl]-3-(oxan-4-yl)-2-[(oxan-4-yl)methyl]propanoate (34)**

**(Cas No. 1567845-22-0)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.85 (d,  $^3J_{\text{HH}} = 8.8$  Hz, 2H), 7.53 (d,  $^3J_{\text{HH}} = 8.8$  Hz, 2H), 4.16 (d,  $^3J_{\text{HH}} = 7.2$  Hz, 1H), 4.12 (d,  $^3J_{\text{HH}} = 7.2$  Hz, 1H), 3.86–3.78 (m, 4H), 3.30–3.18 (m, 4H), 2.47 (tt,  $^3J_{\text{HH}} = 8.0$  Hz, 4.8 Hz, 1H), 2.11 (dd,  $^2J_{\text{HH}} = 14.4$  Hz,  $^3J_{\text{HH}} = 5.6$  Hz, 2H), 2.02 (dd,  $^2J_{\text{HH}} = 14.4$  Hz,  $^3J_{\text{HH}} = 5.6$  Hz, 2H), 1.46–1.32 (m, 4H), 1.32–1.17 (m, 11H), 1.08–1.00 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  175.0, 148.8, 138.9, 127.5, 127.3, 67.7, 61.0, 52.9, 43.4, 34.3, 33.9, 32.8, 31.5, 13.8, 5.8. Anal. Calcd for  $\text{C}_{25}\text{H}_{36}\text{O}_6\text{S}$ : C, 64.63; H, 7.81; S, 6.90. Found: C, 64.62; H, 7.80; S, 6.78.



**[Figure 3-8]**

A reactor was charged with PhCl (241.05 kg) and AlCl<sub>3</sub> (36.20 kg) and cooled to -15-0 °C. The temperature was maintained between -15 °C and 0 °C, and ethyl chloro oxalate (37.10 kg) was added to the mixture dropwise over a period of 1.5 h. After the addition, the mixture was stirred for 1 h. A solution of cyclopropylphenylsulfide **5** (27.20 kg) in PhCl (60.35 kg) was added to it dropwise over a period of 2.5 h at -15-0 °C. After addition, the mixture was warmed to 10-20 °C and stirred for 2 h. The resulting mixture was transferred to a second reactor that contained the purified water (326 kg) over a period of 2.5 h at 5-30 °C. The first reactor and the line were washed with PhCl (30.20 kg). After quenching the reaction mixture, the aqueous layer was separated and extracted with EtOAc (122.90 kg), while the first organic layer was concentrated under vacuum at 50-60 °C until no further distillate could be collected, and dissolved in EtOAc (172.05 kg). The organic layers were collected, washed with 24.6% *aq.* NaCl (159.20 kg), 5.1% *aq.* NaHCO<sub>3</sub> (139.10 kg), and 24.6% *aq.* NaCl (159.20 kg) and concentrated under vacuum at 35-45 °C until no further distillate could be collected. The residue was dissolved in THF (72.45 kg) and concentrated under vacuum at 35-45 °C until no further distillate could be collected. The residue **6** was dissolved in THF (120.90 kg) and a suspension of NaBH(OAc)<sub>3</sub> in THF, which was prepared in another reactor with NaBH<sub>4</sub> (13.70 kg) and AcOH (87.00 kg) in THF (133.05 kg), was added to it dropwise over a period of 1.5 h at 25-35 °C. Another reactor and the line were washed with THF (18.15 kg). The mixture was heated to 45-50 °C and stirred for 2 h. After cooling below 25 °C, the resulting mixture was washed with a 15% *aq.* NaCl (136.40 kg) and concentrated under vacuum at 35-45 °C until no further distillate could be collected. The residue was dissolved in EtOAc (245.30 kg), washed with a mixture of NaCl (6.80 kg) and NaHCO<sub>3</sub> (13.60 kg) in purified water (116 kg) twice and a 15% *aq.* NaCl (136.40 kg), and concentrated under vacuum at 45-55 °C until no further distillate could be collected. The residue was dissolved in toluene (47.10 kg) and concentrated under vacuum at 45-55 °C until no further distillate could be collected. The residue was diluted in toluene (71.50 kg) and heated to 50-60 °C. After dissolution, *n*-heptane (93.05 kg) was added to the solution and the resulting solution was cooled to 25-35 °C slowly over a period of 2.0 h. After crystallization, the resulting

slurry was aged for 1.0 h at 25–35 °C, and cooled to 5–15 °C slowly over a period of 2 h. *n*-Heptane (93.05 kg) was added to the slurry dropwise over a period of 1 h. After aging for 5 h at 5–15 °C, the resulting slurry was filtered by centrifuge. The filter cake was washed with a cold mixture of toluene (12.00 kg) and *n*-heptane (28.00 kg). The cake was dried using conical dryer under vacuum at 45–55 °C for 13.5 h to give **29** as a pale yellow crystal (34.15 kg; 75% yield; 97.20% HPLC area%).

A reactor was charged with CH<sub>3</sub>CN (79.85 kg), **29** (33.95 kg) and NaI (64.50 kg), and it was warmed to 30–35 °C. Me<sub>3</sub>SiCl (58.40 kg) was added to the mixture dropwise over a period of 0.5 h. After the addition, the mixture was stirred for 11 h. The resulting mixture was quenched with 20% *aq.* NaHSO<sub>3</sub> (81.30 kg). The resulting solution was extracted with EtOAc (122.00 kg, 122.10 kg) twice. The organic layers were collected, washed with a 10% *aq.* NaCl (169.00 kg), 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (169.00 kg), 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (169.00 kg), and 10% *aq.* NaCl (169.00 kg), and concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue **25** was dissolved in acetone (53.75 kg) and THF (151.10 kg), and a 23.4% *aq.* oxone<sup>®</sup> was added to it dropwise over a period of 3.5 h at 15–25 °C. After stirring for 2 h, EtOAc (245.00 kg) was added to the resulting mixture. The resulting suspension was filtered by centrifuge, and the filter cake was washed with EtOAc (61.80 kg). The filtrate was transferred to a reactor, and 9.5% *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added to it over a period of 45 min at 15–30 °C, and the resulting mixture was stirred for 40 min. After settling for 35 min, the aqueous layer was separated, and extracted with EtOAc (122.10 kg). The organic layers were collected, washed with a 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (135.50 kg) and 10% *aq.* NaCl (135.50 kg), and concentrated under vacuum at 35–45 °C until no further distillate could be collected. The residue was dissolved in toluene (47.10 kg), and concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue was diluted in EtOAc (76.55 kg), and heated to 50–70 °C. After dissolution, the resulting solution was cooled to 40–45 °C slowly over a period of 1 h. After crystallization, the resulting slurry was aged for 1.5 h at 40–50 °C, cooled to 5–15 °C slowly over a period of 3.5 h, and stirred for 3 h. *n*-Heptane (116.05 kg) was added to the slurry dropwise over a period of 1 h. After aging for 1 h at 5–15 °C, the resulting slurry was filtered by centrifuge, and the

filter cake was washed with a cold mixture of EtOAc (21.60 kg) and *n*-heptane (32.55 kg). The cake was dried using conical dryer under vacuum at 45–55 °C for 6.5 h to give **26** as a pale-yellow crystal (28.90 kg; 80% yield; 99.89% HPLC area %).

A reactor was charged with tetrahydro-2*H*-pyran-4-ylmethanol **24** (22.75 kg), toluene (137.00 kg) and Et<sub>3</sub>N (22.70 kg), and it was cooled to 0–10 °C. A solution of methanesulfonyl chloride (24.60 kg) in toluene (59.00 kg) was added to the mixture dropwise over a period of 0.5 h. After the addition, the mixture was warmed to 20–30 °C. After stirring for 1.5 h, purified water (114 kg) was added to the resulting mixture. The aqueous layer was separated, and extracted with toluene (58.80 kg). The organic layers were collected, and concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue **33** was dissolved in acetone (53.75 kg), NaI (73.20 kg) was added to it portionwise over a period of 45 min, and warmed to 55–65 °C. After stirring for 5 h, purified water (182 kg) was added to the resulting mixture. The resulting solution was concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue was dissolved in EtOAc (163.80 kg), washed with 17.9% *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (101.25 kg), dried over MgSO<sub>4</sub> (2.30 kg), and filtered by centrifuge. The filter cake was washed with EtOAc (27.30 kg). The filtrate was concentrated under vacuum at 25–35 °C until no further distillate could be collected. The residue **27** was taken directly into the next step without further purification (93% assay yield).

A reactor was charged with **26** (28.70 kg) and THF (128.05 kg) and cooled to –10–0 °C. The temperature was maintained between –10 °C and 0 °C, and a 20.5 % solution of LiHMDS in THF (93.30 kg) was added to the mixture dropwise over a period of 1.5 h. After the addition, the mixture was stirred for 1 h. A solution of **27** (33.90 kg) in THF (51.10 kg) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 20.55 kg) was added to the mixture dropwise over a period of 1 h at –10–0 °C. After addition, the mixture was warmed to 15–25 °C and stirred for 2 h. An 8% aqueous solution of NaOH (100.15 kg) was added to the resulting mixture containing **28**, and the resulting solution was warmed to 45–55 °C. After stirring for 4 h, the organic layer was separated and extracted with 10% *aq.* NaCl (143.40 kg). The

aqueous layers were collected, acidified by 35% *aq.* HCl (34.20 kg), and extracted with EtOAc (131.25 kg, 130.05 kg) twice. The organic layers were collected, washed with a 10% *aq.* NaHSO<sub>3</sub> (143.40 kg), dried over MgSO<sub>4</sub> (2.85 kg), and filtered on activated charcoal (1.45 kg). The filter cake was washed with EtOAc (80.80 kg). The filtrate was transferred to a reactor and concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue was dissolved in *i*-BuOAc (99.40 kg) and concentrated under vacuum at 45–55 °C until no further distillate could be collected. The residue was diluted in *i*-BuOAc (124.30 kg) and heated to 90–110 °C. After dissolution, the resulting solution was cooled to 35–45 °C slowly over a period of 1 h. After crystallization, the slurry was aged for 1 h at 35–45 °C, warmed to 73–83 °C, and cooled to 5–15 °C slowly over a period of 4.5 h. *n*-Heptane (98.25 kg) was added to the slurry dropwise over a period of 3.5 h. (After the addition, the slurry was emulsified immediately.) The emulsion was concentrated under vacuum at 45–55 °C until no further distillate could be collected. Toluene (124.10 kg) was added to the residue in the reactor, and the mixture was warmed to 85–95 °C. After dissolution, the resulting solution was cooled to 45 °C over a period of 4 h and stirred for 0.5 h at 40–45 °C. After cooling to 15 °C, the resulting slurry was aged at 10–15 °C for 2 h, filtered by centrifuge. The filter cake was washed with cold toluene (49.70 kg). The cake was dried using a conical dryer under vacuum at 45–55 °C for 4 h to give crude **2** as a pale yellow crystal containing toluene with a weight of 32.25 kg (65% assay yield, 96.97% HPLC area %).

A reactor was charged with *i*-BuOAc (49.85 kg) and the crude **2** (32.25 kg) and heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4.5 h. After the resulting slurry was aged at 40–45 °C for 0.5 h, *n*-heptane (39.30 kg) was added to it dropwise over 1 h, and the resulting slurry was cooled to 15 °C slowly over a period of 2 h. After stirring at 10–15 °C for 1 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.90 kg) and *n*-heptane (19.60 kg). The wet cake (28.70 kg) was transferred to a reactor that contained *i*-BuOAc (50.05 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 3 h. The resulting slurry was aged at 40–45 °C for 0.5 h, *n*-heptane (39.30

kg) was added to it dropwise over 1 h, and the resulting slurry was then cooled to 15 °C slowly over a period of 1 h. After stirring at 40–45 °C for 1 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.90 kg) and *n*-heptane (19.60 kg). The wet cake (27.25 kg) was transferred to a reactor that contained *i*-BuOAc (49.80 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4.5 h. After the resulting slurry was aged at 40–45 °C for 0.5 h, *n*-heptane (39.35 kg) was added to it dropwise over 1 h, and the resulting slurry was cooled to 15 °C slowly over a period of 2 h. After stirring at 10–15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.95 kg) and *n*-heptane (19.65 kg). The wet cake (26.50 kg) was transferred to a reactor that contained *i*-BuOAc (49.85 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 3.5 h. The resulting slurry was warmed to 78 °C slowly over a period of 1 h. After stirring at 78 °C for 0.5 h, the slurry was cooled to 15 °C slowly over a period of 5.5 h. After stirring at 10–15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with cold *i*-BuOAc (24.90 kg). The wet cake (23.95 kg) was transferred to a reactor that contained *i*-BuOAc (49.75 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4 h. The resulting slurry was warmed to 73 °C slowly over a period of 0.5 h. After stirring at 73–76 °C for 0.5 h, the slurry was cooled to 15 °C slowly over a period of 5.5 h. After stirring at 10–15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with cold *i*-BuOAc (24.85 kg). The cake was dried using a conical dryer under vacuum at 45–55 °C for 4.5 h to give **2** as a colorless crystal (20.50 kg; 57% yield; 99.94% HPLC area %).

**[Figure 3-9]**

**(Entry 2)**

The residue **25** (47.40 g) was dissolved in acetone (100 mL) and THF (250 mL). To a resulting solution was added a solution of oxone<sup>®</sup> (182.7 g, 0.297 mol) in H<sub>2</sub>O (600 mL) dropwise over 1.5 h at 20 °C. After stirring at 30 °C for 2 h, the resulting suspension was diluted with EtOAc (400 mL), filtered, and washed with EtOAc (100 mL). The filtrate was quenched with 10% *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (200 mL) at 25 °C. The resulting solution was separated, and the aqueous layer was extracted with EtOAc (200 mL). The organic layers were collected, washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (200 mL) and 10% *aq.* NaCl (200 mL), and concentrated under vacuum. The residue was dissolved in EtOAc (125 mL) at 60 °C. The solution was cooled down to 10 °C slowly for crystallization. After crystallization, *n*-heptane was added dropwise at 10 °C, the resulting slurry was stirred at 10 °C for 1 h, filtered, washed with EtOAc/*n*-heptane (35 mL/70 mL), and dried under vacuum to give the compound **26** as a colorless crystal (46.23 g; 86.9% yield from **29**). To a solution of **26** (40.00 g, 0.149 mol) in THF (200 mL) was added a 20.5% solution of LiHMDS in THF (133.9 g, 0.164 mol) at -5 °C dropwise over 30 min. After stirring at -5 °C for 1 h, a solution of **27** (43.81 g, 0.194 mol) and DMPU (28.7 g, 0.224 mol) in THF (80 mL) was added dropwise to the solution over 15 min at -5 °C. After stirring at 20 °C for 3 h, 2 mol/L *aq.* NaOH (140 mL) was added, and the reaction mixture was warmed to 50 °C. After stirring at 50 °C for 3 h, the resulting solution was separated, and the organic layer was extracted with 10% *aq.* NaCl (200 mL). The aqueous layers were collected, washed with toluene (200 mL), and acidified by 35% *aq.* HCl (40 mL). The aqueous layer was extracted with EtOAc (200 mL) twice, and organic layers were washed with 10% *aq.* NaHSO<sub>3</sub> (200 mL), dried over MgSO<sub>4</sub> (40.0 g), filtered on activated coal (2.0 g), and washed with EtOAc (80 mL). After the filtrate was concentrated under vacuum, the residue was dissolved in *i*-BuOAc (160 mL) and the solution was concentrated under vacuum again. The residue was dissolved in *i*-BuOAc (160 mL) at 90 °C. The solution was cooled down slowly to 40 °C for crystallization. After crystallization, the slurry was stirred at 75 °C for 1 h, and cooled down to 10 °C. After cooling, *n*-heptane

was added to the slurry, which was stirred at 10 °C for 3 h. A crystal was filtered, washed with *i*-BuOAc/*n*-heptane (40 mL/40 mL), and dried under vacuum to give the compound **2** as a colorless crystal (40.02 g; 79.3% yield).

### (Entry 3)

The residue **25** (21.41 g) was dissolved in acetone (45 mL) and THF (112 mL). To a resulting solution was added a solution of oxone<sup>®</sup> (82.23 g) in H<sub>2</sub>O (270 mL) dropwise over 40 min at 20 °C. After stirring at 30 °C for 2 h, the resulting suspension was diluted with EtOAc (180 mL), filtered, and washed with EtOAc (45 mL). The filtrate was quenched with 10% *aq.* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (90 mL) at 25 °C for 24 h. The resulting solution was separated, and the aqueous layer was extracted with EtOAc (90 mL). The organic layers were collected, washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (90 mL), 10% *aq.* NaHCO<sub>3</sub> (90 mL), 10% *aq.* NaCl (90 mL), 10% *aq.* NaHCO<sub>3</sub> (90 mL), and 10% *aq.* NaCl (90 mL), and concentrated under vacuum. The residue was dissolved in EtOAc (56 mL) at 60 °C. The solution was cooled down to 10 °C slowly for crystallization. After crystallization, *n*-heptane (113 mL) was added dropwise at 10 °C, the resulting slurry was stirred at 10 °C for 1 h, filtered, washed with EtOAc/*n*-heptane (16 mL/32 mL), and dried under vacuum to give **26** as a colorless crystal (19.74 g; 82.5% yield from **29**). To a solution of **26** (5.00 g, 0.019 mol) in THF (25 mL) was added a 20.5% solution of LiHMDS in THF (20.5 mL) at −5 °C dropwise over 8 min. After stirring at −5 °C for 7 min, a solution of **27** (5.48 g) and DMPU (3.58 g) in THF (10 mL) was added to the solution over 2 min at −5 °C. After stirring at 25 °C for 3 h, 8% *aq.* NaOH (17.4 g) was added, and the reaction mixture was warmed to 50 °C. After stirring at 50 °C for 3 h, the resulting solution was separated, and the organic layer was extracted with 10% *aq.* NaCl (25 mL). The aqueous layers were collected, and acidified by 35% *aq.* HCl (5 mL). The aqueous layer was extracted with EtOAc (25 mL) twice, and organic layers were washed with 10% *aq.* NaHSO<sub>3</sub> (25 mL), dried over MgSO<sub>4</sub> (0.50 g), filtered on activated coal (0.25 g), and washed with EtOAc (10 mL). After the filtrate was concentrated under vacuum, the residue was dissolved in *i*-BuOAc (20 mL) and the

solution was concentrated under vacuum again. The residue was dissolved in *i*-BuOAc (20 mL) at 90 °C. The solution was cooled down slowly to 40 °C for crystallization. After crystallization, the slurry was stirred at 80 °C for 5 min, and cooled down to 10 °C. After cooling, *n*-heptane (25 mL) was added to the slurry, which was stirred at 10 °C for 14 h. A crystal was filtered, washed with *i*-BuOAc/*n*-heptane (5 mL/5 mL), and dried under vacuum to give **2** as a colorless crystal (4.68 g; 74.2% yield).

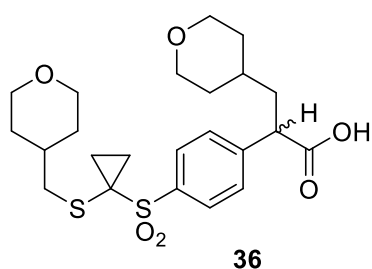
#### (Entry 4)

The residue **25** (21.41 g) was dissolved in acetone (45 mL) and THF (112 mL). To a resulting solution was added a solution of oxone<sup>®</sup> (82.23 g) in H<sub>2</sub>O (270 mL) dropwise over 40 min at 20 °C. After stirring at 30 °C for 2 h, the resulting suspension was diluted with EtOAc (180 mL), filtered, and washed with EtOAc (45 mL). The filtrate was quenched with 10% *aq.* NaHSO<sub>3</sub> (90 mL) at 25 °C for 24 h. The resulting solution was separated, and the aqueous layer was extracted with EtOAc (90 mL). The organic layers were collected, washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (90 mL), 10% *aq.* NaHCO<sub>3</sub> (90 mL), 10% *aq.* NaCl (90 mL), 10% *aq.* NaHCO<sub>3</sub> (90 mL), and 10% *aq.* NaCl (90 mL), and concentrated under vacuum. The residue was dissolved in EtOAc (56 mL) at 60 °C. The solution was cooled down to 10 °C slowly for crystallization. After crystallization, *n*-heptane (113 mL) was added dropwise at 10 °C, the resulting slurry was stirred at 10 °C for 1 h, filtered, washed with EtOAc/*n*-heptane (16 mL/32 mL), and dried under vacuum to give **26** as a colorless crystal (19.63 g; 82.0% yield from **29**). To a solution of **26** (5.00 g, 0.019 mol) in THF (25 mL) was added a 20.5% solution of LiHMDS in THF (20.5 mL) at –5 °C dropwise over 8 min. After stirring at –5 °C for 7 min, a solution of **27** (5.48 g) and DMPU (3.58 g) in THF (10 mL) was added to the solution over 2 min at –5 °C. After stirring at 25 °C for 3 h, 8% *aq.* NaOH (17.4 g) was added, and the reaction mixture was warmed to 50 °C. After stirring at 50 °C for 3 h, the resulting solution was separated, and the organic layer was extracted with 10% *aq.* NaCl (25 mL). The aqueous layers were collected, and acidified by 35% *aq.* HCl (5 mL). The aqueous layer was extracted with EtOAc (25 mL) twice, and organic layers were washed with 10% *aq.* NaHSO<sub>3</sub> (25 mL),



dried over  $\text{MgSO}_4$  (0.50 g), filtered on activated coal (0.25 g), and washed with EtOAc (10 mL). After the filtrate was concentrated under vacuum, the residue was dissolved in *i*-BuOAc (20 mL) and the solution was concentrated under vacuum again. The residue was dissolved in *i*-BuOAc (20 mL) at 90 °C. The solution was cooled down slowly to 40 °C for crystallization. After crystallization, the slurry was stirred at 80 °C for 5 min, and cooled down to 10 °C. After cooling, *n*-heptane (25 mL) was added to the slurry, which was stirred at 10 °C for 14 h. A crystal was filtered, washed with *i*-BuOAc/*n*-heptane (5 mL/5 mL), and dried under vacuum to give the compound **2** as a colorless crystal (4.92 g; 78.0% yield).

**3-(Oxan-4-yl)-2-[4-(1-[(oxan-4-yl)methyl]sulfanyl)cyclopropane-1-sulfonyl]phenyl]propanoic acid (**36**) (Cas No. 1567845-21-9)**



$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.91 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 7.53 (d,  $^3J_{\text{HH}} = 8.4$  Hz, 2H), 5.27 (bs, 1H), 3.98–3.90 (m, 4H), 3.81 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H), 3.39–3.26 (m, 4H), 2.63 (dd,  $^3J_{\text{HH}} = 11.6$  Hz, 6.6 Hz, 1H), 2.58 (dd,  $^3J_{\text{HH}} = 11.6$  Hz, 7.0 Hz, 1H), 2.15–2.06 (m, 1H), 1.98–1.92 (m, 2H), 1.81–1.72 (m, 1H), 1.72–1.56 (m, 5H), 1.50–1.38 (m, 1H), 1.38–1.13 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.7, 144.7, 137.1, 129.9, 128.5, 67.6, 67.6, 67.6, 48.2, 45.1, 40.3, 40.0, 34.4, 32.7, 32.6, 32.5, 32.3, 32.3, 30.9, 17.1, 17.0. Anal. Calcd for  $\text{C}_{23}\text{H}_{32}\text{O}_6\text{S}_2$ : C, 58.95; H, 6.88; S, 13.68. Found: C, 58.95; H, 6.83; S, 13.52.

**[Figure 3-10]**

To a solution of **2** (15.00 g, 44.3 mmol), and Et<sub>3</sub>N (0.19 mL) in toluene (75 mL) was added SOCl<sub>2</sub> (4.20 mL) at 40 °C. After stirring for 4 h, the reaction mixture was concentrated at 50 °C under vacuum. The residue **8** was dissolved in toluene (45 mL), the solution was concentrated at 50 °C under vacuum. The residue **8** was dissolved in toluene (45 mL) and cooled to −10 °C. Et<sub>3</sub>N (12.4 mL) was added to the solution at −10 °C. After stirring at −10 °C for 1 h, the reaction mixture was cooled down to −78 °C, to the yellow solution was added dropwise a solution of (*R*)-pantolactone (6.92 g) in THF (60 mL) over 20 minutes. After stirring at −78 °C for 15 h, the reaction solution was warmed to 0 °C, the resulting mixture was washed with 20% *aq.* citric acid (75 g) and 20% *aq.* NaCl (60 g), and concentrated at 50 °C under vacuum. The residue (***R,R***-**10**) was dissolved in MeOH (45 mL), and the solution was added to the mixture of 30% *aq.* H<sub>2</sub>O<sub>2</sub> (5.79 g) and 4N *aq.* LiOH (13.3 mL) in MeOH (30 mL) at 0-3 °C. After stirring for 1 h, the reaction mixture was quenched with 10% *aq.* Na<sub>2</sub>SO<sub>3</sub> (150 mL). After warming to 20 °C and adding EtOAc (75 mL) and H<sub>2</sub>O (90 mL), the resulting solution was separated. The water layer was washed with toluene (75 mL). After warming to 50 °C and adding EtOAc (150 mL), 35% *aq.* HCl (15 mL) and EtOAc (75 mL x 2) were added to it. The resulting mixture was washed with 20% *aq.* NaCl (60 g) and concentrated at 50 °C under vacuum. The residue (***R***)-**2** was dissolved in *i*-BuOAc (60 mL), the solution was concentrated at 50 °C under vacuum. The residue (***R***)-**2** was dissolved in *i*-BuOAc (45 mL) and at 110 °C. The solution was cooled to 20 °C slowly. After stirring at 20 °C for 14 h, a crystal was filtered, and washed with *i*-BuOAc (15 mL), dried at 50 °C for 2 h under vacuum to give (***R***)-**2** as a colorless crystal (9.82 g, 65.5 % yield from **2**, 99.90:0.10 er).

**[Figure 3-11]**

To a solution of **2** (5.00 g, 14.8 mmol), and Et<sub>3</sub>N (0.06 mL) in toluene (25 mL) was added SOCl<sub>2</sub> (1.40 mL) at 40 °C. After stirring for 4 h, the reaction mixture was concentrated at 50 °C under vacuum. The residue **8** was dissolved in toluene (15 mL), the solution was concentrated at 50 °C under vacuum. The residue **8** was dissolved in toluene (40 mL) and cooled to −10 °C. Et<sub>3</sub>N (4.1 mL) was added to the solution at −10 °C. After stirring at −10 °C for 1 h, the reaction mixture was cooled down to −78 °C, to the yellow solution was added dropwise a solution of (*R*)-pantolactone (2.31 g) in THF (20 mL) over 20 minutes. After stirring at −78 °C for 14 h, the reaction solution was warmed to 0 °C, the resulting mixture was washed with 2N *aq.* HCl (25 mL) and concentrated at 50 °C under vacuum. The residue (***R,R***)-**10** was dissolved in the mixture of 5N *aq.* HCl (50 mL) and AcOH (10 mL). After stirring at 100 °C for 16 h, the reaction mixture was extracted with EtOAc (30 mL) was added to it. After separation, the organic layer was washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (25 mL x 4), the aqueous layers were collected. The aqueous layer was acidified by 35% *aq.* HCl (20 mL), and extracted with EtOAc (25 mL x 3), and collected organic layers were washed with 20% *aq.* NaCl (25 mL). The organic layer was concentrated at 50 °C under vacuum. The residue (***R***)-**2** was dissolved in *i*-BuOAc (20 mL), the solution was concentrated at 50 °C under vacuum. The residue (***R***)-**2** was dissolved in *i*-BuOAc (25 mL) and at 110 °C. The solution was cooled to 20 °C slowly. After stirring at 20 °C for 16 h, a crystal was filtered, and washed with *i*-BuOAc (15 mL), dried at 50 °C for 2 h under vacuum to give (***R***)-**2** as a colorless crystal (2.76 g, 65.5 % yield from **2**, 99.85:0.15 er).

**[Figure 3-12]**

A reactor was charged with toluene (87.85 kg), **2** (20.25 kg) and Et<sub>3</sub>N (181.95 g), and it was warmed to 35–40 °C. SOCl<sub>2</sub> (9.25 kg) was added to the reaction mixture. After stirring at 40–45 °C for 3 h, the reaction mixture was concentrated under vacuum at 45–46 °C until no further distillate could be collected. The residue was dissolved in toluene (35.35 kg) and the solution was concentrated under vacuum at 46 °C until no further distillate could be collected. The residue was dissolved in toluene (141.15 kg) and cooled to –6 °C. Et<sub>3</sub>N (12.14 kg) was added to the solution and stirred at –10–0 °C for 12 h. After cooling to –77–74 °C. A solution of (*R*)-pantolactone (9.40 kg) in THF (73.25 kg) was added dropwise to the yellow solution over a period of 2.5 h, and the resulting mixture was stirred for 2 h. After warming to –5 °C, citric acid monohydrate (22.20 kg) and purified water (40.60 kg) were added to the reaction solution. After warming to 20 °C, the resulting solution was separated. The organic layer was washed with purified water (40.60 kg) and 10% *aq.* NaCl (81.60 kg), and concentrated under vacuum at 48–51 °C until no further distillate could be collected. The residue was dissolved in MeOH (48.25 kg), and concentrated under vacuum at 50–51 °C until no further distillate could be collected, to give the residue **(*R,R*)-10**. Another reactor was charged with 35.4% H<sub>2</sub>O<sub>2</sub> (8.05 kg) and purified water (40.65 kg), and was cooled to 5 °C. A solution of lithium hydroxide monohydrate (3.00 kg, 71.5 mol) in purified water (20.30 kg) was added dropwise. The resulting lithium peroxide solution was transferred to a second reactor containing a solution of **(*R,R*)-10** in MeOH (96.50 kg) dropwise over 1 h at 0–3 °C. After stirring at –1–3 °C for 1.5 h, a solution of Na<sub>2</sub>SO<sub>3</sub> (18.30 kg) in purified water (163.50 kg) was added dropwise to the resulting solution over a period of 1.5 h at 8–9 °C. After warming to 35 °C, lithium hydroxide monohydrate (3.80 kg) was added to the solution. After stirring at 38–40 °C for 2.5 h, the resulting solution was washed with toluene (87.90 kg), and acidified by 35% *aq.* HCl (27.50 kg). The aqueous layer was extracted with EtOAc (91.35 kg, 91.35 kg, 91.25 kg) three times, and the collected organic layers were washed with 10% *aq.* NaCl (81.75 kg), dried over MgSO<sub>4</sub> (4.05 kg), and filtered. After the filtrate was concentrated at 50 °C under vacuum, the residue was dissolved in *i*-BuOAc (70.30

kg), and the solution was concentrated at 50–51 °C under vacuum. The residue was dissolved in *i*-BuOAc (87.95 kg) at 110 °C. The solution was cooled slowly to 85 °C for crystallization. After crystallization, the suspension was stirred at 85–81 °C for 1.5 h, and cooled slowly to 15 °C over a period of 8 h. After stirring at 15–11 °C for 3 h, a crystal was filtered, washed with *i*-BuOAc (35.20 kg), and dried at 46–51 °C for 6 h under vacuum to give (**R**)-**2** as a colorless crystal (16.20 kg; 80.0% yield from **2**, 99.84:0.16 er).

The dr of (**R,R**)-**10** was determined by HPLC. HPLC Conditions : Wavelength: 230 nm, Column: Waters, xBridge™ C18 4.6 mm × 75 mm, 2.5 μm particle size, Column heater temperature: 40 °C, Mobile phase A: H<sub>2</sub>O/CH<sub>3</sub>CN/TFA (950:50:1), B: CH<sub>3</sub>CN/H<sub>2</sub>O/TFA (800:200:1), 0-24 min (B 0-80%), 24-26min (B 80%), 26-36min (B 0%), Flow rate: 1.0 mL/minute, Injection volume: 10 μL, Integration time: For 26 minutes after injection.

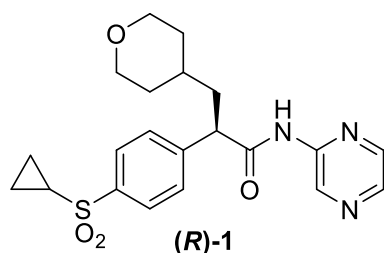
The er was determined by an HPLC system. The setup of the HPLC system was as follows: Wavelength: 230 nm; Column: DAICEL, CHIRALPAK IC, 4.6 mm × 15 cm, 5 μm particle size; Column heater temperature: 25 °C; Mobile phase: Hexane/Ethanol/TFA (700:300:0.5); Flow rate: 0.5 mL/minute; Injection volume: 10 μL; Integration time: 40 min after injection. Sample solution: Weigh accurately 25.02 mg of sample into a 50 mL volumetric flask. Partially fill the flask with ethanol and mix well until dissolved. Dilute up to the mark with ethanol, and manually mix it thoroughly.

A reactor was charged with toluene (69.30 kg), (**R**)-**2** (16.00 kg) and NMP (141 g), and it was warmed to 35–40 °C. SOCl<sub>2</sub> (7.35 kg) was added to the reaction mixture. After stirring at 40–45 °C for 4 h, the reaction mixture was concentrated under vacuum at 45–46 °C until no further distillate could be collected. The residue was dissolved in toluene (27.80 kg) and the solution was concentrated under vacuum at 46 °C until no further distillate could be collected. The residue was dissolved in toluene (57.15 kg). The resulting mixture was transferred to a second reactor that contained 2-aminopyradine (4.95 kg), pyridine (37.40 kg), and THF (71.35 kg) over a period of 1.5 h at 20–30 °C. After stirring at 20 °C for 2 h, 20% *aq.* HCl (87.60 kg) was added to the reaction solution over a period of 1 h at 20–

30 °C. The resulting solution was extracted with EtOAc (143.90 kg), washed with 10% *aq.* Na<sub>2</sub>CO<sub>3</sub> (81.10 kg), washed with 10% *aq.* NaCl (87.95 kg), dried over MgSO<sub>4</sub> (8.05 kg), filtered on activated coal (798.92 g), and the remaining solid was washed with EtOAc (92.35 kg). After the filtrate was concentrated under vacuum, the residue was dissolved in MeOH (63.45 kg) and the solution was concentrated under vacuum again. The residue was dissolved in MeOH (38.10 kg) at 55 °C. The dissolved solution was cooled slowly to 40 °C and seed crystal (8.04 g) was added for crystallization. After crystallization, the suspension was cooled slowly to –10 °C over a period of 5 h. After stirring at –10 °C for 1 h, a crystal was filtered and washed with MeOH (25.25 kg). Wet crystal was dissolved in 2-propanol (125.00 kg) at 80 °C. The solution was cooled slowly to 60 °C and seed crystal (8.05 g) was added for crystallization. After crystallization, the suspension was cooled slowly to –5 °C over a period of 10 h. After stirring at –5 °C for 5 h, a crystal was filtered, washed with 2-propanol (25.05 kg), and dried under vacuum to give the compound (**R**)-**1** as a colorless crystal (11.80 kg; 60.0% yield, 100:<0.05 er). The er was determined by HPLC system. The set up of the HPLC system as follows: Wavelength: 235 nm, Column: DAICEL, CHIRALPAK AD-3, 4.6 mm × 25 cm, 3 µm particle size; Column heater temperature: 40 °C; Mobile phase: Hexane/Ethanol (700:300); Flow rate: 1.0 mL/minute; Injection volume: 10 µL; Integration time: 35 min after injection. Sample solution: Weigh accurately about 20.22 mg of sample into a 20 mL volumetric flask. Partially fill the flask with ethanol and mix well until dissolved. Dilute upto the mark with ethanol, and manually mix it thoroughly.

