令和 2 年度

博士論文

生物活性天然物の立体発散的合成研究

Study of Stereodivergent Synthesis of Biologically Active Natural Products

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目次

発表論文

Total Synthesis and Absolute Configuration of (–)-Gummiferol
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Total Synthesis, Structural Elucidation, and Structure−Cytotoxic Activity Relationship of (−)-Gummiferol
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（第 3 章）

本文中で用いた略号

Ac	acetyl	MTPA	α-methoxy-α-(trifluoromethyl)phenylacety
Bn	benzyl	*n*	normal
Bu	butyl	NMO	*N*-methylmorpholine *N*-oxide
cat	catalyst	NOE	nuclear Overhauser effect
CSA	10–camphorsulfonic acid	P	a protective group
DIPT	diisopropyl tartrate	*p*	para
DIBAL-H	diisobutylaluminum hydride	Ph	phenyl
DIPEA	*N,N*-diisopropylethylamine	Piv	pivaloyl
DMAP	4-(dimethylamino)pyridine	PMB	paramethoxybenzyloxy
DMF	*N,N*-dimethylformamide	PT	
D.M.P.	Dess-Martin periodinane	py	pyridine
DMSO	dimethyl sulfoxide	PPTS	pyridinium paratoluenesulfonate
dr	diastereomeric ratio	Pr	propyl
EC_{50}	effective concentration at 50%	quant.	quantitative
Et	ethyl	R	an alkyl group
eq	equivalent	rt	room temperature
HMBC	hetero-nuclear multiple-bond connectivity	Red-Al	sodium bis (2-methoxyethoxy)aluminum
HMDS	1,1,1,3,3,3-hexamethyldisilazane		hydride
HMQC	hetero-nuclear multiple quantum coherence	*t*	tertialy
i	iso	TBDPS	tertialybutyldiphenylsilyl
IC_{50}	inhibitory concentration at 50%	TBS	tertialybutyldimethylsilyl
LD_{99}	lethal dose at 99%	TES	triethylsilyl
LDA	lithium diisopropylamide	Tf	trifluoromethanesulfonyl
*m*CPBA	metachloroperoxybenzoic acid	THF	tetrahydrofuran
Me	methyl	TPAP	tetrapropylammonium perruthenate
MS	molecular sieves	Ts	paratoluenesulfonyl

第 1 章　　序論

天然物は、創薬および農薬・香料等の開発におけるリード化合物の貴重な供給源であり、多くの天然物はそれらの立体異性体と共存している。

天然物構造に基づく医薬品を創製するためには、生合成では得られない天然物の構造類縁体を合成し、構造活性相関試験を実施する必要がある。

天然物の構造解明及び構造活性相関研究を進めるためには、天然物及びその立体異性体を供給するための合理的な合成経路を確立する必要がある。複数の立体異性体が考えられる場合は、構造の確認/解明と構造活性相関研究の両方の観点から、天然物のすべての立体異性体にアクセスするための効率的な合成経路を開発することが重要となる。

二つのキラル中心を有する目的化合物**1a-1d**を合成する場合を考える[1]。**1a-1d**に到達する合成法は、**Figure 1-1**に示すように、それぞれ独立した経路(a：独立的合成)と分岐経路(b：発散的合成)の二つの合成法がある。

独立した経路(a)では、4つの目的化合物**1a-1d**が異なる出発物質からそれぞれ独立して合成される。発散的合成(b)では、**1a-1d**は同じ出発物質から合成される。この合成法では、**2a**と**2b**は共通の中間体からの分岐により合成される。また、**1a**、**1b**及び**1c**、**1d**は、それぞれ**2a**及び**2b**から得られる共通の中間体から合成される。発散的合成では、4つの合成対象化合物**1a-1d**すべてを統一的に供給し、合成後期に共通の合成中間体からの分岐点を設定することにより、合成をより効率的に行うことができる。

複数の不斉点をもつ天然物のすべての立体異性体を合成する際は、効率よく合成できる発散的合成が望まれる。

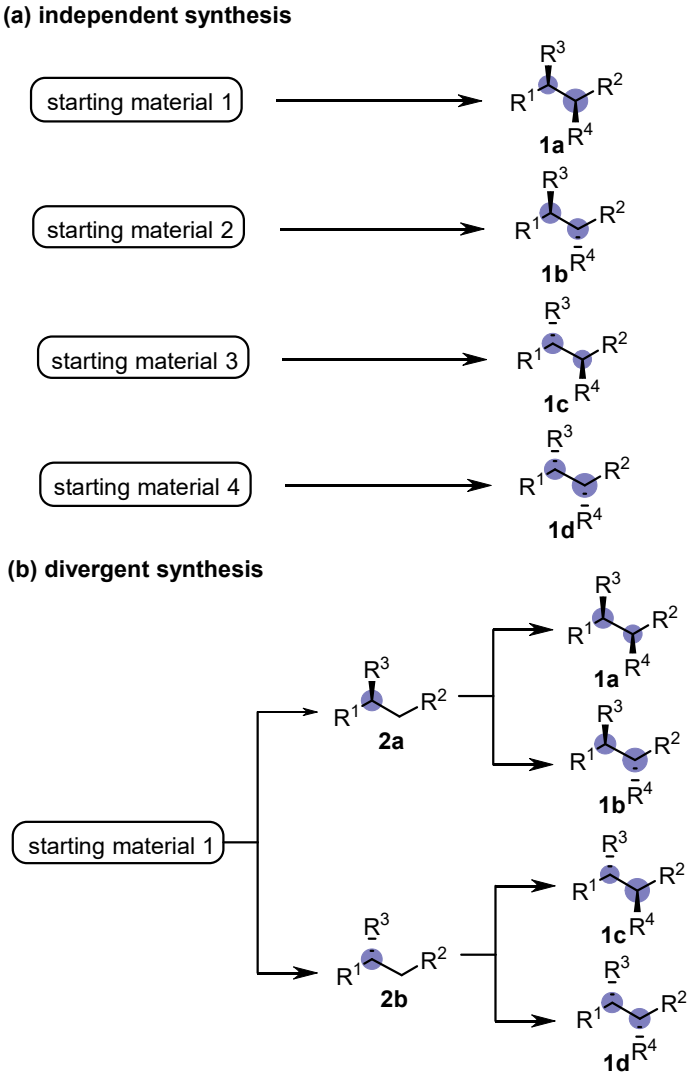


Figure 1-1. Schematic overview of independent and divergent synthesis.

天然物や医薬品の合成に向けた立体発散的合成のアプローチの例を提示する。

レボキセチンの全４立体異性体の立体発散的合成 [2]

レボキセチン(**5**)(**Figure 1-2**)は強力かつ選択的なノルエピネフリン再取り込み阻害薬(NRI)であり、現在、(2*S,* 3*S*)-及び(2*R,* 3*R*)-エナンチオマーのラセミ混合物として、 Edronax, Prolift, Vestra, Norebox,及び Integex の商品名で 60 カ国以上で抗うつ薬として販売されている。また、レボキセチンはパニック障害、注意欠陥多動性障害(ADHD)、ナルコレプシー、コカイン依存性障害の治療にも有用であることが明らかになっている。

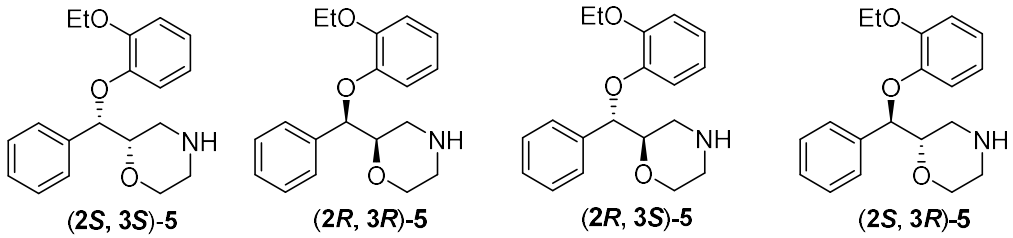
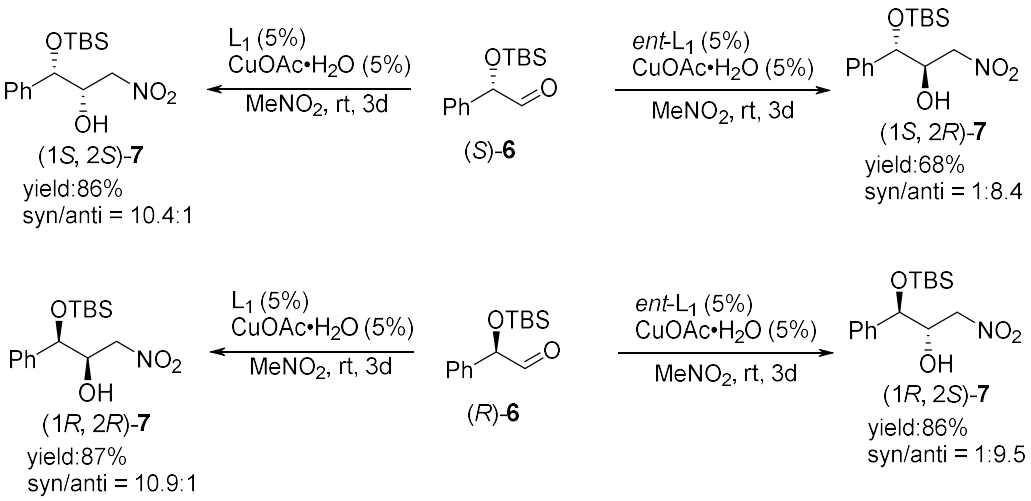


Figure 2. Structures of the four stereoisomers of reboxetine **5**.

いくつかの研究では、(*S, S*)- レボキセチンがノルエピネフリントランスポーター(NET)に対して、その(*R, R*)-エナンチオマーよりも有意に活性で選択的であることが報告されている。このため、(*S, S*)-レボキセチンの合成のために、過去10年間にわたり、化学的分割、加水分解速度論的分割、キラルプール法、不斉エポキシ化及びジヒドロキシル化、及び不斉移動水素化に基づくいくつかの方法が開発されてきた。レボキセチンは、何種類かの副作用が報告されており、立体化学に基づく原因解明が求められる。また、(*S, R*)及び(*R, S*)-レボキセチンも(*S, S*)-レボキセチンに非常に類似したNETに対する親和性を持つことが分かってきた。(*S, R*)-及び(*R, S*)- レボキセチン類縁体も新規NRIの候補として適切であると考えられることから、レボキセチン及びその類縁体のすべての立体異性体を簡便かつ確実に合成することができれば、より有効性及び安全性の高い抗うつ薬の研究開発が大いに促進されると考えられる。

Chengらは銅触媒Cu-L_1 and及びCu-*ent*-L_1 (**Figure 1-3**)を用いてキラルなアルデヒド(*S*)-又は(*R*)-**6**とニトロメタンとのジアステレオ選択的ニトロアルドール反応を行うことで、抗うつ薬レボキセチンの全4種の立体異性体を多様に調製した(**Scheme 1-1**)。



Scheme 1-1. Diastereoserective Henry reactions

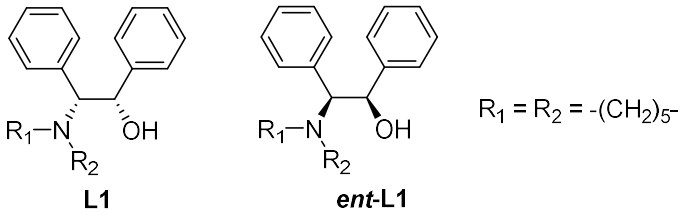
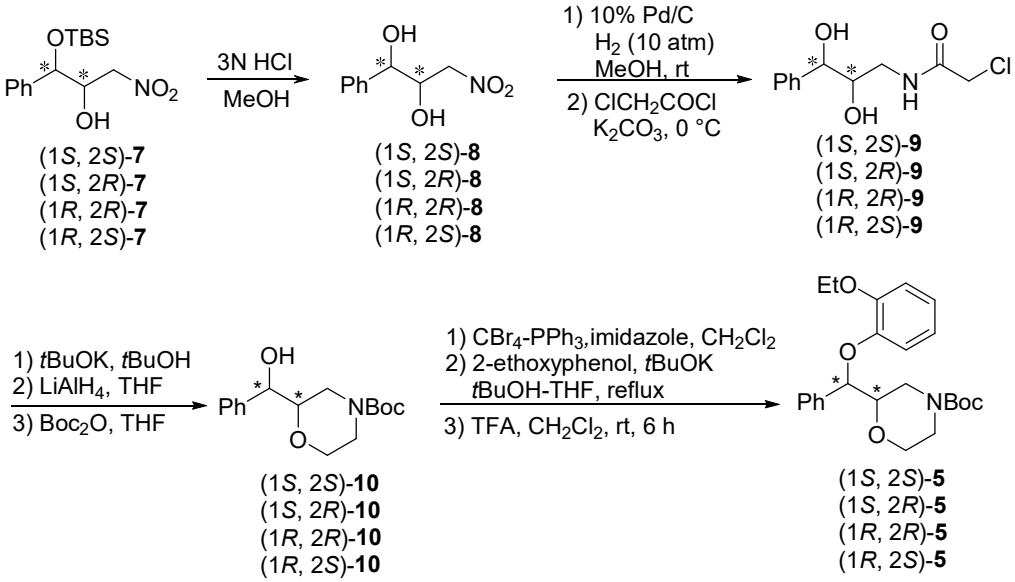


Figure 1-3. Chiral amino alcohol ligands L_1 and *ent*-L_1.