**(R)-2-[4-(Cyclopropylsulfonyl)phenyl]-N-pyrazin-2-yl-3-(tetrahydro-2H-pyran-4-yl)**

**propanamide ((R)-1)** (CAS No.745051-65-4)



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.53 (d, <sup>5</sup>J<sub>HH</sub> = 1.0 Hz, 1H), 8.36 (d, <sup>3</sup>J<sub>HH</sub> = 2.6 Hz, 1H), 8.21 (dd, <sup>3</sup>J<sub>HH</sub> = 2.6 Hz, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 1H), 7.91 (d, <sup>4</sup>J<sub>HH</sub> = 1.6 Hz, 1H), 7.90 (d, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, 2H), 7.56 (d, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz, 2H), 3.96-3.90 (m, 2H), 3.80 (t, <sup>3</sup>J<sub>HH</sub> = 7.4 Hz, 1H), 3.31 (tdd, <sup>3</sup>J<sub>HH</sub> = 11.8 Hz, 3.1 Hz, 2.4 Hz, 2H), 2.47 (tt, <sup>3</sup>J<sub>HH</sub> = 7.9 Hz, 4.9 Hz, 1H), 2.26-2.18 (m, 1H), 1.86-1.79 (m, 1H), 1.64-1.55 (m, 2H), 1.52-1.29 (m, 5H), 1.08-1.02 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 170.8, 148.0, 144.8, 142.1, 140.5, 139.9, 137.0, 128.8, 128.3, 67.7, 67.7, 50.3, 40.6, 33.0, 32.9, 32.7, 32.7, 6.09, 6.07. Anal. Calcd for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>S: C, 60.70; H, 6.06; N, 10.11; S, 7.72. Found: C, 60.66; H, 5.98; N, 10.10; S, 7.73. [α]<sub>D</sub><sup>20</sup> -51.4 (c 1.08, MeOH)

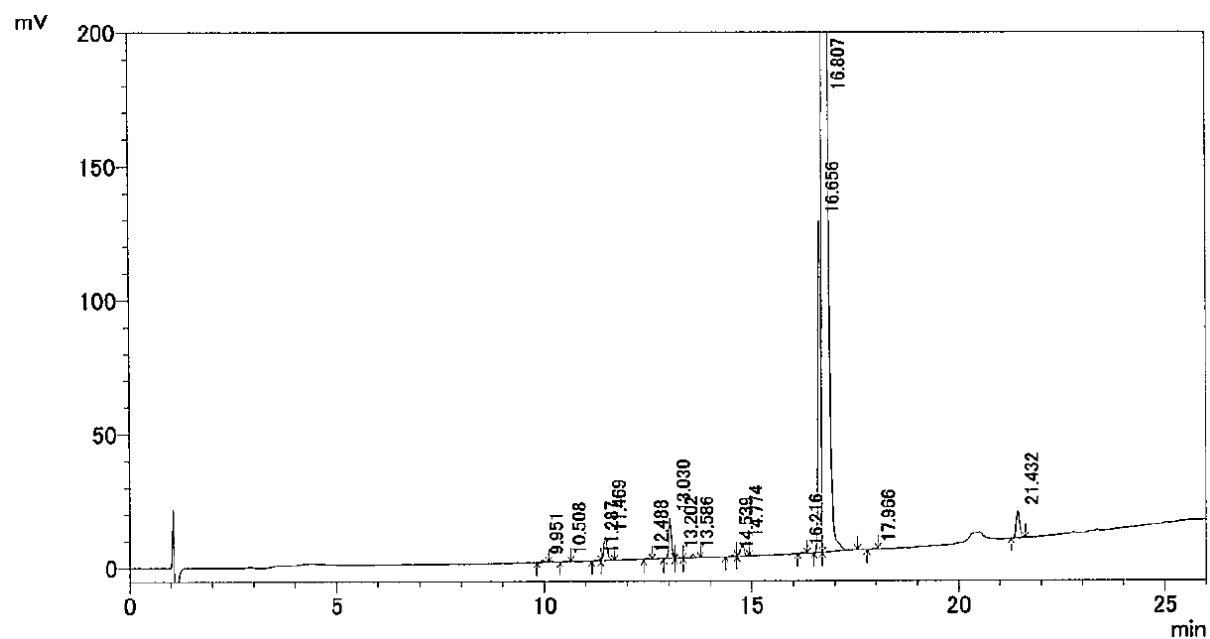




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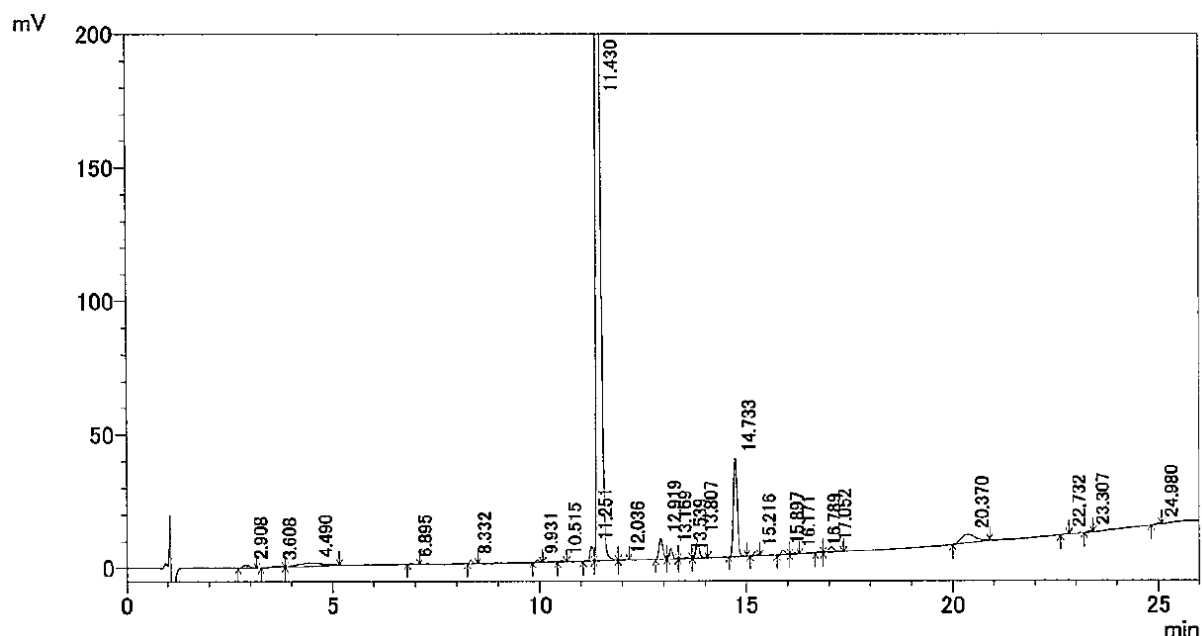
[Figure 2-3]

(R,R)-10



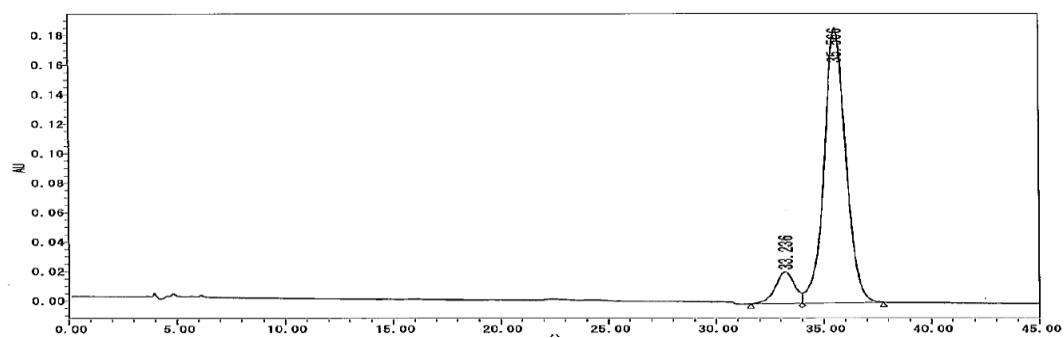
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	9.951	4984	711	0.074	0.070	
2	10.508	2811	379	0.042	0.037	
3	11.287	2696	445	0.040	0.044	
4	11.469	47833	8656	0.710	0.854	V
5	12.488	2196	415	0.033	0.041	V
6	13.030	75260	15160	1.117	1.496	V
7	13.202	9037	1545	0.134	0.152	V
8	13.586	9070	1391	0.135	0.137	V
9	14.539	2757	431	0.041	0.043	
10	14.774	26200	4568	0.389	0.451	V
11	16.216	2853	492	0.042	0.049	V
12	16.656	635775	124221	9.435	12.258	
13	16.807	5859617	844592	86.958	83.345	SV
14	17.966	2705	393	0.040	0.039	
15	21.432	54669	9966	0.811	0.983	
合計		6738464	1013366	100.000	100.000	

(R)-2 before purification

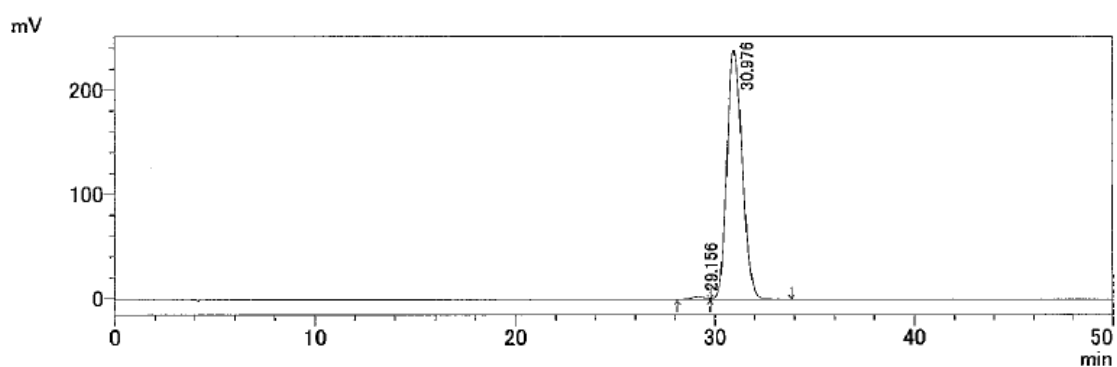


ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.908	14001	1162	0.296	0.144	
2	3.608	11285	495	0.239	0.061	
3	4.490	50699	1068	1.073	0.132	V
4	6.895	2340	458	0.050	0.057	
5	8.332	7524	1320	0.159	0.164	V
6	9.931	4859	852	0.103	0.105	
7	10.515	2005	383	0.042	0.047	V
8	11.251	28867	5663	0.611	0.701	
9	11.430	4143132	729272	87.703	90.319	V
10	12.036	2537	227	0.054	0.028	V
11	12.919	48150	7864	1.019	0.974	V
12	13.169	23382	3942	0.495	0.488	V
13	13.539	3398	597	0.072	0.074	V
14	13.807	40559	7185	0.859	0.890	
15	14.733	217226	36970	4.598	4.579	
16	15.216	7080	1350	0.150	0.167	
17	15.897	10518	1798	0.223	0.223	
18	16.171	2144	333	0.045	0.041	V
19	16.789	2757	395	0.058	0.049	
20	17.052	21431	1992	0.454	0.247	V
21	20.370	72425	2951	1.533	0.366	
22	22.732	2427	401	0.051	0.050	
23	23.307	2816	415	0.060	0.051	V
24	24.980	2498	350	0.053	0.043	
合計		4724059	807443	100.000	100.000	

**(R)-2 before crystallization**



**(R)-2 after crystallization**

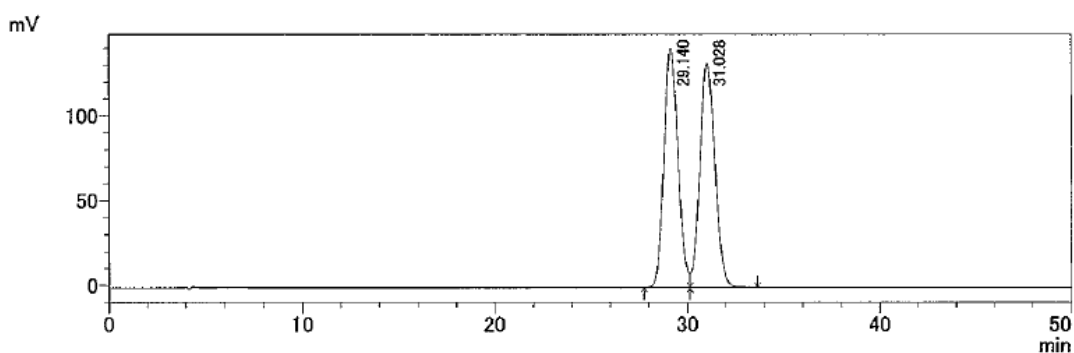


1 Det.A Ch1/230nm

検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	29.156	140451	2942	1.082	1.215	
2	30.976	12842381	239209	98.918	98.785	V
合計		12982832	242152	100.000	100.000	

**参考：ラセミ体**



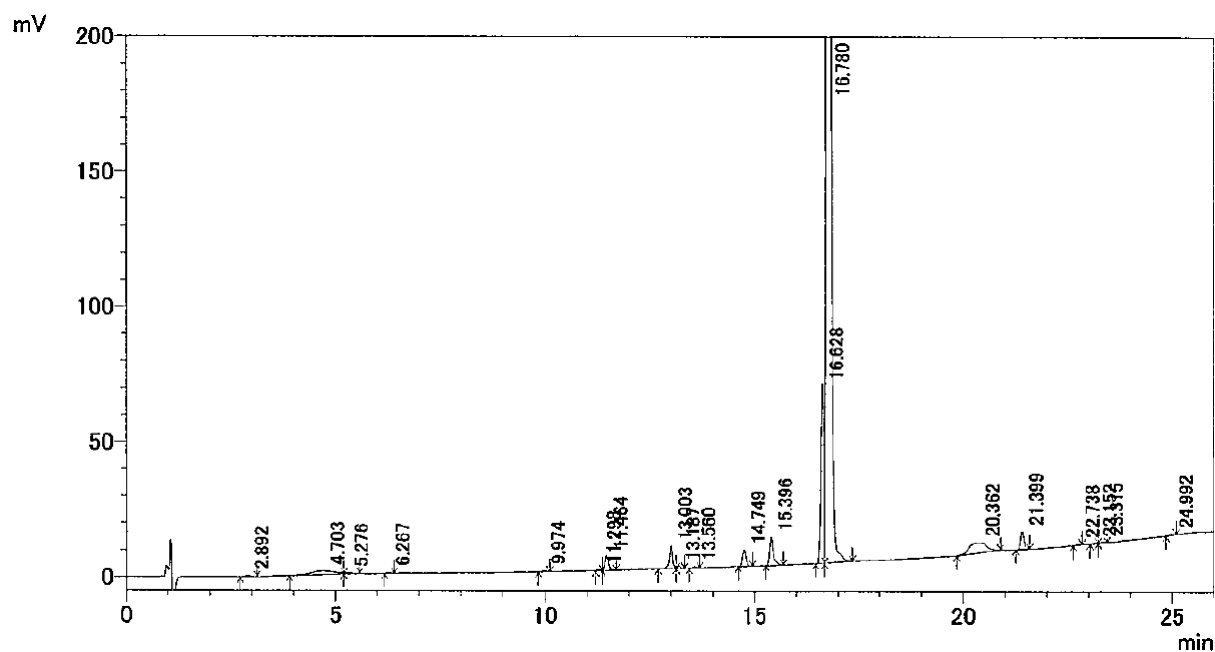
1 Det.A Ch1/230nm

検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	29.140	7152913	141311	49.751	51.692	
2	31.028	7224612	132059	50.249	48.308	V
合計		14377525	273370	100.000	100.000	

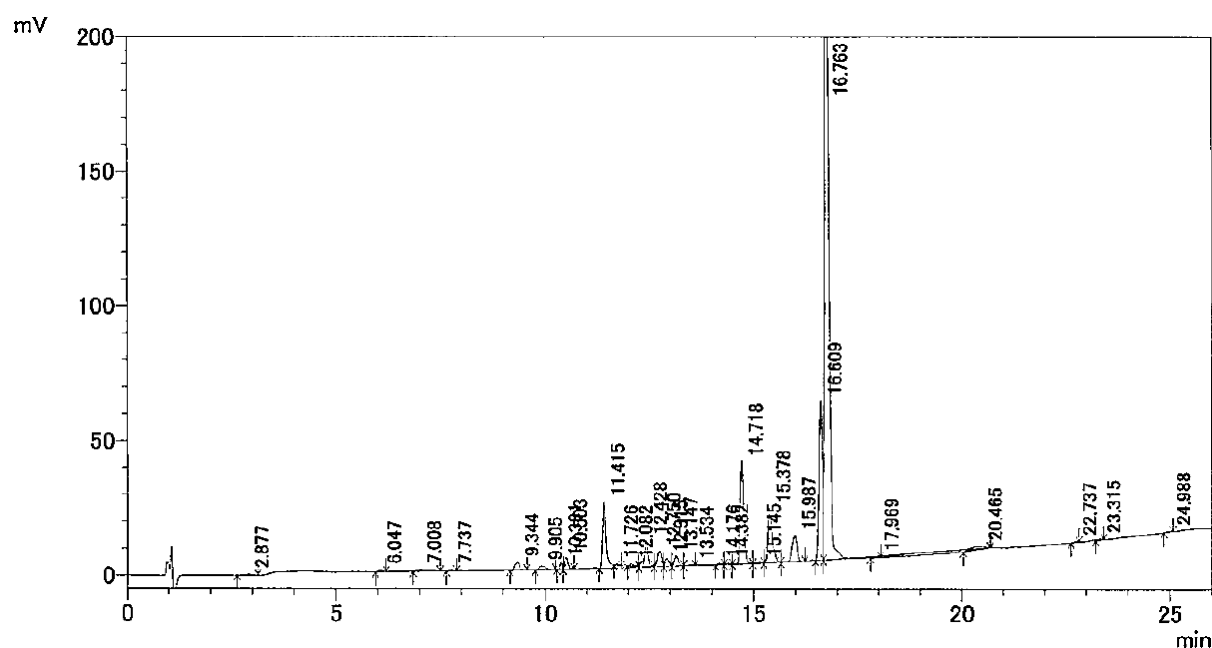
[Figure 2-4]

(Entry 1)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.892	5100	459	0.113	0.063	
2	4.703	54939	1343	1.218	0.186	
3	5.276	5919	483	0.131	0.067	V
4	6.267	2835	522	0.063	0.072	
5	9.974	3567	532	0.079	0.074	
6	11.298	2168	380	0.048	0.053	V
7	11.464	30544	5492	0.677	0.759	V
8	13.003	47675	8515	1.057	1.177	
9	13.187	4828	809	0.107	0.112	V
10	13.560	3211	568	0.071	0.079	
11	14.749	35395	6117	0.785	0.846	V
12	15.396	64903	10527	1.439	1.456	V
13	16.628	347451	66444	7.702	9.188	
14	16.780	3742325	608626	82.957	84.159	V
15	20.362	111306	3842	2.467	0.531	
16	21.399	36506	6669	0.809	0.922	V
17	22.738	3050	509	0.068	0.070	
18	23.152	2464	366	0.055	0.051	
19	23.315	3955	553	0.088	0.077	V
20	24.992	2997	427	0.066	0.059	
合計		4511137	723183	100.000	100.000	

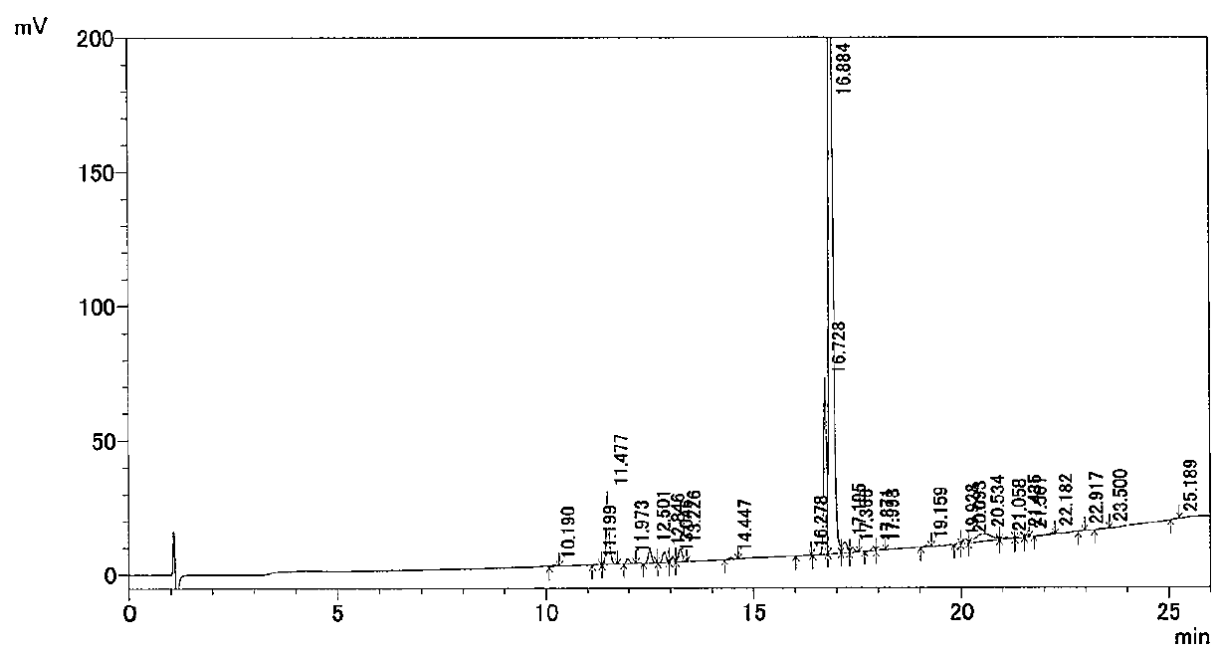
## (Entry 2)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.877	4406	324	0.158	0.069	
2	6.047	3692	643	0.132	0.136	
3	7.008	11477	598	0.412	0.127	V
4	7.737	2032	451	0.073	0.096	
5	9.344	21913	2881	0.786	0.610	
6	9.905	13450	1346	0.482	0.285	
7	10.381	11894	2600	0.426	0.551	
8	10.503	22182	4393	0.795	0.931	V
9	11.415	174250	24411	6.248	5.172	SV
10	11.726	2178	513	0.078	0.109	T
11	12.082	5351	773	0.192	0.164	TV
12	12.428	61379	9897	2.201	2.097	V
13	12.750	38236	5581	1.371	1.182	V
14	12.915	19578	2975	0.702	0.630	V
15	13.147	22880	3858	0.820	0.817	V
16	13.534	2383	232	0.085	0.049	V
17	14.176	3374	564	0.121	0.119	
18	14.382	3047	564	0.109	0.120	V
19	14.718	224639	38075	8.055	8.067	V
20	15.145	2497	333	0.090	0.071	V
21	15.378	141757	20379	5.083	4.318	V
22	15.987	79081	9814	2.835	2.079	V
23	16.609	324095	59247	11.621	12.552	
24	16.763	1556538	279301	55.810	59.173	SV
25	17.969	2319	273	0.083	0.058	TV
26	20.465	27775	972	0.996	0.206	T
27	22.737	2153	364	0.077	0.077	
28	23.315	2256	332	0.081	0.070	V
29	24.988	2161	308	0.077	0.065	
合計		2788974	472005	100.000	100.000	

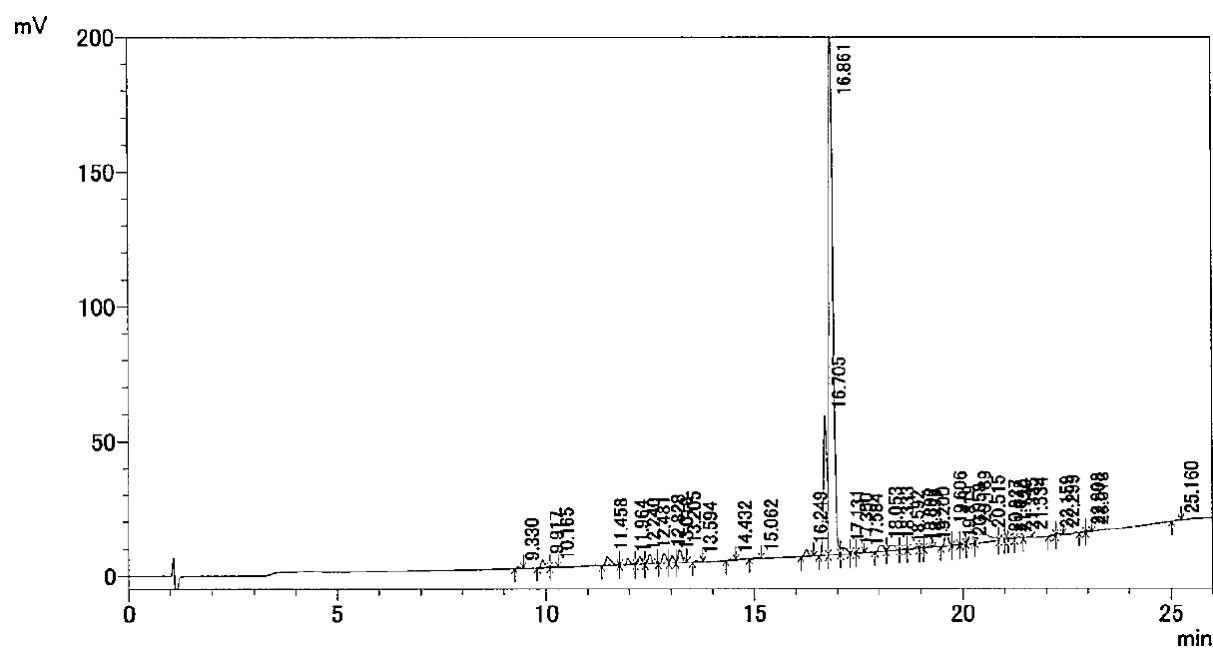
[Figure 2-5]

(Entry 1)



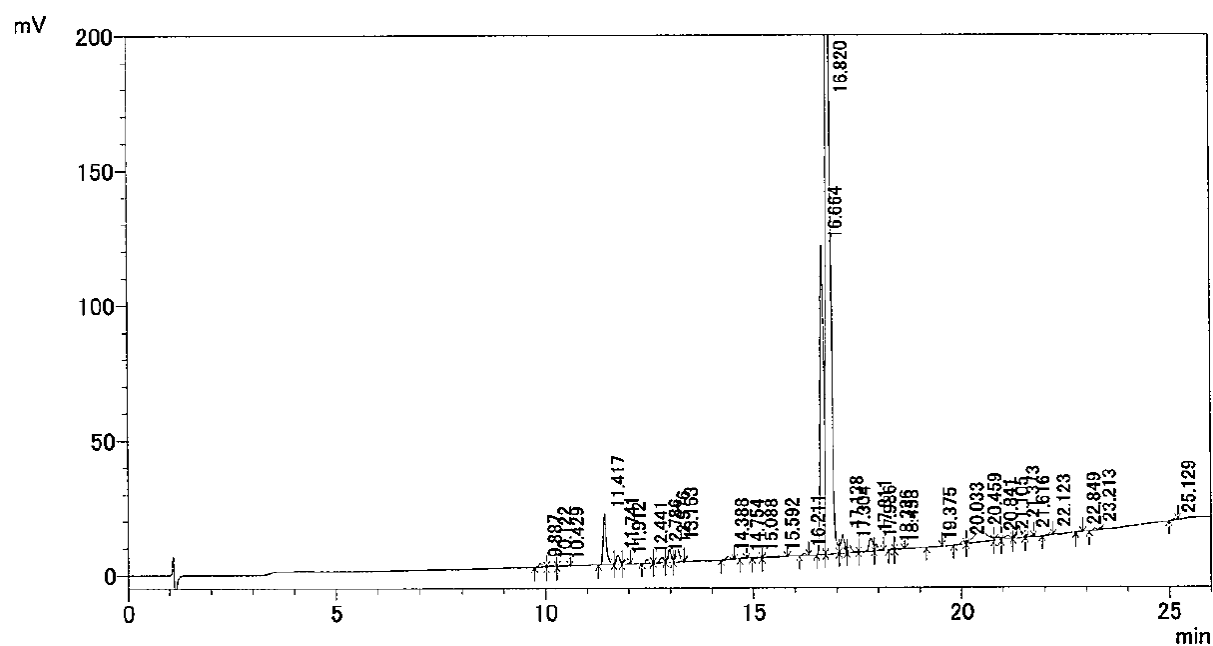
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	10.190	2579	499	0.097	0.114	V
2	11.199	2427	445	0.091	0.102	V
3	11.477	150973	27345	5.659	6.268	
4	11.973	10682	1855	0.400	0.425	V
5	12.501	31604	5613	1.185	1.287	V
6	12.846	23074	3914	0.865	0.897	
7	13.046	7659	1453	0.287	0.333	V
8	13.226	27777	4724	1.041	1.083	V
9	14.447	4870	688	0.183	0.158	
10	16.278	3318	459	0.124	0.105	
11	16.728	358187	66088	13.426	15.148	
12	16.884	1843278	304339	69.092	69.758	V
13	17.195	32852	4117	1.231	0.944	V
14	17.366	12153	1794	0.456	0.411	V
15	17.871	7489	1289	0.281	0.296	V
16	17.998	6841	1130	0.256	0.259	V
17	19.159	5050	679	0.189	0.156	V
18	19.928	3991	776	0.150	0.178	
19	20.093	9412	1450	0.353	0.332	V
20	20.534	81657	2963	3.061	0.679	V
21	21.058	13174	691	0.494	0.158	V
22	21.435	11954	1711	0.448	0.392	V
23	21.561	4524	776	0.170	0.178	V
24	22.182	5255	652	0.197	0.149	V
25	22.917	2028	303	0.076	0.069	V
26	23.500	2923	229	0.110	0.053	
27	25.189	2138	297	0.080	0.068	
合計		2667868	436277	100.000	100.000	

(Entry 2)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	9.330	2799	603	0.132	0.176	
2	9.917	18443	2913	0.873	0.853	
3	10.165	2741	518	0.130	0.152	V
4	11.458	28630	3278	1.355	0.960	
5	11.964	13815	2494	0.654	0.730	V
6	12.240	15139	2820	0.716	0.826	V
7	12.481	20699	3612	0.979	1.057	V
8	12.828	23469	3863	1.110	1.131	
9	13.019	15632	2759	0.740	0.808	V
10	13.205	29306	4816	1.387	1.410	V
11	13.594	4291	737	0.203	0.216	V
12	14.432	3055	468	0.145	0.137	
13	15.062	2769	326	0.131	0.095	V
14	16.249	15319	2477	0.725	0.725	V
15	16.705	289818	51930	13.713	15.200	
16	16.861	1351905	226394	63.966	66.267	V
17	17.131	21643	2333	1.024	0.683	V
18	17.350	4656	635	0.220	0.186	V
19	17.584	2777	244	0.131	0.072	V
20	18.053	19068	2338	0.902	0.684	
21	18.333	21327	2095	1.009	0.613	V
22	18.592	2074	381	0.098	0.112	V
23	18.892	3863	760	0.183	0.222	V

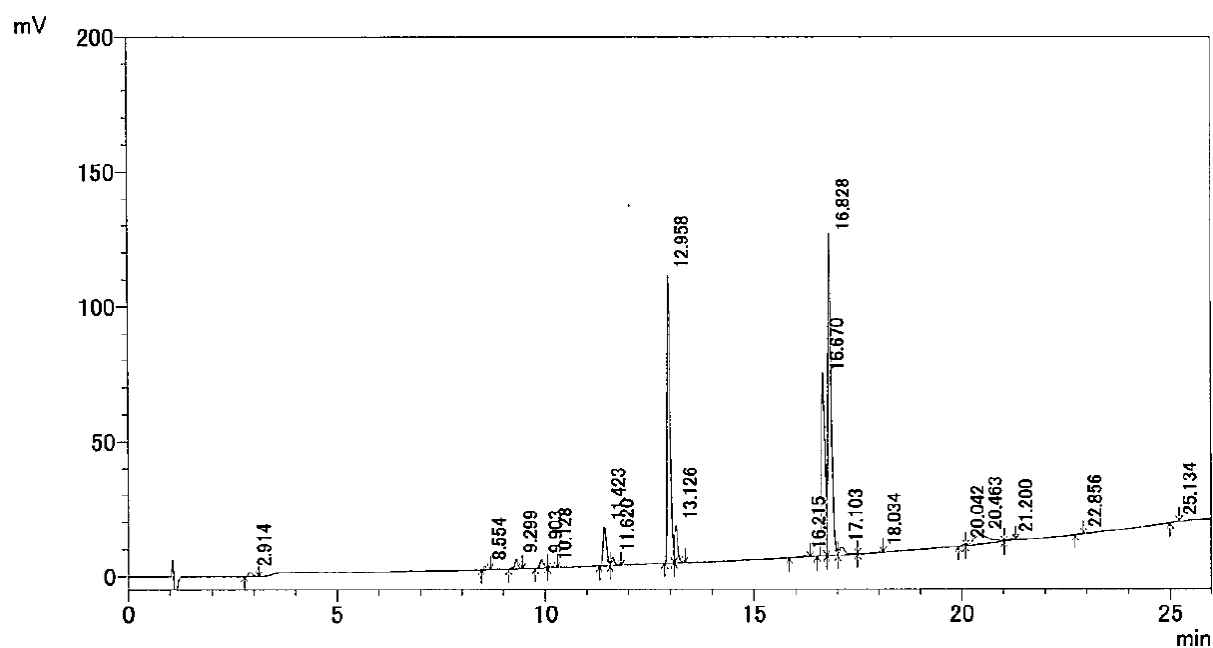
(Entry 3)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	9.887	8814	1420	0.243	0.239	
2	10.122	3451	555	0.095	0.093	V
3	10.429	2528	238	0.070	0.040	V
4	11.417	108154	18767	2.978	3.161	V
5	11.741	17147	3428	0.472	0.577	V
6	11.912	7885	1299	0.217	0.219	V
7	12.441	7705	1361	0.212	0.229	
8	12.786	10113	1773	0.278	0.299	V
9	12.976	24243	4704	0.667	0.792	V
10	13.163	34644	5785	0.954	0.974	V
11	14.388	7648	1041	0.211	0.175	
12	14.754	2945	485	0.081	0.082	V
13	15.088	2734	311	0.075	0.052	V
14	15.592	2268	107	0.062	0.018	V
15	16.211	5265	926	0.145	0.156	V
16	16.664	637102	114858	17.541	19.343	
17	16.820	2453912	402645	67.561	67.809	V
18	17.138	48279	6876	1.329	1.158	V
19	17.304	19347	2874	0.533	0.484	V
20	17.811	29511	4941	0.813	0.832	V
21	17.936	15658	2766	0.431	0.466	V
22	18.336	2197	412	0.060	0.069	V
23	18.458	2948	324	0.081	0.055	V



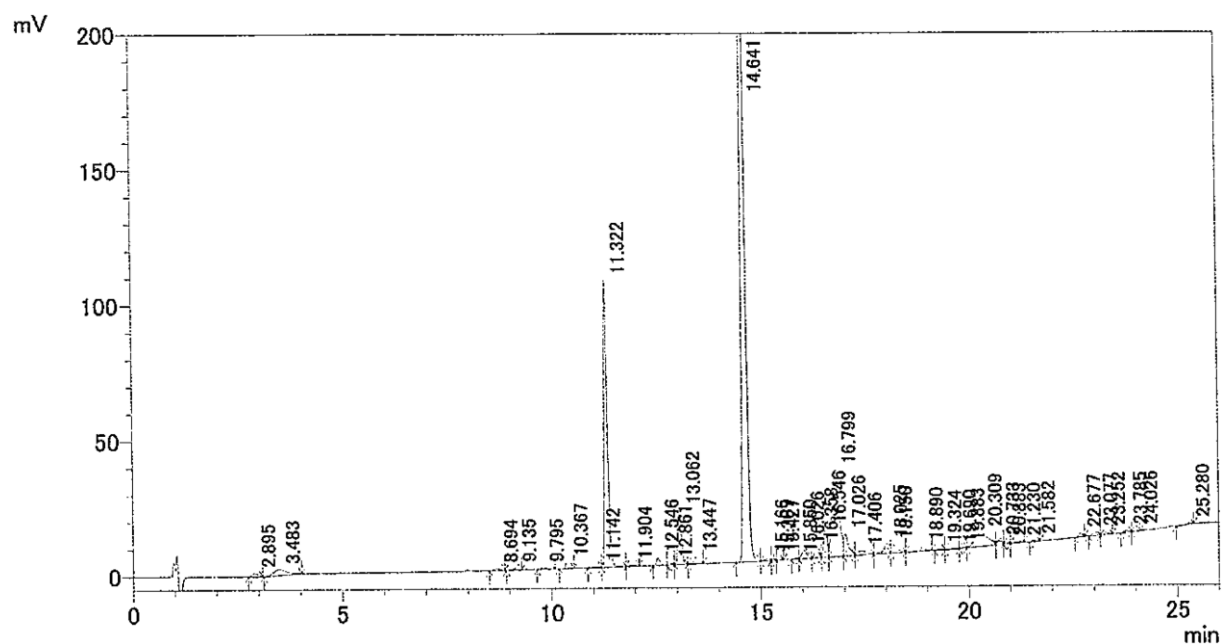
(Entry 4)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.914	9150	1467	0.451	0.424	
2	8.554	6267	1366	0.309	0.395	
3	9.299	19991	3625	0.985	1.049	
4	9.903	18978	3309	0.935	0.957	
5	10.128	4010	561	0.198	0.162	V
6	11.423	81075	14608	3.996	4.226	V
7	11.620	16855	3103	0.831	0.898	V
8	12.958	560082	107170	27.606	31.006	V
9	13.126	71941	13846	3.546	4.006	V
10	16.215	4837	685	0.238	0.198	
11	16.670	386560	68035	19.053	19.683	
12	16.828	718518	119980	35.415	34.712	V
13	17.103	28840	2665	1.422	0.771	V
14	18.034	2597	143	0.128	0.041	V
15	20.042	3495	615	0.172	0.178	
16	20.463	86565	3174	4.267	0.918	V
17	21.200	4737	660	0.233	0.191	V
18	22.856	2199	339	0.108	0.098	
19	25.134	2128	293	0.105	0.085	
合計		2028825	345644	100.000	100.000	

[Figure 2-7]

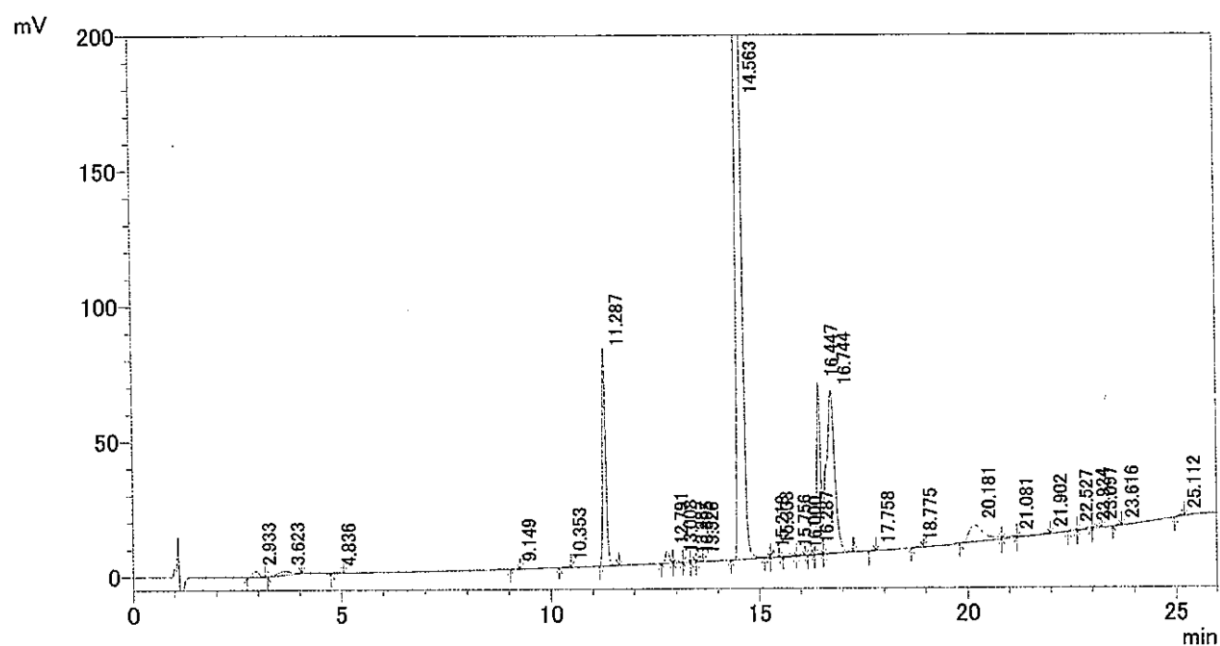
(Entry 1)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.895	12249	1166	0.340	0.220	V
2	3.483	47000	2083	1.306	0.393	
3	8.694	5461	686	0.152	0.129	
4	9.135	5050	752	0.140	0.142	
5	9.795	5116	460	0.142	0.087	
6	10.367	12750	2332	0.354	0.440	
7	11.142	2374	236	0.066	0.045	V
8	11.322	589870	105831	16.389	19.974	V
9	11.904	3518	389	0.098	0.073	V
10	12.546	15934	2799	0.443	0.528	
11	12.861	2987	537	0.083	0.101	V
12	13.062	123790	20400	3.439	3.850	V
13	13.447	15825	2335	0.440	0.441	V
14	14.641	1870584	304835	51.972	57.532	
15	15.166	7818	933	0.217	0.176	V
16	15.307	3583	656	0.100	0.124	V
17	15.427	4774	840	0.133	0.158	V
18	15.850	2176	343	0.060	0.065	
19	16.026	25658	3180	0.713	0.600	V
20	16.358	32409	4160	0.900	0.785	
21	16.546	59960	10184	1.666	1.922	V
22	16.799	387991	32029	10.780	6.045	V
23	17.026	63835	8019	1.774	1.513	V