7に対し、TBS基の脱保護を行い**8**とした(**Scheme 1-2**)。**8**のニトロ基を接触水素化によりアミノ基へ変換後、2当量の炭酸カリウムの存在下でのクロロアセチルクロリドと反応させ、クロロアセトアミド**9**を得た。*t*BuOK(2.5当量)で処理することによりモルホリノンに変換され、$LiAlH_4$により還元後、Boc保護することでモルホリンのBoc-アミド**10**を得た。最後に2級アルコールのブロモ化、エーテル化、Boc基の脱保護を行うことでレボキセチンの合成を達成した。



Scheme 1-2. Asynmetric synthesis of reboxetine **5**

この合成経路では、アルデヒド(*S*)-**6**から総収率30.5%で(*S, S*)-レボキセチンを与えた。さらに、ここで開発した合成アプローチを用いれば、市販で入手できるフェノール類が豊富にあるため、構造的に多様なレボキセチン類縁体を簡便に調製することができる。本研究が新規NRIの研究開発を促進することが望まれる。

1-ヒドロキシメチルピロリジン アルカロイドの全立体異性体の立体発散的合成[3]

1-ヒドロキシメチルピロリジン アルカロイドの全ての可能な立体異性体、すなわち(+)-イソレトロネカノール、(–)-イソレトロネカノール、(+)-ラブルニン、及び(–)-トラケランタミジンは、種々の開花植物の抽出物中に見出された。これら 4 種の立体異性体のエステル誘導体は、抗炎症活性、抗コリン活性、抗寄生虫活性、及び抗真菌活性などの生物活性を示す。ピロリジジンアルカロイドの一つである(–)-イソレトロネカノールはそのアミド誘導体に変換され、それらは強力かつ選択的な 5-HT 4 受容体作動薬であることが判明している。そのため、これらの生物学的重要性を考慮して、1-ヒドロキシメチルピロリジン アルカロイドの不斉合成法の開発が求められる **(Figure 1-4)**。

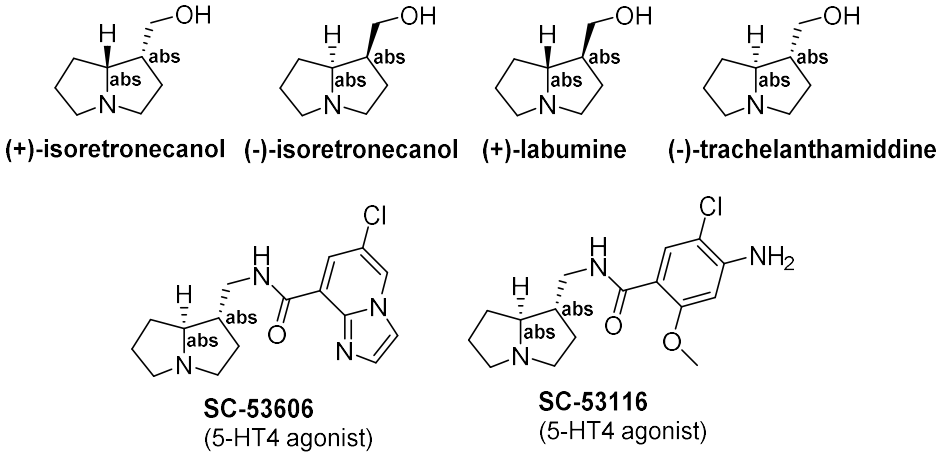
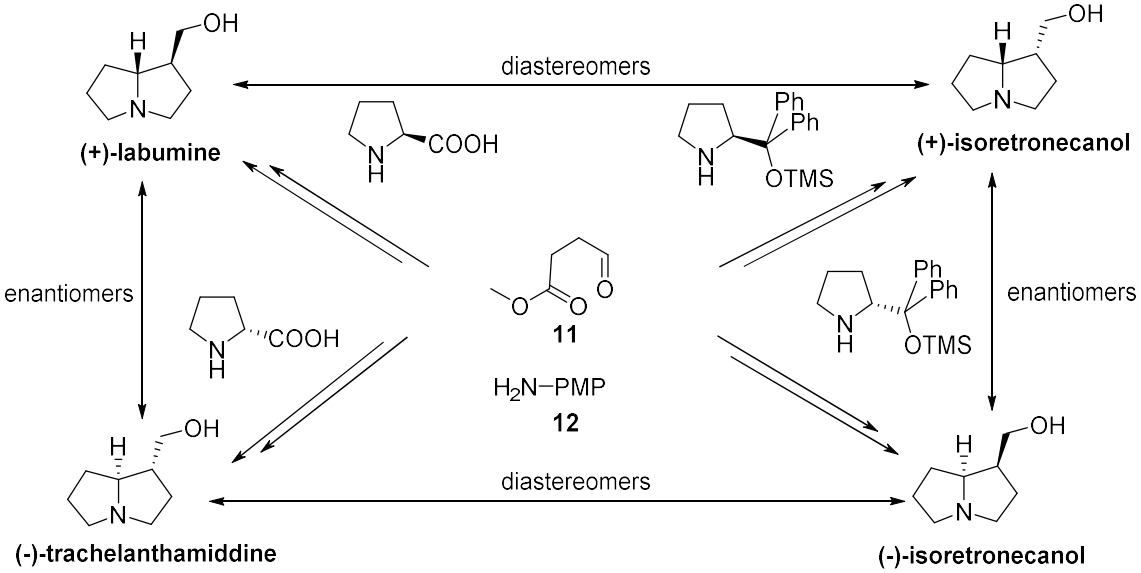


Figure 1-4. Structures of pyrrolizidine alkaloids and their derivatives.

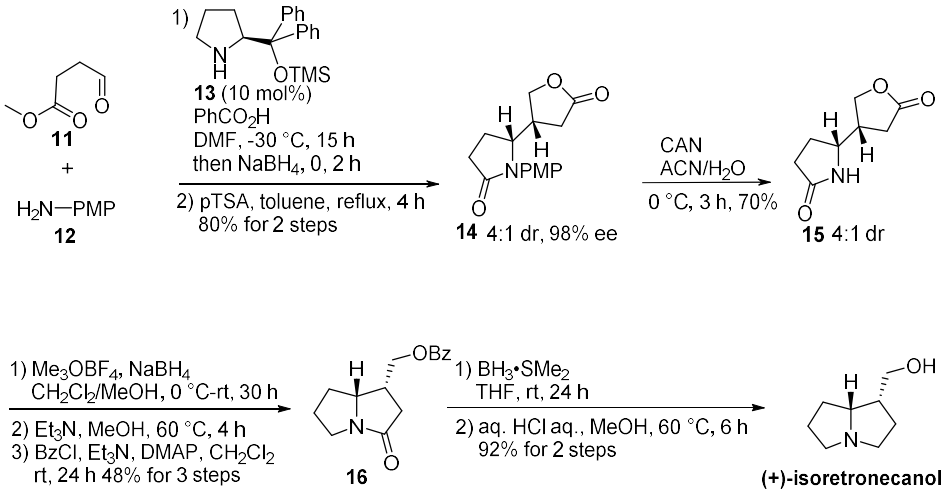
4-oxobutanoate とPMP-アミンを全立体異性体合成の共通中間体として設定した(**Scheme 3**)。$PhCO_2H$の存在下、不斉自己Mannich反応の最適化を行い、4種の立体異性体を作り分けることを計画した。



Scheme 1-3. Synthesis strategy of four stereoisomers of pyrrolizidine alkaloids.

(+)-イソレトロネカノールの合成について示す(**Scheme 1-4**)。4-oxobutanoate **11** と PMP-amine **12** 存在下、触媒 **13** 及び $PhCO_2H$ を作用させ、-30℃で不斉自己 Mannich 反応を行った。Mannich 付加物は反応条件下で不安定であったため、$NaBH_4$ で還元し、 p-TSA を用いて環化することで、80%の単離収率、dr 比 4:1 及び 98% ee で PMP-ラクタム **14** を得ることに成成した。CAN を用いて PMP-ラクタム **14** の PMP 基の除去を行い、ラクタム **15** を得た。ラクタム **15** の選択的

還元を Me_3OBF_4 と $NaBH_4$ を用いて達成して粗生成物を得た。さらに MeOH 中 NEt_3 を用いて環化し二環性ラクタムとし、一級アルコールを Bz 基で保護して二環性ラクタム **16** を 3 段階で 48%の収率で得た。BH_3・SMe_2 を用いた二環性ラクタム **16** の還元とそれに続くベンゾイル基の除去により(+)-イソレトロネカノールの合成を達成した。



Scheme 4. Asymmetric synthesis of (+)-Isoretronecanol

同様の手法でマンニッヒ反応の不斉触媒を変更することで、同一の中間体 4-oxobutanoate **11** と PMP-amine **12** から、4 種の立体異性体の初の立体発散的合成に成功した。

構造解明を目的としたソランデラクトンIの合成[4]

ソランデラクトン I (**17**)は 1996 年にヒドロ虫 Solanderia secunda から単離された 8 員環ラクトンである(**Figure 1-5**)。シクロプロピル部位及び、ラクトン部位の C7、C8 及び C10 位における相対配置は詳細な NMR スペクトル解析により決定したが、 C13 及び C14 位におけるビシナルジオール基の立体化学は解明されなかった。
そこで、Pietruszka らは、ソランデラクトンの 4 つの可能なジアステレオマーすべての合成を試みた(**Scheme 1-6**)。

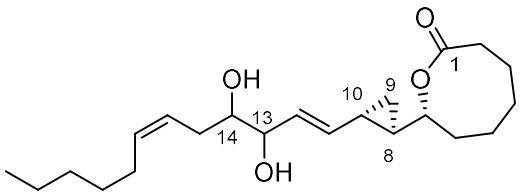
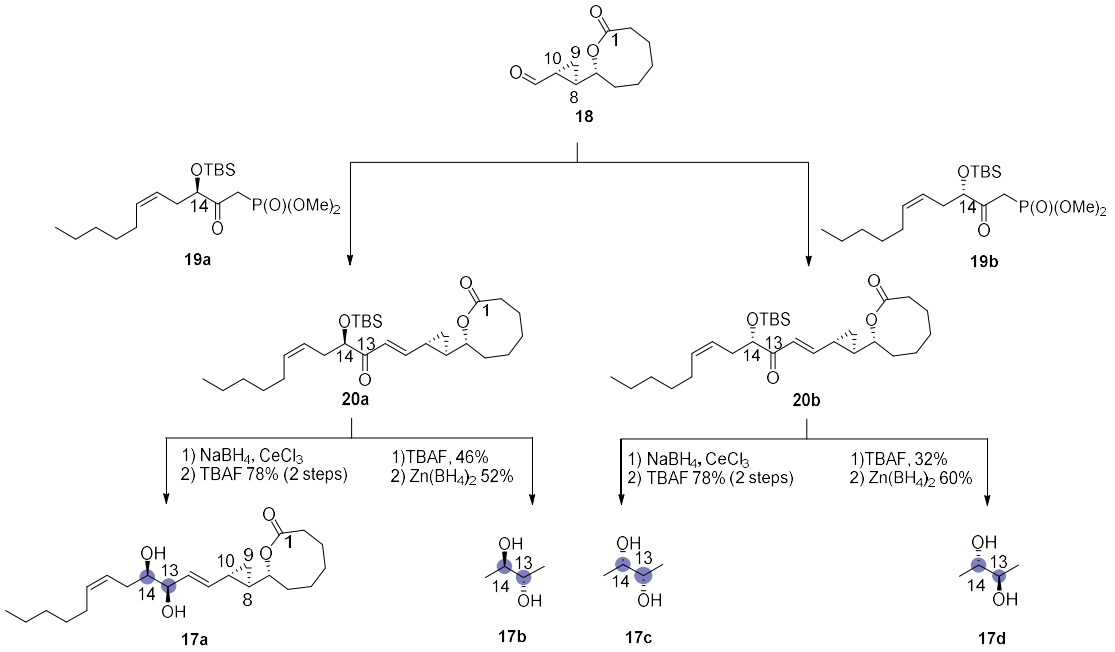


Figure 5. Relative configuration of solandelactone I (**17**).

アルデヒド**18** とL-及びD-セリンから調製した光学活性なホスホネート**19a** 及び**19b** との Horner-Wadsworth-Emmons 反応を行いα，β-不飽和ケトン **20a** 及び **20b** を得た。これは C14 位の立体異性体を与える最初の分岐点である。続いて、第二の分岐により C13 位の立体異性体を作り分けた。すなわち、**20a** に対し、$NaBH_4/CeCl_3$ を用いて Felkin-Anh 型の 1,2-還元を行った後、TBS 基の除去を行い *syn*-ジオール **17a** を合成した。TBS エーテル **20a** の脱保護後、得られたα-ヒドロキシケトンの $Zn(BH_4)_2$ によるキレート制御ジアステレオ選択的還元により *anti*-ジオール **17b** を得ることに成功した。並行して、α-シロキシケトン **20b** のジアステレオ選択的還元によってそれぞれ *syn*-ジオール **17c** と *anti*-ジオール **17d** を合成した。



Scheme 6. Stereodivergent synthesis of **17a**–**17d**.

合成した **17a-17d** とソランデラクトン I の NMR データ及び比旋光度を比較した結果、**17c** が天然物データとよく一致したことから、ソランデラクトン I の構造を **17c** に示すものであることを明らかにした。

天然物の構造決定や構造活性相関を研究する際に、効率よく全ての立体異性体を作り分けられる合成経路の設計が重要になる。立体発散的合成は、合成の終盤に分岐点を設定することで、より短工程化することが可能となる。

標的化合物の全ての立体異性体を多様な方法で供給することは、天然物の構造解明及び活性相関の研究を加速させ、また、新しい合成戦略及び反応を開発する機会を提供する。

このような背景から、生物活性天然物の構造決定を目的とした立体発散的合成、および構造活性相関に関する研究を行うこととした。

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(1) (a) Nájera, C.; Foubelo, F.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2020**, *18*, 1232. (b) Takamura, H. *Tetrahedron Lett.* **2018**, *59*, 955.
(2) Liu, C.; Lin, Z. W.; Zhou, Z. H.; Chen, H. B. *Org. Biomol. Chem.* **2017**, *15*, 5395.
(3) Sarkale A. M.; Appayee, C. *Org. Lett.* **2020**, *22*, 4355.
(4) Eichenauer, N. C.; Tschersich, R.; Pietruszka, J. *J. Nat. Prod.* **2015**, *78*, 2782.

第 2 章　(–)-グンミフェロールの全合成・絶対立体配置決定・構造活性相関

2 – 1　　序論

(–)-グンミフェロールは 1995 年に Wall らの研究グループにより、アフリカ大陸のジンバブエに生息する *Adenia gunmmifera* の葉から単離された [1]。本化合物はガン細胞に対し毒性を示すことが知られており、中でもマウス白血病 P388 細胞（ED_{50}:0.03 μg/mL）やヒト膠芽腫 U373 細胞（ED_{50}:0.05 μg/mL）に対し強い細胞毒性を有している。トリアセチレン及びジエポキシド部分を特徴とする(–)-グミフェロールの平面構造(**Figure 2-1**)は、詳細な NMR スペクトル解析により判明している。C8–C9 位、C10–C11 位の 2 つのエポキシドは、カップリング定数（$^3J_{8,9}$ 及び $^3J_{10,11}$ = 2.0 Hz）の観測からトランス配置であると決定された。しかし、天然からの供給量は微量であり、グンミフェロールの立体構造、すなわち 2 つの隣接エポキシド部分の絶対配置は明らかにされなかった。

そこで本化合物の絶対立体配置の決定および生物活性発現部位の解明を目的として合成研究を行うこととした。本章では、(–)-グンミフェロールの考えられる 2 つのジアステレオマーの立体選択的合成と、構造決定について論述する。さらに、グンミフェロールの構造的に単純化された類縁体の合成と、合成されたグンミフェロール、その立体異性体のヒト癌細胞に対する増殖阻害活性についても報告する。

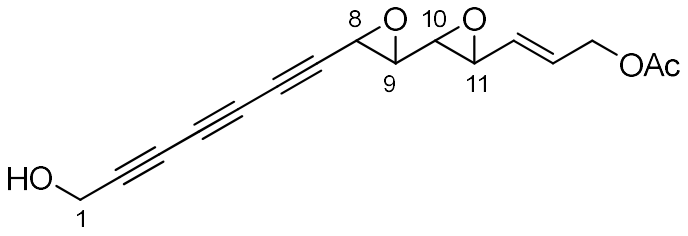


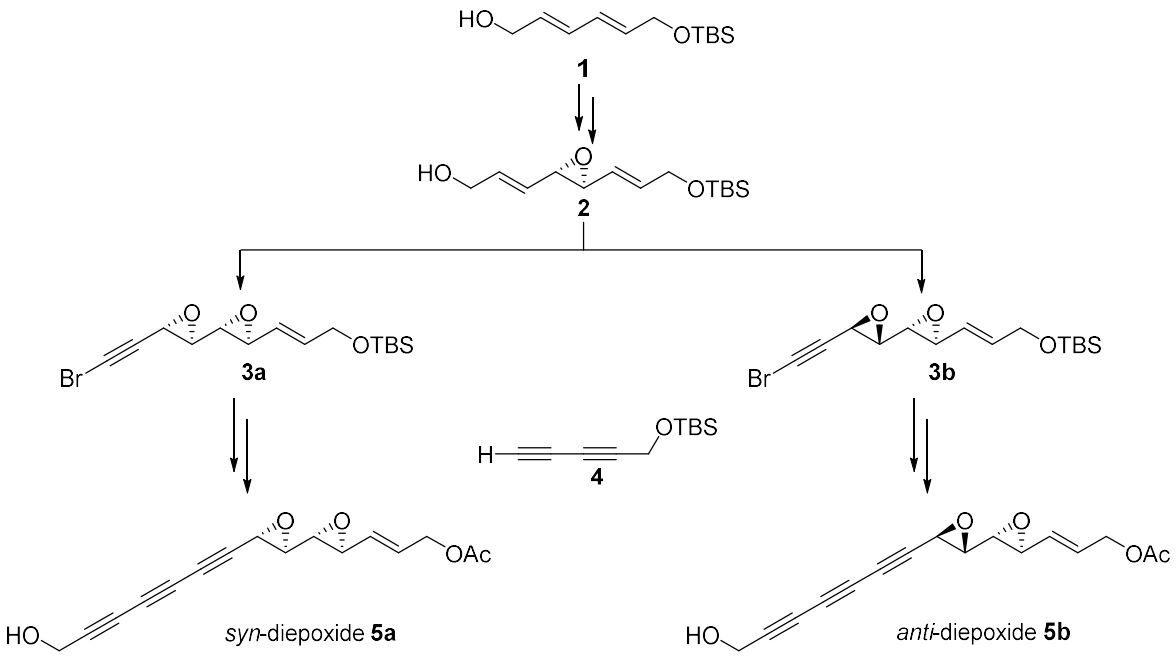
Figure 2-1. Planar structure of (–)-gummiferol.

2 – 2　　合成戦略

(–)-グンミフェロールは立体化学が不明な連続した二つのエポキシドがあるため、四つの可能な立体異性体が考えられる。しかしそのうちの二つはエナンチオマーであるため、比旋光度の比較により判別することが可能である。よって考えられる四つ立体異性体のうち二つを化学合成することとした。次の二点を考慮に入れて、合成戦略を考えた。1、考えられる二つのジアステレオマーを立体選択的に合成できること。2、合成した各種立体異性体それぞれの立体構造を決定できること。

合成戦略を示す(**Scheme 2-1**)。まず、アリルアルコール **1** を合成する [2]。アリルアルコール **1** に対し、Sharpless–Katsuki 不斉エポキシ化 [3] を含む数段階の変換を行い、二種類の立体異性体の合成に関して共通中間体であるアリルアルコール **2** を合成する。**2** に対し、*syn*-および *anti*-ジエポキシド部位を構築した後、さらに数段階の変換を行うことでブロモアセチレン **3a**、**3b** とする。これらと別途合成したジアセチレン **4** とのカップリング反応 [4] を行い、トリアセチレン部位を構築し、*syn*-ジエポキシド **5a** および *anti*-ジエポキシド **5b** を合成することを考えた。

Scheme 2-1

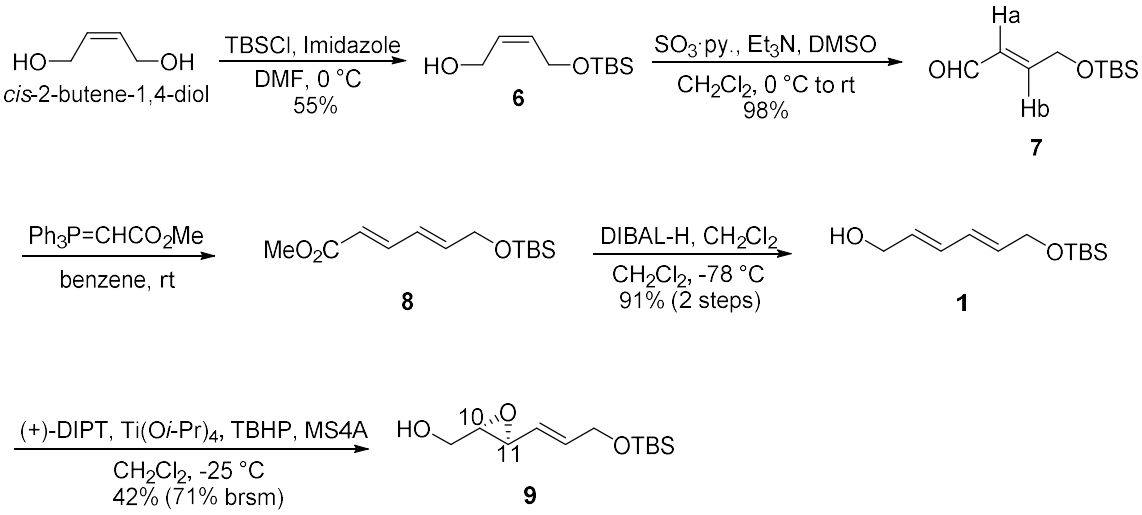


2 – 3　　*syn*-ジエポキシドの立体選択的合成

2－3－1　エポキシアルコールの合成

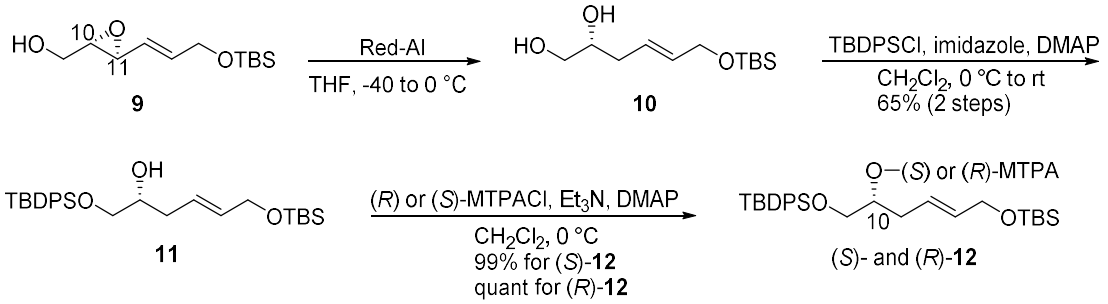
まず始めにエポキシアルコール 9 の合成について示す (Scheme 2-2)。出発原料である cis-2-butene-1,4-diol の片方のヒドロキシ基のみを TBS 基で保護しシリルエーテル 6 とした。次に、アルコール 6 を Parikh–Doering 酸化 5 したところ、オレフィンの異性化が進行し、所望の α,β-不飽和アルデヒド 7 を得た。なお、Ha、Hb のカップリング定数が JHa,Hb＝15.4 Hz であることにより、トランス体であることを確認した。続いて、Wittig 反応により二炭素増炭し、不飽和エステル 8 とした後、DIBAL-H 還元を行い、アリルアルコール 1 を得た。アリルアルコール 1 に対し(+)-DIPT を用いて、官能基選択的およびエナンチオ選択的に Sharpless–Katsuki 不斉エポキシ化反応 3 を行い、エポキシアルコール 9 を単一の立体異性体として合成することが出来た。