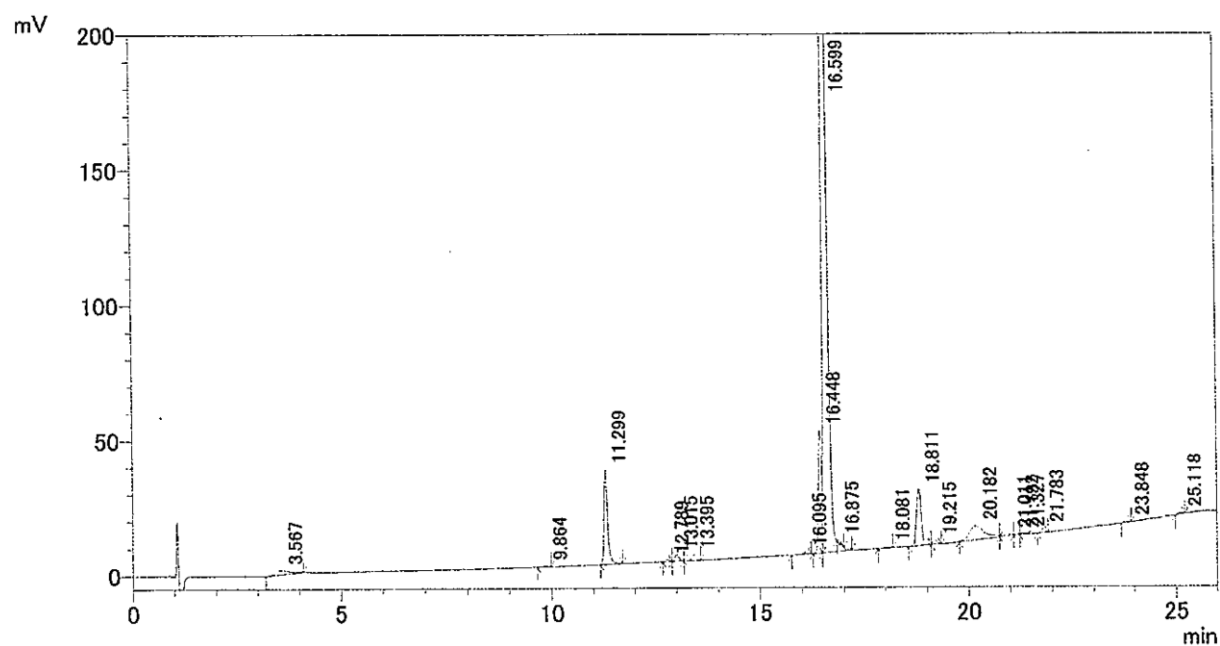
(Entry 2)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.933	22377	2066	0.331	0.213	
2	3.623	32801	1377	0.485	0.142	
3	4.836	2774	343	0.041	0.035	
4	9.149	2855	573	0.042	0.059	V
5	10.353	2091	368	0.031	0.038	
6	11.287	439740	81061	6.506	8.367	V
7	12.791	28550	4698	0.422	0.485	
8	13.008	9283	1472	0.137	0.152	V
9	13.287	4653	832	0.069	0.086	V
10	13.395	5173	852	0.077	0.088	V
11	13.526	2830	478	0.042	0.049	V
12	14.563	4750259	732128	70.275	75.567	S
13	15.218	5918	1206	0.088	0.125	T
14	15.333	14566	2573	0.215	0.266	TV
15	15.756	8897	1319	0.132	0.136	T
16	16.000	2563	446	0.038	0.046	TV
17	16.287	10259	2034	0.152	0.210	T
18	16.447	374786	63516	5.545	6.556	TV
19	16.744	838323	60406	12.402	6.235	TV
20	17.758	2252	338	0.033	0.035	
21	18.775	2204	253	0.033	0.026	
22	20.181	155511	6193	2.301	0.639	
23	21.081	11546	669	0.171	0.069	V

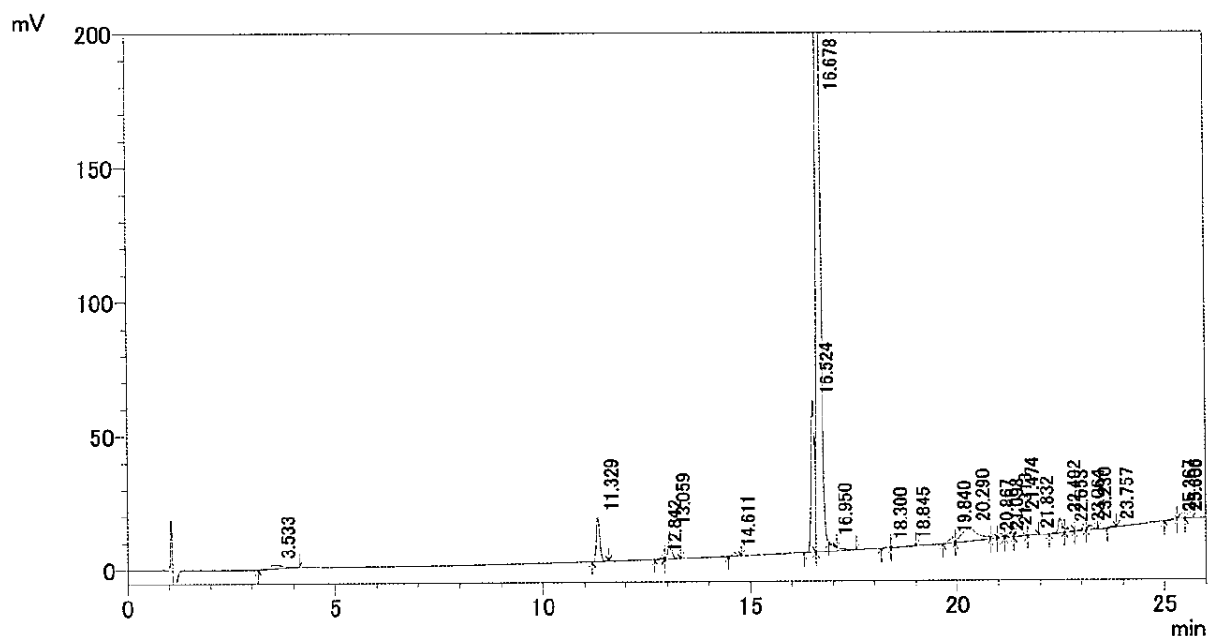
(Entry 3)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.567	37326	1528	0.891	0.236	
2	9.864	2666	343	0.064	0.053	
3	11.299	207377	35111	4.948	5.415	
4	12.789	3750	725	0.089	0.112	
5	13.015	14126	2323	0.337	0.358	V
6	13.395	12432	2143	0.297	0.330	V
7	16.095	6449	878	0.154	0.135	
8	16.448	236878	45260	5.651	6.980	
9	16.599	3327858	527877	79.396	81.409	SV
10	16.875	3659	624	0.087	0.096	T
11	18.081	3035	277	0.072	0.043	V
12	18.811	163913	21034	3.911	3.244	
13	19.215	7287	1296	0.174	0.200	V
14	20.182	130453	5156	3.112	0.795	
15	21.011	11170	620	0.266	0.096	V
16	21.192	3486	415	0.083	0.064	V
17	21.327	4489	542	0.107	0.084	V
18	21.783	9126	1502	0.218	0.232	
19	23.848	2388	259	0.057	0.040	
20	25.118	3599	513	0.086	0.079	
合計		4191466	648424	100.000	100.000	

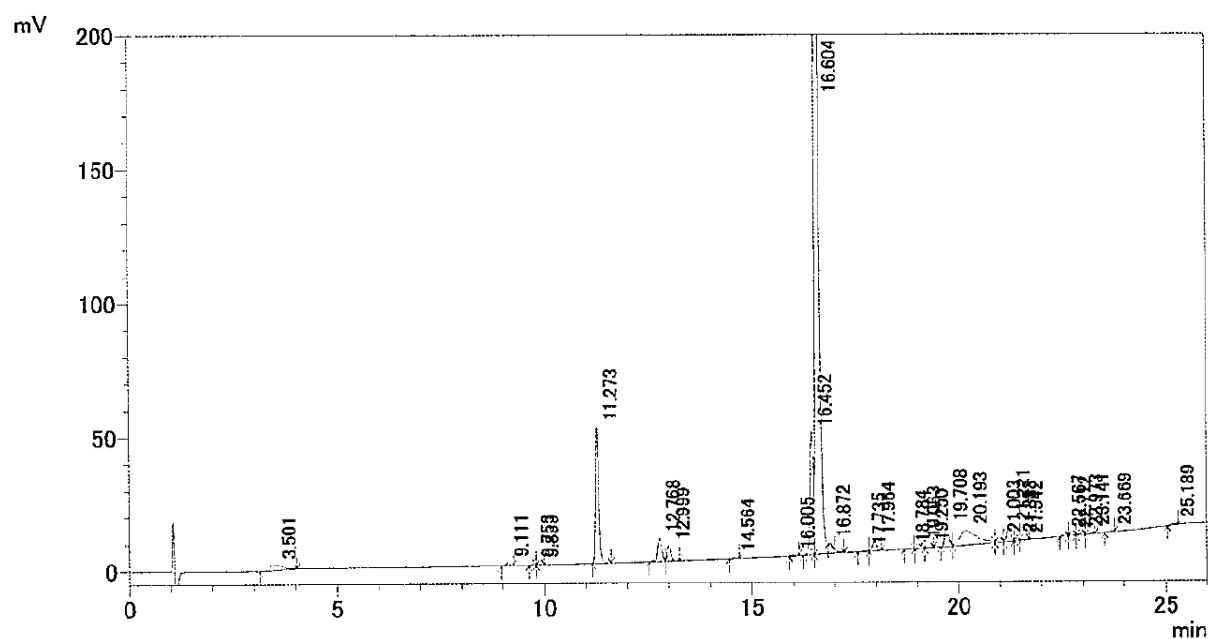
(Entry 4)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.533	41647	1649	1.235	0.323	
2	11.329	95789	17007	2.841	3.332	
3	12.842	3095	489	0.092	0.096	
4	13.059	63964	10314	1.897	2.021	V
5	14.611	8409	1291	0.249	0.253	
6	16.524	318376	56606	9.442	11.090	
7	16.678	2507577	391663	74.367	76.730	SV
8	16.950	5434	872	0.161	0.171	T
9	18.300	4802	740	0.142	0.145	
10	18.845	3375	299	0.100	0.059	V
11	19.840	12251	1491	0.363	0.292	
12	20.290	134265	5148	3.982	1.009	V
13	20.867	6716	767	0.199	0.150	V
14	21.098	5384	590	0.160	0.116	V
15	21.313	15418	2197	0.457	0.430	V
16	21.474	58676	7812	1.740	1.531	V
17	21.832	3197	337	0.095	0.066	V
18	22.492	37166	5337	1.102	1.046	
19	22.653	9867	1387	0.293	0.272	V
20	23.064	7955	902	0.236	0.177	V
21	23.230	12336	1396	0.366	0.273	V
22	23.757	3094	489	0.092	0.096	
23	25.267	4697	611	0.139	0.120	

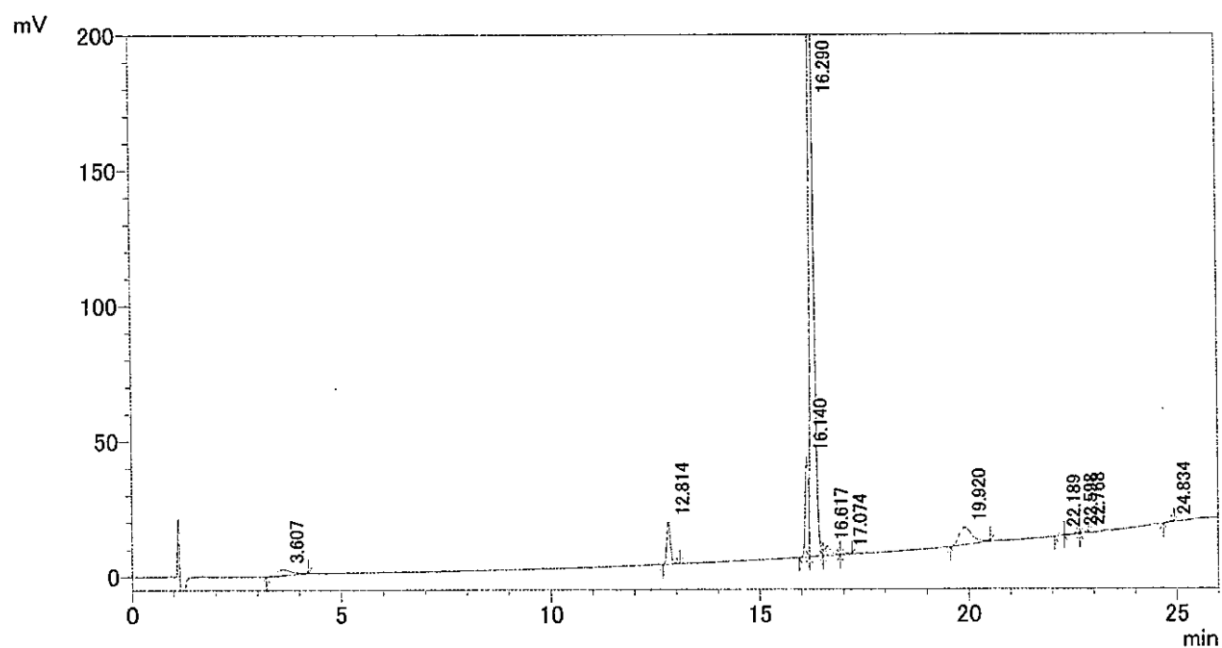
(Entry 5)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.501	46070	2009	1.263	0.359	
2	9.111	5788	1094	0.159	0.196	
3	9.753	3833	665	0.105	0.119	
4	9.833	2582	543	0.071	0.097	V
5	11.273	286479	50868	7.855	9.097	V
6	12.768	58521	8763	1.605	1.567	
7	12.999	36048	5693	0.988	1.018	V
8	14.564	2989	503	0.082	0.090	
9	16.005	2265	354	0.062	0.063	V
10	16.452	255458	46087	7.005	8.242	
11	16.604	2612275	410247	71.628	73.366	SV
12	16.872	3688	518	0.101	0.093	T
13	17.735	2640	327	0.072	0.058	
14	17.964	24153	3935	0.662	0.704	V
15	18.784	2144	303	0.059	0.054	V
16	19.063	10409	1600	0.285	0.286	
17	19.250	2630	275	0.072	0.049	V
18	19.708	49282	7232	1.351	1.293	
19	20.193	150929	5468	4.138	0.978	V
20	21.003	11654	1384	0.320	0.247	V
21	21.221	34978	5381	0.959	0.962	V
22	21.383	4735	781	0.130	0.140	V
23	21.542	2324	253	0.064	0.045	V

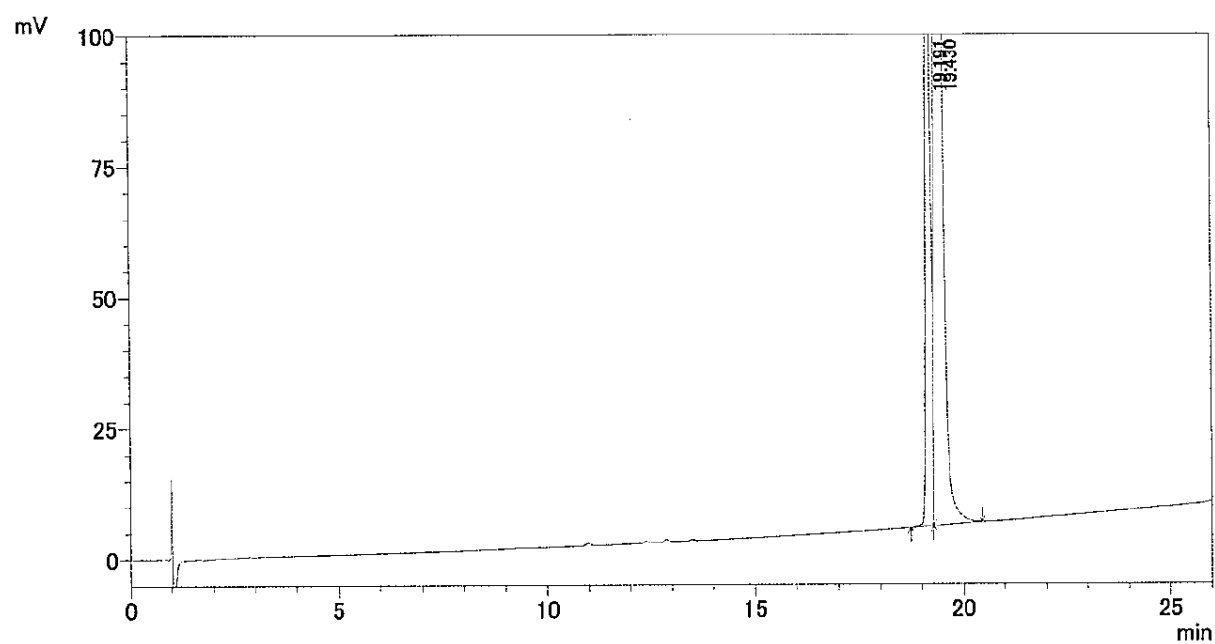
(Entry 6)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.607	54959	2194	2.167	0.555	
2	12.814	93414	15689	3.683	3.967	
3	16.140	191405	36761	7.546	9.294	
4	16.290	1996406	327934	78.705	82.913	V
5	16.617	38440	3460	1.515	0.875	V
6	17.074	5434	585	0.214	0.148	V
7	19.920	138153	6297	5.446	1.592	
8	22.189	5470	809	0.216	0.205	
9	22.598	4048	503	0.160	0.127	V
10	22.768	4932	734	0.194	0.186	V
11	24.834	3906	549	0.154	0.139	
合計		2536566	395516	100.000	100.000	

(Entry 7)

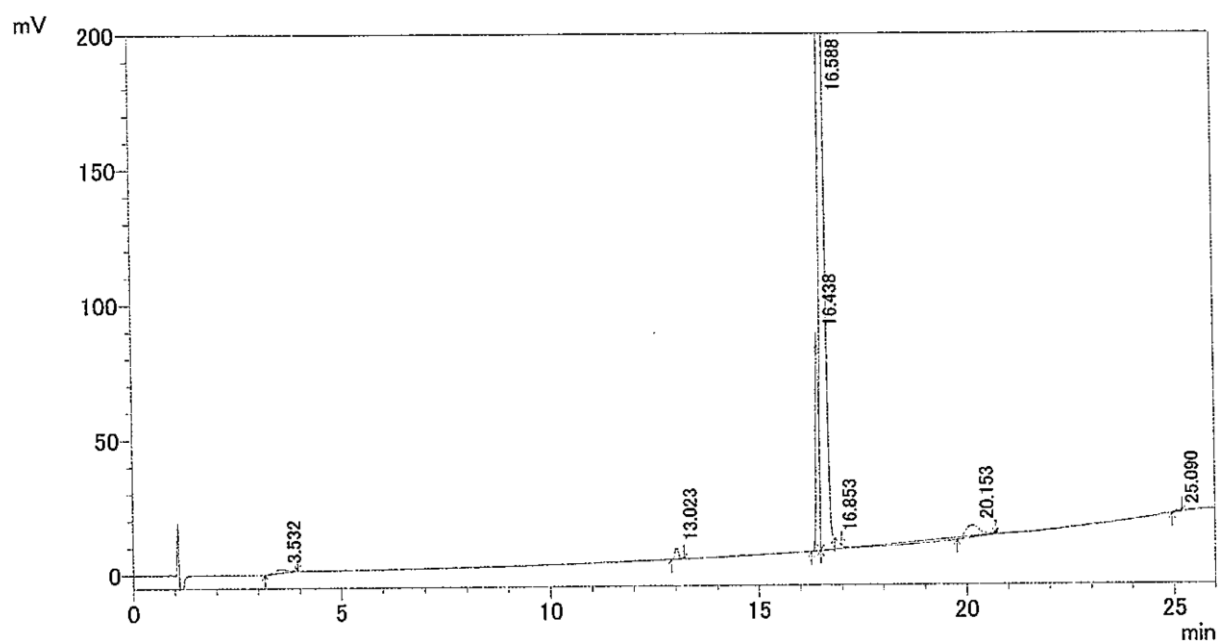


検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	19.191	1131481	145467	15.003	16.251	
2	19.430	6410409	749659	84.997	83.749	V
合計		7541891	895126	100.000	100.000	



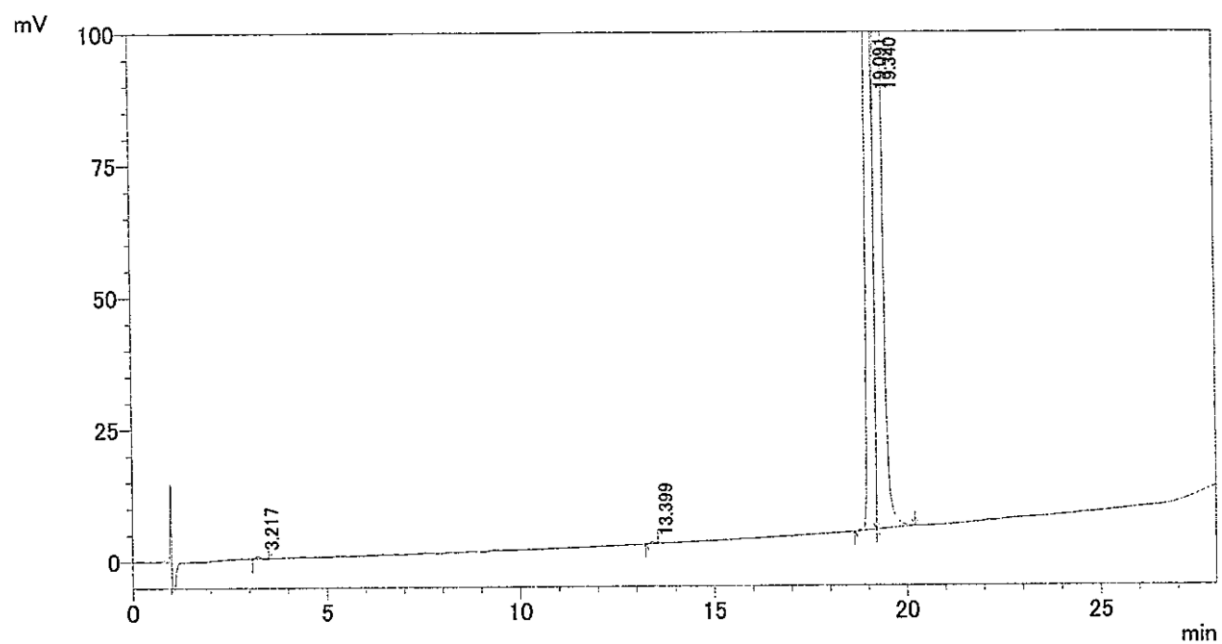
(Entry 8)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.532	29735	1317	0.719	0.198	
2	13.023	26819	4505	0.649	0.679	V
3	16.438	426511	80988	10.314	12.199	
4	16.588	3536550	571556	85.519	86.089	SV
5	16.853	4047	558	0.098	0.084	T
6	20.153	107925	4441	2.610	0.669	T
7	25.090	3800	549	0.092	0.083	
合計		4135387	663913	100.000	100.000	

(Entry 9)

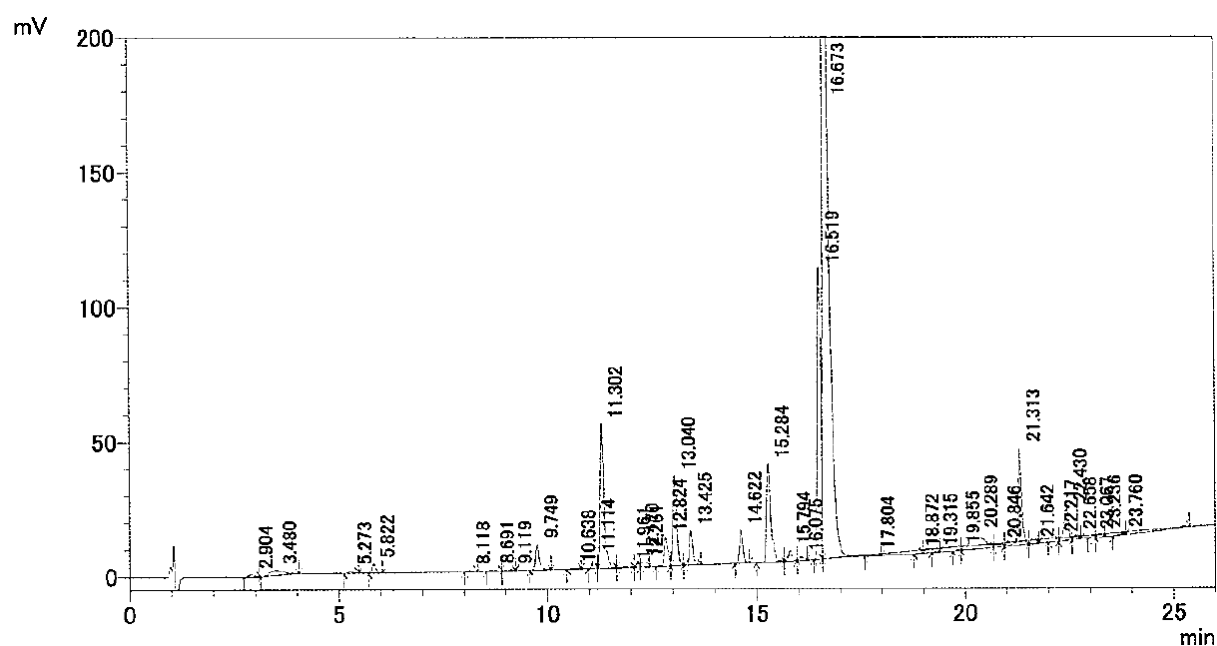


検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.217	3685	464	0.049	0.052	
2	13.399	2710	346	0.036	0.039	
3	19.091	3658832	451530	48.669	50.335	
4	19.340	3852506	444718	51.246	49.575	V
合計		7517733	897058	100.000	100.000	

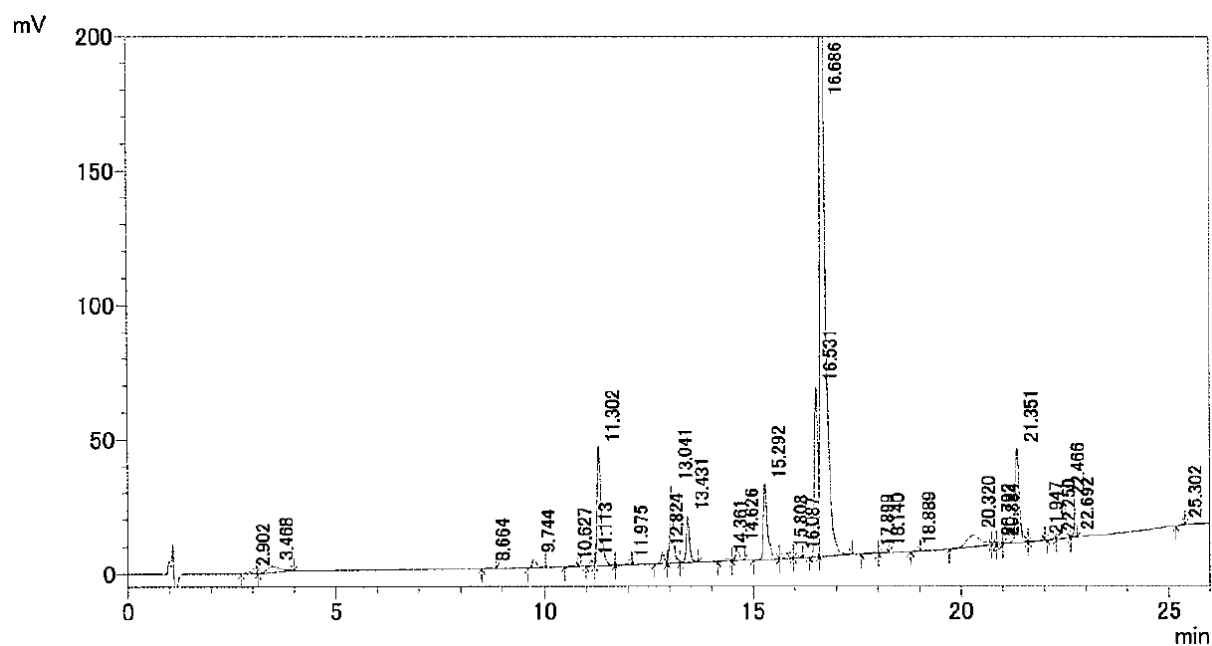
[Figure 2-8]

(Entry 1)



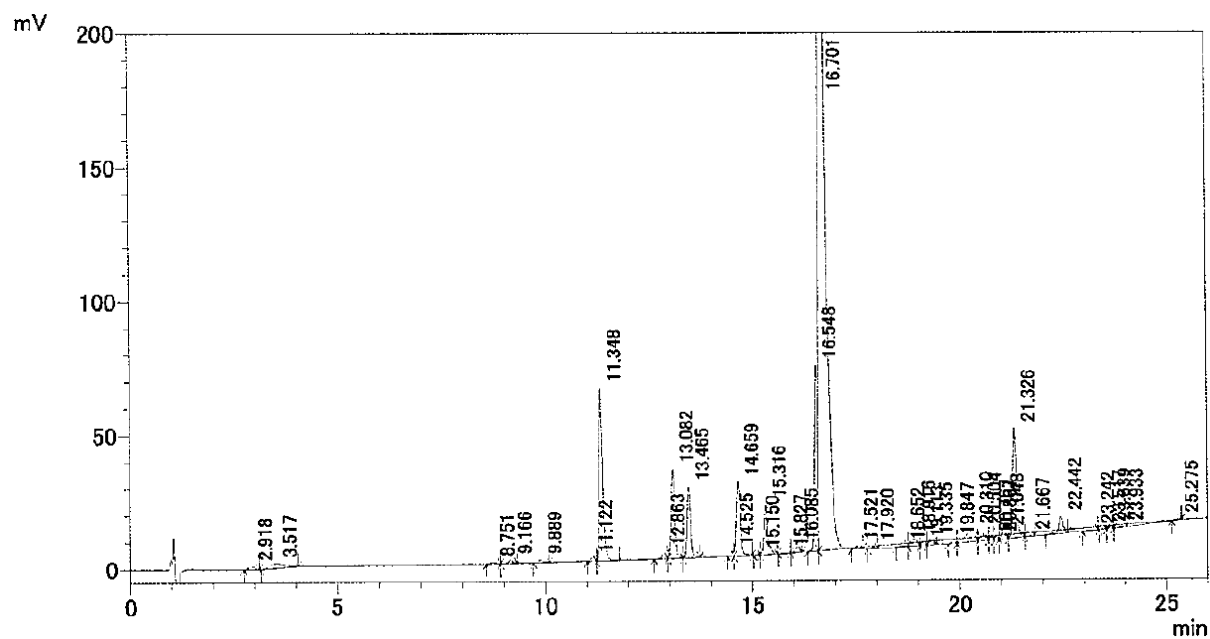
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.904	9315	914	0.157	0.101	
2	3.480	45273	1922	0.765	0.212	
3	5.273	6498	947	0.110	0.104	
4	5.822	20067	3450	0.339	0.380	
5	8.118	3181	483	0.054	0.053	V
6	8.691	5057	633	0.085	0.070	
7	9.119	2533	429	0.043	0.047	
8	9.749	64301	9646	1.086	1.064	
9	10.638	3506	317	0.059	0.035	
10	11.114	23004	4104	0.388	0.452	V
11	11.302	326001	53992	5.505	5.953	V
12	11.961	6272	788	0.106	0.087	V
13	12.170	9744	1855	0.165	0.205	V
14	12.261	8311	1651	0.140	0.182	V
15	12.824	68419	10738	1.155	1.184	
16	13.040	206930	33420	3.495	3.685	V
17	13.425	76219	12673	1.287	1.397	V
18	14.622	72794	12191	1.229	1.344	V
19	15.284	244455	36393	4.128	4.013	
20	15.794	25117	4025	0.424	0.444	V
21	16.075	7380	1235	0.125	0.136	V
22	16.519	591739	108894	9.993	12.007	
23	16.673	3578155	543861	60.427	59.968	SV

(Entry 2)



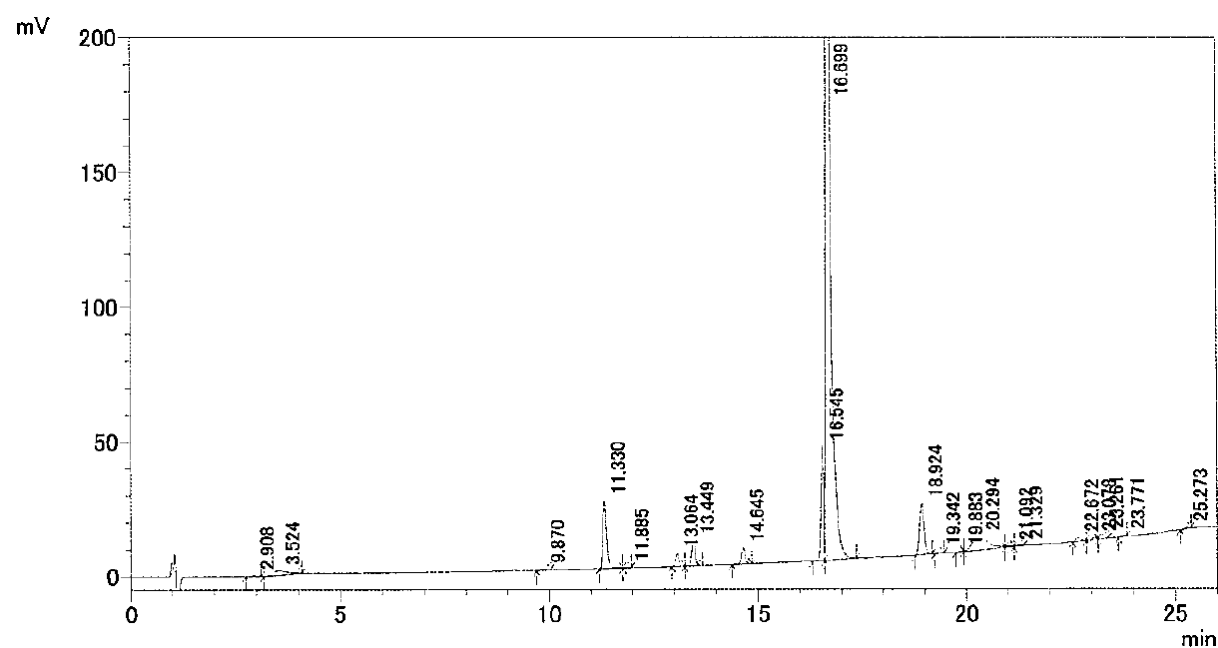
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.902	6790	652	0.150	0.099	
2	3.468	52327	2351	1.156	0.358	
3	8.664	4034	496	0.089	0.076	V
4	9.744	23340	3378	0.516	0.515	
5	10.627	2449	258	0.054	0.039	V
6	11.113	9965	1803	0.220	0.275	V
7	11.302	269274	44359	5.951	6.762	V
8	11.975	2772	378	0.061	0.058	V
9	12.824	26270	4320	0.581	0.659	
10	13.041	173368	28673	3.831	4.371	V
11	13.431	101345	17376	2.240	2.649	V
12	14.361	7386	1170	0.163	0.178	
13	14.626	31059	5208	0.686	0.794	V
14	15.292	184686	28036	4.082	4.274	
15	15.808	11633	1865	0.257	0.284	V
16	16.087	4802	837	0.106	0.128	V
17	16.531	346229	63103	7.652	9.620	
18	16.686	2804529	392911	61.979	59.898	V
19	17.899	3872	331	0.086	0.050	
20	18.140	3095	411	0.068	0.063	V
21	18.889	3064	491	0.068	0.075	V
22	20.320	108265	4583	2.393	0.699	
23	20.792	6185	967	0.137	0.147	V

## (Entry 3)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.918	10959	1092	0.158	0.106	
2	3.517	39967	1637	0.577	0.159	
3	8.751	4903	585	0.071	0.057	
4	9.166	7578	1301	0.109	0.126	V
5	9.889	9840	999	0.142	0.097	V
6	11.122	8022	1082	0.116	0.105	V
7	11.348	377172	64697	5.447	6.280	V
8	12.863	16121	2621	0.233	0.254	
9	13.082	207387	33508	2.995	3.253	V
10	13.465	158346	26749	2.287	2.597	V
11	14.525	9153	1795	0.132	0.174	V
12	14.659	174625	27824	2.522	2.701	V
13	15.150	2592	420	0.037	0.041	
14	15.316	122529	19061	1.770	1.850	V
15	15.827	2176	243	0.031	0.024	
16	16.085	15013	2272	0.217	0.221	
17	16.548	378304	69499	5.464	6.747	V
18	16.701	4857718	704157	70.158	68.356	SV
19	17.521	7440	1055	0.107	0.102	T
20	17.920	3569	602	0.052	0.058	T
21	18.652	3099	331	0.045	0.032	T
22	18.916	22508	2762	0.325	0.268	TV
23	19.113	5215	761	0.075	0.074	TV

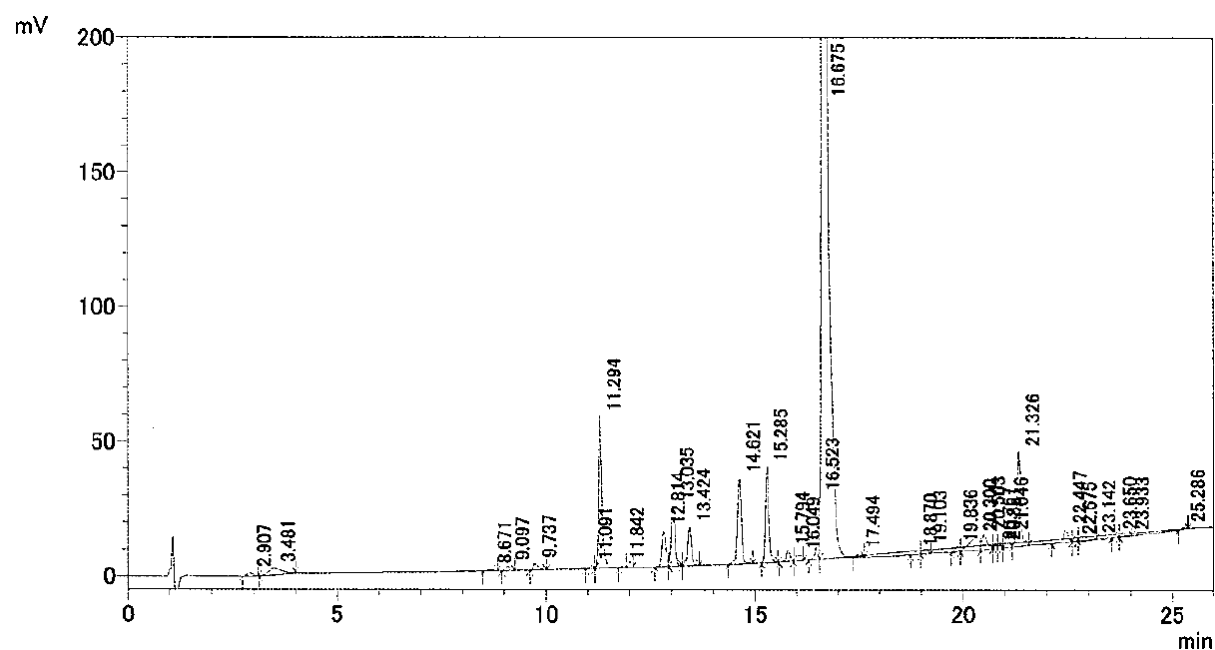
(Entry 4)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.908	3917	371	0.114	0.077	
2	3.524	38634	1587	1.121	0.330	
3	9.870	4706	417	0.137	0.087	V
4	11.330	154819	25390	4.493	5.275	V
5	11.885	2585	307	0.075	0.064	V
6	13.064	28992	4810	0.841	0.999	V
7	13.449	55824	9440	1.620	1.961	V
8	14.645	37186	6142	1.079	1.276	
9	16.545	233186	43006	6.768	8.934	
10	16.699	2558708	359215	74.261	74.626	V
11	18.924	148164	19058	4.300	3.959	
12	19.342	5041	927	0.146	0.193	
13	19.883	2263	361	0.066	0.075	
14	20.294	132084	5055	3.833	1.050	V
15	21.092	3738	217	0.108	0.045	V
16	21.329	2752	221	0.080	0.046	V
17	22.672	9277	1267	0.269	0.263	
18	23.078	5157	825	0.150	0.171	V
19	23.261	11951	1761	0.347	0.366	V
20	23.771	3039	481	0.088	0.100	
21	25.273	3529	499	0.102	0.104	
合計		3445552	481356	100.000	100.000	