Scheme 2-2



続いて合成したエポキシアルコール **9** の構造決定を行った(**Scheme 2-3**)。エポキシアルコール **9** に対し、Red-Al を用いて位置選択的にエポキシドを開環したところ[6]、望みの 1,3-ジオールではなく、反応性の高いアリル位で開環が進行した 1,2-ジオール **10** が単一で得られたので、**10** を用いて構造決定を進めることとした。**10** に対し、一級ヒドロキシ基のみを TBDPS 基で保護しシリルエーテル **11** を合成した。さらに、(*S*)-又は(*R*)- MTPA エステル **12** へと誘導した[7]。

Scheme 2-3



改良モッシャー法により、C10 位のヒドロキシ基の立体化学の確認を行った(**Figure 2-2**)。その結果(*S*)-体と(*R*)-体の化学シフトの差が C10 位の左側でマイナス、右側でプラスの値を示したことから、アルコール **11** の立体化学は望みのものであり、そのことによって、エポキシアルコール **9** が目的の立体化学を有することを確認した。

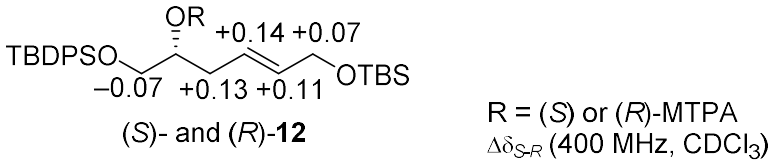
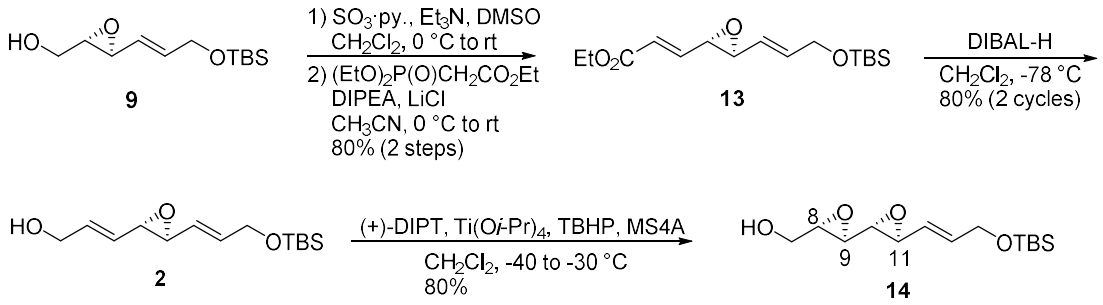


Figure 2-2. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**12**.

2－3－2　ジエポキシアルコールの合成

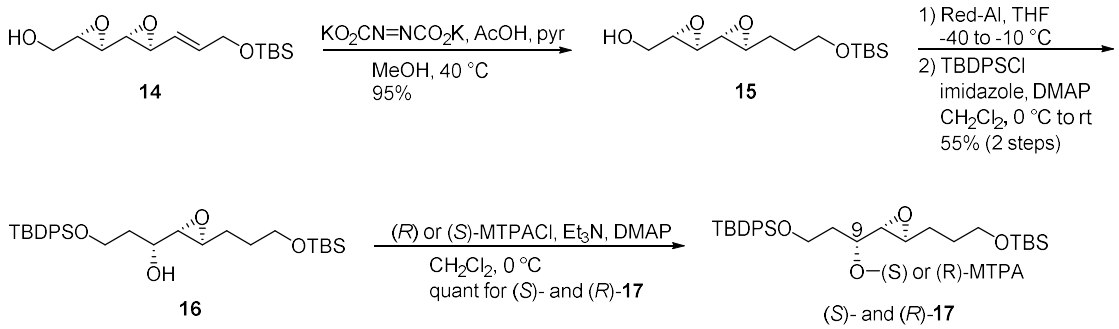
ジエポキシアルコール **14** の合成を行った(**Scheme 2-4**)。得られたエポキシアルコール **9** に対して Parikh–Doering 酸化 [5] によりアルデヒドとした後に Horner–Wadsworth–Emmons 反応 [8] を行い、エステル **13** を得た。続いて、2.2 当量の DIBAL-H を用いて、アリルアルコール **2** への還元を試みたが、エポキシドの開環した副生成物を生じた。そのため、1.2 当量の DIBAL-H を用い段階的な還元を行うことで、目的のアリルアルコール **2** を 2 ステップ 80%の収率で合成することが出来た。アリルアルコール **2** に対して、(+)-DIPT を用いて二度目の不斉エポキシ化を行い、収率良くかつ単一のジアステレオマーとしてジエポキシアルコール **14** を合成することに成功した。

Scheme 2-4



次に、**14** の C8–C9 位のエポキシドの構造決定を行った(**Scheme 2-5**)。C11 位の反応性を下げるため、ジエポキシアルコール **14** をジイミド還元によりアルカン **15** へと変換した。続いて Red-Al を用いて位置選択的にエポキシドの開環を行い 1,3-ジオールとした後に、一級ヒドロキシ基のみを TBDPS 基で保護し **16** を合成した。さらに、二級アルコールを(*S*)-又は(*R*) -MTPA エステル **17** へと誘導した。

Scheme 2-5



前述と同様に改良モッシャー法により、C9 位の立体化学の確認を行った(**Figure 2-3**)。その結果(*S*)-体と(*R*)-体のケミカルシフトの差が C9 位の左側でプラス、右側でマイナスの値を示したため、アルコール **16** の立体化学は望みのものであり、そのことによって、ジエポキシアルコール **14** が目的の立体化学であることを確認した。

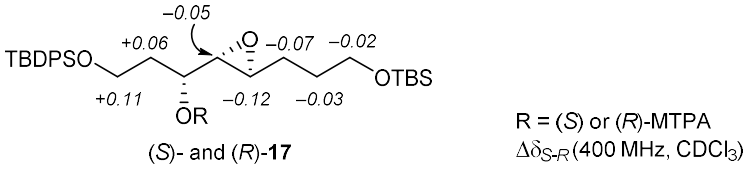


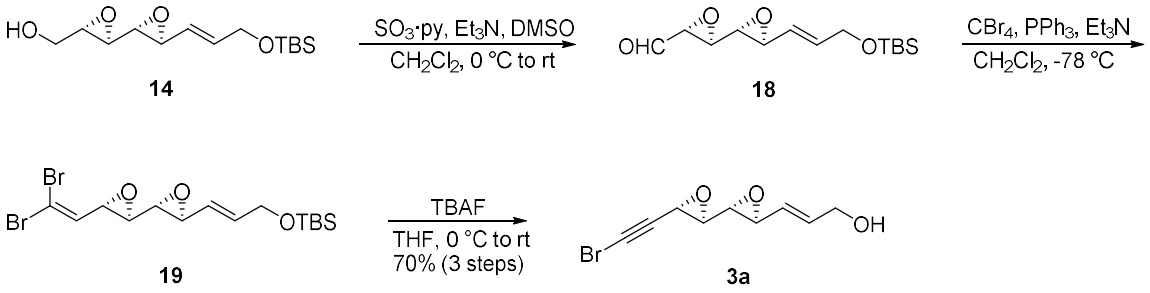
Figure 2-3. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**17**.

2－3－3　ブロモアセチレンの合成

続いて、ブロモアセチレン **3a** の合成を行った(Scheme 2-6)。まず、得られたジエポキシアルコール **14** に対し、Parikh–Doering 酸化 [5] を行いアルデヒド **18** へと変換後、従来の Corey–Fuchs 法によるジブロモオレフィン化を試みた [9]。しかし、目的化合物は全く得られず、エポキシドが開環した副生成物が得られた 10。種々条件検討を行った結果、添加物として Et_3N を加えたところ、目的化合物 **19** を 91%の高収率で合成することに成功した [11a]。Et_3N の添加は、エポキシドが開環する副反応を抑制する効果があると考えられる。具体的には、ホスホラスイリドを形成する際に生じるトリフェニルホスフィンダイブロマイドが強い求核剤として働くので、Et_3N で配位子交換を行うことで、トリフェニルホスフィンを再生し、求核性を低減させていると考える。また、トリフェニルホスフィンダイブロマイドは系中に水が存在しますと水と反応し臭化水素が発生し、酸性となるため、これを中和する働きもあるのではないかと考えました。

系中に少量の水が含まれる際に生じる HBr をトラップし、アリールエポキシドが開環する副反応を抑制すること、
その後、過剰量の TBAF を用い、TBS 基の除去と脱臭化水素によるアルキンの形成を同時に行い [11b]、ブロモアセチレン **3a** へと変換した。

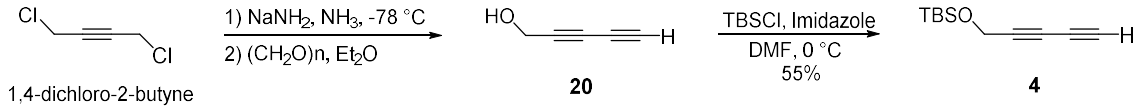
Scheme 2-6



2–3–4　ジアセチレンの合成およびカップリングの検討

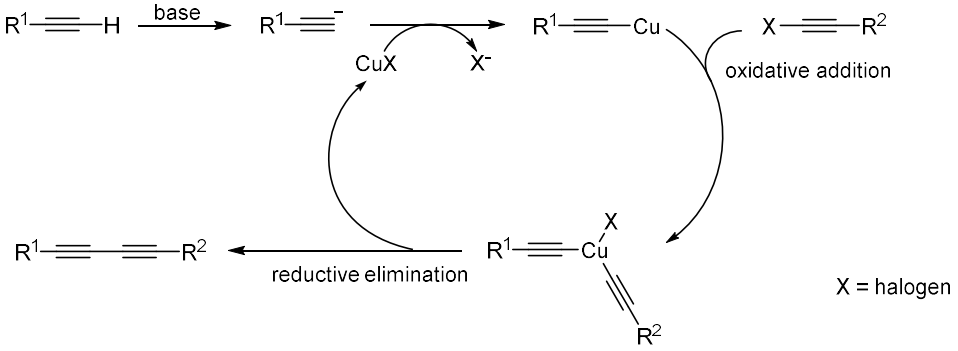
得られたブロモアセチレン **3a** のカップリングパートナーであるジアセチレン **4** の合成を行った [12](**Scheme 2-7**)。まず、1,4-dichloro-2-butyne に対し、$NaNH_2$、NH_3 を用いてナトリウムアセチリドへ変換した後、パラホルムアルデヒドと反応させることで、ジアセチレン **20** を合成した。続いて、ヒドロキシ基を TBS 基で保護しジアセチレン **4** を得た。

Scheme 2-7



次に、トリアセチレン部位構築に用いる Cadiot–Chodkiewicz カップリング反応 [13] の詳細を説明する。本反応はアミン塩基と臭化銅(I)のような銅(I)塩を触媒として、末端アルキンとハロゲン化アルキンとをカップリングさせる化学反応であり、この反応によってジアセチレンが得られる。反応機構は次のように提唱されている(**Scheme 2-8**)。末端水素の塩基による脱プロトン化に次いで銅(I)アセチリドが形成される。生じた銅(I)アセチリドにハロアルキンが酸化的付加し銅(III)錯体を形成後、還元的脱離を経て、新しい炭素 - 炭素結合が生成する。

Scheme 2-8. Mechanism proposed for Cadiot–Chodkiewicz coupling



得られたブロモアセチレン **3a** とジアセチレン **4** の Cadiot–Chodkiewicz カップリング反応 [13] の検討を行った(Scheme 2-9、Table 2-1)。ブロモアセチレン **3a**(1.0 equiv)、ジアセチレン **4** (1.1 equiv)に対し、Alami 法に従い CuI、(PPh3)2PdCl2 を用いて反応を行ったが 13、反応が汚くなり目的化合物は得られなかった(entry 1)。そこで、CuCl、NH2OH•HCl、$EtNH_2$ を用いて、室温で反応を行ったところ [14]、望みのカップリング体を得ることが出来た(entry 2)。しかしこの段階では精製が困難であったため、生じたヒドロキシ基をアセチル化することでアセテート **21** を 2 ステップ 20%で合成することに成功した。望みのカップリング体 21 を合成することが出来たが、カップリングの際にエポキシドにジアセチレンが付加したと思われる副生成物が得られた。そこで、カップリング反応の温度を 0 °C へ下げて反応を行ったところ 2 ステップ 40%と収率が向上した(entry 3)。さらに–78 °C と低温で反応を行ったところ、目的のカップリング体 **21** を 2 ステップ 67%の収率で合成することが出来た(entry 4)。

Scheme 2-9

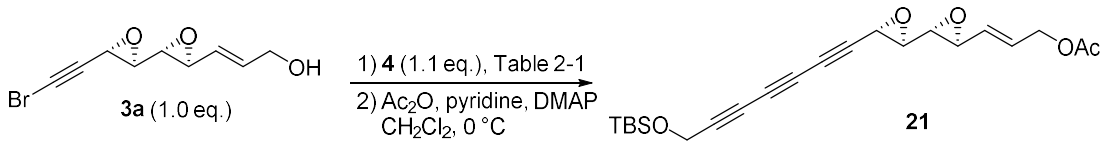


Table 2-1. Cadiot–Chodkiewicz Coupling between **3a** and **4**

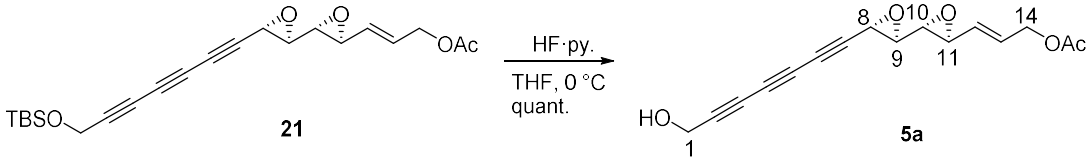
entry	conditions	yield (%)[a]
1	CuI, $(Ph_3P)_2PdCl_2$, pyrrolidine, rt	0
2	CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, rt	20
3	CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 0°C	40
4	CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, -78°C	67

[a] Isolated yield in two steps.

2–3–5　*syn*-ジエポキシドの合成

最後に、*syn*-ジエポキシド **5a** の合成を行った **(Scheme 2-10)**。得られたアセテート **21** に対し HF•pyridine を用いて TBS 基を除去することで、*syn*-ジエポキシド **5a** を合成することに成功した。

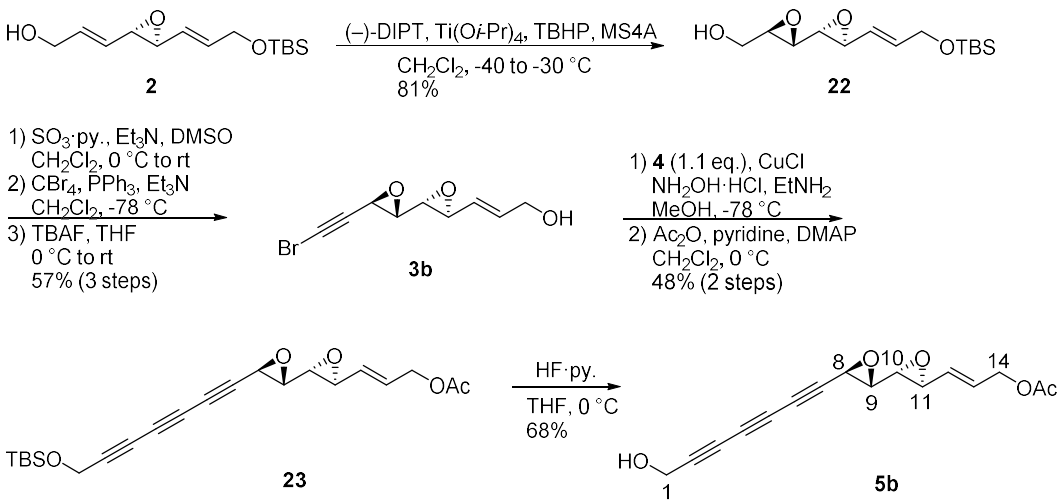
Scheme 2-10



2–4　*anti*-ジエポキシドの立体選択的合成

syn-ジエポキシド **5a** の合成を完了したため、前述の方法に従って *anti*-ジエポキシド **5b** の立体選択的合成を行った**(Scheme 2-11)**。まず、共通中間体であるアリルアルコール **2** に対し、(–)-DIPT を用いて Sharpless–Katsuki 不斉エポキシ化 [3] を行い、単一のジアステレオマーとしてジエポキシド **22** を合成した。次に、**22** に対し Parikh–Doering 酸化 [5] によりアルデヒドとした後、ジブロモオレフィン化、TBS 基の除去と脱臭化水素化を同時に行い、ブロモアセチレン **3b** を 3 ステップ 57%の収率で合成することが出来た。Cadiot–Chodkiewicz カップリング反応 [13] により、ジアセチレン **4** と連結しトリアセチレン骨格を構築した後に、生じたアルコールをアセチル化し **23** を得た。最後に、TBS 基の除去を行い、*anti*-ジエポキシド **5b** を合成することに成功した。

Scheme 2-11



2–5　(–)-グンミフェロールの絶対立体配置の決定

(–)-グンミフェロールの 2 つの候補化合物の合成が完了したので、相対立体配置を決定するために天然物データと合成した *syn*-および *anti*-ジエポキシドの ^{1}H および ^{13}C NMR スペクトルデータの比較を行った。その結果、*syn*-ジエポキシド **5a** の ^{1}H および ^{13}C NMR スペクトルデータは天然物データとよく一致した(**Table 2-2**)。一方、*anti*-ジエポキシド **5b** の ^{1}H および ^{13}C NMR スペクトルデータは天然物データとは一致しないことが分かった(**Table 2-3**)。特に、*anti*-ジエポキシド **5b** の C9、C10 位のプロトンおよびカーボンの化学シフトの差は大きく異なった。その値はそれぞれ $\Delta\delta_{N-S}$ = +0.08 (H-9)、+0.12 (H-10)、–1.23 (C-9)、–0.88 (C-10)であった。

Table 2-2. ^{1}H and ^{13}C NMR Chemical Shifts of Natural (–)-Gummiferol and the Synthetic Product **5a**[a]

	^{1}H NMR			^{13}C NMR		
position	natural[b]	**5a**[c]	$\Delta\delta_{N-S}$[d]	natural[b]	**5a**[c]	$\Delta\delta_{N-S}$[d]
1	4.34	4.36	-0.02	51.31	51.51	-0.02
2				77.20	77.21	-0.01
3				70.12	70.41	-0.29
4				62.43	62.60	-0.17
5				62.80	62.74	+0.06
6				69.00	68.99	+0.01
7				73.90	73.99	-0.09
8	3.46	3.44	+0.02	43.05	43.06	-0.01
9	3.35	3.34	+0.01	57.46	57.49	-0.03
10	3.04	3.02	+0.02	56.20	56.22	-0.02
11	3.39	3.38	+0.01	55.15	55.11	+0.04
12	5.49	5.49	0	129.37	129.31	+0.06
13	6.05	6.04	+0.01	130.53	130.44	+0.09
14	4.58	4.59	-0.01	63.55	63.50	+0.05
14-*C*OCH$_3$				170.77	170.47	+0.34
14-CO*C*H$_3$	2.09	2.08	+0.01	20.87	20.90	-0.03

[a] Chemical shifts are reported in ppm with reference to tetramethylsilane. [b] Recorded at 500 MHz (125 MHz). [c] Recorded at 400 MHz (100 MHz). [d] δ_N and δ_S are chemical shifts of the natural product and the synthetic product, respectively.

Table 2-3. ^{1}H and ^{13}C NMR Chemical Shifts of Natural (–)-Gummiferol and the Synthetic Product **5b**[a]

	^{1}H NMR			^{13}C NMR		
position	natural[b]	**5b**[c]	$\Delta\delta_{N\text{-}S}$[d]	natural[b]	**5b**[c]	$\Delta\delta_{N\text{-}S}$[d]
1	4.34	4.36	-0.02	51.31	51.52	-0.21
2				77.20	77.20	0
3				70.12	70.41	-0.29
4				62.43	62.81	-0.38
5				62.80	62.55	+0.25
6				69.00	69.20	-0.20
7				73.90	73.69	+0.12
8	3.46	3.43	+0.03	43.05	43.47	-0.42
9	3.35	3.27	+0.08	57.46	58.69	-1.23
10	3.04	2.92	+0.12	56.20	57.08	-0.88
11	3.39	3.35	+0.04	55.15	55.86	-0.71
12	5.49	5.48	+0.01	129.37	129.05	+0.32
13	6.05	6.04	+0.01	130.53	130.50	+0.03
14	4.58	4.58	0	63.55	63.45	+0.10
14-*C*OCH$_3$				170.77	170.39	+0.38
14-CO*CH$_3$*	2.09	2.08	+0.01	20.87	20.90	-0.03

[a] Chemical shifts are reported in ppm with reference to tetramethylsilane. [b] Recorded at 500 MHz (125 MHz). [c] Recorded at 400 MHz (100 MHz). [d] δ_N and δ_S are chemical shifts of the natural product and the synthetic product, respectively.

(–)-グンミフェロールの絶対立体化学を決定するため、比旋光度の値の比較を行った。天然物の値が$[\alpha]^{25}_{D}$ －170 (*c* 0.2, CH_3OH)であるのに対し、合成した *syn*-ジエポキシド **5a** は$[\alpha]^{25}_{D}$ －62.5 (*c* 0.07, CH_3OH)だった。この結果から、(–)-グンミフェロールの絶対立体配置は **Figure 2-3** に示すものであることを明らかにした。

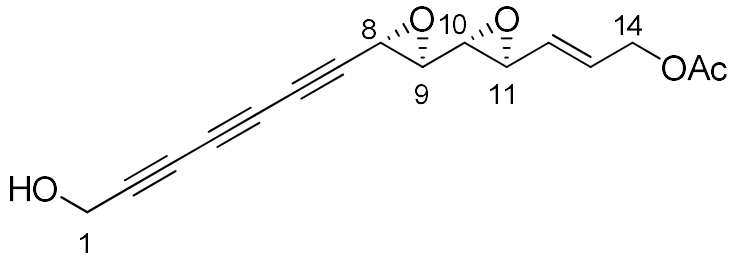


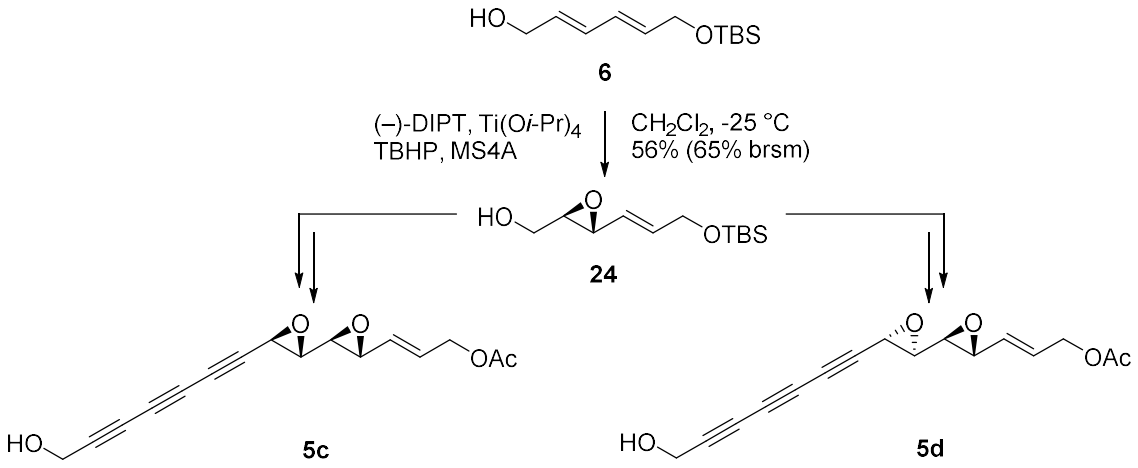
Figure 2-3. Absolute configuration of (–)-gummiferol.