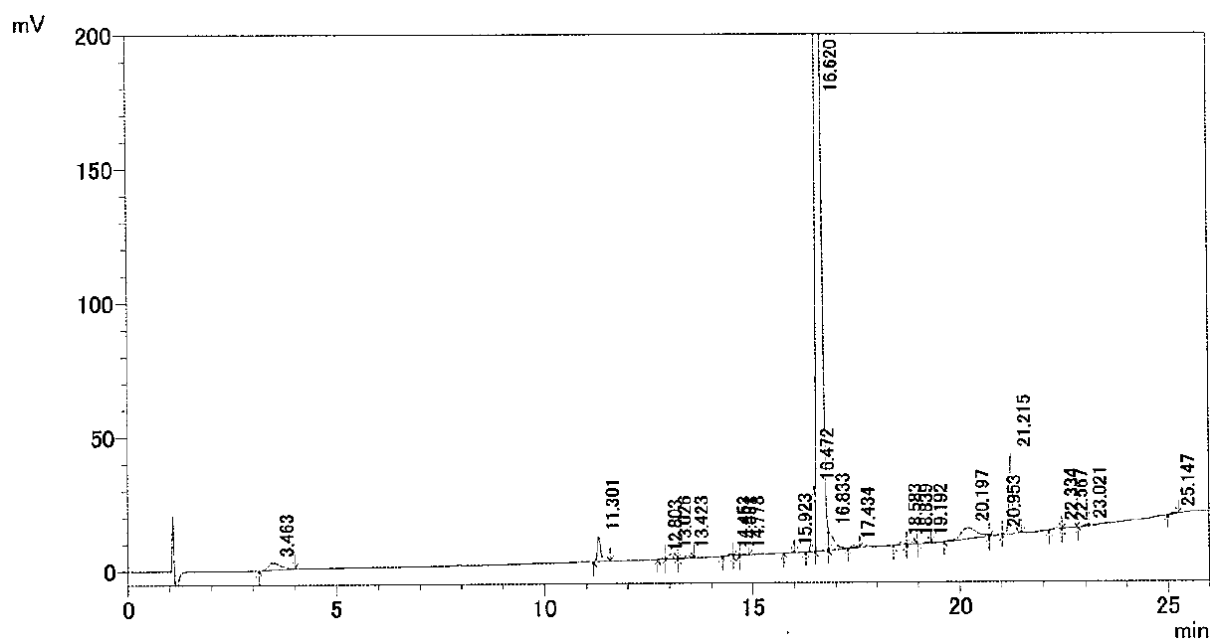
[Figure 2-10]

(Entry 1)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.907	10684	1014	0.156	0.099	
2	3.481	49609	2252	0.724	0.220	
3	8.671	4425	556	0.065	0.054	
4	9.097	9426	1734	0.137	0.170	
5	9.737	19384	2399	0.283	0.235	
6	11.091	7700	1069	0.112	0.105	V
7	11.294	327033	56930	4.770	5.573	SV
8	11.842	4095	680	0.060	0.067	T
9	12.814	80965	13345	1.181	1.306	
10	13.035	138784	22558	2.024	2.208	V
11	13.424	84675	14234	1.235	1.393	V
12	14.621	198534	31654	2.896	3.098	V
13	15.285	205933	35640	3.004	3.489	V
14	15.794	23707	4056	0.346	0.397	
15	16.049	12819	1958	0.187	0.192	V
16	16.523	116533	23229	1.700	2.274	V
17	16.675	5083601	744266	74.145	72.852	SV
18	17.494	8324	1190	0.121	0.116	T
19	18.870	4978	861	0.073	0.084	TV
20	19.103	11391	1874	0.166	0.183	TV
21	19.836	9622	1576	0.140	0.154	T
22	20.300	85128	4751	1.242	0.465	TV
23	20.503	48286	5450	0.704	0.533	TV

(Entry 2)

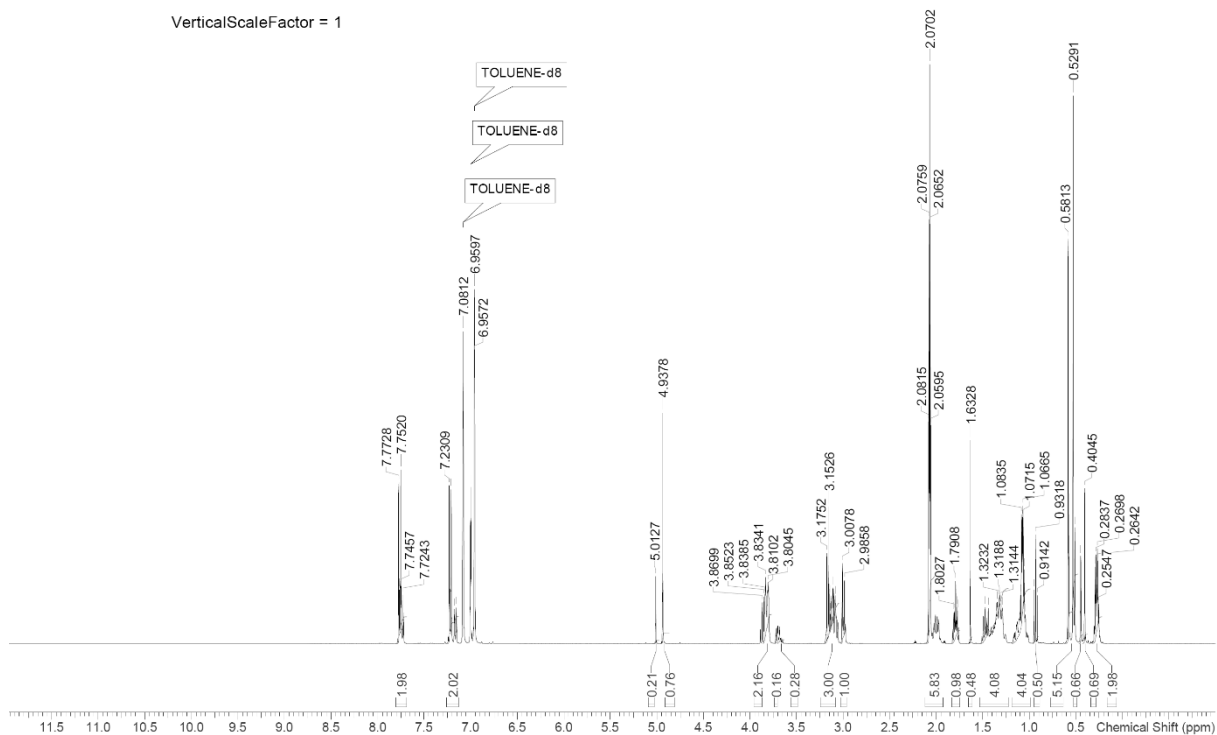


ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.463	59076	2650	1.106	0.350	
2	11.301	56033	9342	1.049	1.235	
3	12.803	3283	591	0.061	0.078	V
4	13.026	10625	1653	0.199	0.219	V
5	13.423	8558	1371	0.160	0.181	V
6	14.453	4102	662	0.077	0.087	
7	14.591	2535	386	0.047	0.051	V
8	14.778	2830	363	0.053	0.048	V
9	15.923	2383	323	0.045	0.043	V
10	16.472	121902	24022	2.282	3.175	
11	16.620	4644737	667664	86.968	88.253	V
12	16.833	63047	7010	1.180	0.927	SV
13	17.434	6282	819	0.118	0.108	T
14	18.583	9601	1205	0.180	0.159	
15	18.839	6392	834	0.120	0.110	V
16	19.192	2738	433	0.051	0.057	
17	20.197	110933	4019	2.077	0.531	
18	20.953	9693	616	0.181	0.081	V
19	21.215	196707	30177	3.683	3.989	V
20	22.334	7105	968	0.133	0.128	
21	22.567	3276	305	0.061	0.040	V
22	23.021	5044	612	0.094	0.081	
23	25.147	3873	507	0.073	0.067	

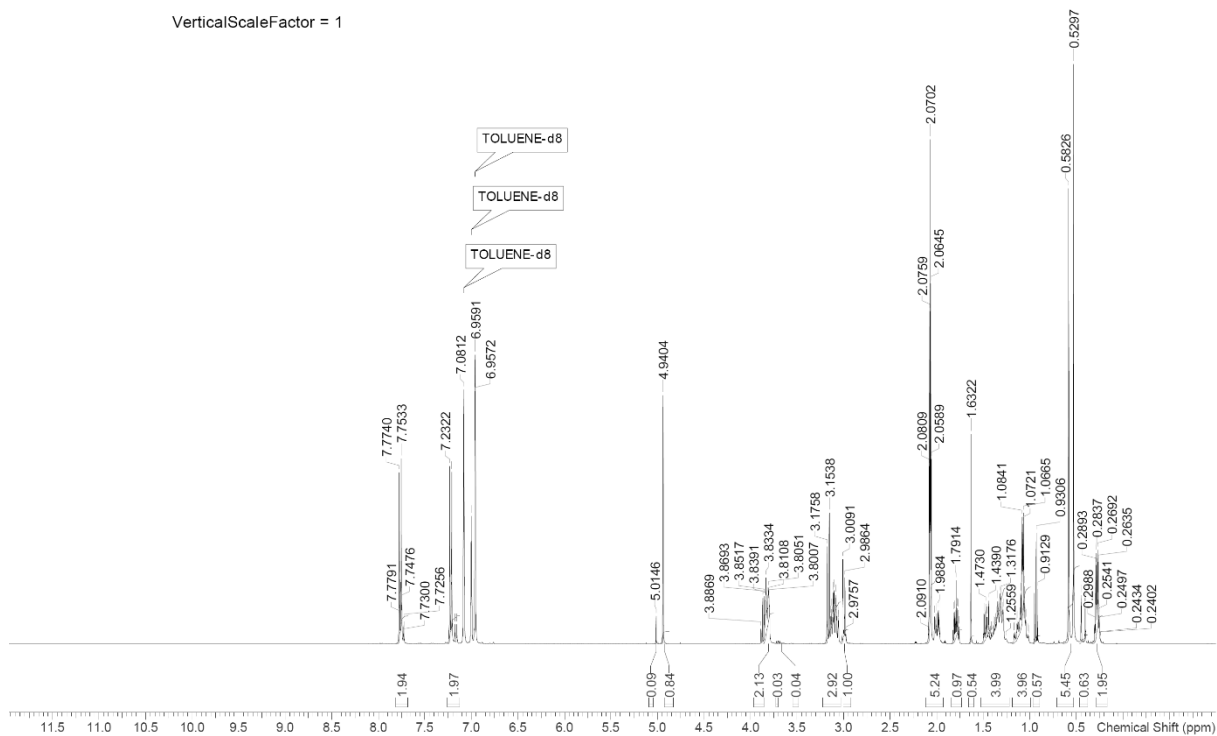


[Figure 2-11]

(Entry 1)



(Entry 2)



VerticalScaleFactor = 1

Chemical Shift (ppm)

Integration values: 1.96, 1.99, 2.09, 2.08, 1.00, 5.36, 0.97, 0.40, 4.03, 4.00, 0.44, 6.48, 1.96

Peak labels: 7.7765, 7.7715, 7.7501, 7.7451, 7.7224, 7.2272, 7.0812, 6.9585, 5.0083, 4.9328, 3.8687, 3.8504, 3.8385, 3.8328, 3.8278, 3.8095, 3.8045, 3.7995, 3.1683, 3.1463, 2.9964, 2.9757, 2.9663, 2.0903, 1.9871, 1.7851, 1.6310, 1.4699, 1.4365, 1.3157, 1.0822, 1.0652, 0.9239, 0.9123, 0.3988, 0.4907, 0.2843, 0.2490, 0.2453, 0.2786, 0.2648, 0.2591, -0.5782, -0.5240, -0.5240

TOLUENE-d8

TOLUENE-d8

TOLUENE-d8

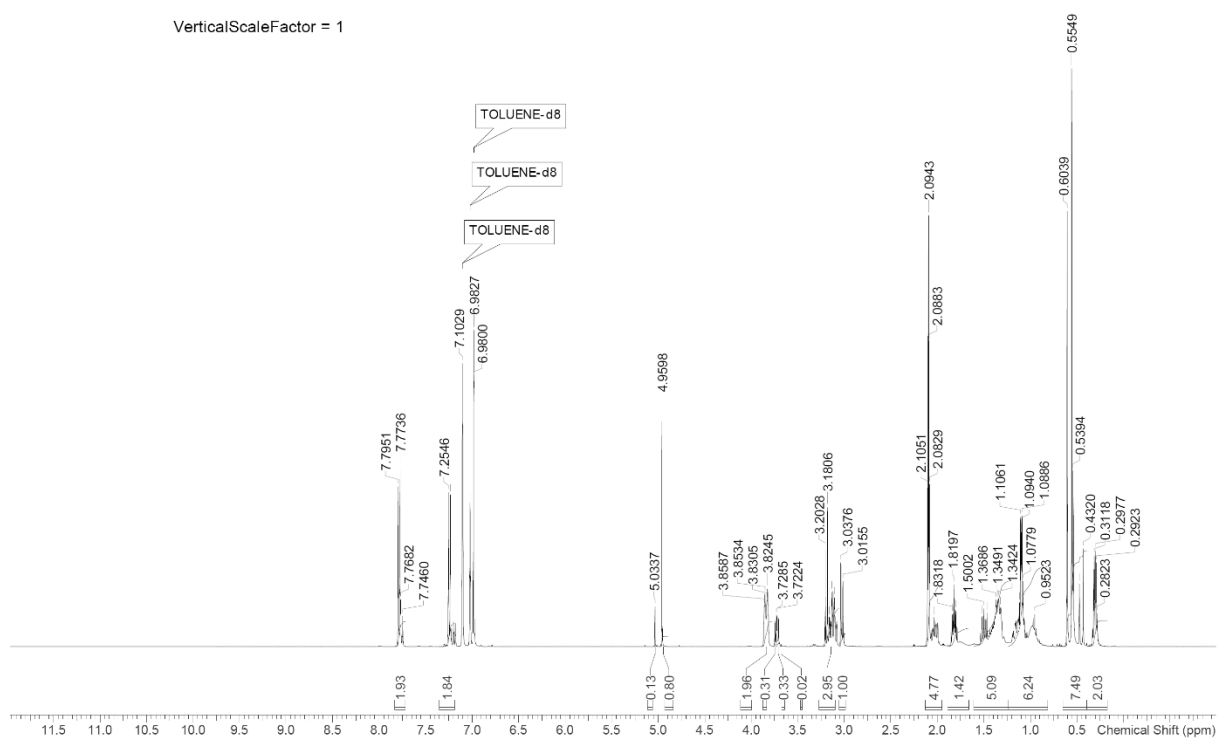
<sup>1</sup>H NMR spectrum (400 MHz, DMSO-d<sub>6</sub>) of 1,3-bis(4-ethoxyphenyl)propan-2-one. The x-axis represents the chemical shift in ppm, ranging from 0 to 10. The spectrum shows several characteristic peaks:

- Aromatic protons (7.4–7.8 ppm, multiplet, integral 2.00).
- Protons α to the ketone (3.6–3.9 ppm, multiplet, integral 2.19).
- Ethoxy methyl protons (~1.2 ppm, quartet, integral 6.40).
- Ethoxy methylene protons (~0.9 ppm, triplet, integral 6.41).
- Solvent peaks for DMSO-d<sub>6</sub> (2.50, 2.69, and 2.97 ppm).

Key peak data (Chemical Shift, ppm):

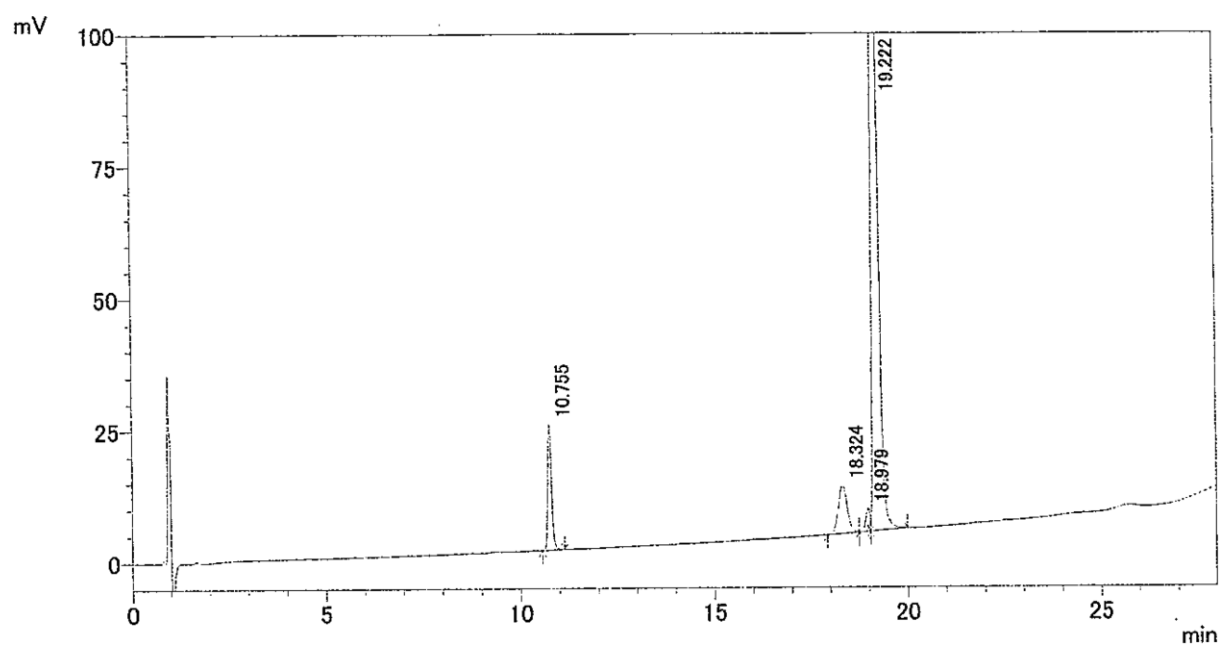
Chemical Shift (ppm)	Integration
7.740, 7.742, 7.756	2.00
7.2309, 7.2259	1.96
7.0837, 6.9591, 6.9516	2.00
4.9396	0.98
3.8718, 3.8542, 3.8360, 3.8121, 3.8070, 3.8020	2.19
3.1740, 3.1519, 3.1060, 3.0047, 2.9627	2.03
2.0834, 2.0771, 2.0670, 2.0614	6.40
1.6341, 1.4743, 1.4403, 1.3156, 1.0957, 1.0797, 1.0734, 1.0677, 0.9331, 0.9155	6.41
0.2883, 0.2837, 0.2837, 0.2635	2.00

[Figure 2-12]



[Figure 2-13]

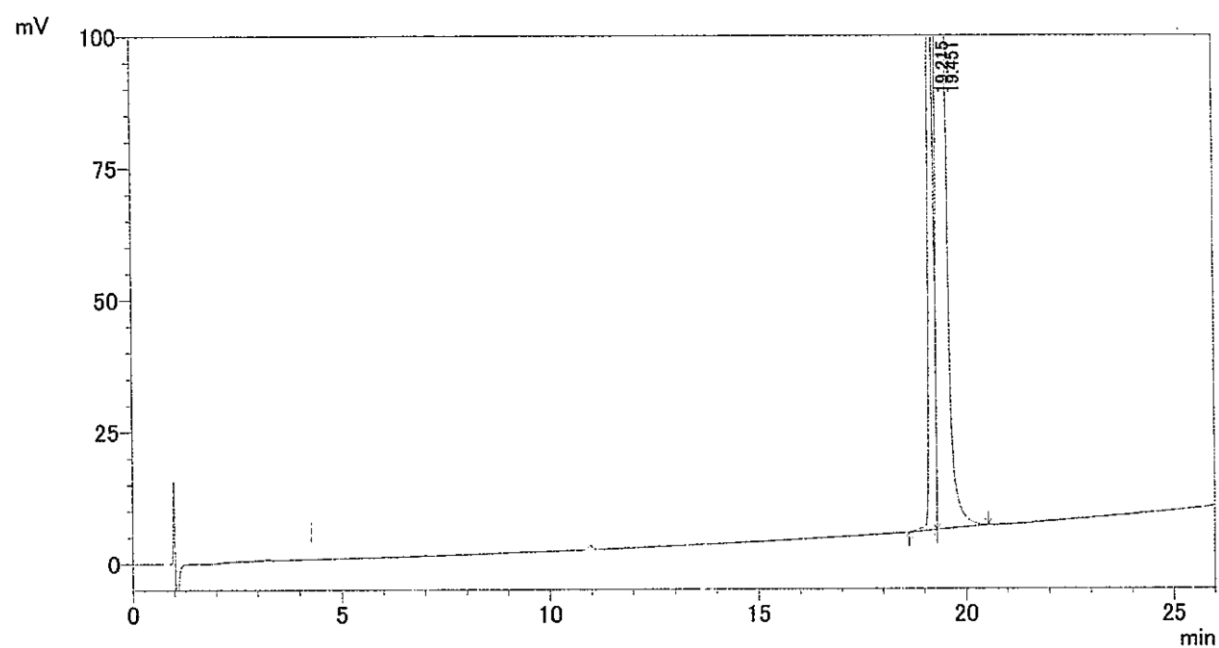
(Entry 1)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	10.755	163402	23979	5.920	7.364	
2	18.324	146719	9225	5.316	2.833	
3	18.979	33092	4376	1.199	1.344	V
4	19.222	2416808	288048	87.565	88.459	V
合計		2760021	325628	100.000	100.000	

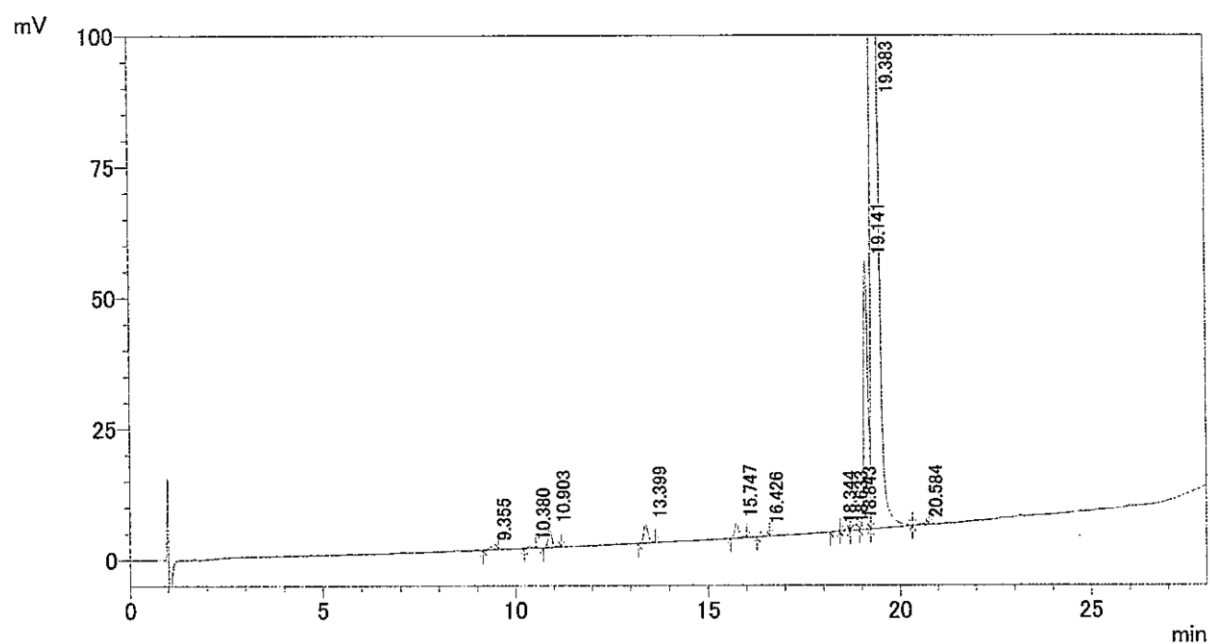
(Entry 2)



検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	19.215	1168525	151505	11.297	12.684	
2	19.451	9174724	1042905	88.703	87.316	V
合計		10343249	1194410	100.000	100.000	

(Entry 3)

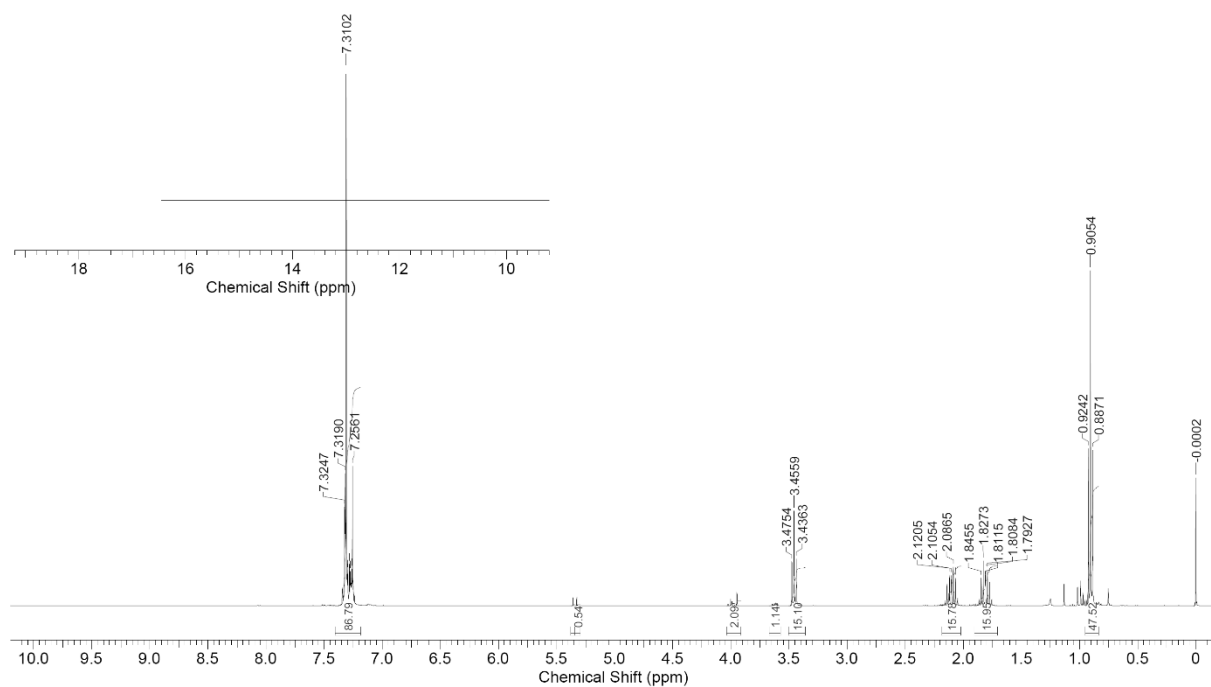


検出器A Ch1 230nm

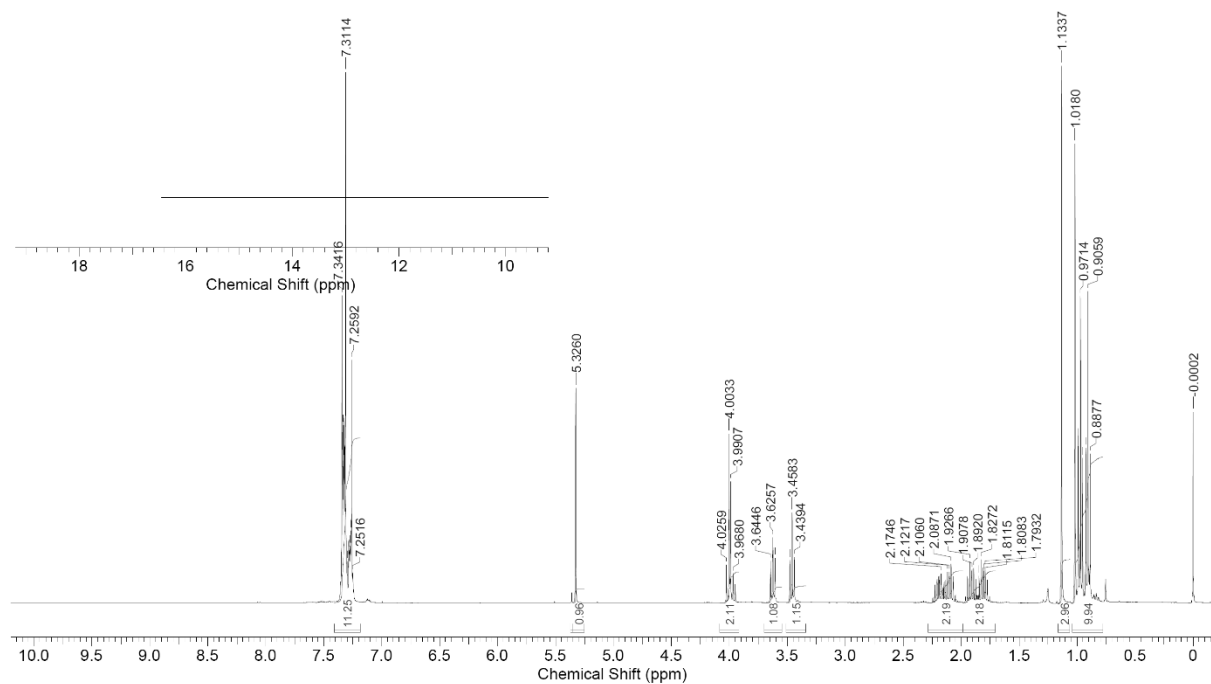
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	9.355	4670	588	0.089	0.094	
2	10.380	2353	337	0.045	0.054	
3	10.903	25351	3623	0.480	0.576	
4	13.399	27839	3519	0.528	0.559	
5	15.747	21224	2813	0.402	0.447	
6	16.426	8820	1244	0.167	0.198	
7	18.344	3412	445	0.065	0.071	
8	18.633	4265	344	0.081	0.055	V
9	18.843	10031	985	0.190	0.157	V
10	19.141	399367	51216	7.569	8.141	V
11	19.383	4765311	563721	90.316	89.608	V
12	20.584	3647	263	0.069	0.042	V
合計		5276290	629098	100.000	100.000	

[Figure 2-14]

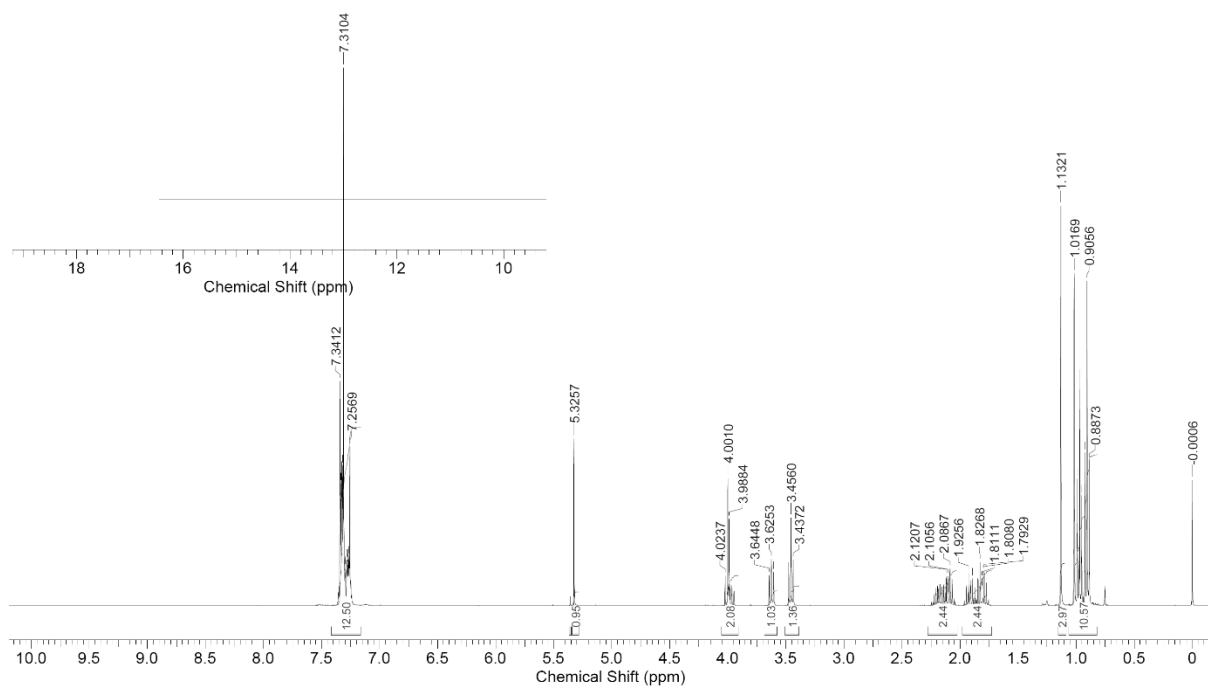
(Entry 1)



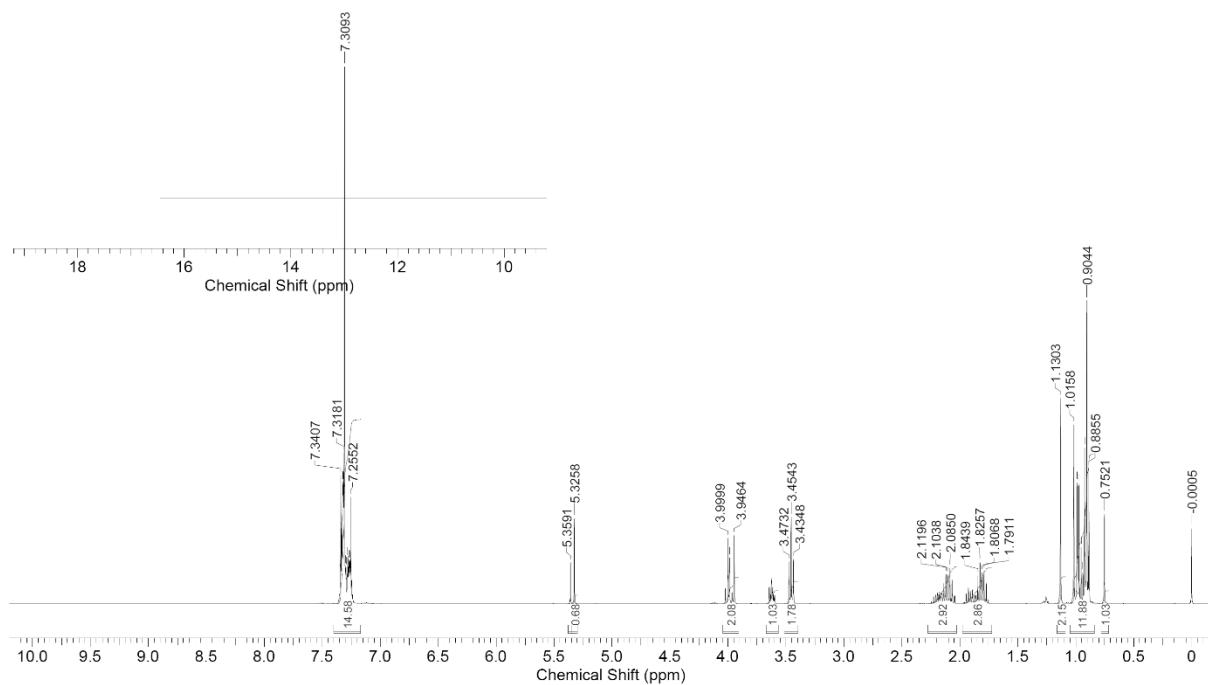
(Entry 2)