2−6　(–)-グンミフェロールの構造活性相関

2−6−1　(–)-グンミフェロールの立体異性体の合成

(–)-グンミフェロールの絶対立体配置を決定することができたため、グンミフェロールの構造活性相関を明らかにすることとした。はじめに、ジエポキシド部位が生物活性に及ぼす影響を解明するために、(–)-グンミフェロールの残り 2 つの立体異性体 **5c**、**5d** を合成することとした(**Scheme 2-12**)。すなわち、アリルアルコール **6** に対し(–)-DIPT を用いた Sharpless–Katsuki 不斉エポキシ化反応 [3] を行い、エポキシアルコール **24** へと誘導後、前述と同様の方法で *syn*-ジエポキシド **5c** および *anti*-ジエポキシド **5d** を合成した [15]。

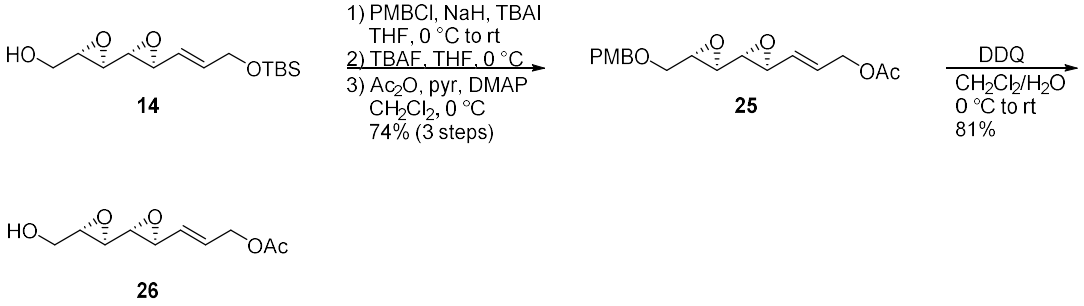
Scheme 2-12



2−6−2　構造単純化類縁体の合成

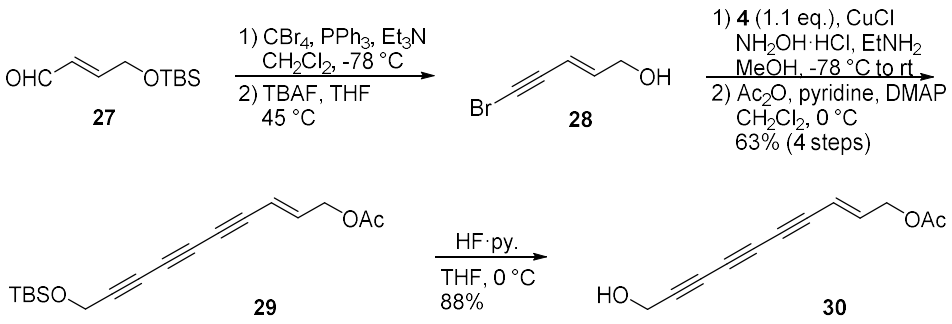
次にジエポキシド部位およびトリアセチレン骨格に対応する構造単純化類縁体の合成を行った。まずはジエポキシド部位を有する構造単純化類縁体 **26** の合成を示す(**Scheme 2-13**)。(–)-グンミフェロールの合成中間体であるエポキシアルコール **14** に対し PMB 保護を行い、続いて TBS 基を除去しアルコールを得た。得られたアルコールをアセチル化しアセテート **25** とした。DDQ を作用させ PMB 基を除去し、目的のジエポキシド **26** を合成した。

Scheme 2-13



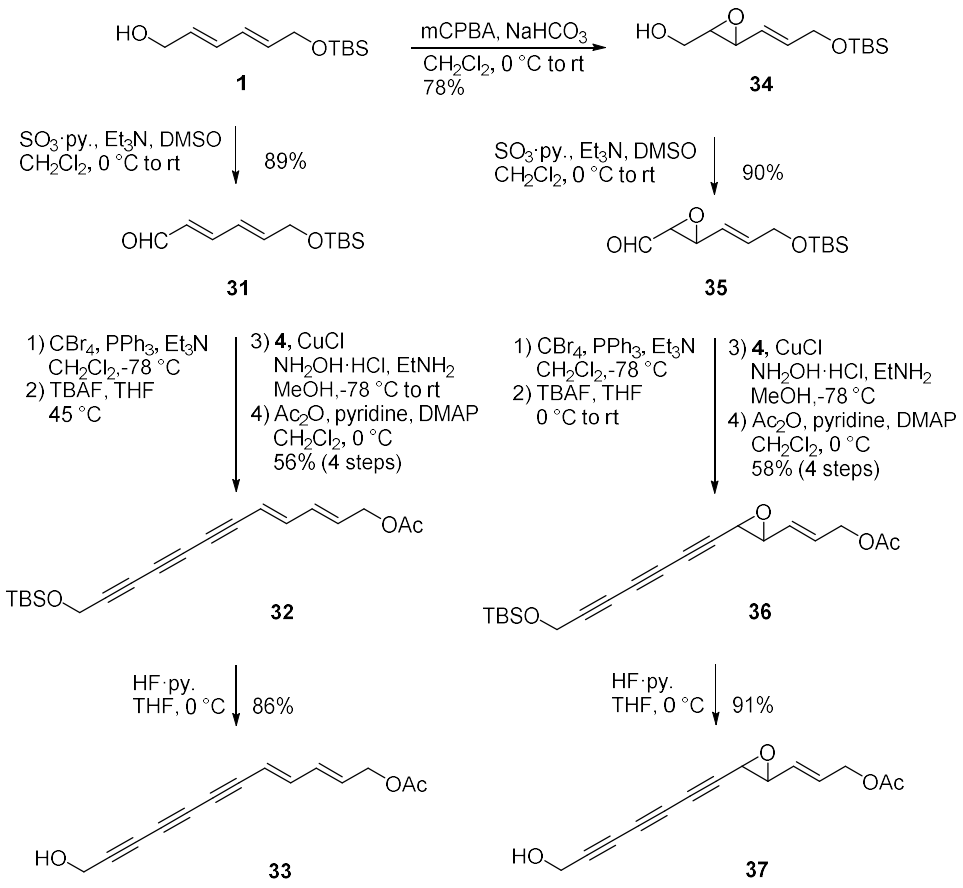
続いてトリアセチレン骨格を有する構造単純化類縁体 **30**、**33**、**37** の合成に着手した。既知のアルデヒド **27** [16] に対し、改良した Corey–Fuchs 法によりジブロモオレフィンへと変換後、過剰量の TBAF を用い、TBS 基の脱保護と脱臭化水素によるアルキンの形成を同時に行い、ブロモアセチレン **28** へと変換した(**Scheme 2-14**)。Cadiot–Chodkiewicz カップリング反応 [13] により、ブロモアセチレン **28** とジアセチレン **4** とを連結し、生じたアルコールをアセチル化することでアセテート **29** を 4 ステップ 63%の収率で得た。TBS 基の除去を行い、1 つ目の構造単純化トリアセチレン化合物 **30** を合成することに成功した。

Scheme 2-14



他の二つの構造単純化類縁体 **33**、**37** も同様に合成した(**Scheme 2-15**)。ジエノール **1** を Parikh–Doering 酸化 [5] によりアルデヒド **31** へ変換した。続く 4 ステップの変換を行いトリアセチレン **32** を合成した。すなわち、(1) Et_3N 存在下 CBr_4 と PPh_3 を作用させ 1 炭素増炭、(2) ワンポットでの TBS 基の除去と脱臭化水素によるアルキンの形成、(3) ブロモアルキンと **4** との Cadiot–Chodkiewicz カップリング反応 [13]、(4)生じたアルコールのアセチル化を行うことで **32** を 4 ステップ 56%の収率で得た。最後に TBS エーテルの脱保護を行い、**30** より 2 炭素増炭されたトリアセチレン化合物 **33** を合成することに成功した。**37** の合成も共通中間体であるジエノール **1** より行った。**1** に対し *m*-CPBA を用いた位置選択的なエポキシ化を行いラセミのエポキシアルコール **34** を得た。**34** を Parikh–Doering 酸化 [5] によりアルデヒド **35** へ誘導後、前述と同様に 4 ステップの変換を行いトリアセチレン **36** を合成した。**36** に対し HF•py.を用いて TBS 基を除去することで、3 つ目の構造単純化トリアセチレン化合物 **37** を合成することに成功した。なお **37** は **33** のモノエポキシ化体である。

Scheme 2-15



2−6−3　活性評価

(–)-グンミフェロール(**5a**)とその立体異性体 **5b**、**5c**、**5d**、およびその構造単純化類縁体 **26**、**29**、**30**、**32**、**33**、**36**、**37** の細胞生存率評価を行った。ヒト急性骨髄性白血病 HL60 細胞およびヒト子宮頸がん HeLa S_3 細胞を用いた MTT アッセイを用いて、これらの化合物の増殖阻害活性を評価した。細胞を 96 ウェルプレートで種々の濃度の化合物で 72 時間処理した結果を示す(**Table 2-4)**、**Figure 2-4.**。

興味深いことに、 (–)-グンミフェロール(**5a**)およびその立体異性体 **5b**、**5c**、**5d** は、ジエポキシド部位の立体構造が異なるにも関わらずに同様の活性(HL60…IC_{50}: 1.22–3.61 μM、HeLa S_3…IC_{50}: 6.76–19.1 μM)を示した。構造単純化したジエポキシド化合物 **26** は、HL60 および HeLa S_3 細胞の両方に対して不活性であった(IC_{50}>100 μM)。一方で、構造単純化されたトリアセチレン化合物 **30** は増殖阻害活性(HL60…IC_{50}: 12.3 μM、HeLa S3…IC_{50}: 31.6 μM)を保持していた。他の二つのトリアセチレン化合物 **33** および **37** の生物活性は **30** のそれと比較してわずかに増加することが証明された。また、**30**、**33**、**37** の TBS 保護体 **29**、**32**、**36** においても二つの細胞に対する細胞毒性に顕著な低下は見られなかった。アルコール **30** と比較して、その TBS 保護体 **29** の方が活性が高い原因としては、保護基によって化合物の水溶性が下がった結果、細胞膜透過性が高くなり活性が上昇したと考えられる。一方、アルコール **33**、**37** と比較して、その TBS 保護体である **32**、**36** の方が活性が低下した。その原因としては、保護基のような大きな構造が化合物のターゲットとの相互作用を阻害したためと考えられる。以上の結果から、構造活性相関に関して次の二つの結論を導いた。

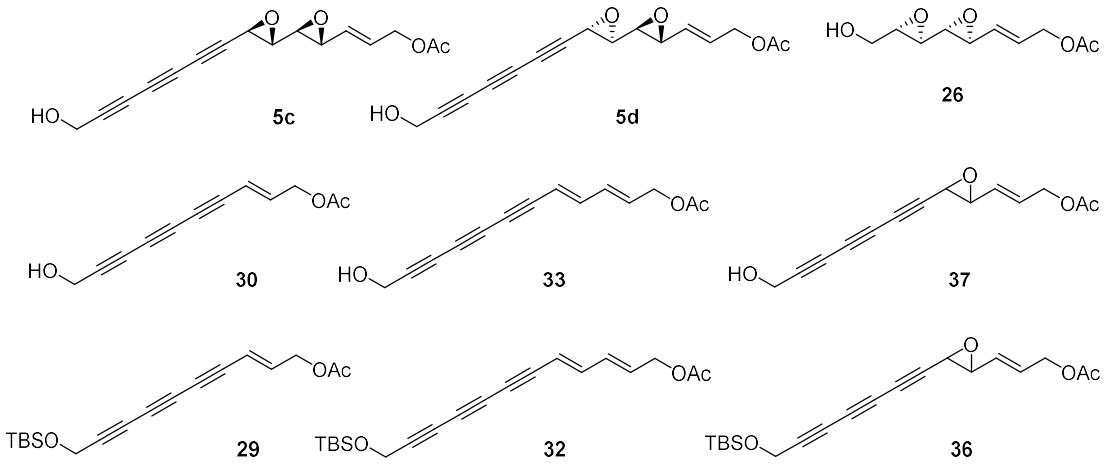
(1) ジエポキシドの立体化学は、増殖阻害活性にほとんど影響しない。
(2) トリアセチレン骨格は細胞毒性を発現するために不可欠である。

Table 2-4. Growth-Inhibitory Activity of (–)-Gummiferol, Its Stereoisomers, and Its Structural Analogues against Human Cancer Cells[a]

compounds	HL60	HeLa S_3
5a	1.22	6.76
5b	1.62	8.61
5c	1.23	6.68
5d	3.61	19.1
26	>100	>100
30	12.3	31.6
33	4.63	22.4
37	4.75	17.4
29	4.48	19.3
32	19.4	50.9
36	7.40	20.6

[a] IC_{50} values in μM

Figure 2-4. The structures of synthetic products.