**(Entry 3)**

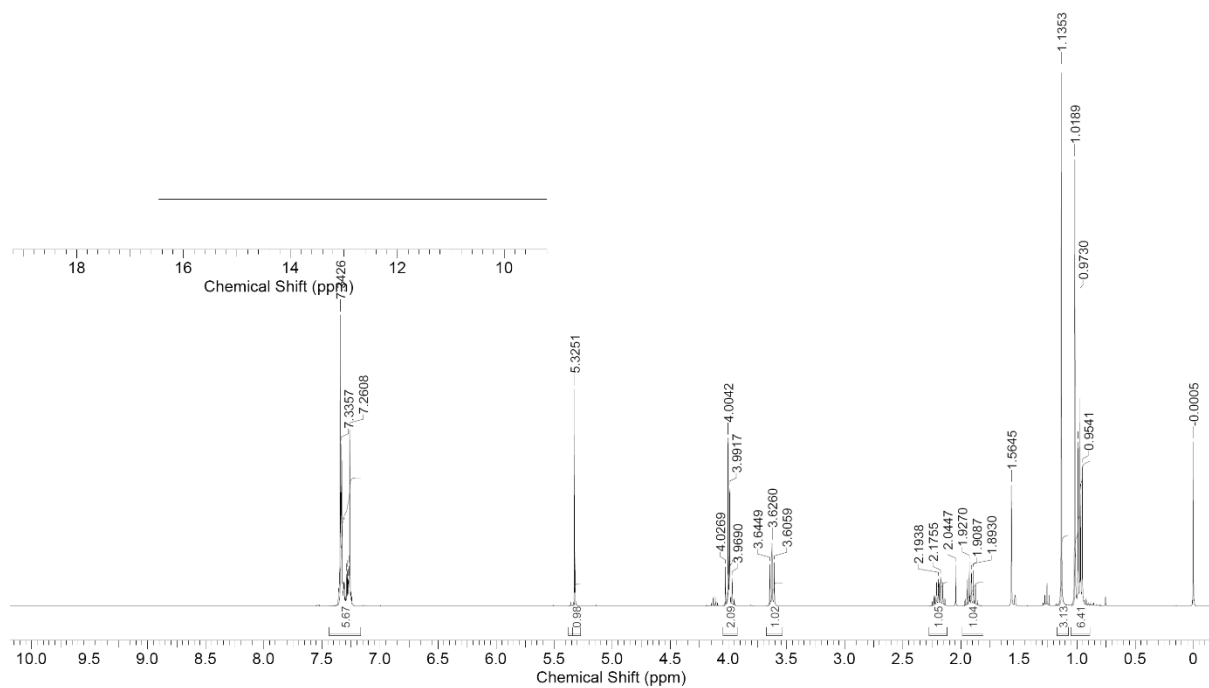


**(Entry 4)**

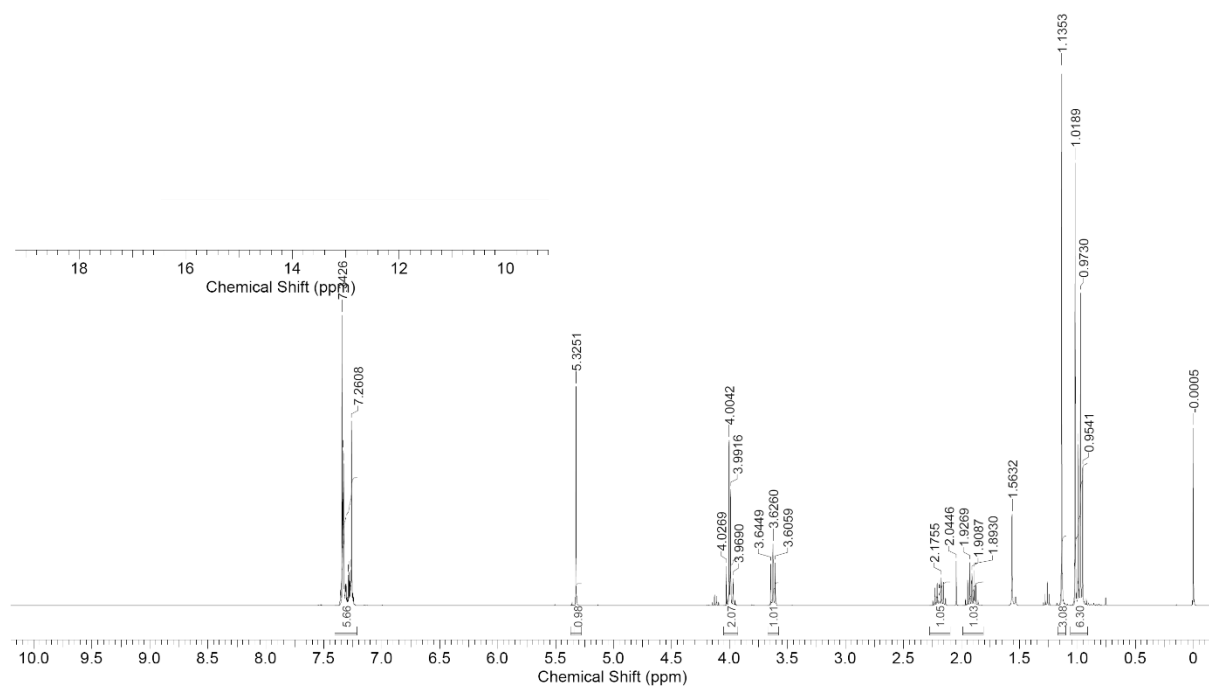




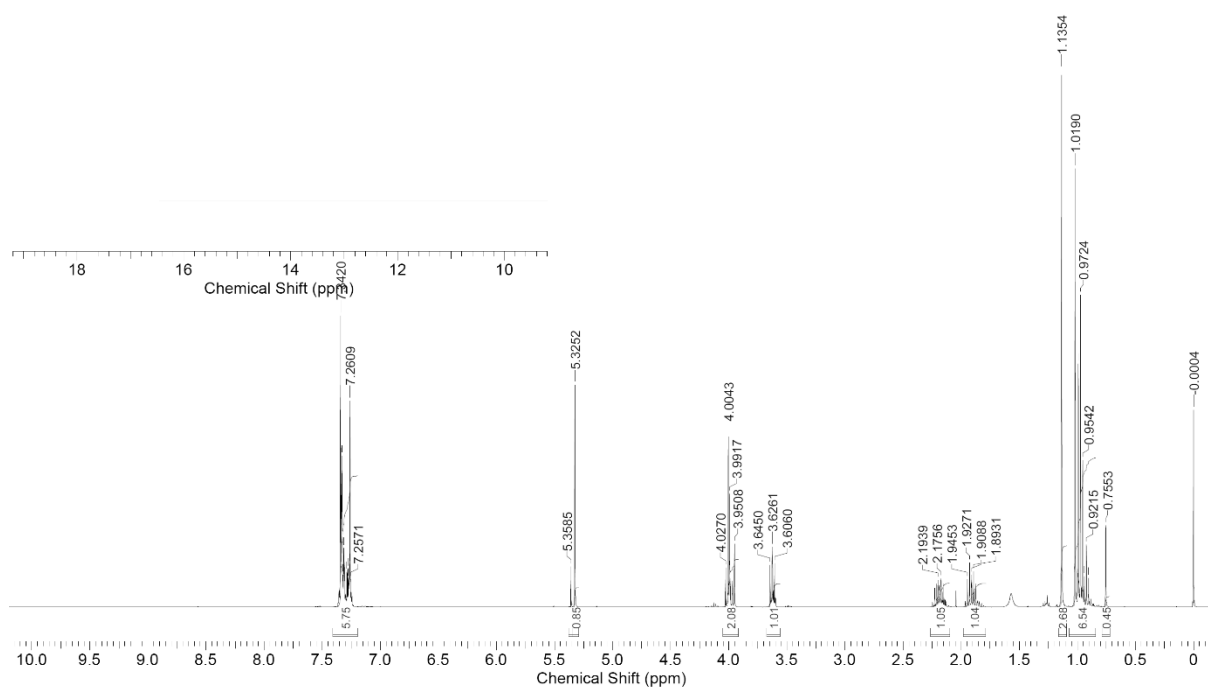
**(Entry 5)**



**(Entry 6)**

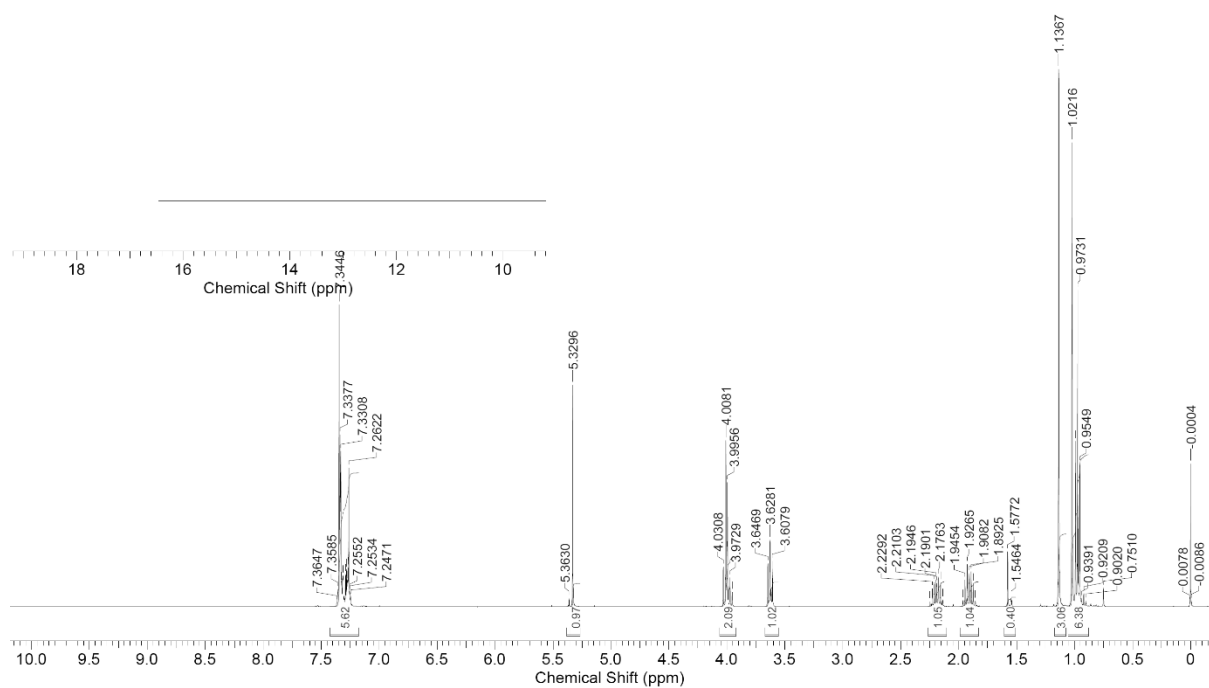


(Entry 7)

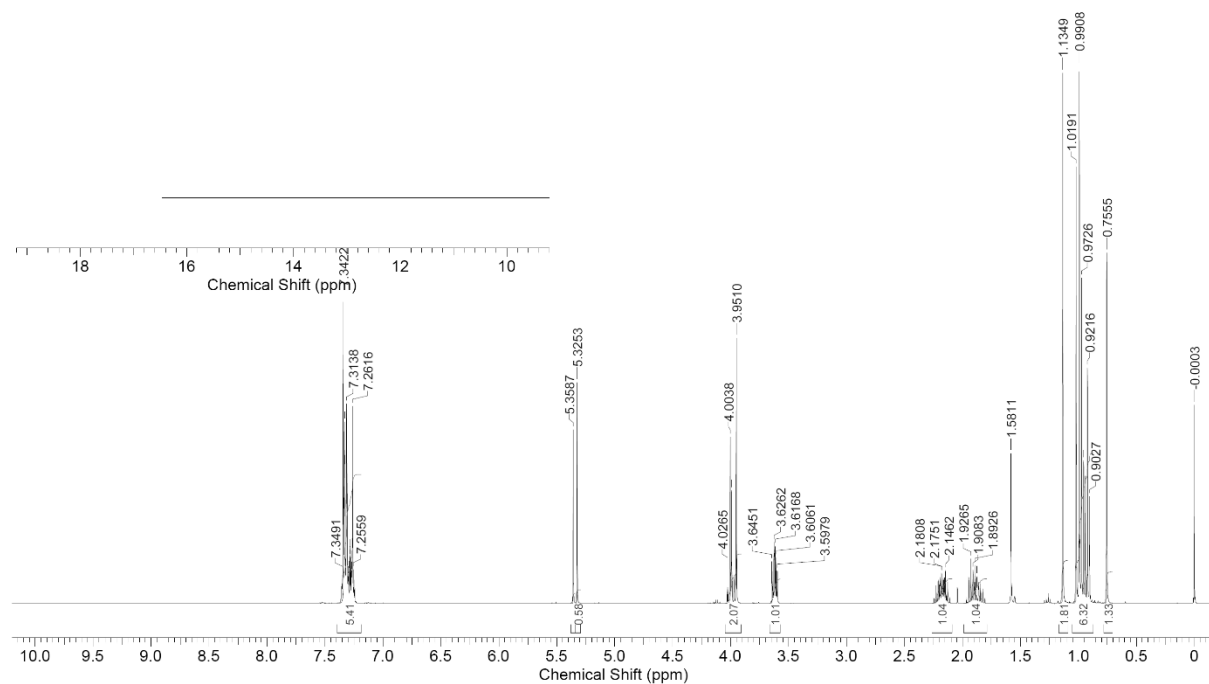


[Figure 2-15]

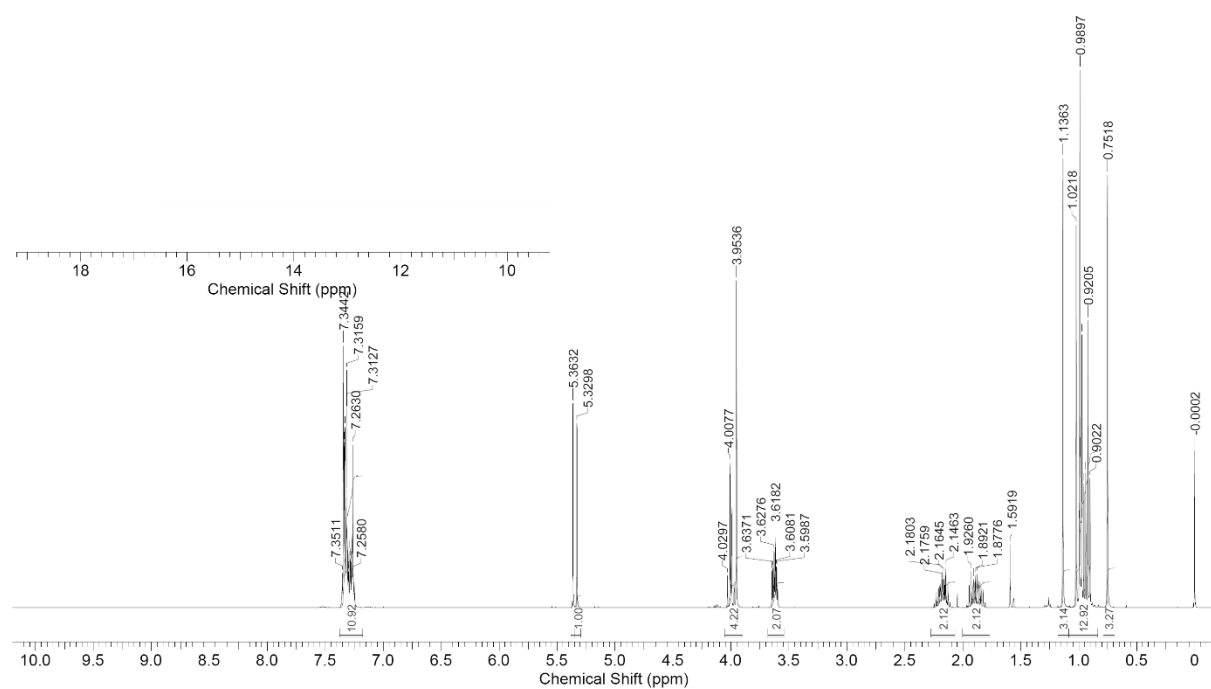
(Entry 1)



(Entry 2)

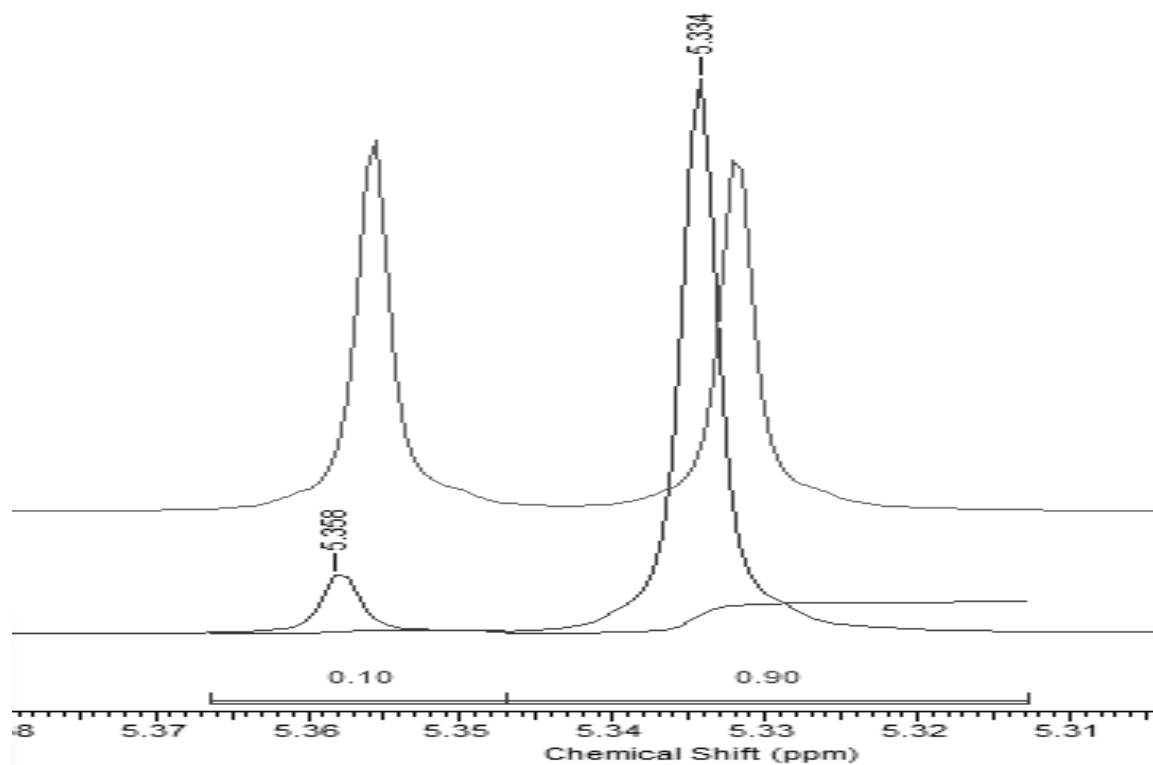
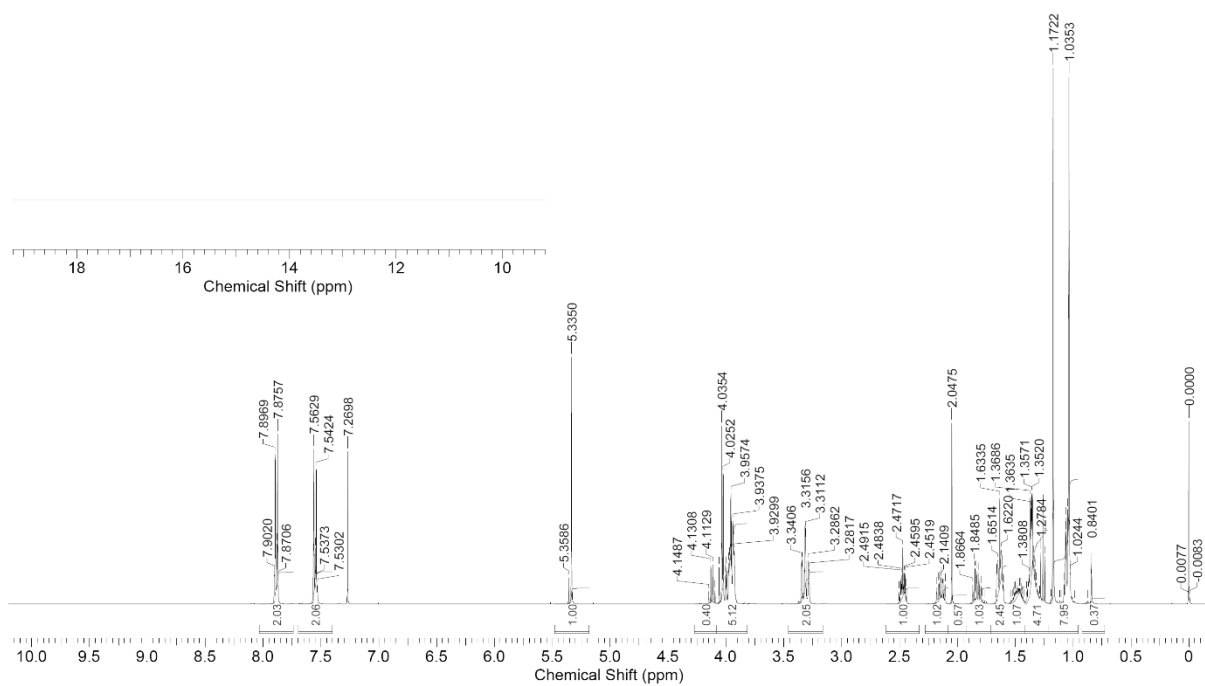


**(Entry 3)**

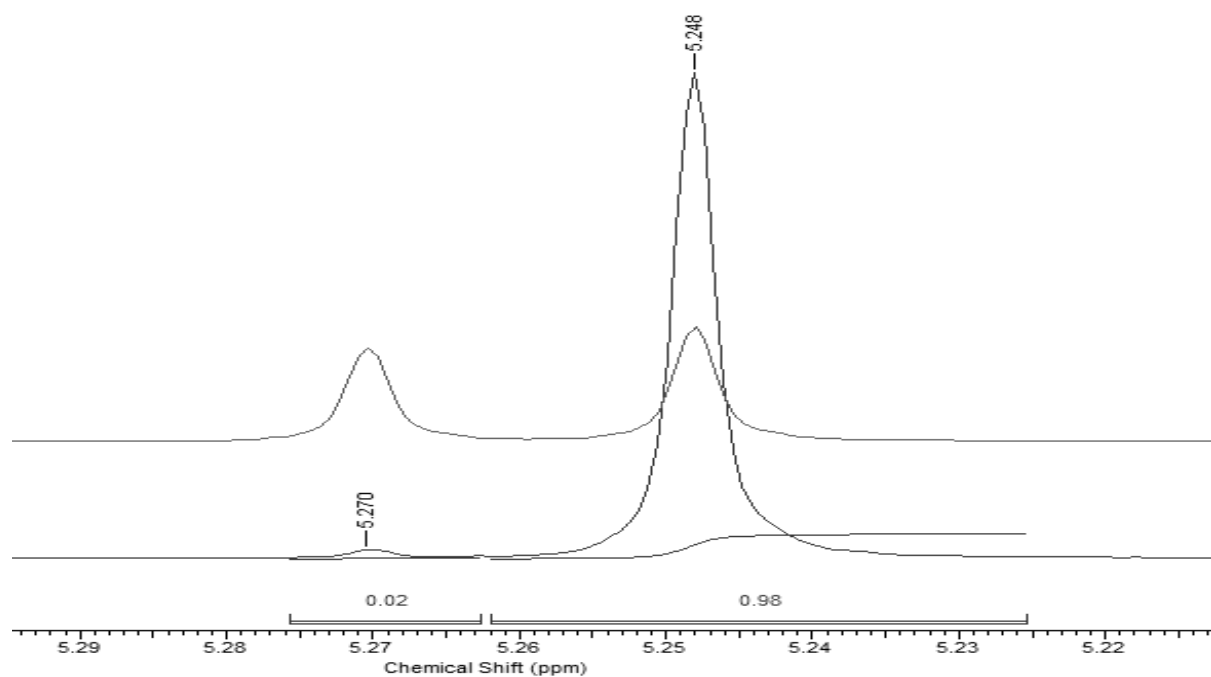
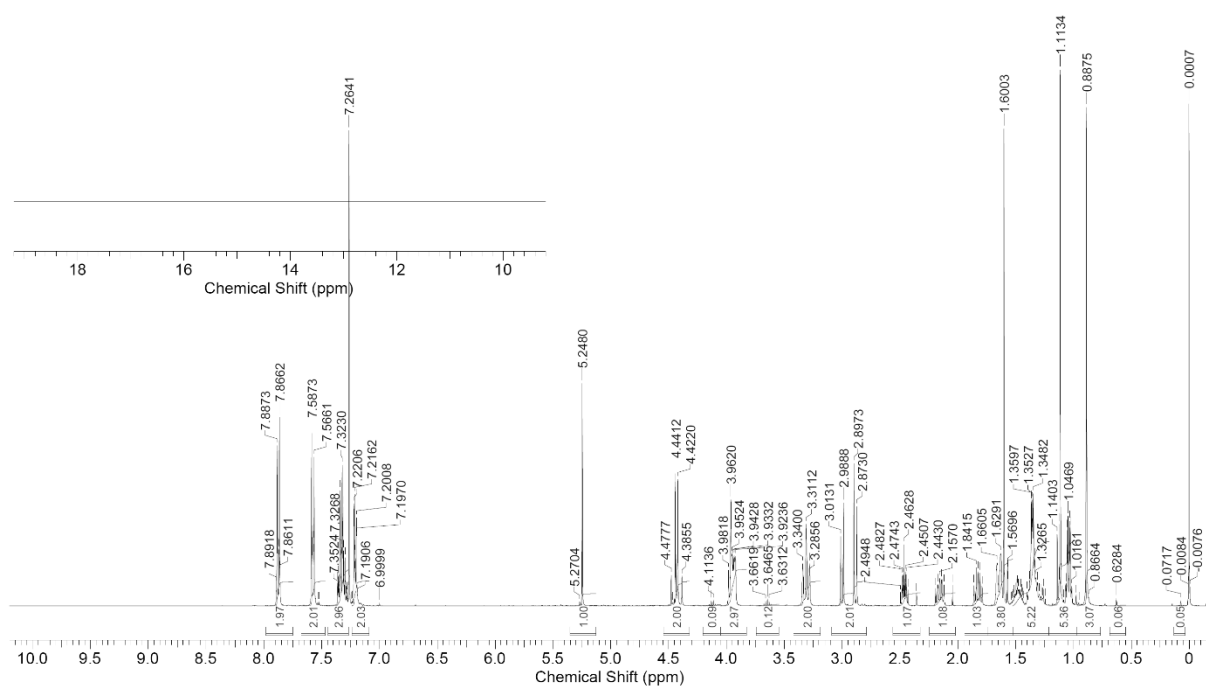


[Figure2-16]

(*R,R*)-10

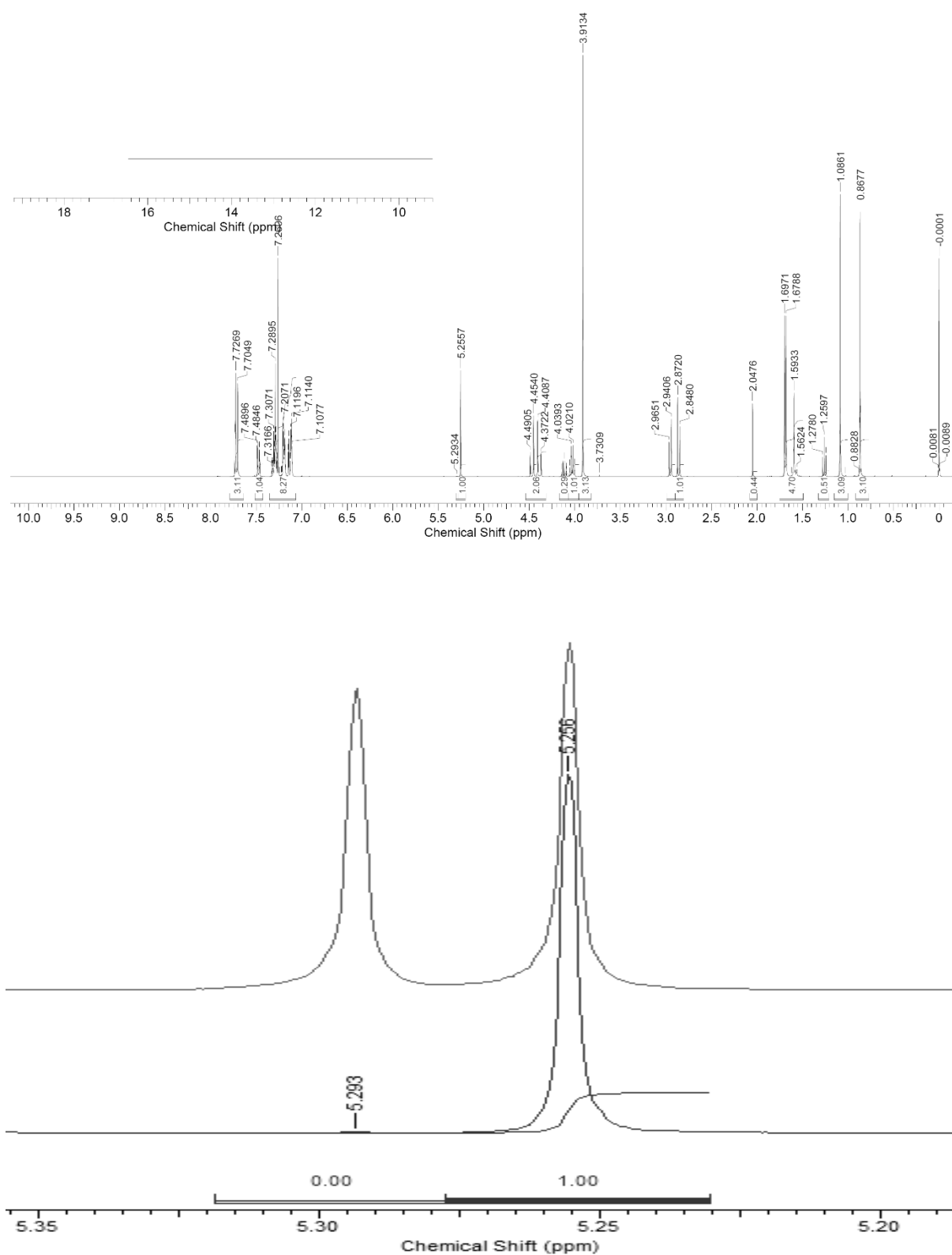


**(R,R)-15**

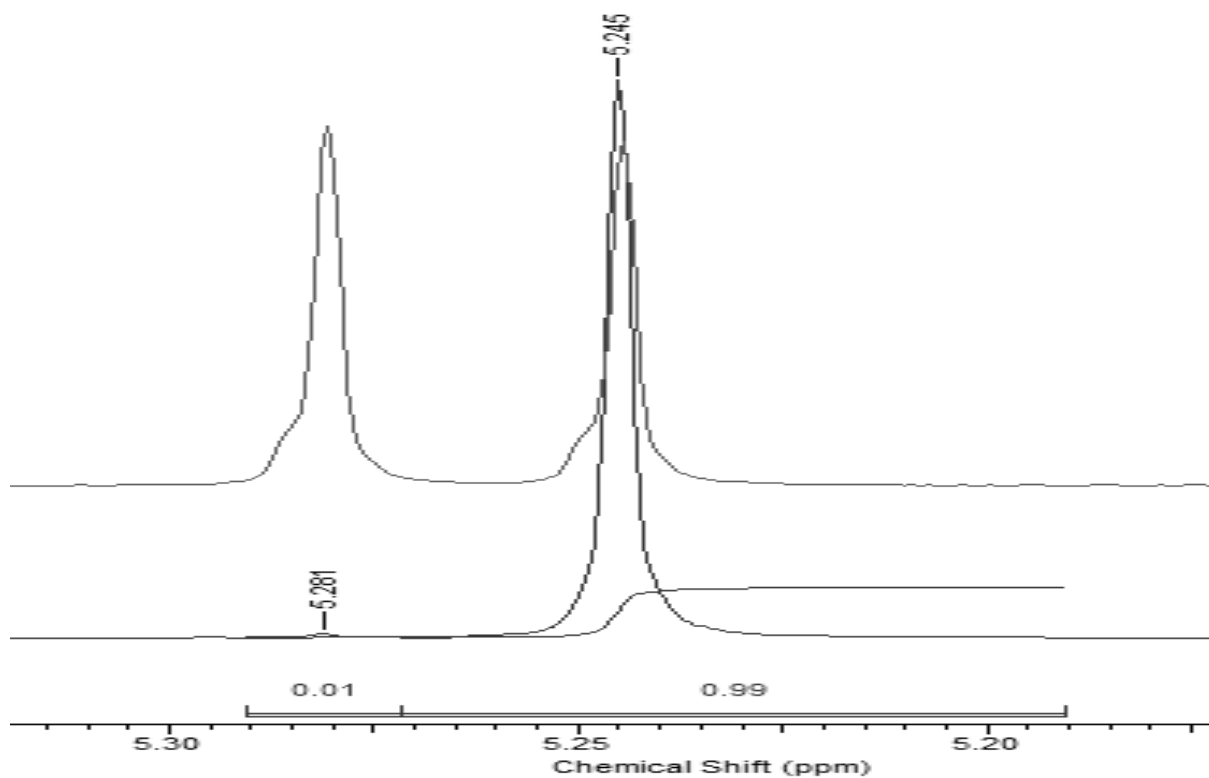
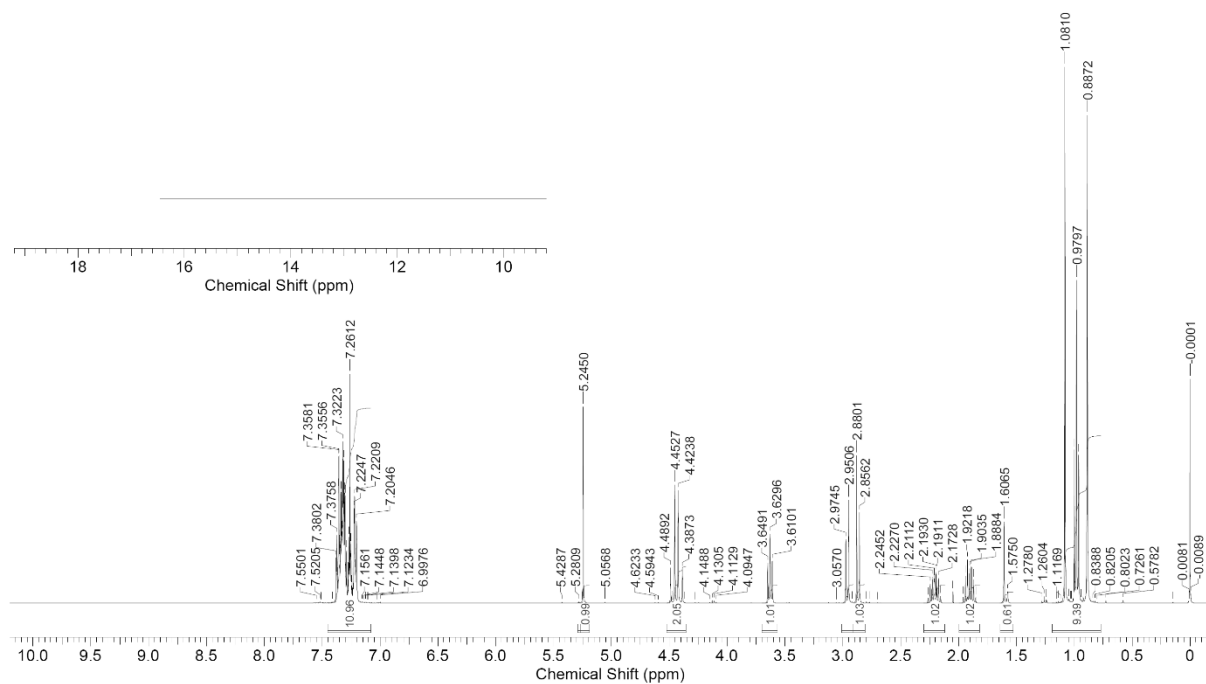


[Figure 2-17]

(*R,R*)-16

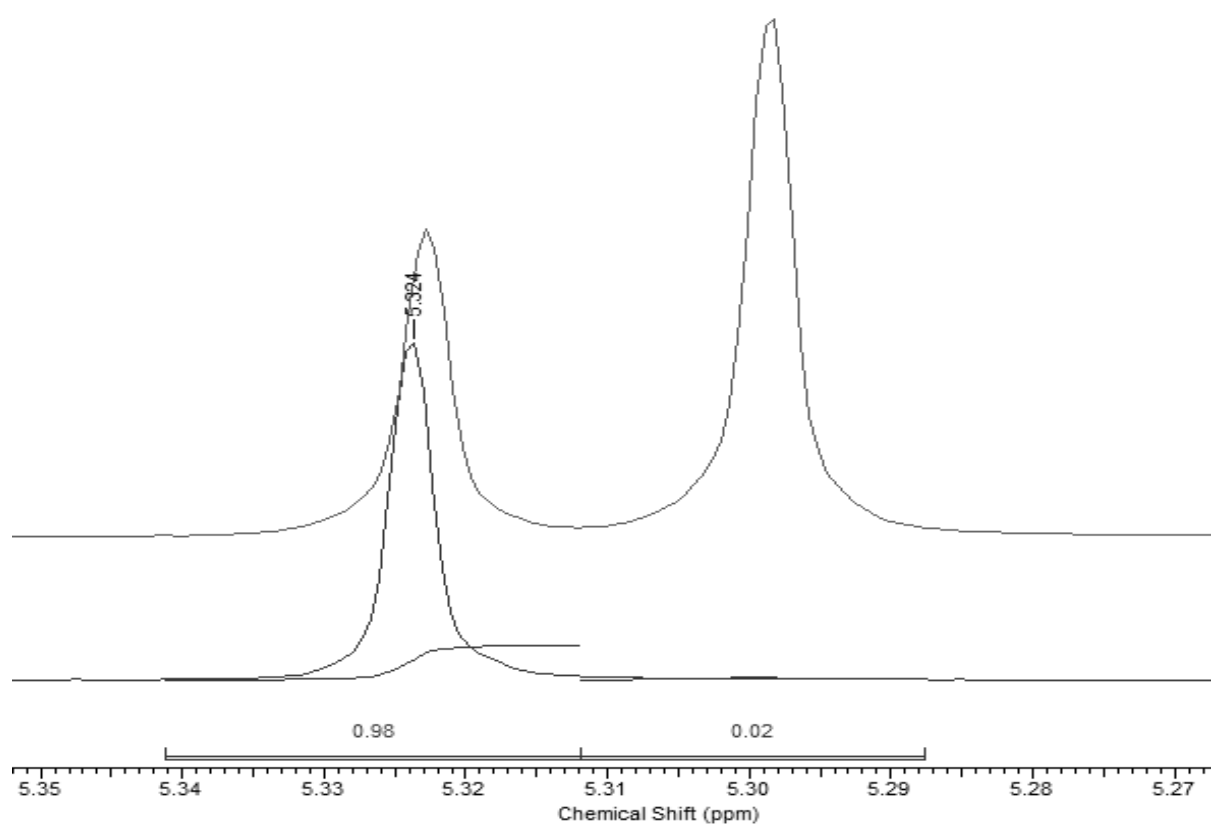
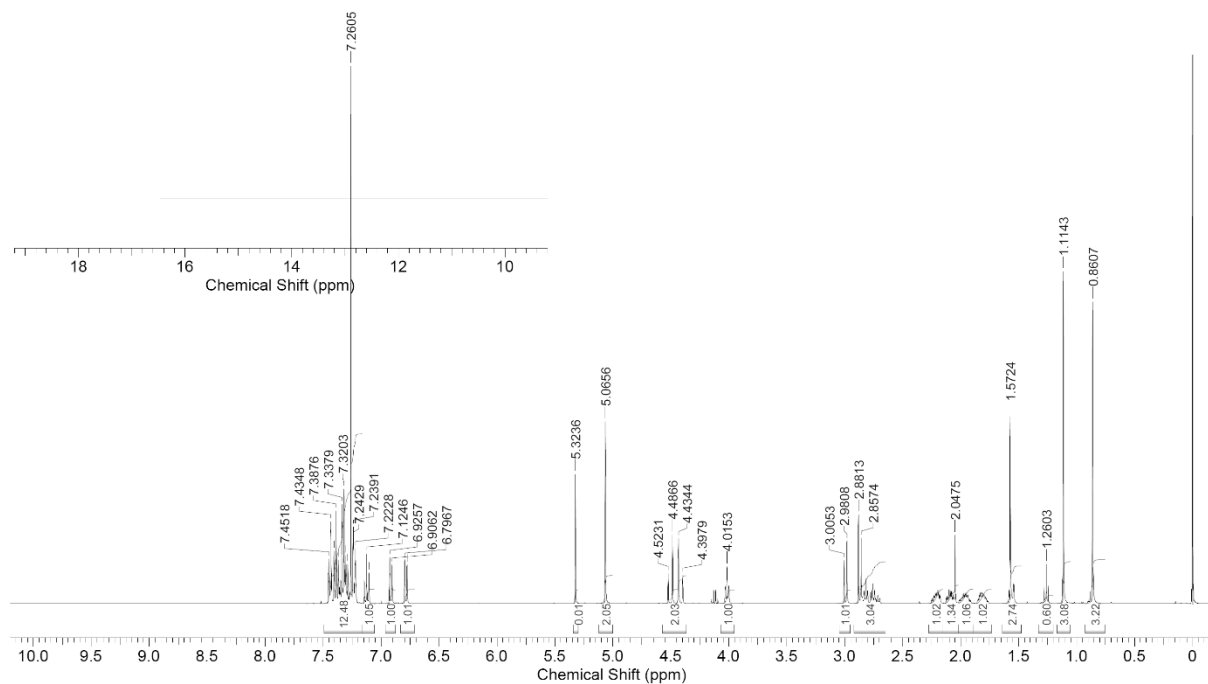