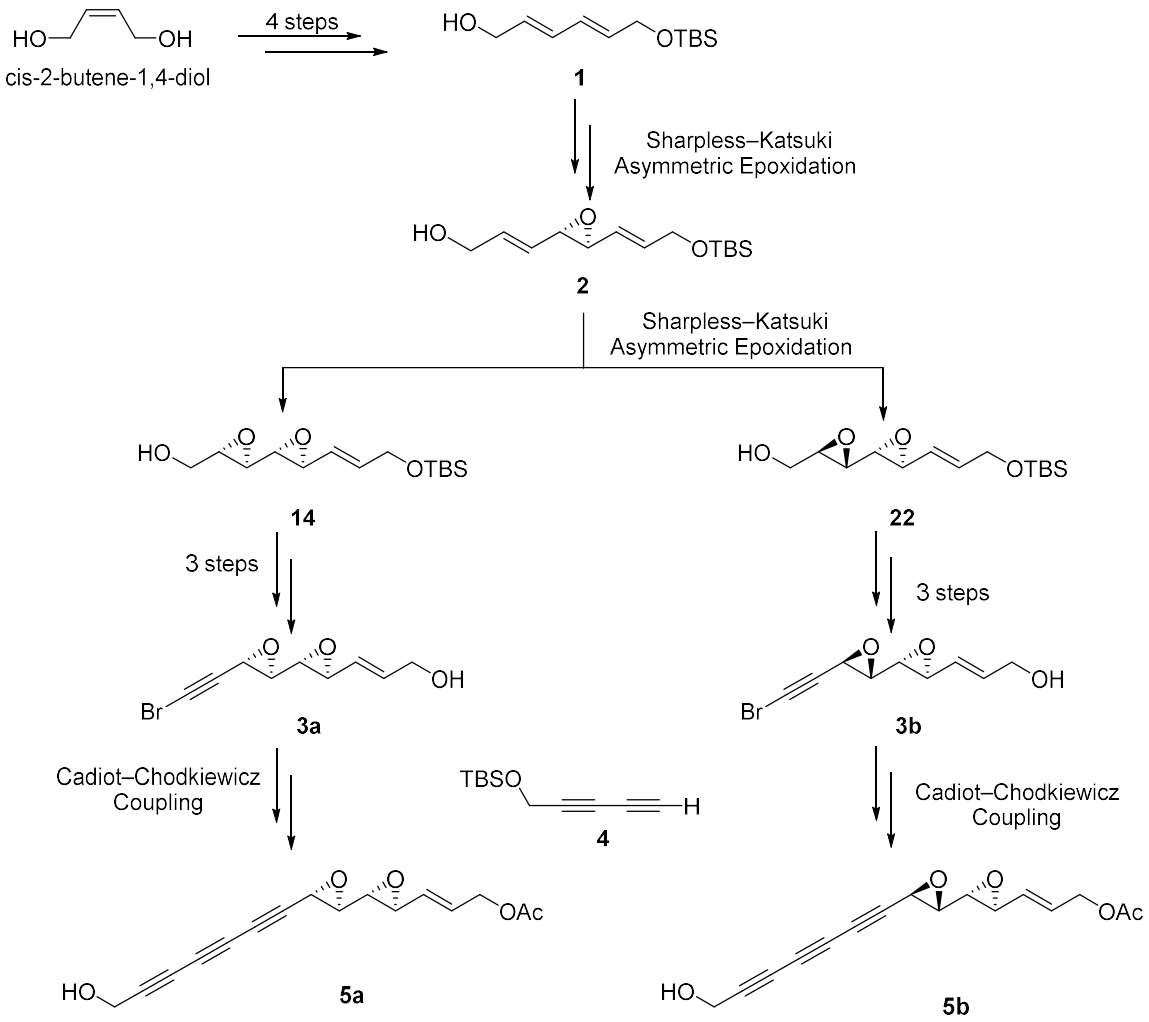
2–7　まとめ

(–)-グンミフェロールの全合成・絶対立体配置決定・構造活性相関のまとめについて示す。(–)-グンミフェロールの絶対立体配置を決定すべく、考えられる 2 つのジアステレオマー**5a**、**5b** を高立体選択的に合成した(**Scheme 2-16**)。出発原料として *cis*-2-butene-1,4-diol を用い、4 段階の変換を経てアリルアルコール **1** を得た。**1** に対して Sharpless–Katsuki 不斉エポキシ化[3] を含む数段階の変換を行い、エポキシアルコール **2** を合成した。続いて **2** に対し(+)-DIPT を用いて二度目の不斉エポキシ化を行いジエポキシアルコール **14** へ変換した。アルコール **14** に対し 3 段階の変換を行うことでブロモアセチレン **3a** を得た。**3a** と別途合成したジアセチレン **4** との Cadiot–Chodkiewicz カップリング反応[13] を行い、トリアセチレン骨格を構築した後、ヒドロキシ基のアセチル化および TBS 基の除去を行い、*syn*-ジエポキシド **5a** の合成に成功した。また、共通中間体 **2** に対し(–)-DIPT を用いた不斉エポキシ化反応を行い、高ジアステレオマー選択的にジエポキシド **22** を合成した。**22** に対して、先述と同様の反応を行うことで、*syn*-ジエポキシド **5b** の合成も達成した。

合成した *syn*-ジエポキシド **5a** および *anti*-ジエポキシド **5b** のそれぞれの ^{1}H および ^{13}C NMR スペクトルデータおよび比旋光度と天然物データを比較することにより、(–)-グンミフェロールが **5a** で示される絶対立体配置を有していることを明らかにした。

さらに、(–)-グンミフェロールの構造活性相関を解明するために **5a**、**5b** とそのエナンチオマー**5c**、**5d** を合成した。さらに、ジエポキシド部位またはトリアセチレン骨格を有する構造単純化類縁体として **26**、**29**、**30**、**32**、**33**、**36**、**37** を合成し、併せて細胞毒性試験を行った(**Figure 2-4**)。合成した 11 個の化合物に対し、ヒト急性骨髄性白血病 HL60 細胞およびヒト子宮頸がん HeLa S_3 細胞に対する増殖抑制活性を評価した。その結果、(1) ジエポキシド部位の立体化学は細胞毒性にほとんど影響しないが、(2) トリアセチレン骨格が生物活性を発現するために不可欠であることの 2 点を明らかにした。

Scheme 2-16


HO
OH
cis-2-butene-1,4-diol
4 steps
HO
OTBS
1
Sharpless–Katsuki
Asymmetric Epoxidation
HO
OTBS
2
Sharpless–Katsuki
Asymmetric Epoxidation
HO
OTBS
14
HO
OTBS
22
3 steps
Br
OH
3a
3 steps
Br
OH
3b
Cadiot–Chodkiewicz
Coupling
TBSO
H
4
Cadiot–Chodkiewicz
Coupling
HO
OAc
5a
HO
OAc
5b

実験項 **(Experimental Section)**

General Methods. Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of argon. Reaction solvents were purchased as dehydrated solvents and stored with active molecular sieves 4A under argon prior to use for reactions. All solvents for work-up procedure were used as received. Analytical thin-layer chromatography (TLC) was performed with aluminium TLC plates (Merck TLC silica gel 60F254). Column chromatography was performed with Fuji Silysia silica gel BW-300 or Kanto Chemical silica gel 60N. Optical rotations were recorded on a JASCO DIP-1000. IR spectra were recorded on a JASCO FT/IR-460 plus. 1H and 13C NMR spectra were recorded on a JEOL JNM-AL400 or Varian 600 MHz spectrometer. Chemical shifts are reported in ppm with reference to the internal residual solvent (1H NMR, CHCl3 7.26 ppm; 13C NMR, CDCl3 77.0 ppm) or tetramethylsilane. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br =broad. Coupling constants (J) are in hertz. High resolution mass spectra were recorded on a Micromass LCT (ESI-TOF-MS) spectrometer.

Epoxy Alcohol 9. To a suspension of powdered MS4A (400 mg) in CH_2Cl_2 (40 mL) were added (+)-DIPT (0.27 mL, 1.32 mmol), Ti(O*i*-Pr)$_4$ (0.26 mL, 0.877 mmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 2.9 mL, 17.4 mmol) at -25 °C. The mixture was stirred at the same temperature for 30 min and a solution of allylic alcohol **1** (2.00 g, 8.77 mmol) in CH_2Cl_2 (5.0 mL + 3.0 mL + 2.0 mL) was added. After the resulting mixture was stirred at –25 °C for 4 h, the reaction was quenched with 3 M aqueous NaOH. The mixture was stirred at room temperature for 1 h. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1) gave epoxy alcohol **9** (901 mg, 42%) as a light yellow oil and allylic alcohol **1** (816 mg, 41% recovery). Epoxy alcohol **9**: R_f = 0.39 (hexane/EtOAc = 1:1); $[\alpha]^{25}_{D}$ –27.1 (*c* 0.10, $CHCl_3$); IR (neat) 3434, 2954, 2928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (dt, *J* = 15.4, 4.4 Hz, 1 H), 5.50 (ddt, *J* = 15.4, 8.0, 2.0 Hz, 1 H), 4.20 (dd, *J* = 4.4, 2.0 Hz, 2 H), 3.96 (ddd, *J* = 12.7, 5.4, 2.4 Hz, 1 H), 3.70 (ddd, *J* = 12.7, 7.8, 3.9 Hz, 1 H), 3.44 (dd, *J* = 8.0, 2.4 Hz, 1 H), 3.09 (dt, *J* = 3.9, 2.4 Hz, 1 H), 1.60 (dd, *J* = 7.8, 5.4 Hz, 1 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 125.9, 62.8, 61.2, 60.0, 55.3,

26.0, 18.6, –5.2, –5.2; HRMS (ESI–TOF) calcd for $C_{12}H_{24}O_3SiNa$ $(M + Na)^+$ 267.1393, found 267.1385.

TBDPS Ether 11. To a solution of epoxy alcohol **9** (50.0 mg, 0.205 mmol) in THF (2.0 mL) was added Red-Al (65% in toluene, 0.31 mL, 1.00 mmol) at –40 °C. After the mixture was stirred at 0 °C for 5 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was diluted with EtOAc and washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 2:1) gave diol **10** (40.5 mg), which was used for the next reaction without further purification.

To a solution of diol **10** obtained above (40.5 mg, 127 μmol) in CH_2Cl_2 (1.5 mL) were added DMAP (32.6 mg, 0.237 mmol), imidazole (32.2 mg, 0.474 mmol), and TBDPSCl (82 μL, 0.316 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1, 10:1, 4:1) gave TBDPS ether **11** (61.9 mg, 65% in two steps) as a yellow oil: R_f = 0.67 (hexane/EtOAc = 4:1); $[\alpha]^{22}_D$ +1.2 (*c* 0.77, $CHCl_3$); IR (neat) 3412, 2956, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (m, 4 H), 7.44–7.37 (m, 6 H), 5.67–5.56 (m, 2 H), 4.10 (d, *J* = 3.7 Hz, 2 H), 3.78–3.75 (m, 1 H), 3.67 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.54 (dd, *J* = 10.2, 6.8 Hz, 1 H), 2.43 (brs, 1 H), 2.23 (t, *J* = 6.4 Hz, 2 H), 1.07 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.1, 132.2, 129.7, 127.7, 126.2, 71.5, 67.4, 63.7, 36.1, 26.9, 26.0, 19.3, 18.5, –5.0; HRMS (ESI–TOF) calcd for $C_{28}H_{44}O_3Si_2Na$ $(M + Na)^+$ 507.2727, found 507.2733.

MTPA Ester (*S*)-12. To a solution of alcohol **11** (2.8 mg, 5.77 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (1.4 mg, 11.5 μmol), Et_3N (1.1 μL, 8.00 μmol), and (*R*)-MTPACl (1.3 μL, 6.93 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 45:1) gave MTPA ester (*S*)-**12** (4.0 mg, 99%) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 10:1); $[\alpha]^{23}_D$ –7.7 (*c* 0.19,

$CHCl_3$); IR (neat) 2954, 2928, 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.32 (m, 15 H), 5.64–5.52 (m, 2 H, H-12 and H-13), 5.25–5.20 (m, 1 H, H-10), 4.06 (d, J = 4.4 Hz, 2 H, H_2-14), 3.74–3.66 (m, 2 H, H_2-9), 3.54 (s, 3 H), 2.55–2.41 (m, 2 H, H_2-11), 1.01 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 135.5, 135.4, 133.4, 133.0, 132.8, 132.2, 129.7, 129.5, 129.4, 128.2, 127.6, 127.6, 127.4, 124.2, 77.2, 76.8, 64.0, 63.4, 55.5, 33.5, 26.8, 26.0, 19.2, 18.5, –5.2; HRMS (ESI–TOF) calcd for $C_{38}H_{51}F_3O_5Si_2Na$ $(M + Na)^+$ 723.3125, found 723.3130.