**(*R,R*)-17**

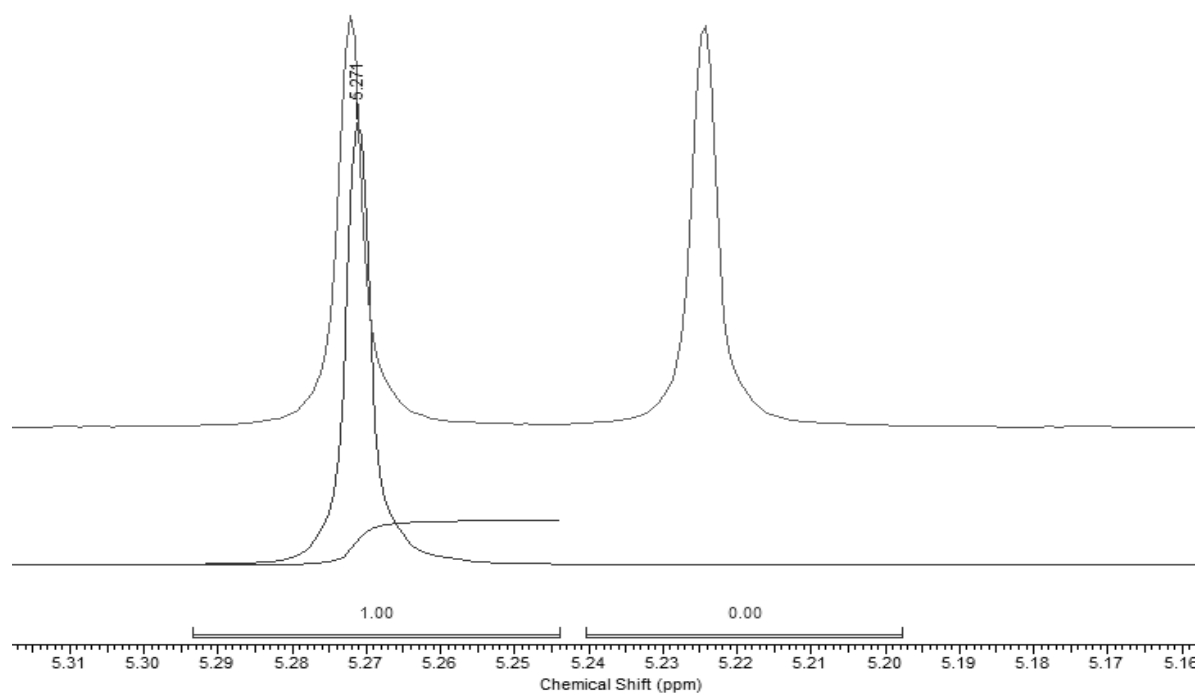
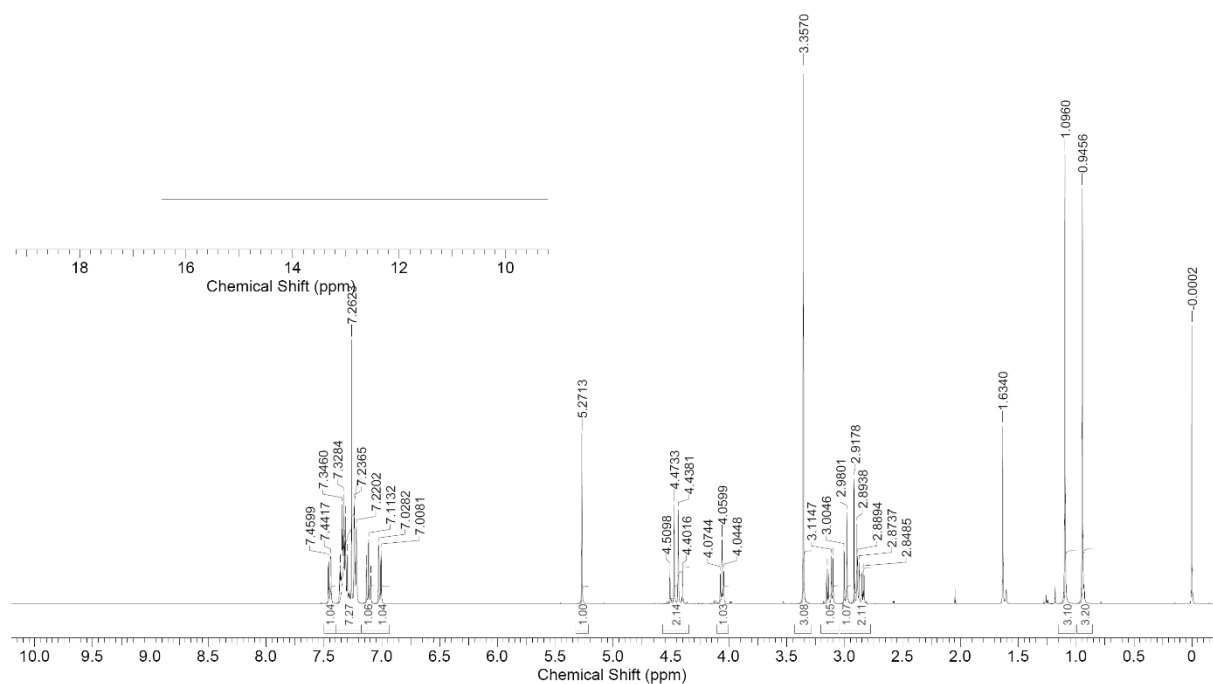




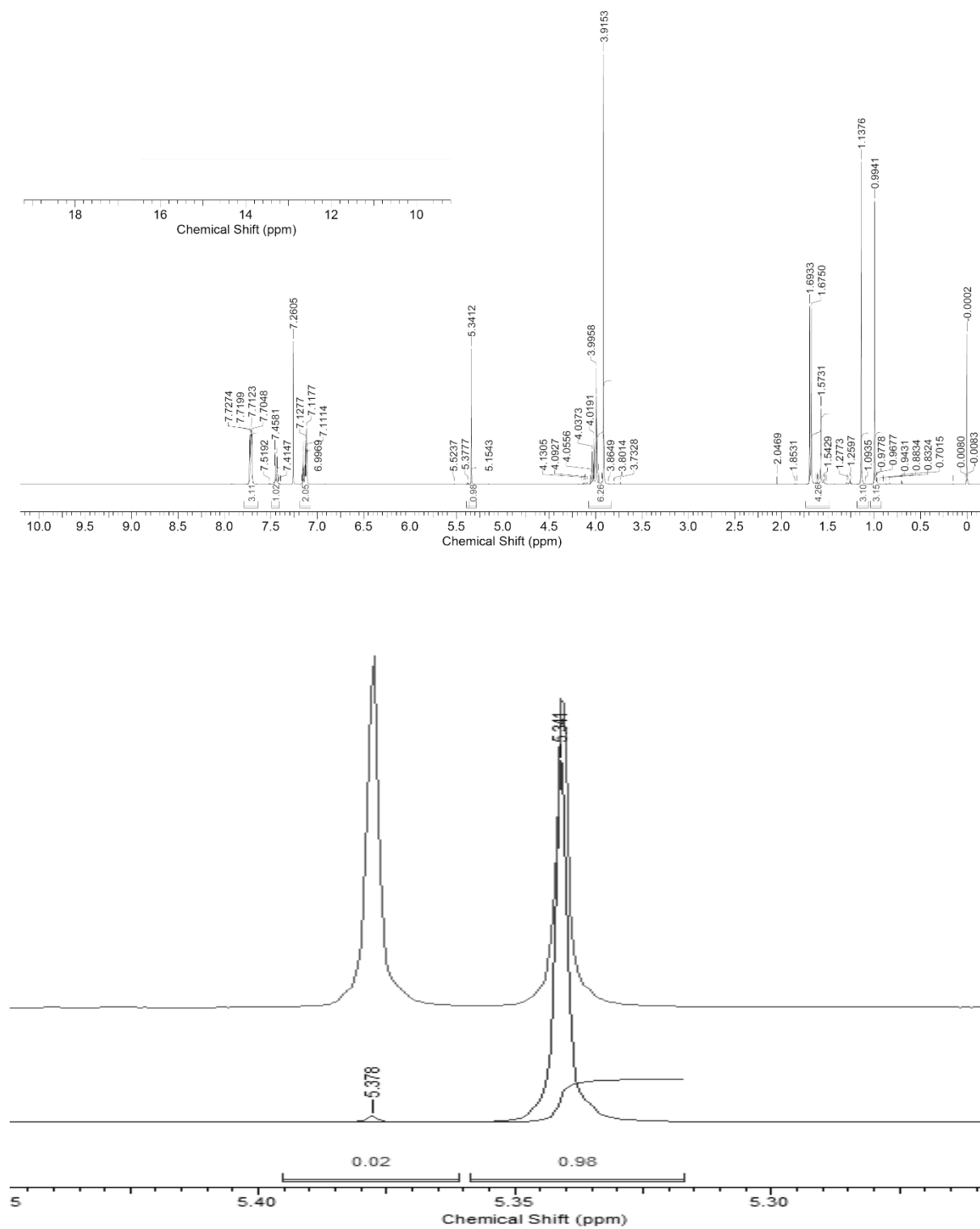
**(R,R)-18**



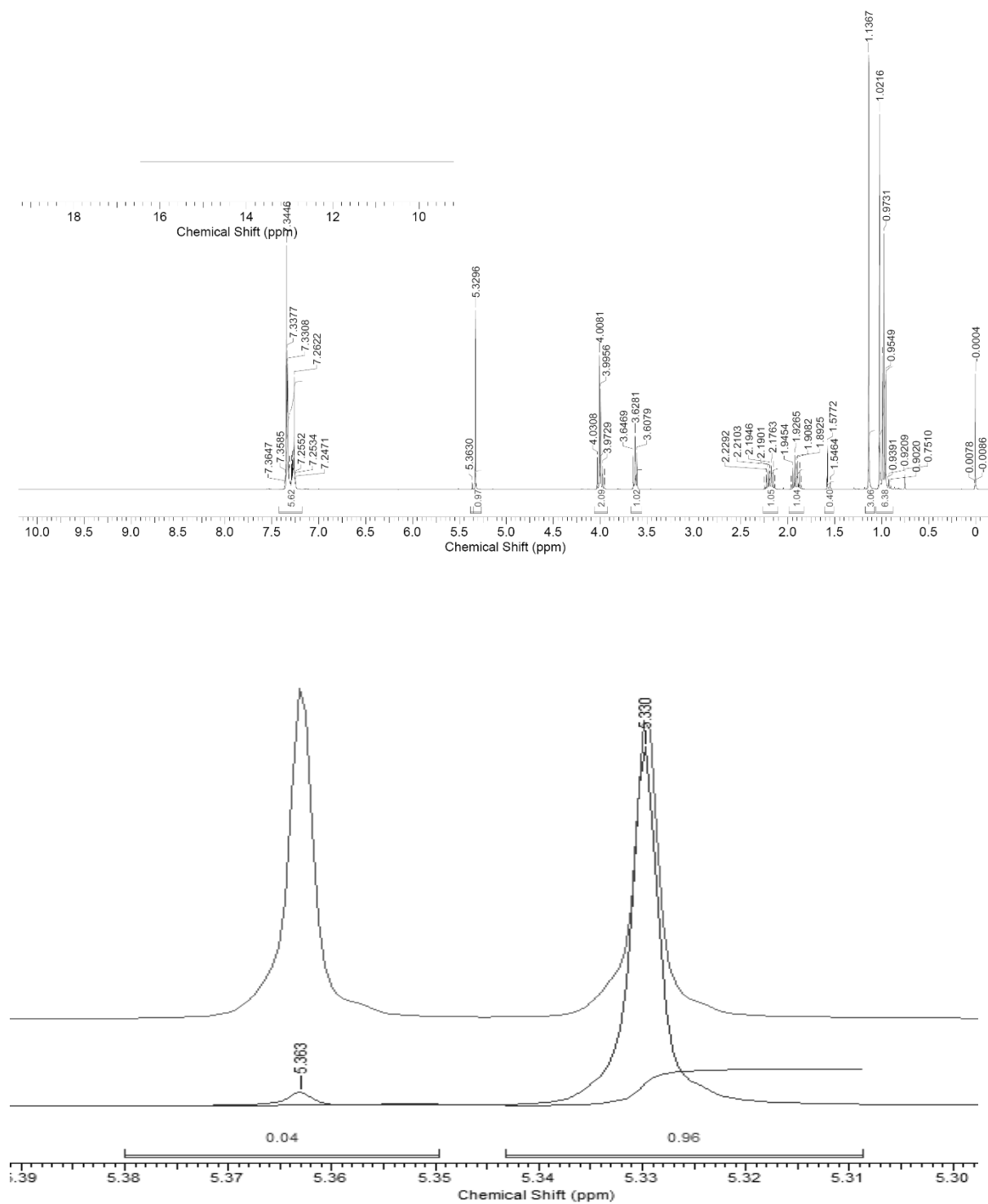
**(R,R)-19**



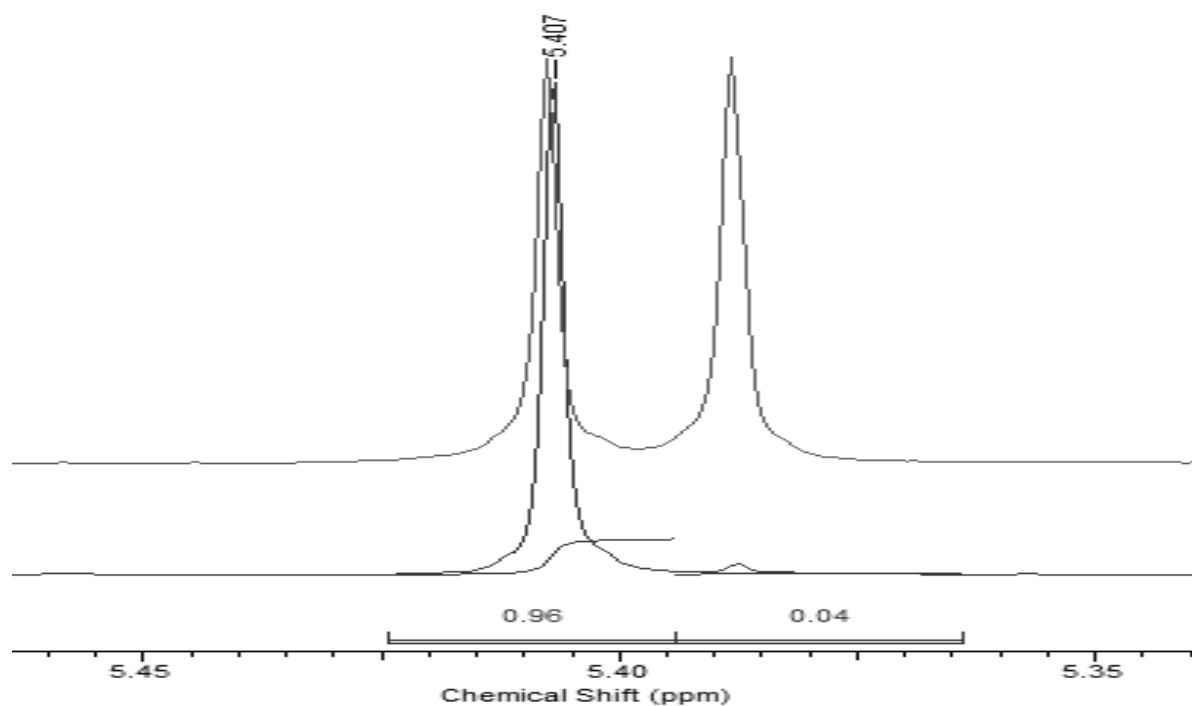
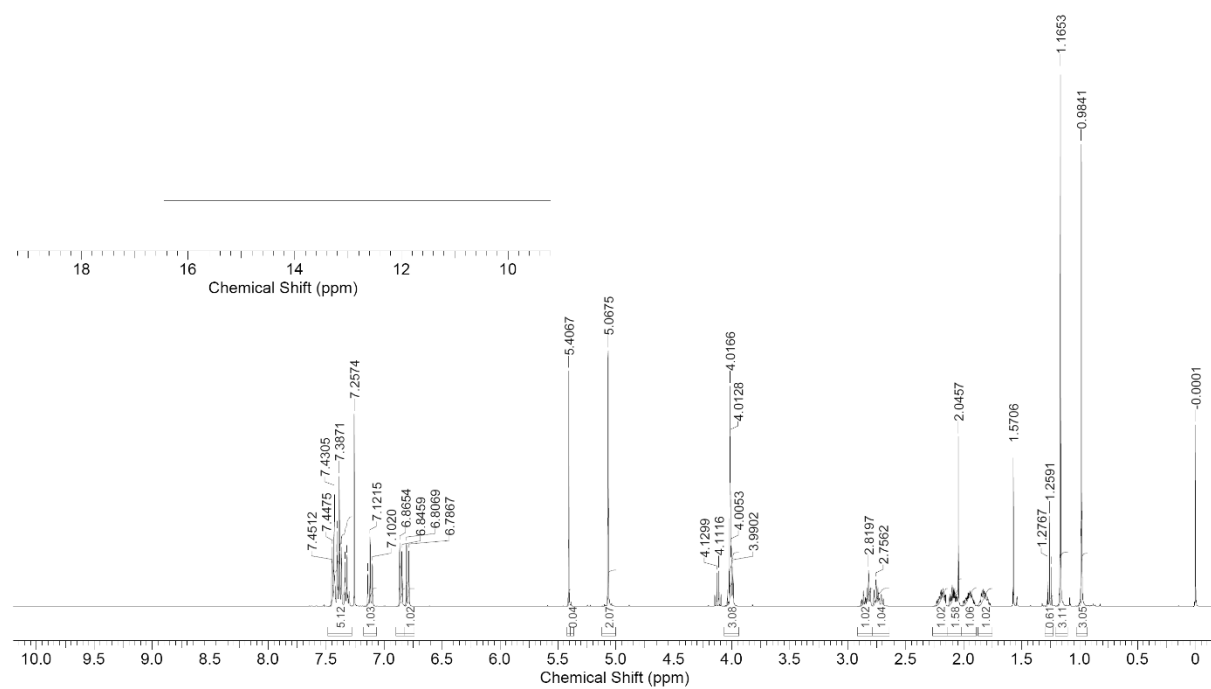
**(R,R)-20**



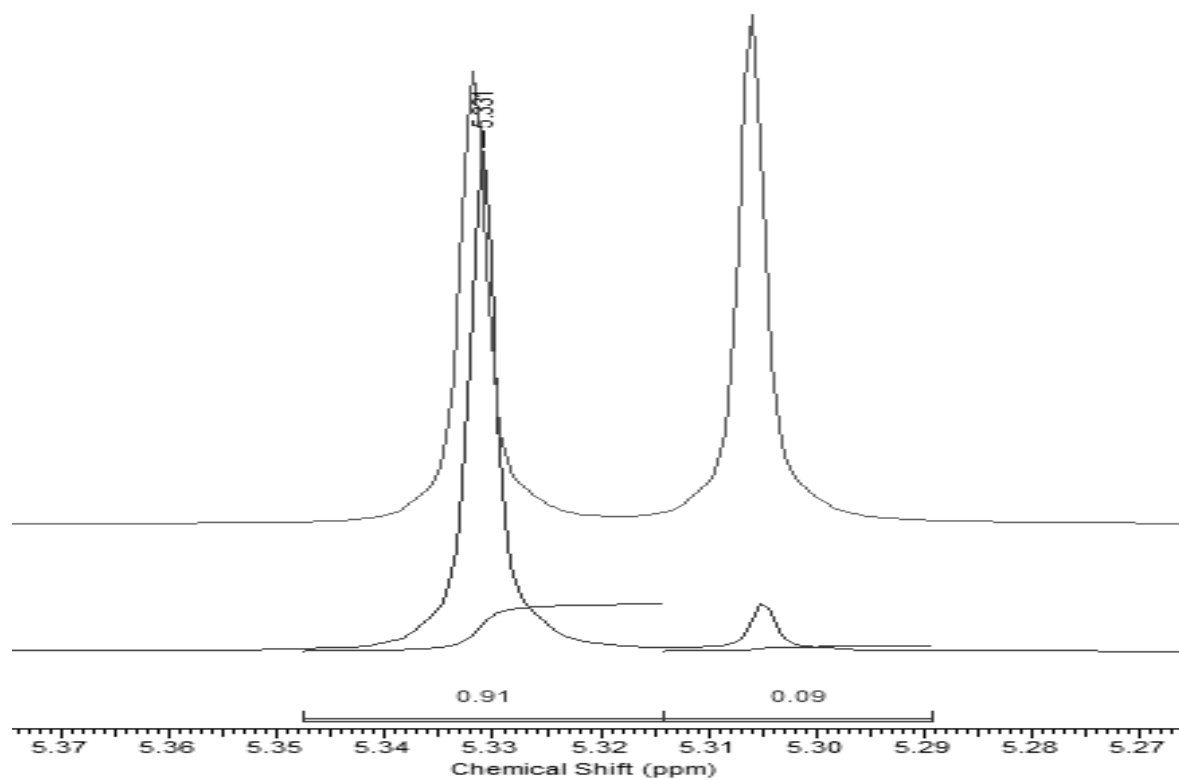
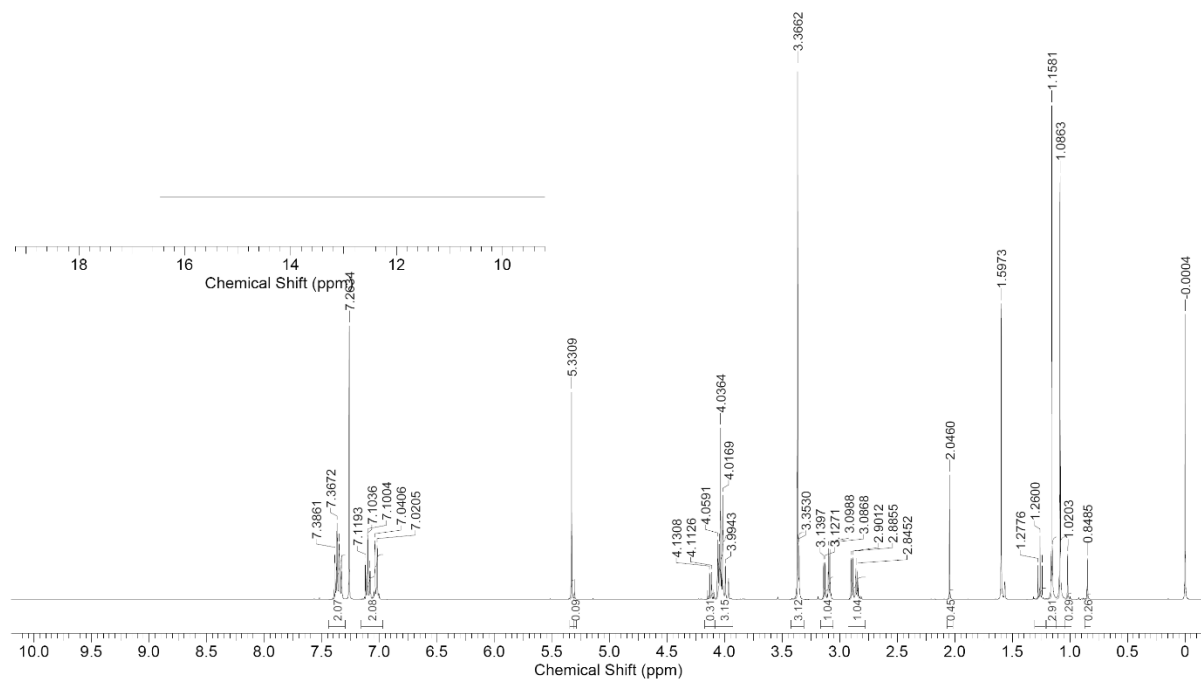
**(*R,R*)-13**



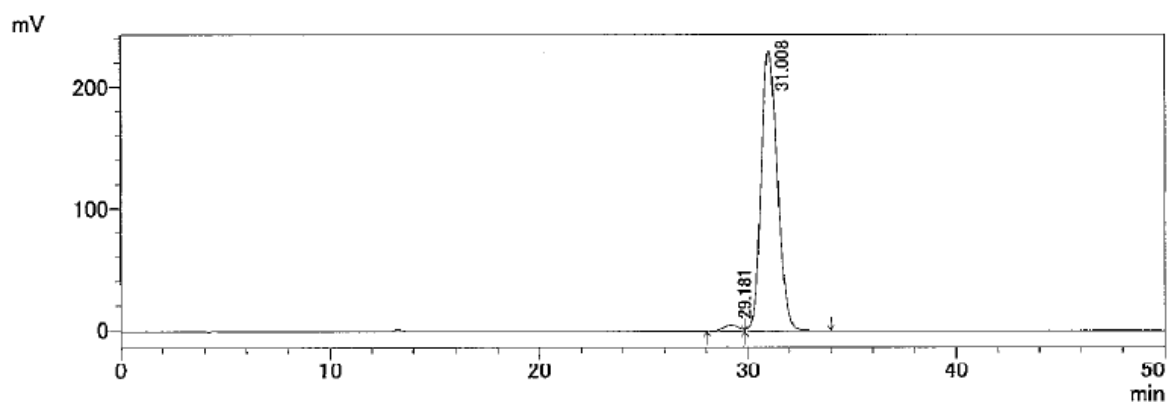
**(*R,R*)-21**



**(*R,R*)-22**



[Figure 2-18]

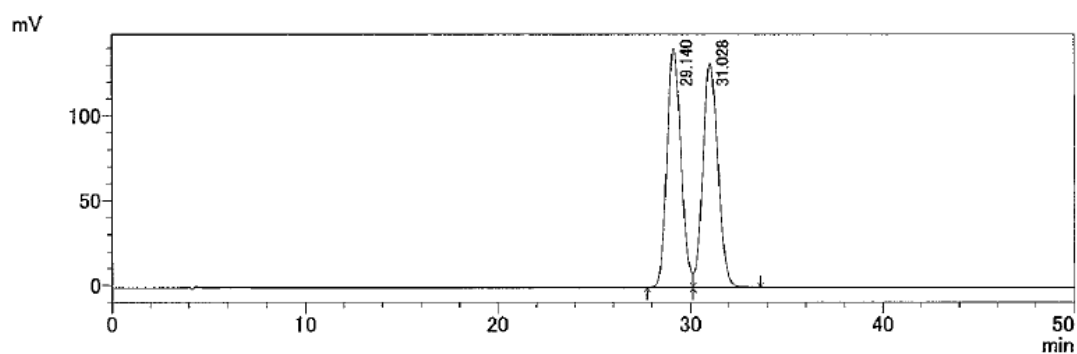


1 Det.A Ch1/230nm

検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	29.181	240838	4904	1.871	2.077	
2	31.008	12630296	231249	98.129	97.923	V
合計		12871134	236153	100.000	100.000	

参考：ラセミ体



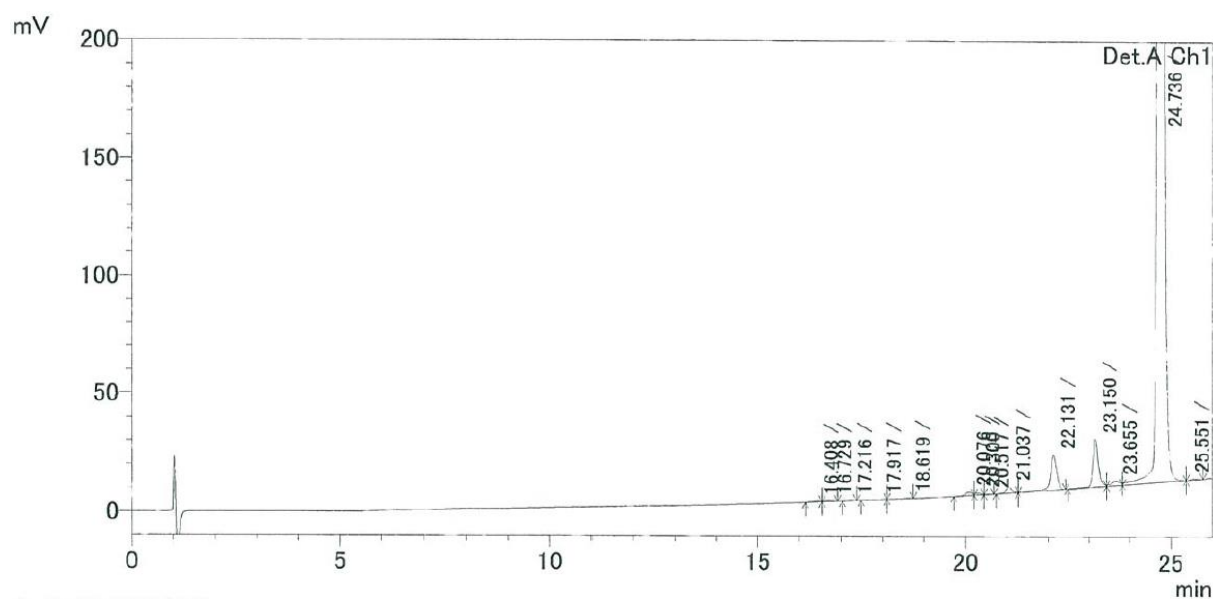
1 Det.A Ch1/230nm

検出器A Ch1 230nm

ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	29.140	7152913	141311	49.751	51.692	
2	31.028	7224612	132059	50.249	48.308	V
合計		14377525	273370	100.000	100.000	

[Figure 3-4]

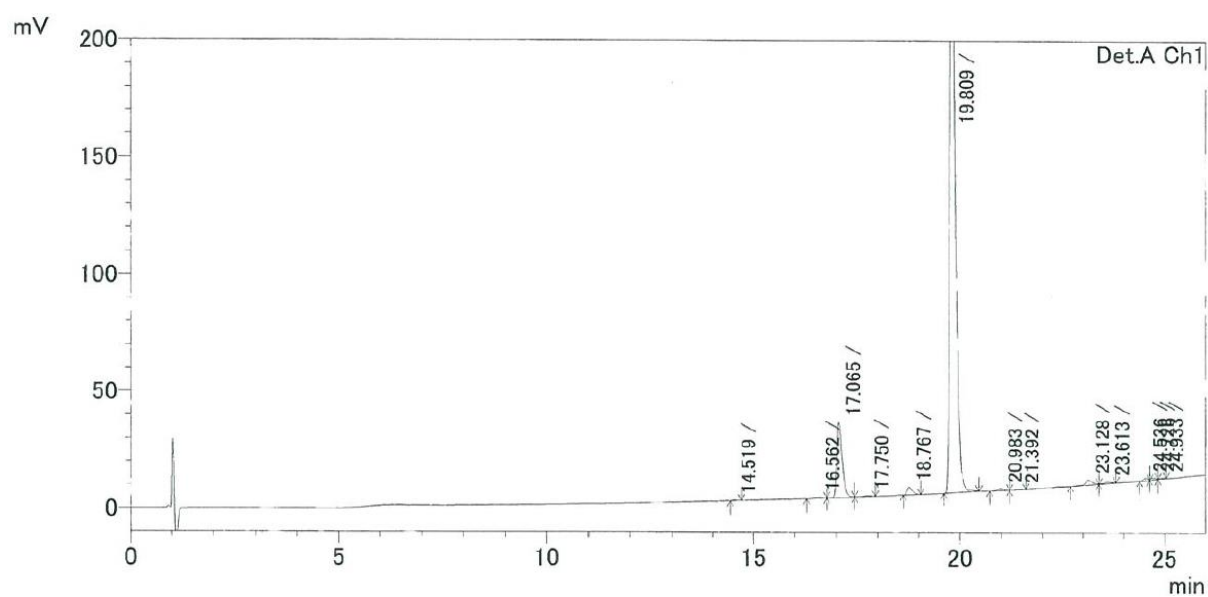
Compound 6



ピーク#	保持時間	面積	高さ	面積%	マーク
1	16.408	4746	347	0.067	
2	16.729	6093	407	0.086	V
3	17.216	1972	219	0.028	
4	17.917	1201	50	0.017	
5	18.619	1709	180	0.024	
6	20.076	17000	1469	0.241	
7	20.300	9132	907	0.130	V
8	20.517	1356	167	0.019	V
9	21.037	26710	2790	0.379	
10	22.131	160198	14606	2.274	V
11	23.150	189122	19659	2.685	
12	23.655	29433	1909	0.418	V
13	24.736	6590220	676381	93.550	V
14	25.551	5668	546	0.080	V
合計		7044559	719640	100.000	

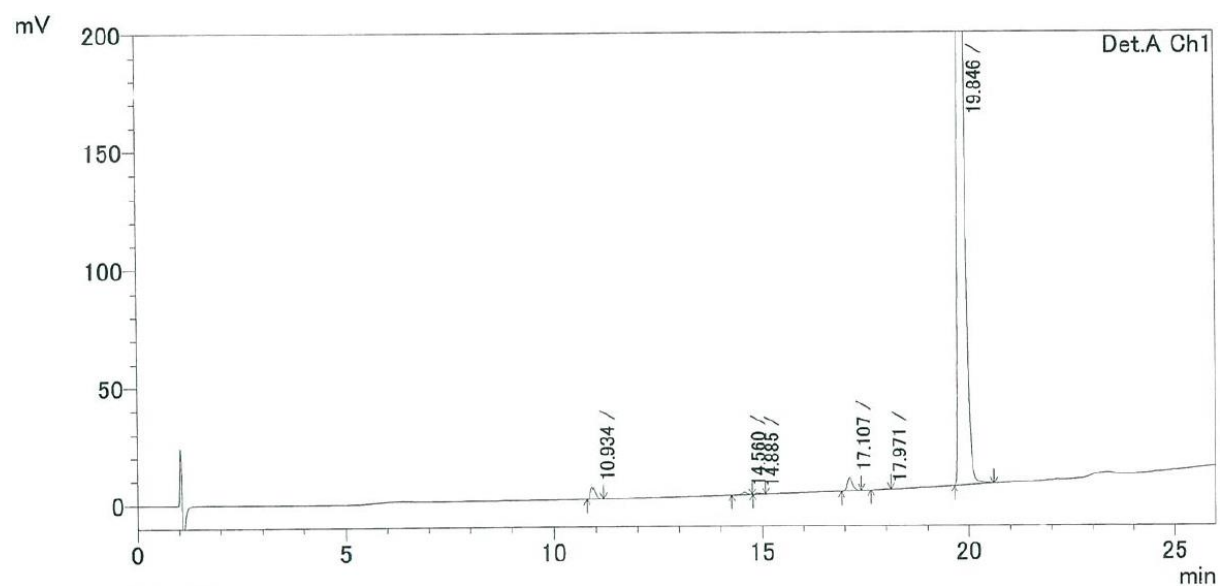


# Compound 29



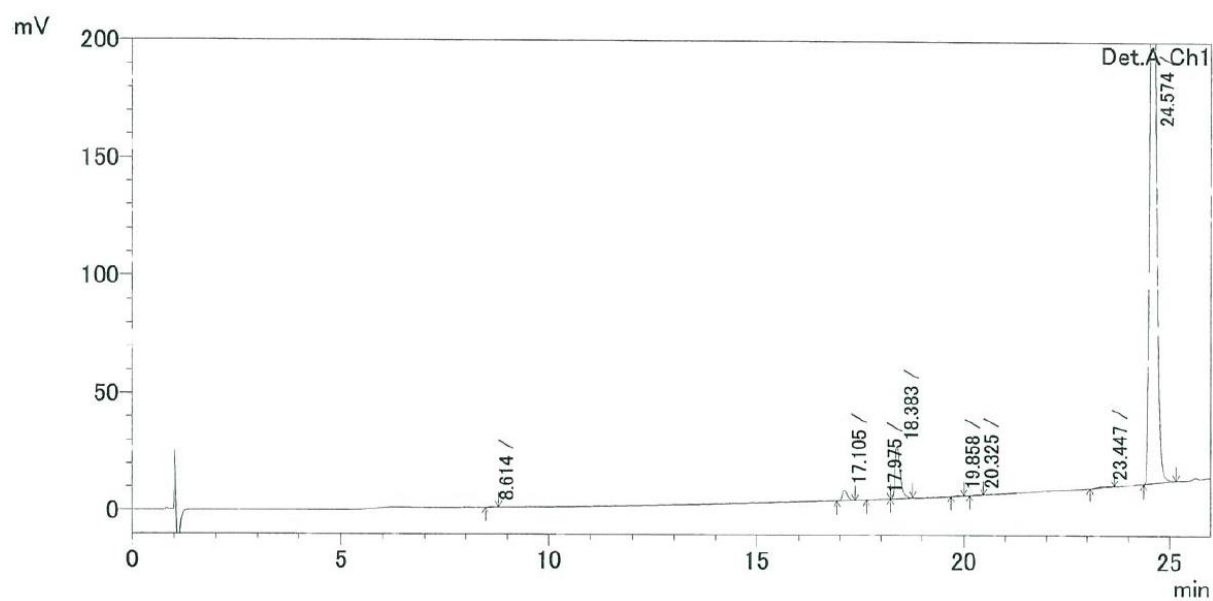
ピーク#	保持時間	面積	高さ	面積%	マーク
1	14.519	3108	410	0.112	V
2	16.562	5936	432	0.215	
3	17.065	290901	32244	10.517	V
4	17.750	3573	296	0.129	V
5	18.767	29419	3313	1.064	V
6	19.809	2366794	258919	85.568	S
7	20.983	9151	850	0.331	
8	21.392	1565	194	0.057	V
9	23.128	27427	2226	0.992	
10	23.613	8786	684	0.318	V
11	24.536	8944	1040	0.323	
12	24.726	7237	832	0.262	V
13	24.933	3126	404	0.113	V
合計		2765966	301842	100.000	

# Compound 29 after crystallization



ピーク#	保持時間	面積	高さ	面積%
1	10.934	34433	5112	0.792
2	14.560	8241	1000	0.189
3	14.885	3916	496	0.090
4	17.107	50955	5753	1.171
5	17.971	2487	227	0.057
6	19.846	4250002	461000	97.700
合計		4350035	473589	100.000

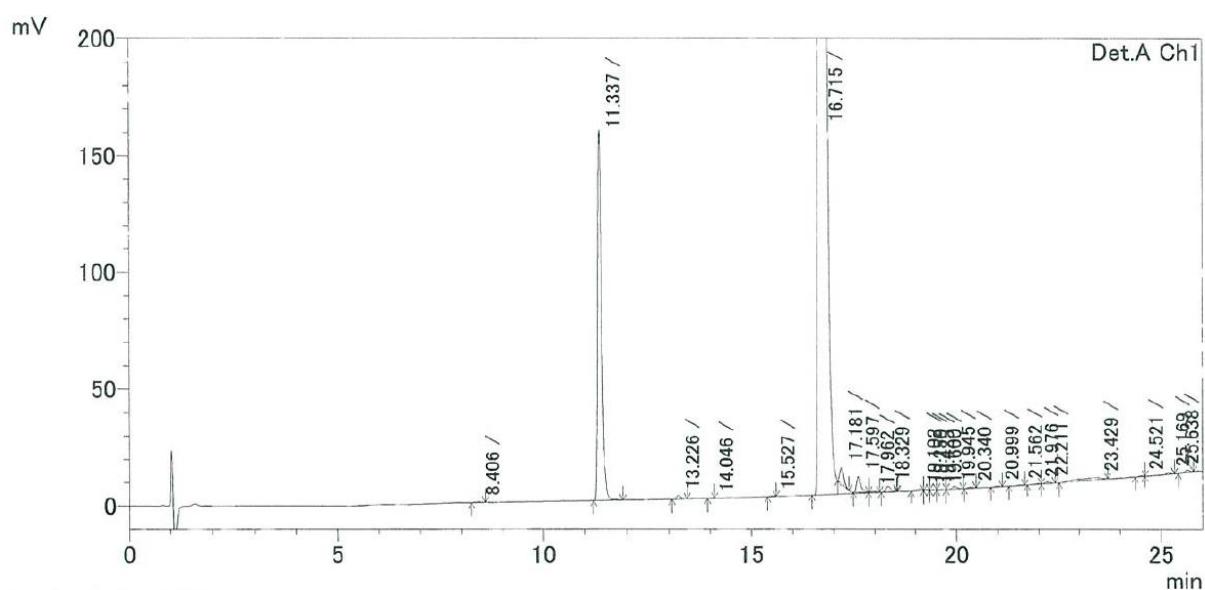
# Compound 25



ピーク#	保持時間	面積	高さ	面積%	マーク
1	8.614	1780	225	0.049	
2	17.105	37801	4406	1.049	
3	17.975	1186	86	0.033	
4	18.383	193066	22347	5.358	
5	19.858	2112	252	0.059	
6	20.325	2217	218	0.062	
7	23.447	10568	496	0.293	
8	24.574	3354683	328493	93.097	
合計		3603412	356522	100.000	

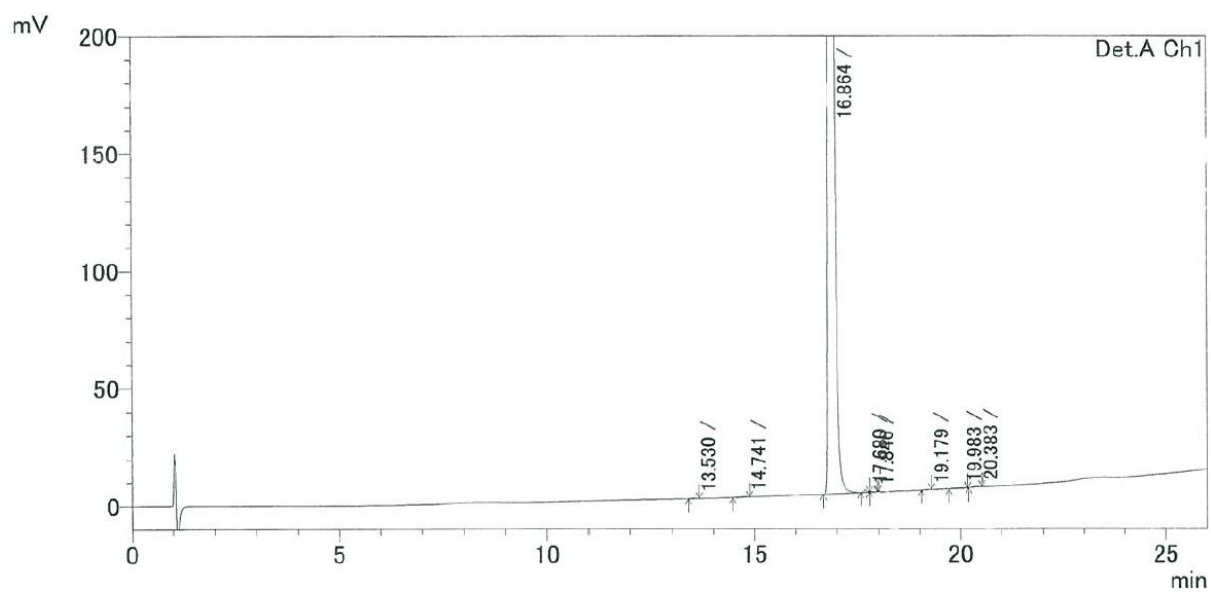
[Figure 3-5]

Compound 26



ピーク#	保持時間	面積	高さ	面積%	マーク
1	8.406	2251	261	0.018	
2	11.337	1097472	159146	8.878	S
3	13.226	11286	1660	0.091	
4	14.046	1120	185	0.009	V
5	15.527	2420	305	0.020	V
6	16.715	11024664	1004702	89.187	S
7	17.181	48480	6927	0.392	T
8	17.597	48845	6813	0.395	T
9	17.962	4135	495	0.033	TV
10	18.329	20304	2343	0.164	T
11	19.102	7032	840	0.057	
12	19.250	2632	416	0.021	V
13	19.425	1216	169	0.010	V
14	19.600	1340	172	0.011	V
15	19.945	10519	1200	0.085	
16	20.340	4080	488	0.033	
17	20.999	2927	366	0.024	
18	21.562	1462	211	0.012	V
19	21.976	3096	337	0.025	
20	22.211	7302	759	0.059	V
21	23.429	43692	889	0.353	
22	24.521	3024	307	0.024	
23	25.169	4198	633	0.034	V
24	25.638	7734	968	0.063	
合計		12361234	1190591	100.000	

# Compound 26 after crystallization

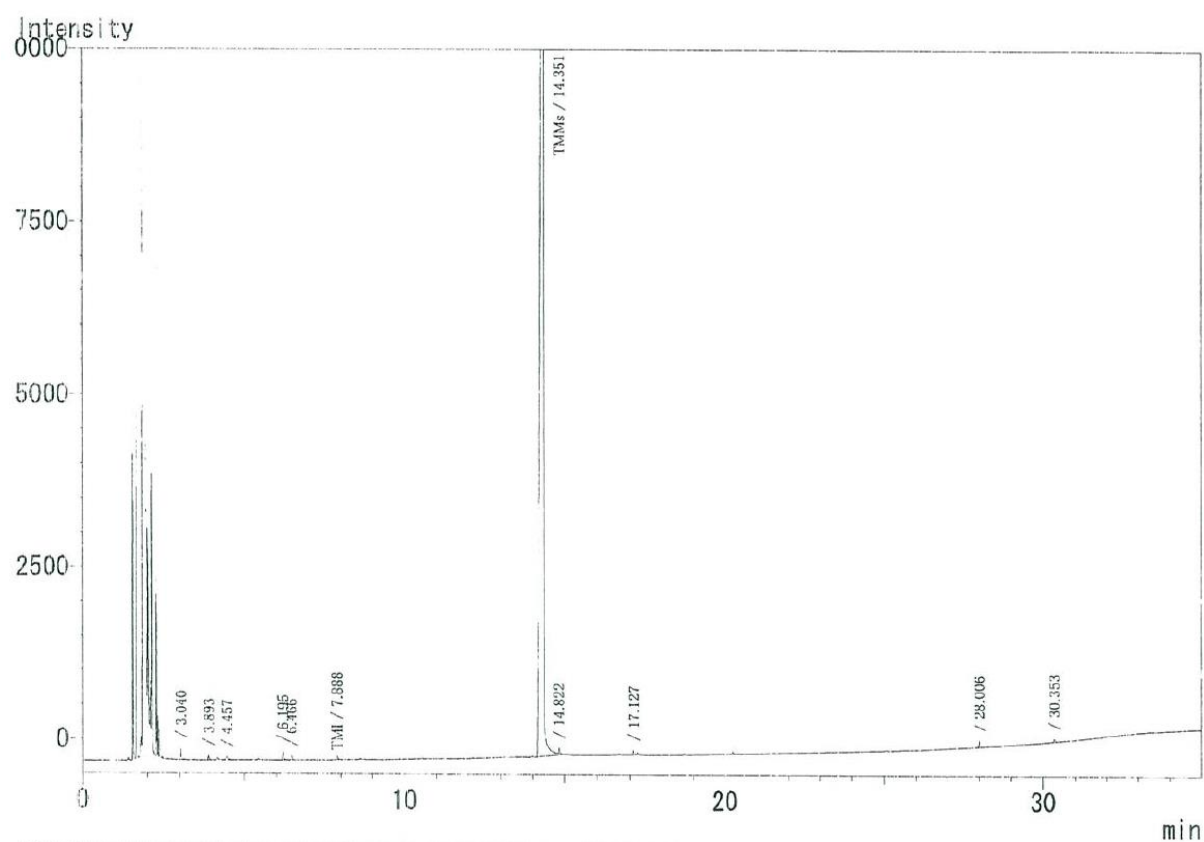


ピーク#	保持時間	面積	高さ	面積%	マーク
1	13.530	1105	175	0.019	
2	14.741	2450	210	0.041	
3	16.864	5893869	689526	99.683	S
4	17.680	6030	961	0.102	T
5	17.846	1840	255	0.031	TV
6	19.179	1363	187	0.023	
7	19.983	1575	102	0.027	
8	20.383	4395	511	0.074	
合計		5912629	691926	100.000	



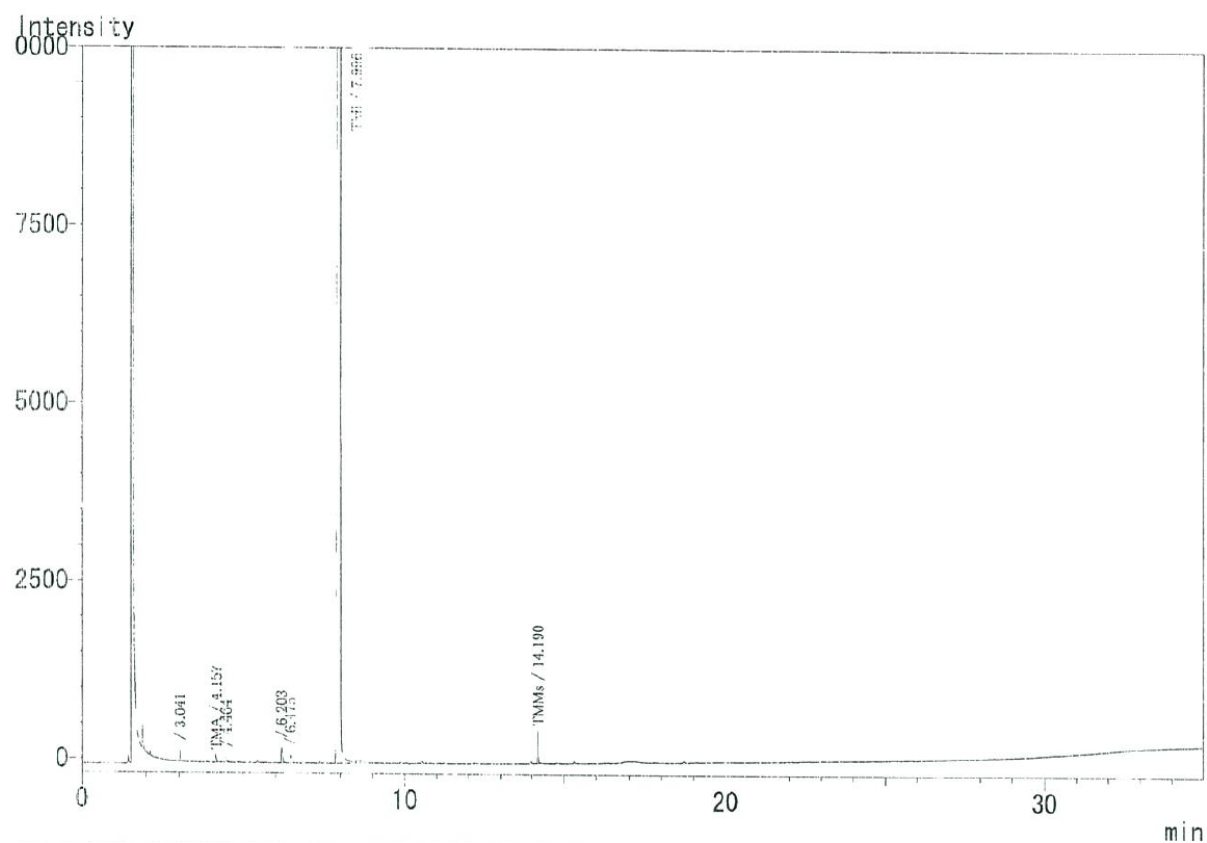
[Figure 3-6]

Compound 33



ピーク番号	保持時間	マーク	面積	面積%	高さ	高さ%
1	3.040		246	0.213	170	0.8614
2	3.893		158	0.137	66	0.3345
3	4.457		183	0.159	52	0.2611
4	6.195		316	0.273	121	0.6121
5	6.466		157	0.135	60	0.3060
6	7.888		160	0.139	64	0.3224
7	14.351	S	113725	98.325	18906	95.8337
8	14.822	T	177	0.153	82	0.4180
9	17.127		175	0.151	64	0.3249
10	28.006		225	0.194	99	0.4994
11	30.353	V	140	0.121	45	0.2266
合計			115662	100.000	19729	100.0000

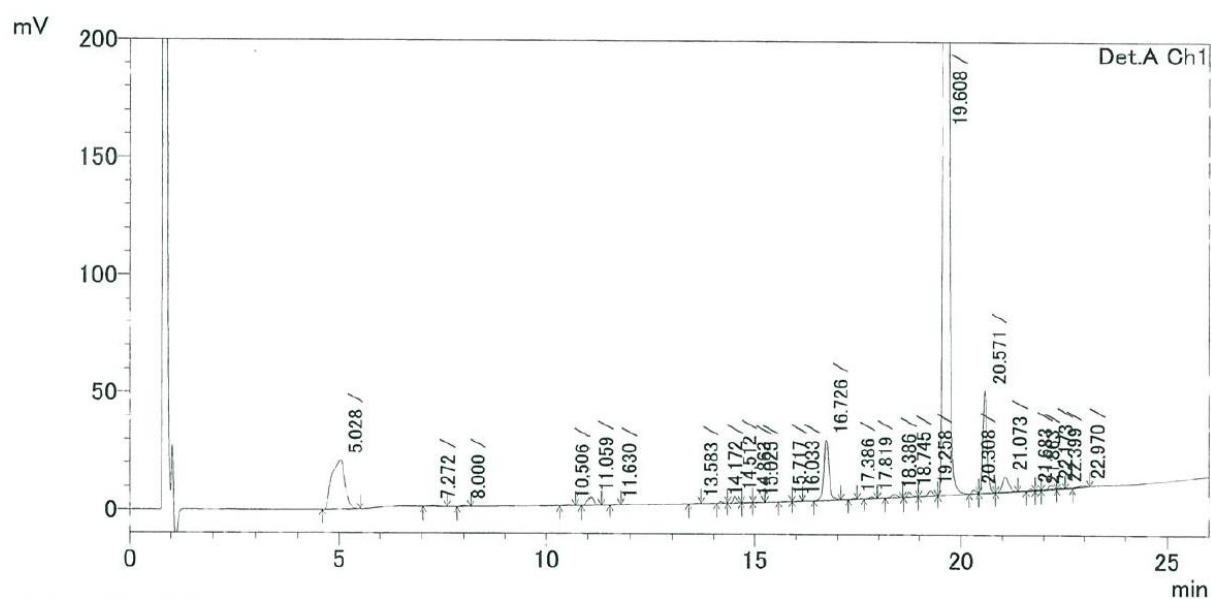
# Compound 27



ピーク番号	保持時間	マーク	面積	面積%	高さ	高さ%
1	3.041		233	0.098	148	0.2903
2	4.157		273	0.115	107	0.2101
3	4.464		232	0.098	79	0.1553
4	6.203		621	0.262	214	0.4209
5	6.475	V	357	0.151	114	0.2242
6	7.996	S	234406	98.862	49751	97.8113
7	14.190	V	981	0.414	452	0.8880
合計			237103	100.000	50865	100.0000

[Figure 3-7]

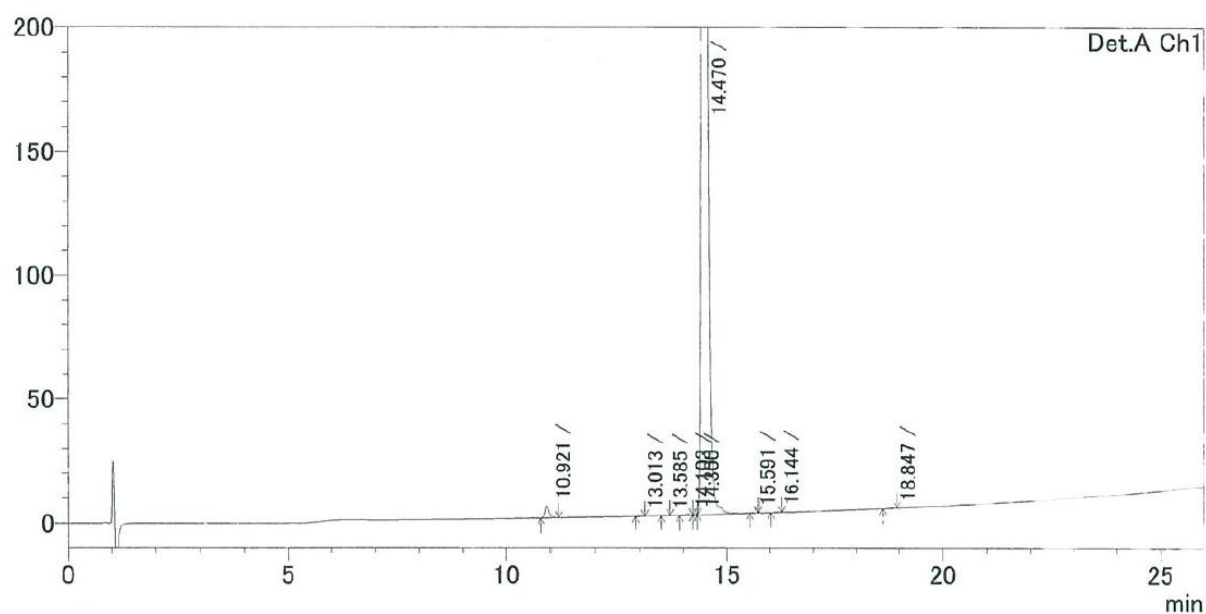
Compound 28



ピーク#	保持時間	面積	高さ	面積%	マーク
1	5.028	453466	20880	6.893	
2	7.272	4684	277	0.071	
3	8.000	3293	433	0.050	
4	10.506	3175	335	0.048	
5	11.059	32399	3388	0.492	
6	11.630	1630	256	0.025	
7	13.583	1513	245	0.023	
8	14.172	4760	740	0.072	
9	14.512	18901	2776	0.287	V
10	14.863	1789	173	0.027	V
11	15.025	1353	160	0.021	V
12	15.717	1576	164	0.024	
13	16.033	1216	131	0.018	
14	16.726	216862	25749	3.296	
15	17.386	2245	345	0.034	
16	17.819	5672	737	0.086	V
17	18.386	13437	1474	0.204	V
18	18.745	16666	2210	0.253	
19	19.258	18222	2446	0.277	V
20	19.608	5331534	686551	81.041	S
21	20.308	11997	1608	0.182	T
22	20.571	314288	43773	4.777	TV
23	21.073	75469	6551	1.147	TV
24	21.683	6839	1032	0.104	T
25	21.863	1780	279	0.027	TV
26	22.173	16611	2151	0.252	TV
27	22.399	4055	571	0.062	TV
28	22.970	13416	991	0.204	T
合計		6578849	806426	100.000	



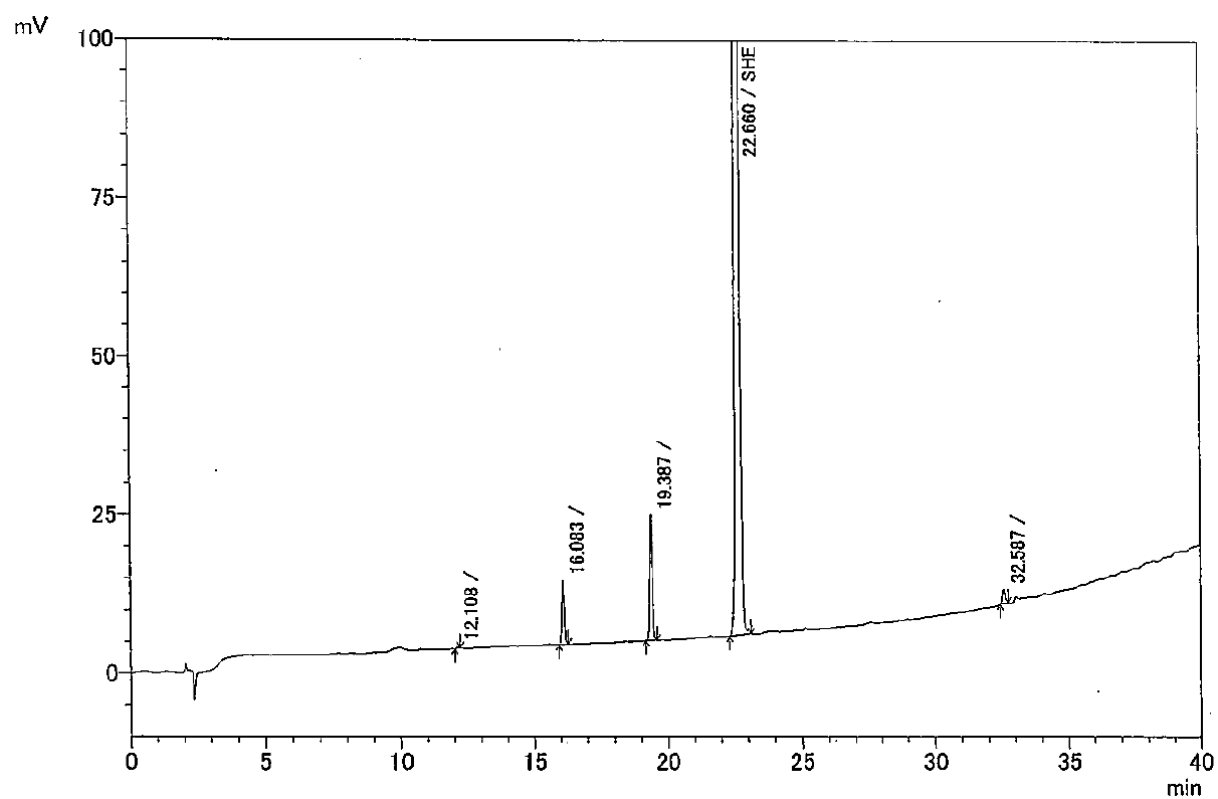
# Compound 2 after crystallization



ピーク#	保持時間	面積	高さ	面積%	マーク
1	10.921	33285	4926	0.476	
2	13.013	2917	458	0.042	V
3	13.585	1119	140	0.016	V
4	14.103	4289	539	0.061	
5	14.300	1294	266	0.019	V
6	14.470	6943243	945965	99.318	SV
7	15.591	1343	223	0.019	TV
8	16.144	1891	274	0.027	
9	18.847	1569	167	0.022	
合計		6990950	952957	100.000	

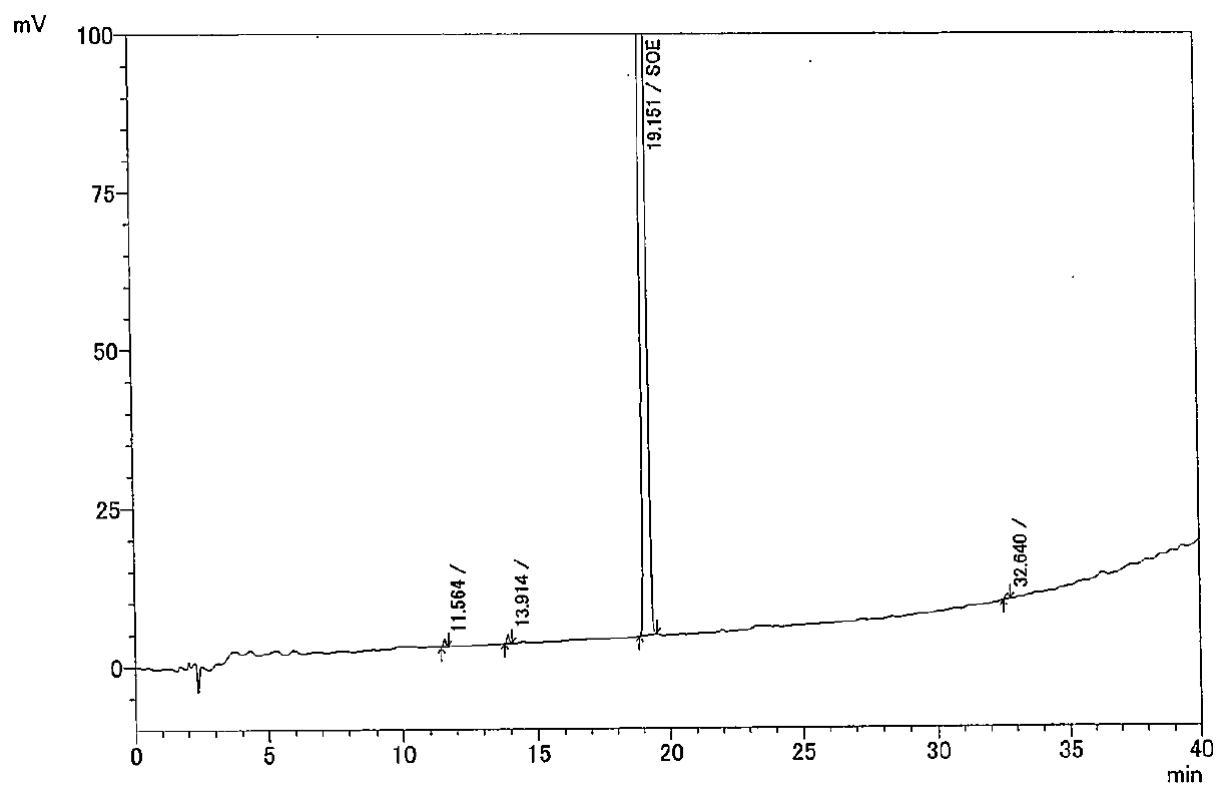
[Figure 3-8]

Compound 29



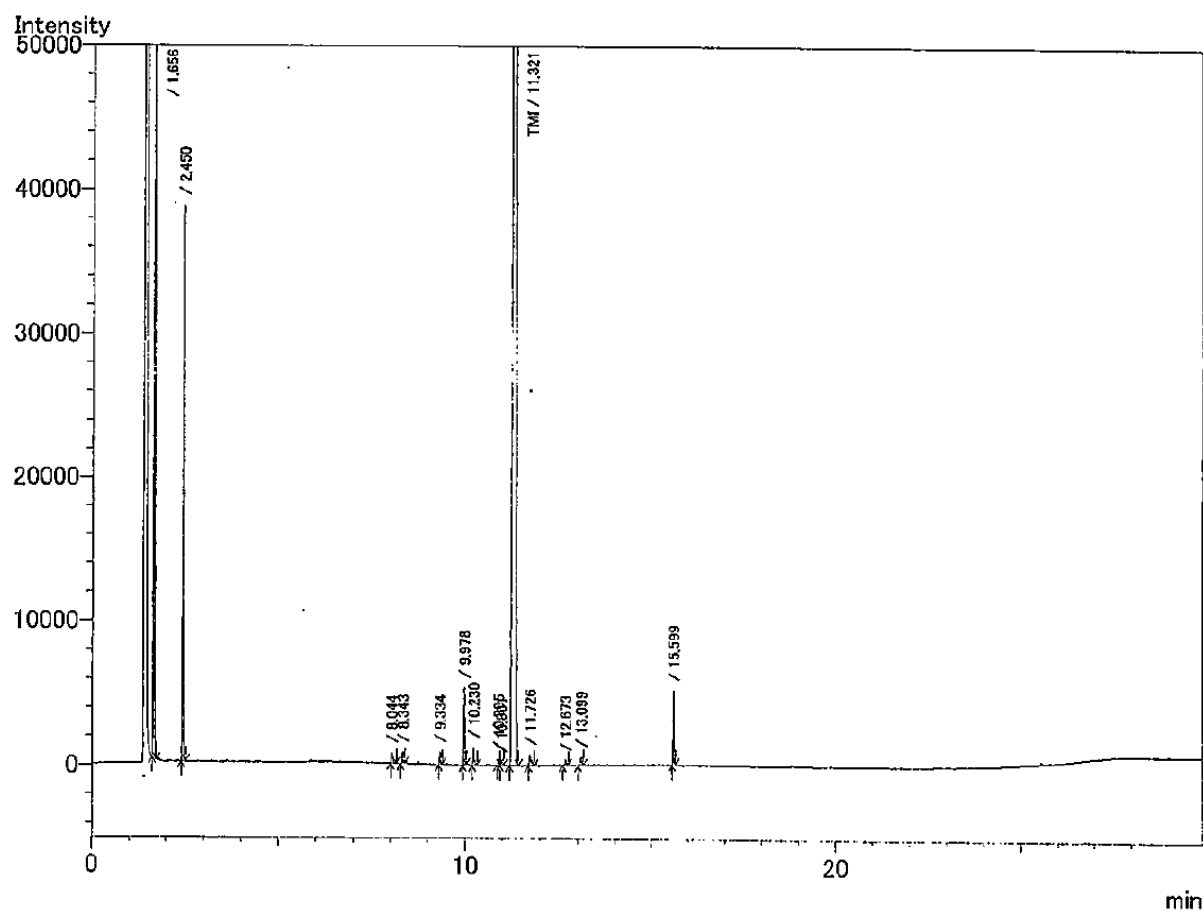
ピーク#	化合物名	保持時間	面積	面積%	マーク
1		12.108	1660	0.022	
2		16.083	56962	0.758	
3		19.387	135259	1.800	
4	SHE	22.660	7307056	97.232	
5		32.587	14129	0.188	
合計			7515066	100.000	

# Compound 26



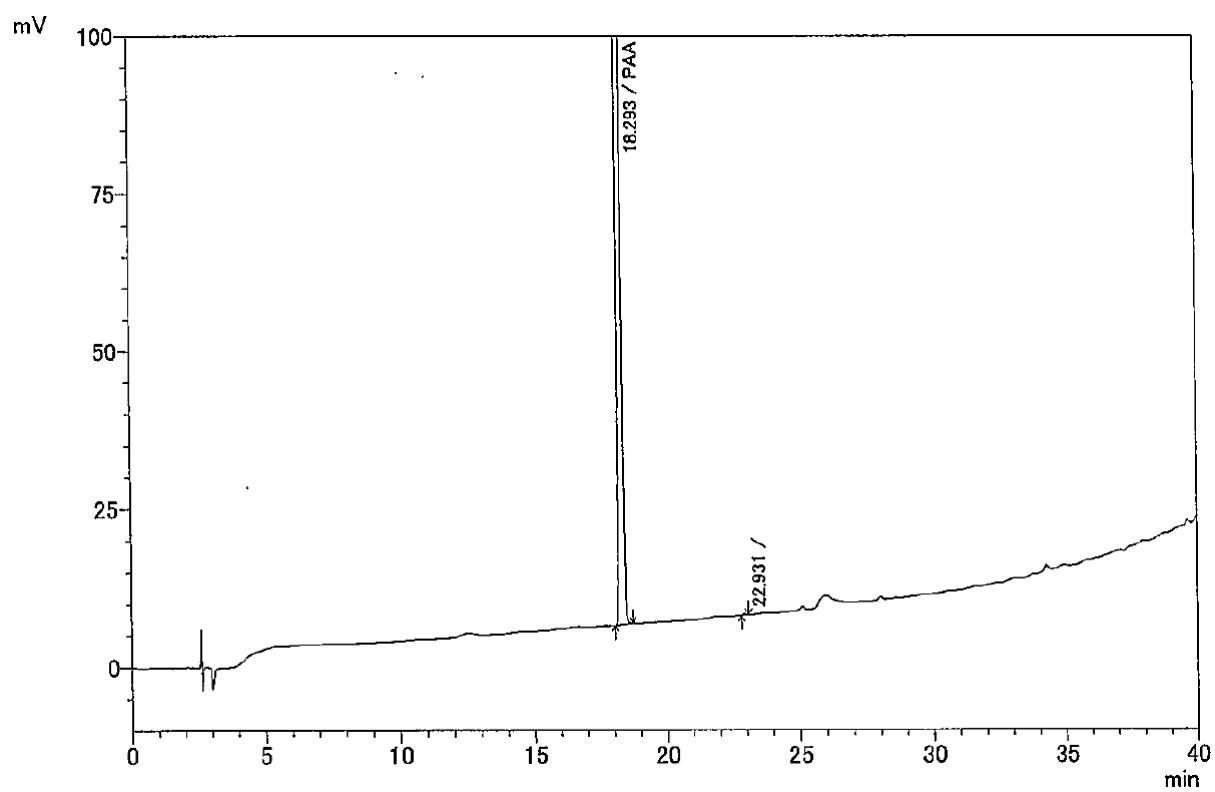
ピーク#	化合物名	保持時間	面積	面積%	マーク
1		11.564	6362	0.053	
2		13.914	8649	0.072	
3	SOE	19.151	11977558	99.823	
4		32.640	6191	0.052	
合計			11998760	100.000	

# Compound 27



ピーク番号	化合物名	保持時間	面積	面積%	マーク
1		1.656	188864	7.350	
2		2.450	77708	3.024	
3		8.044	1690	0.066	
4		8.343	1705	0.066	
5		9.334	1670	0.065	
6		9.978	10847	0.422	
7		10.230	2510	0.098	
8		10.895	1004	0.039	
9		10.961	581	0.023	V
10	TMI	11.321	2269567	88.327	
11		11.726	2236	0.087	
12		12.673	654	0.025	
13		13.099	1228	0.048	
14		15.599	9244	0.360	
合計			2569508	100.000	

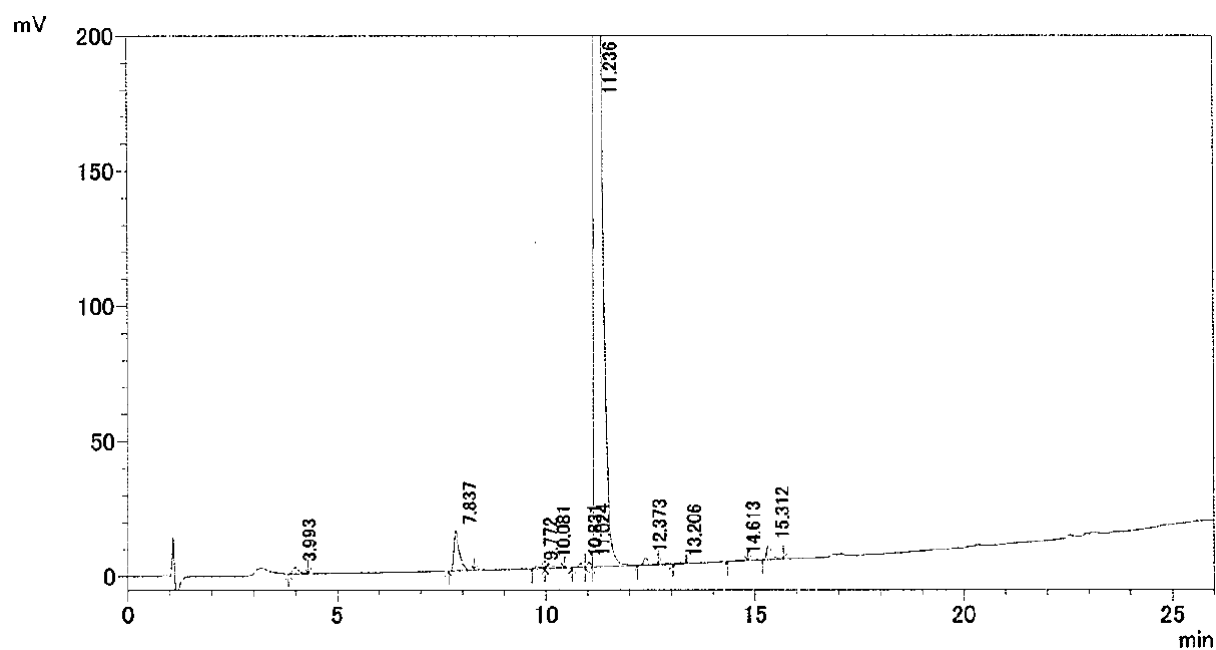
## Compound 2



ピーク#	化合物名	保持時間	面積	面積%	マーク
1	PAA	18.293	4760574	99.957	
2		22.931	2066	0.043	
合計			4762640	100.000	

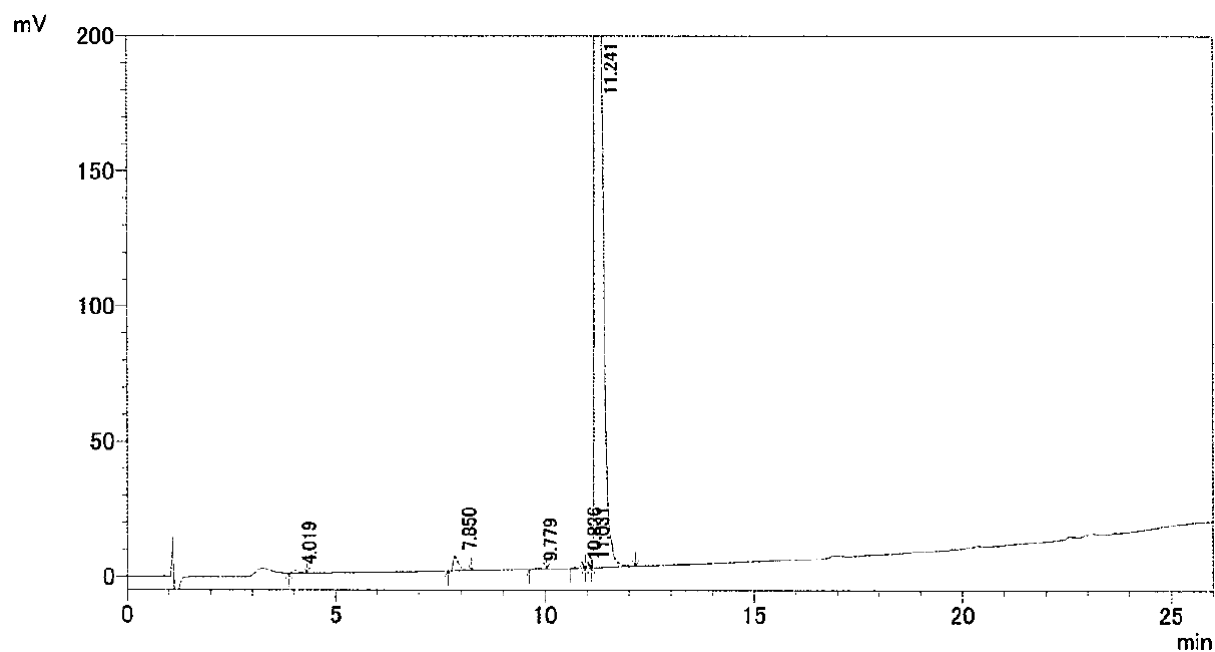
[Figure 3-9]

(Entry 3)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.993	20133	2121	0.331	0.318	
2	7.837	135642	14968	2.228	2.244	
3	9.772	7850	877	0.129	0.132	
4	10.081	15950	1637	0.262	0.246	V
5	10.831	12548	1564	0.206	0.235	
6	11.024	11385	1637	0.187	0.246	V
7	11.236	5806521	635694	95.396	95.320	SV
8	12.373	21463	2455	0.353	0.368	T
9	13.206	2239	203	0.037	0.030	T
10	14.613	4627	343	0.076	0.051	V
11	15.312	48427	5407	0.796	0.811	V
合計		6086784	666907	100.000	100.000	

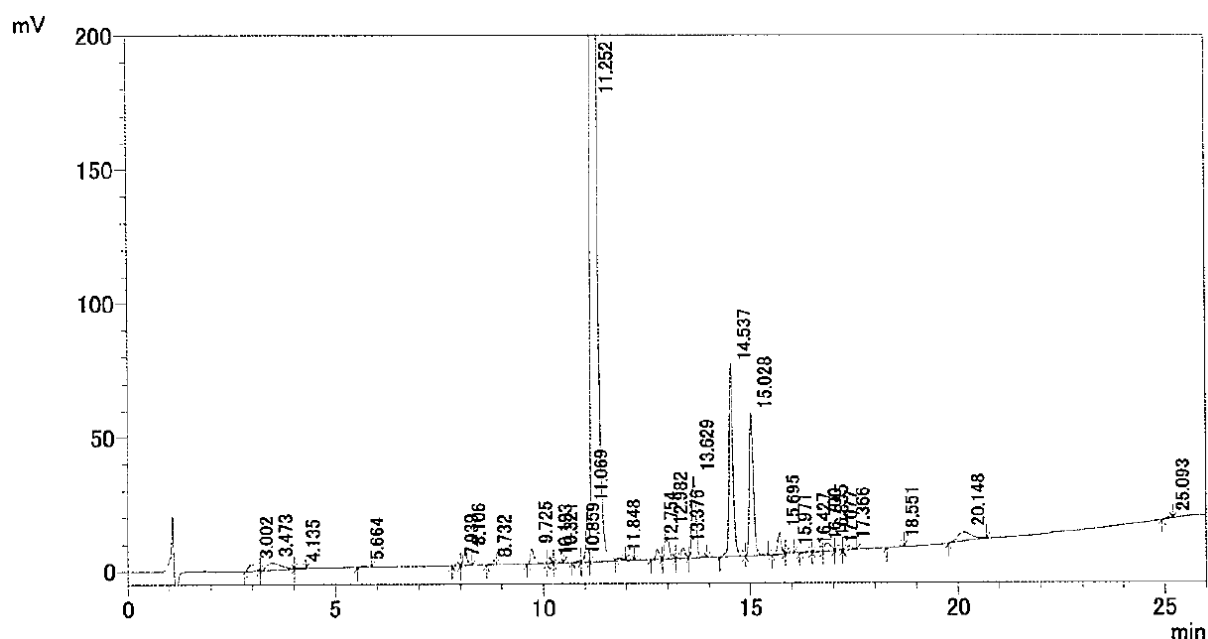
(Entry 4)



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	4.019	9491	1003	0.170	0.164	
2	7.850	48830	5419	0.875	0.885	
3	9.779	6463	722	0.116	0.118	
4	10.836	7808	813	0.140	0.133	
5	11.031	5501	833	0.099	0.136	V
6	11.241	5499882	603624	98.600	98.565	V
合計		5577976	612414	100.000	100.000	

[Figure 3-10]

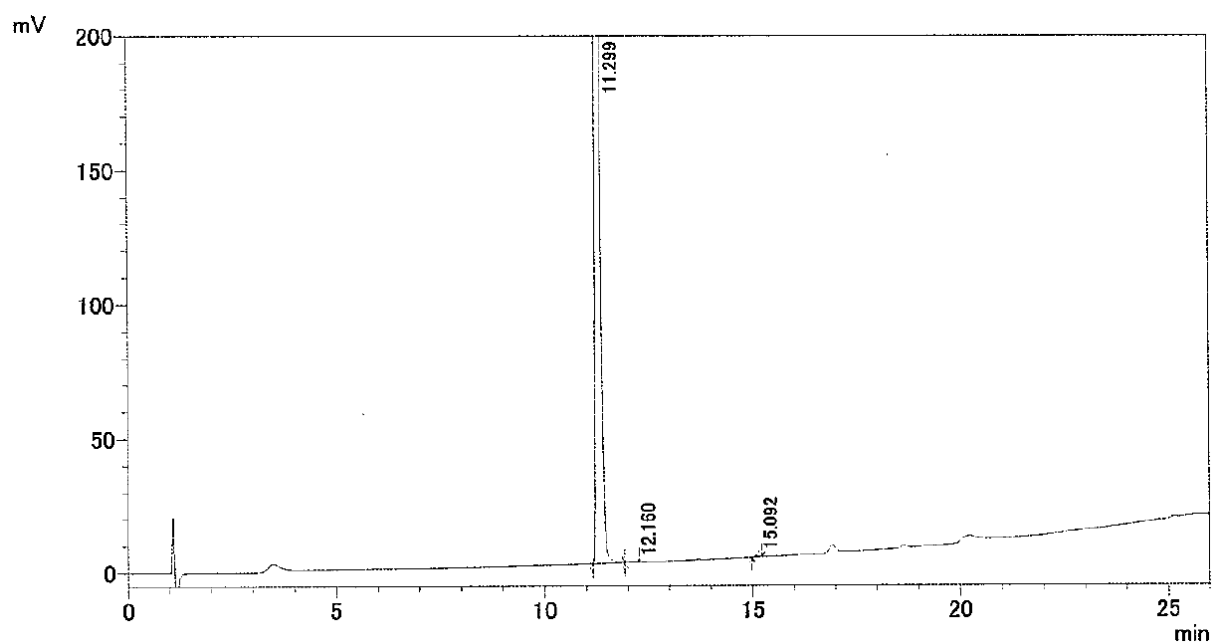
(R)-2 after hydrolysis



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	3.002	27047	2256	0.314	0.200	
2	3.473	64446	2731	0.747	0.242	V
3	4.135	3516	313	0.041	0.028	V
4	5.664	4035	549	0.047	0.049	
5	7.939	6443	1164	0.075	0.103	
6	8.106	35497	5298	0.412	0.470	V
7	8.732	3773	593	0.044	0.053	V
8	9.725	38021	5401	0.441	0.479	
9	10.193	2841	467	0.033	0.041	
10	10.321	7368	998	0.085	0.089	V
11	10.859	4540	533	0.053	0.047	V
12	11.069	112164	20546	1.300	1.824	V
13	11.252	6967740	889041	80.788	78.919	SV
14	11.848	4467	639	0.052	0.057	T
15	12.754	23646	3684	0.274	0.327	
16	12.982	69928	10721	0.811	0.952	V
17	13.376	25421	3936	0.295	0.349	V
18	13.629	193636	30762	2.245	2.731	V
19	14.537	474027	72094	5.496	6.400	
20	15.028	329496	53415	3.820	4.742	V
21	15.695	49807	7846	0.577	0.696	
22	15.971	6936	794	0.080	0.071	V
23	16.427	5224	535	0.061	0.047	V
24	16.700	21283	2003	0.247	0.178	V
25	16.855	35012	3140	0.406	0.279	V
26	17.077	5322	662	0.062	0.059	V
27	17.366	14840	1726	0.172	0.153	V
28	18.551	8200	1004	0.095	0.089	
29	20.148	76422	3195	0.886	0.284	
30	25.093	3596	477	0.042	0.042	
合計		8624693	1126522	100.000	100.000	



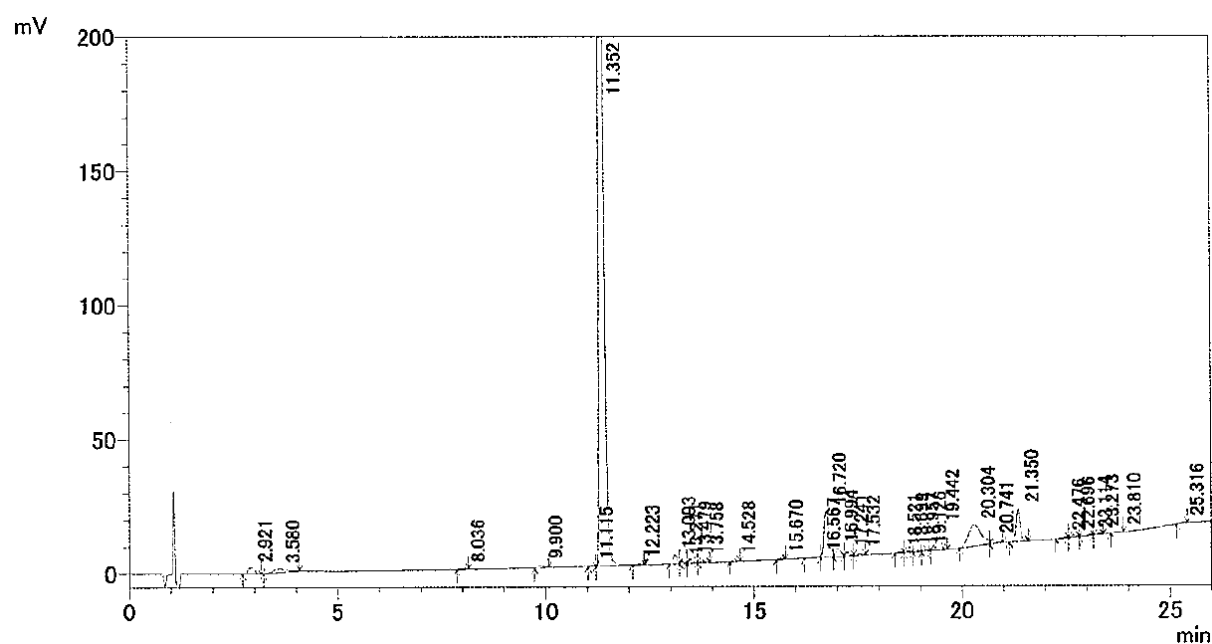
**(R)-2 after crystallization**



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	11.299	4565680	712595	99.882	99.897	V
2	12.160	2360	218	0.052	0.031	V
3	15.092	3050	520	0.067	0.073	
合計		4571090	713333	100.000	100.000	

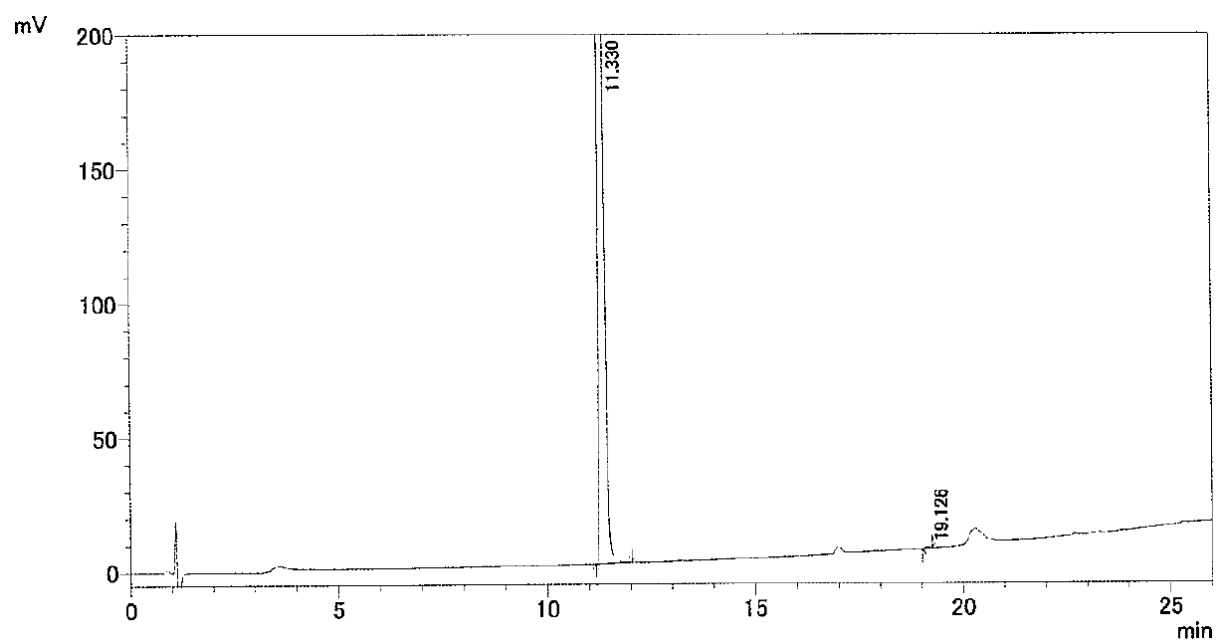
[Figure 3-11]

(R)-2 after hydrolysis



ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	2.921	27508	2280	0.582	0.315	
2	3.580	32921	1347	0.696	0.186	
3	8.036	2749	474	0.058	0.066	
4	9.900	9839	1074	0.208	0.148	
5	11.115	2930	446	0.062	0.062	V
6	11.352	4066849	652040	86.017	90.091	SV
7	12.223	2637	410	0.056	0.057	TV
8	13.093	22204	3298	0.470	0.456	V
9	13.271	5998	826	0.127	0.114	V
10	13.479	8809	1357	0.186	0.188	V
11	13.758	5403	892	0.114	0.123	V
12	14.528	4590	801	0.097	0.111	
13	15.670	3392	461	0.072	0.064	
14	16.567	2582	471	0.055	0.065	
15	16.720	128406	17465	2.716	2.413	V
16	16.994	32743	3110	0.693	0.430	V
17	17.241	10234	1338	0.216	0.185	V
18	17.532	5976	664	0.126	0.092	V
19	18.521	2197	373	0.046	0.052	
20	18.699	2626	460	0.056	0.064	V
21	18.957	2417	412	0.051	0.057	
22	19.126	3377	482	0.071	0.067	V
23	19.442	55777	8342	1.180	1.153	V
24	20.304	170137	7826	3.599	1.081	
25	20.741	13331	1505	0.282	0.208	V
26	21.350	79410	12455	1.680	1.721	
27	22.476	3739	510	0.079	0.070	
28	22.696	5914	825	0.125	0.114	V
29	23.114	2355	426	0.050	0.059	V
30	23.273	4931	673	0.104	0.093	V
31	23.810	2292	225	0.048	0.031	
32	25.316	3695	484	0.078	0.067	
合計		4727967	723754	100.000	100.000	

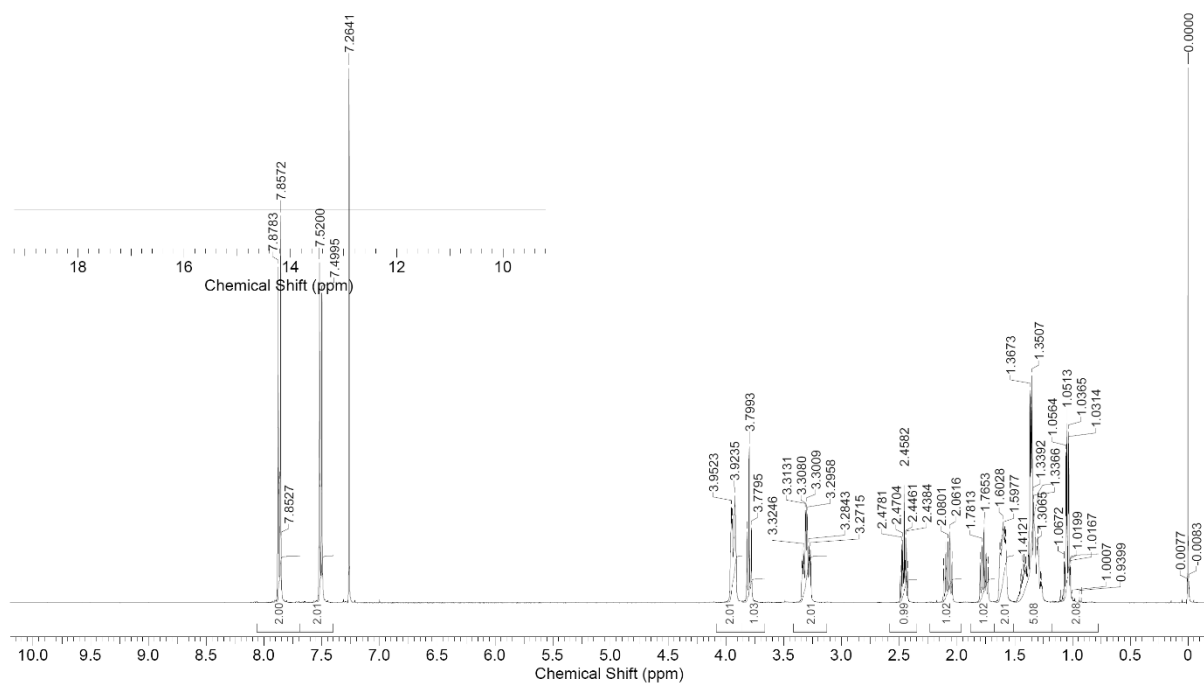
**(R)-2 after crystallization**



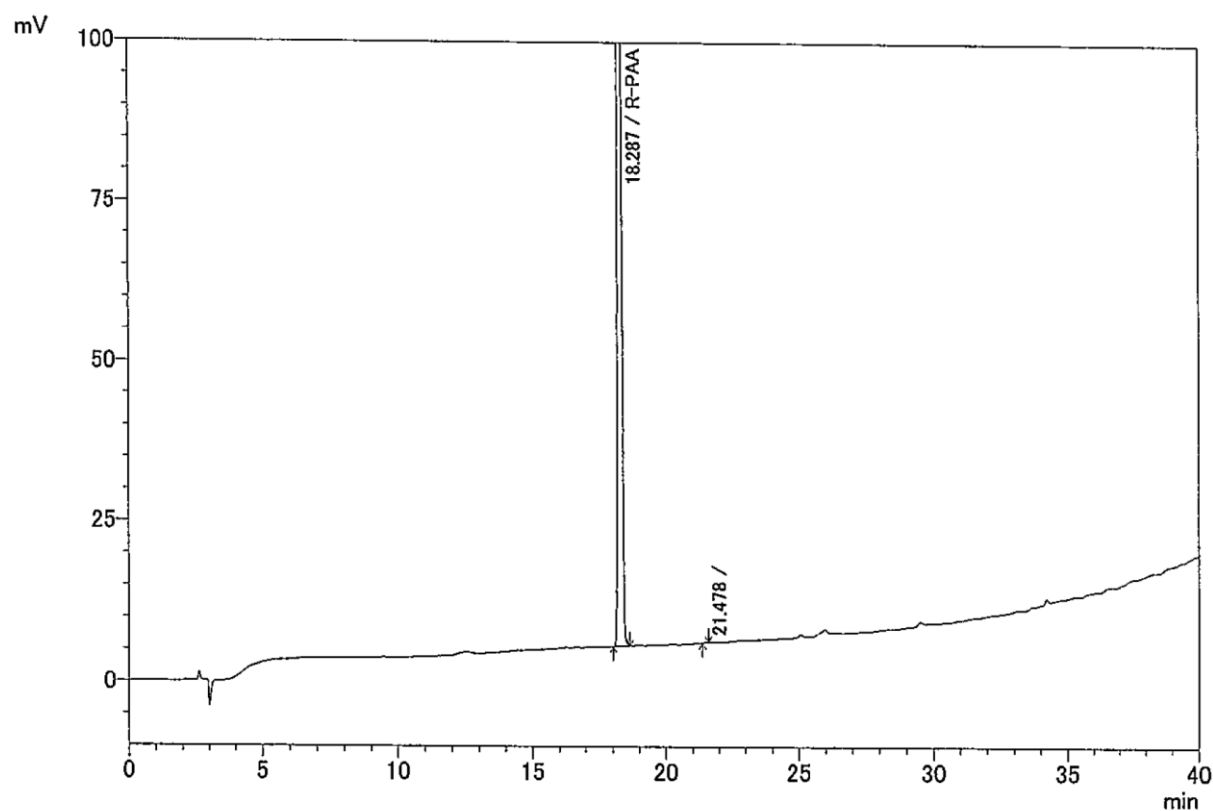
ピーク#	保持時間	面積	高さ	面積%	高さ%	マーク
1	11.330	5407949	809307	99.957	99.957	
2	19.126	2335	352	0.043	0.043	
合計		5410284	809659	100.000	100.000	

[Figure 3-12]

(*R*)-2 after crystallization



**(R)-2 after crystallization**

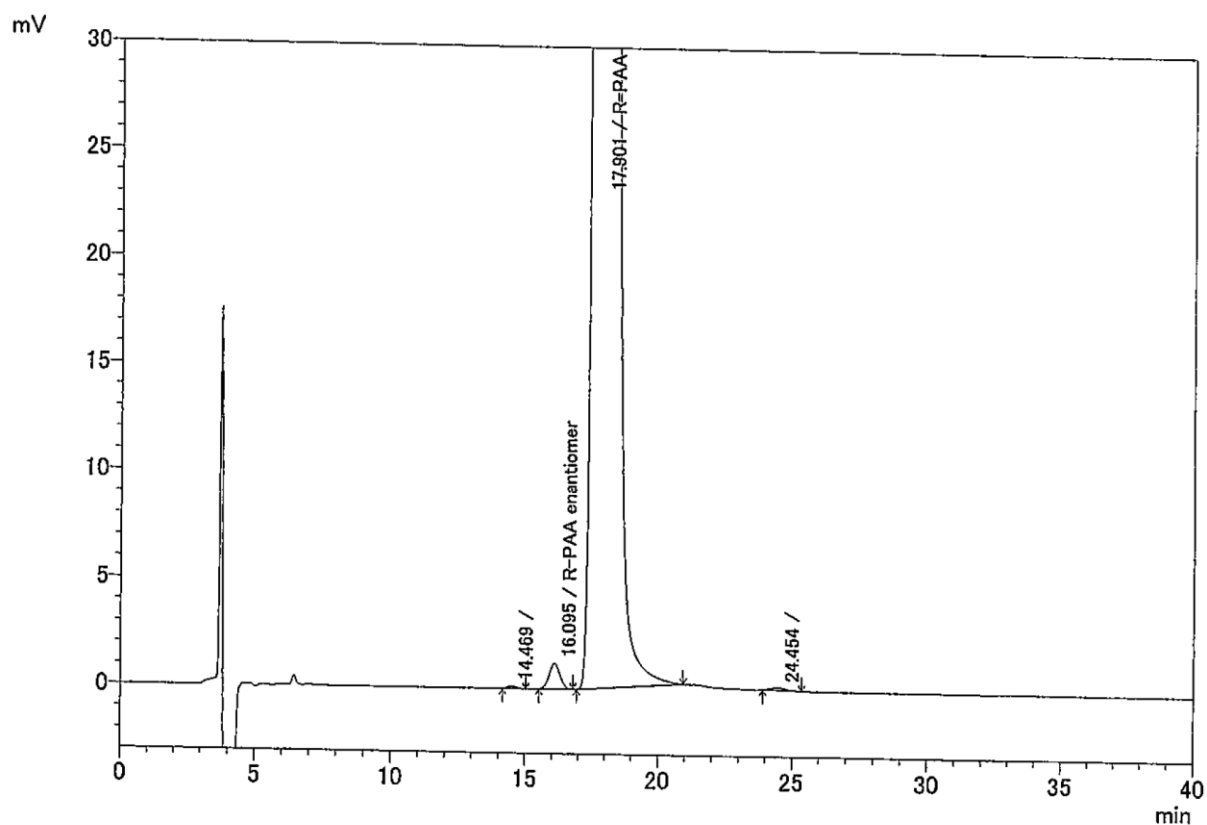


検出器A Ch1 220nm

ピークテーブル

ピーク#	化合物名	保持時間	面積	面積%	マーク
1	R-PAA	18.287	4750963	99.977	
2		21.478	1077	0.023	
合計			4752040	100.000	

(R)-2 after crystallization

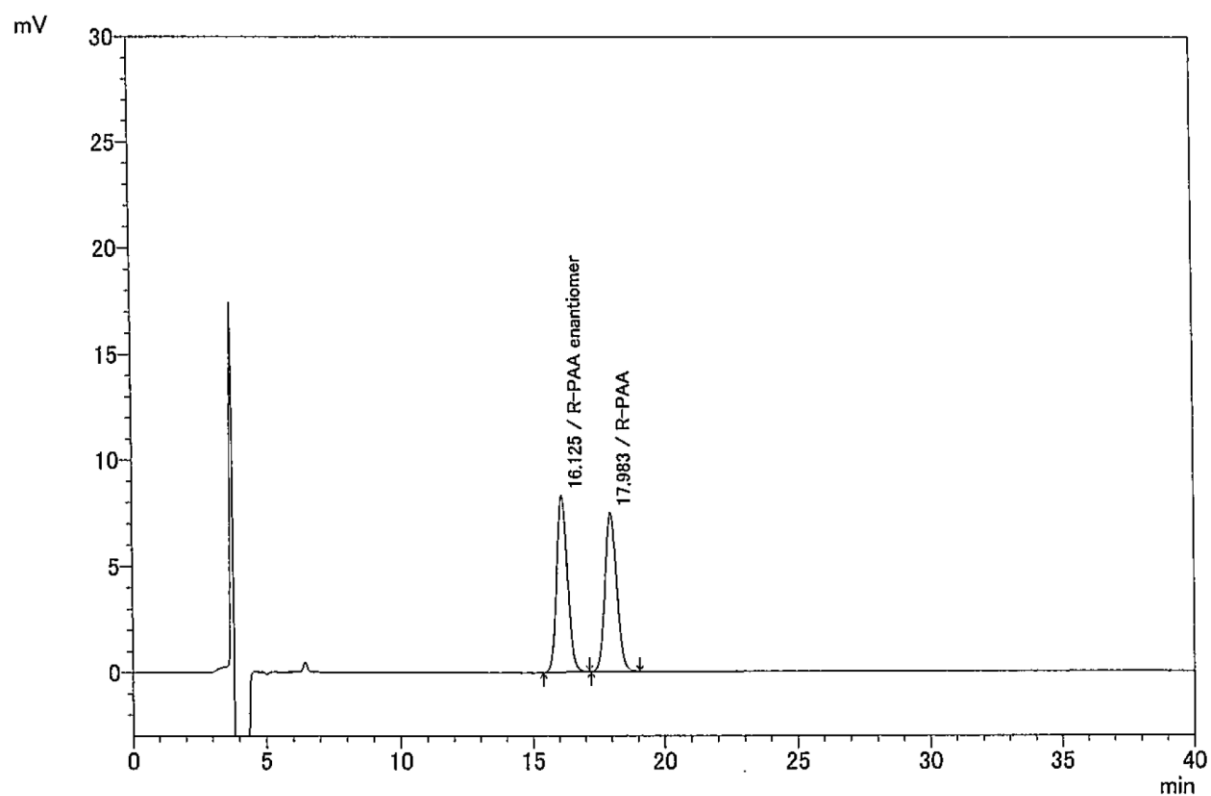


検出器A Ch1 230nm

ピークテーブル

ピーク#	化合物名	保持時間	面積	面積%	マーク
1		14.469	2264	0.010	
2	R-PAA enantiomer	16.095	33528	0.141	
3	R-PAA	17.901	23749200	99.829	
4		24.454	4992	0.021	
合計			23789984	100.000	

参考：ラセミ体 2

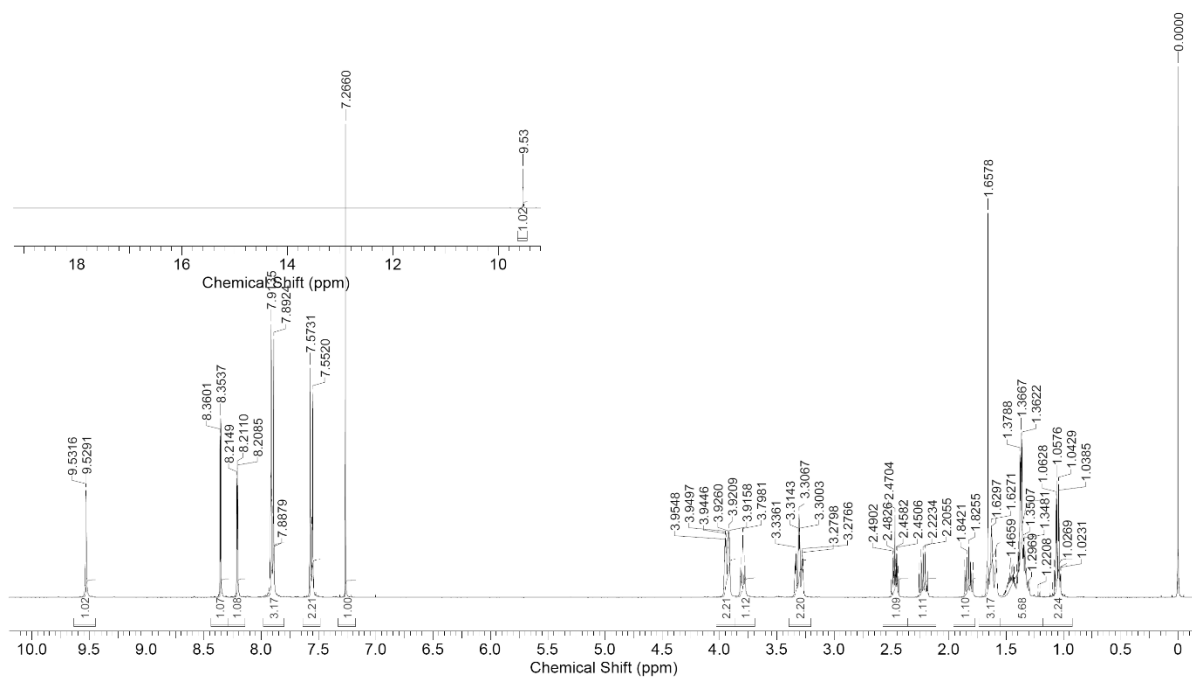


ピークテーブル

検出器A Ch1 230nm

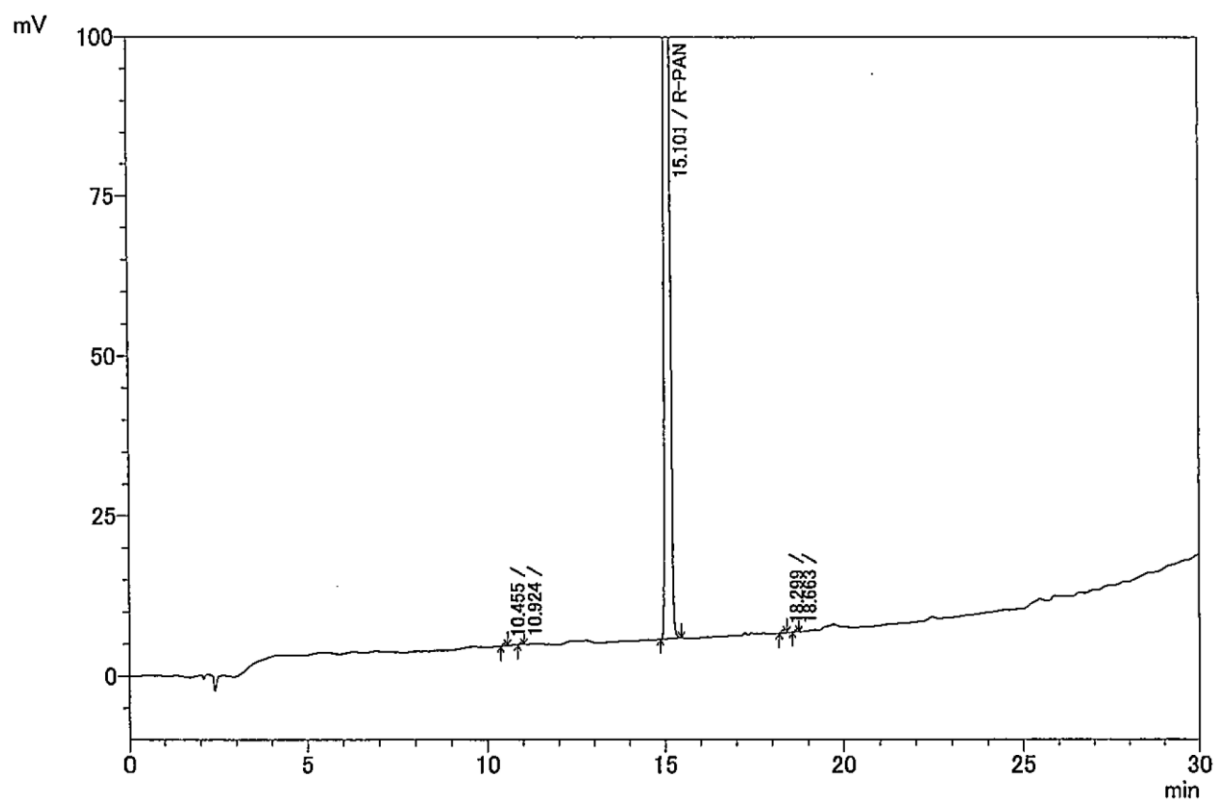
ピーク#	化合物名	保持時間	面積	面積%	分離度	マーク
1	R-PAA enantiomer	16.125	237666	50.017	0.000	
2	R-PAA	17.983	237505	49.983	2.355	
合計			475171	100.000		

**(R)-1 after crystallization**





(R)-1 after crystallization

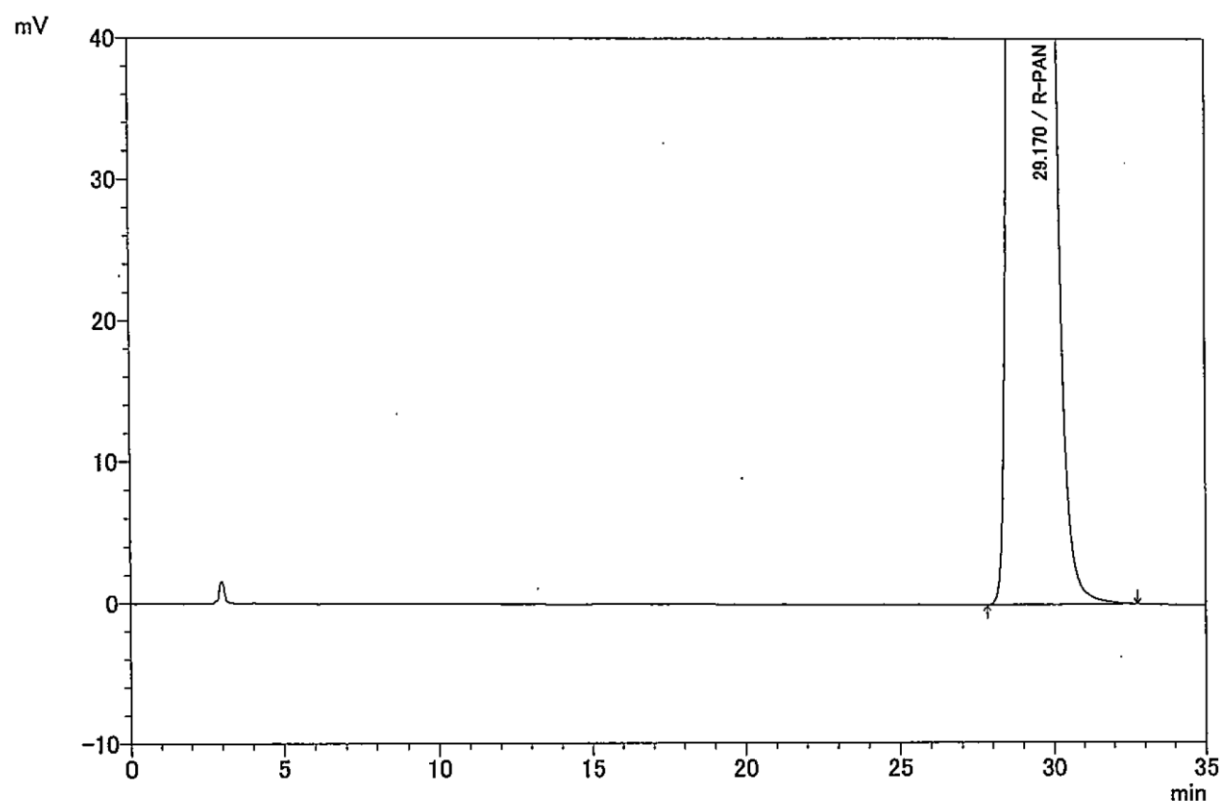


ピークテーブル

検出器A Ch1 220nm

ピーク#	化合物名	保持時間	面積	面積%	マーク
1		10.455	2115	0.025	
2		10.924	1655	0.019	
3	R-PAN	15.101	8583030	99.903	
4		18.299	2722	0.032	
5		18.663	1862	0.022	
合計			8591384	100.000	

**(R)-1 after crystallization**

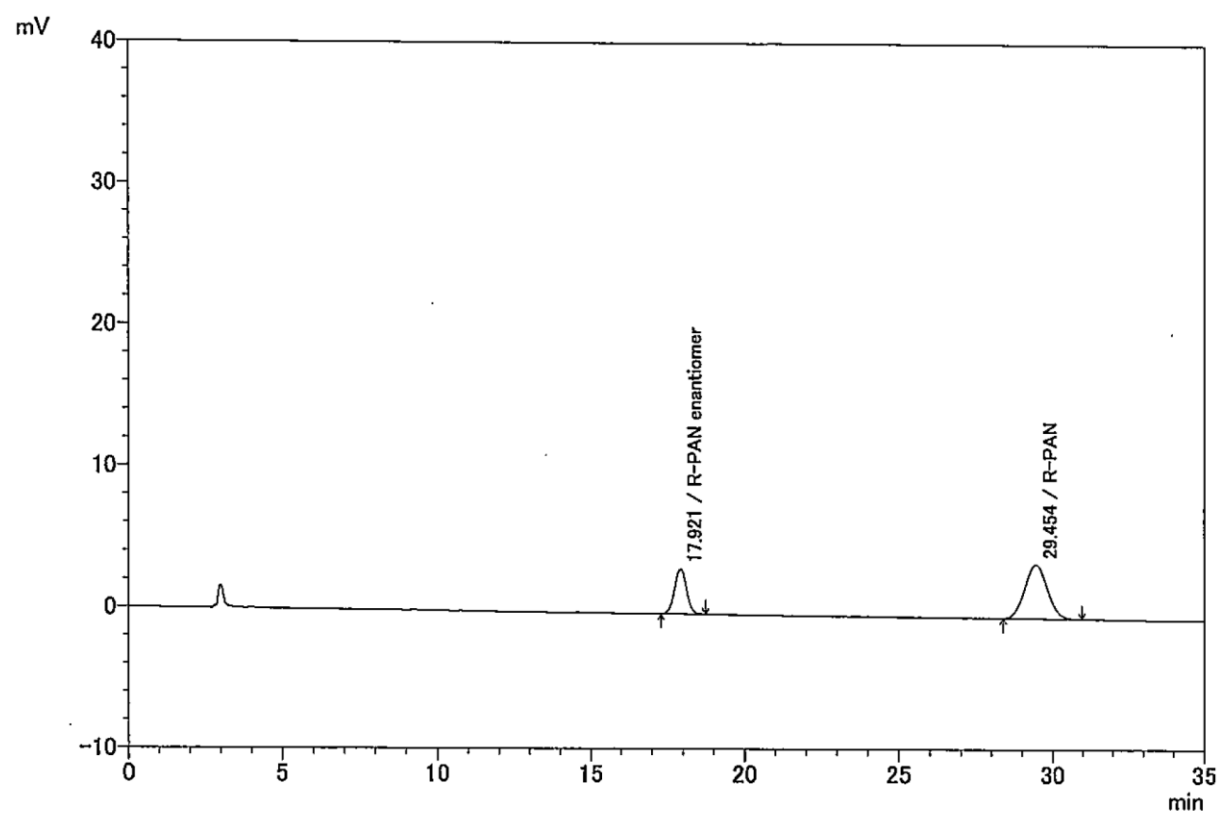


ピークテーブル

検出器A Ch1 235nm

ピーク#	化合物名	保持時間	面積	面積%	マーク
1	R-PAN	29.170	30036521	100.000	
合計			30036521	100.000	

参考：ラセミ体 1



ピークテーブル

検出器A Ch1 235nm

ピーク#	化合物名	保持時間	面積	面積%	分離度	マーク
1	R-PAN enantiomer	17.921	87723	30.549	0.000	
2	R-PAN	29.454	199436	69.451	10.974	
合計			287158	100.000		



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## 主論文目録

本学位論文は、下記の発表論文による。

1. Yamagami, T.; Hatsuda, M.; Utsugi, M.; Kobayashi, R.; Moritani, Y.  
Highly Diastereoselective Esterification of Ketenes Generated In Situ from Acyl Chlorides with  
(*R*)-Pantolactone Derivatives  
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Scalable Synthesis of a Nonracemic  $\alpha$ -Arylpropionic Acid via Ketene Desymmetrization for a  
Glucokinase Activator  
*Org. Process Res. Dev.* **2014**, 18, 437-445.

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