MTPA Ester (*R*)-12.　To a solution of the alcohol **11** (2.8 mg, 5.77 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (1.4 mg, 11.5 μmol), Et_3N (1.1 μL, 8.00 μmol), and (*S*)-MTPACl (1.3 μL, 6.93 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 45:1) gave MTPA ester (*R*)-**12** (4.1 mg, quant) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 10:1); $[\alpha]^{26}_D$ +26.7 (*c* 0.72, $CHCl_3$); IR (neat) 2954, 2930, 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.29 (m, 15 H), 5.53–5.39 (m, 2 H, H-12 and H-13), 5.27–5.20 (m, 1 H, H-10), 4.01–3.98 (m, 2 H, H_2-14), 3.77 (dd, J = 5.6, 2.2 Hz, 2 H, H_2-9), 3.55 (s, 3 H), 2.35 (t, J = 6.3 Hz, 2 H, H_2-11), 1.04 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 135.5, 135.4, 133.3, 133.0, 132.8, 132.4, 129.8, 129.8, 129.4, 128.6, 128.3, 127.7, 127.4, 124.0, 77.2, 76.8, 64.4, 63.4, 55.5, 33.3, 26.8, 26.0, 19.3, 18.4, –5.1; HRMS (ESI–TOF) calcd for $C_{38}H_{51}F_3O_5Si_2Na$ $(M + Na)^+$ 723.3125, found 723.3135.

α,β-Unsaturated Ester 13.　To a solution of alcohol **9** (998 mg, 4.09 mmol) in CH_2Cl_2 (40 mL) and DMSO (13 mL) were added Et_3N (1.3 mL, 12.3 mmol) and SO_3·py. (1.30 g, 8.18 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding aldehyde (865 mg), which was used for the next reaction without further purification.

To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (1.6 mL, 7.12 mmol) in CH_3CN (27 mL) were added DIPEA (1.8 mL, 10.7 mmol), LiCl (602 mg, 14.2 mmol), and the aldehyde obtained

above (865 mg) in CH_3CN (5.0 mL + 3.0 mL + 1.0 mL) at 0 °C. After the mixture was stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave α,β-unsaturated ester **13** (1.02 g, 3.27 mmol, 80% in two steps) as a colorless oil: R_f = 0.63 (hexane/EtOAc = 4:1); $[\alpha]^{22}_D$ –43.2 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2930, 1723, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 15.6, 6.8 Hz, 1 H), 6.13 (d, *J* = 15.6 Hz, 1 H), 6.03 (dt, *J* = 15.3, 4.4 Hz, 1 H), 5.50 (ddt, *J* = 15.3, 7.7, 1.9 Hz, 1 H), 4.22–4.17 (m, 4 H), 3.38–3.32 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.7, 135.8, 125.3, 123.7, 62.7, 60.7, 60.6, 58.2, 26.0, 18.4, 14.3, –5.2, –5.2; HRMS (ESI–TOF) calcd for $C_{16}H_{28}O_4SiNa$ $(M + Na)^+$ 335.1655, found 335.1648.

Allylic Alcohol 2.　To a solution of α,β-unsaturated ester **13** (18.4 mg, 59.0 μmol) in CH_2Cl_2 (1.0 mL) was added DIBAL-H (1.03 M solution in hexane, 63 μL, 64.9 μmol) at –78 °C. After the mixture was stirred at the same temperature for 10 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 20:1, 10:1, 4:1) gave the corresponding aldehyde (16.4 mg), which was used for the next reaction without further purification.

To a solution of the aldehyde obtained above (16.4 mg) in CH_2Cl_2 (1.0 mL) was added DIBAL-H (1.03 M solution in hexane, 63 μL, 64.9 μmol) at –78 °C. After the mixture was stirred at the same temperature for 10 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 10:1, 4:1) gave allylic alcohol **2** (12.7 mg, 80% in two cycles) as a colorless oil: R_f = 0.35 (hexane/EtOAc = 2:1); $[\alpha]^{25}_D$ –32.1 (*c* 0.87, $CHCl_3$); IR (neat) 3409, 2954, 2929, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, *J* = 15.4, 4.4 Hz, 1 H), 6.00 (dt, *J* = 15.4, 4.4 Hz, 1 H), 5.54–5.46 (m, 2 H), 4.20–4.17 (m, 4 H), 3.29–3.27 (m, 2 H), 1.36 (brs, 1 H), 0.91 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.2, 128.0, 126.1, 62.8, 62.7, 59.9, 59.6, 26.0, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{14}H_{26}O_3SiNa$ $(M + Na)^+$ 293.1549, found 293.1545.

Epoxy Alcohol 14. To a suspension of powdered MS4A (130 mg) in CH_2Cl_2 (10 mL) were added (+)-DIPT (0.17 mL, 0.843 mmol), Ti(O*i*-Pr)$_4$ (0.17 mL, 0.562 mmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 1.8 mL, 10.8 mmol) at –30 °C. The mixture was stirred at the same temperature for 30 min and a solution of allylic alcohol **2** (151 mg, 0.558 mmol) in CH_2Cl_2 (3.0 mL + 1.0 mL + 1.0 mL) was added at –40 °C. After the resulting mixture was stirred at –40 °C for 17 h and at –30 °C for further 8 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. After the concentration, the mixture was diluted with Et_2O and 3 M aqueous NaOH was added to the mixture. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **14** (127 mg, 80%) as a colorless oil: R_f = 0.42 (hexane/EtOAc = 1:1); $[\alpha]^{20}_D$ –61.2 (*c* 0.98, $CHCl_3$); IR (neat) 3435, 2954, 2929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 4.4 Hz, 1 H), 5.46 (ddt, *J* = 15.6, 7.8, 2.0 Hz, 1 H), 4.19 (dd, *J* = 4.4, 2.0 Hz, 2 H), 3.96 (ddd, *J* = 12.7, 4.4, 2.2 Hz, 1 H), 3.70 (ddd, *J* = 12.7, 7.8, 3.6 Hz, 1 H), 3.39 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.17 (dt, *J* = 3.6, 2.2 Hz, 1 H), 3.07 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.4, 2.0 Hz, 1 H), 1.82 (brs, 1 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 125.4, 62.7, 60.5, 57.9, 55.7, 55.5, 53.3, 25.9, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{14}H_{26}O_4SiNa$ $(M + Na)^+$ 309.1498, found 309.1496.

Alkane 15. To a mixture of alkene **14** (10.0 mg, 34.9 μmol), pyridine (0.54 mL, 5.58 mmol), and $KO_2CN{=}NCO_2K$ (542 mg, 2.79 mmol) in MeOH (2.0 mL) was added AcOH (0.32 mL, 5.58 mmol) at 40 °C. After the mixture was stirred at the same temperature for 6 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave alkane **15** (9.6 mg, 33.2μmol, 95%) as a yellow oil: R_f = 0.60 (hexane/EtOAc = 1:1); $[\alpha]^{22}_D$ –34.9 (*c* 0.20, $CHCl_3$); IR (neat) 3435, 2954, 2928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99–3.96 (m, 1 H), 3.71–3.69 (m, 3 H), 3.16 (dt, *J* = 4.4, 2.2 Hz, 1 H), 3.04 (dd, *J* = 4.6, 2.2 Hz, 1 H), 3.00–2.97 (m, 1 H), 2.76

(dd, J = 4.6, 2.2 Hz, 1 H), 1.74–1.57 (m, 5 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 60.6, 56.2, 55.9, 55.7, 53.7, 29.1, 28.2, 26.0, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{14}H_{28}O_4SiNa$ $(M + Na)^+$ 311.1655, found 311.1653.

TBDPS Ether 16. To a solution of epoxy alcohol **15** (12.0 mg, 41.5 μmol) in THF (0.6 mL) was added Red-Al (65% in toluene, 62 μL, 0.208 mmol) at –40 °C. After the mixture was allowed to warm to –10 °C for 2 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:1) gave the corresponding diol (11.0 mg), which was used for the next reaction without further purification.

To a solution of the diol obtained above (11.0 mg) in CH_2Cl_2 (0.5 mL) were added DMAP (5.4 mg, 44.0 μmol), imidazole (3.0 mg, 44.0 μmol), and TBDPSCl (7.6 μL, 29.3 μmol) at 0 °C. After the mixture was stirred at room temperature for 7 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave TBDPS ether **16** (12.1 mg, 22.8 μmol, 55% in two steps) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 4:1); $[\alpha]^{24}_D$ –3.2 (*c* 0.33, $CHCl_3$); IR (neat) 3419, 2954, 2929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4 H), 7.46–7.37 (m, 6 H), 3.93–3.80 (m, 3 H), 3.67–3.60 (m, 2 H), 2.99–2.96 (m, 1 H), 2.78 (dd, J = 4.6, 2.2 Hz, 1 H), 2.63 (d, J = 4.6 Hz, 1 H), 1.85–1.75 (m, 2 H), 1.67–1.58 (m, 4 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.5, 129.7, 127.7, 69.6, 62.6, 61.6, 61.5, 55.9, 36.2, 29.8, 29.2, 28.3, 26.9, 26.0, 19.2, –5.2; HRMS (ESI–TOF) calcd for $C_{30}H_{48}O_4Si_2Na$ $(M + Na)^+$ 551.2989, found 551.2988.

MTPA Ester (*S*)-17. To a solution of alcohol **16** (1.7 mg, 3.21 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (0.8 mg, 6.42 μmol), Et_3N (0.6 μL, 4.50 μmol), and (*R*)-MTPACl (0.7 μL, 3.85 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*S*)-**17** (2.5 mg, quant) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 7:1); $[\alpha]^{24}_D$ –14.3 (*c* 0.23,

$CHCl_3$); IR (neat) 2953, 2929, 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4 H), 7.54–7.52 (m, 2 H), 7.39–7.35 (m, 9 H), 5.27–5.22 (m, 1 H, H-9), 3.75–3.70 (m, 2 H, H_2-7), 3.61–3.56 (m, 2 H, H_2-14), 3.47 (s, 3 H), 2.88 (dd, J = 6.5, 2.1 Hz, 1 H, H-10), 2.79–2.76 (m, 1 H, H-11), 2.07–1.88 (m, 2 H, H_2-8), 1.61–1.51 (m, 4 H, H_2-12 and H_2-13), 1.06 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 135.4, 135.4, 133.3, 133.2, 132.1, 130.0, 129.5, 128.3, 127.7, 127.4, 77.2, 73.8, 62.4, 59.4, 58.4, 56.4, 55.4, 33.8, 29.1, 28.2, 26.9, 26.0, 19.2, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{40}H_{55}F_3O_6Si_2Na$ $(M + Na)^+$ 767.3387, found 767.3378.

MTPA Ester (*R*)-17.　To a solution of alcohol **16** (1.3 mg, 2.45 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (0.6 mg, 4.90 μmol), Et_3N (0.5 μL, 3.43 μmol), and (*S*)-MTPACl (0.6 μL, 2.94 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*R*)-**17** (2.0 mg, quant) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 7:1); $[\alpha]^{27}_D$ +28.0 (*c* 0.23, $CHCl_3$); IR (neat) 2954, 2929, 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.70 (m, 1 H), 7.64–7.60 (m, 4 H), 7.53–7.51 (m, 1 H), 7.45–7.29 (m, 9 H), 5.20–5.15 (m, 1 H, H-9), 3.66–3.56 (m, 4 H, H_2-7 and H_2-14), 3.57 (s, 3 H), 2.93 (dd, J = 7.3, 2.0 Hz, 1 H, H-10), 2.91–2.89 (m, 1 H, H-11), 1.93–1.80 (m, 2 H, H_2-8), 1.66–1.51 (m, 4 H, H_2-12 and H_2-13), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 135.5, 135.4, 134.7, 133.4, 133.3, 132.3, 129.7, 129.4, 128.3, 127.7, 127.2, 77.2, 74.5, 62.4, 59.2, 58.5, 57.1, 55.6, 34.0, 29.1, 28.2, 26.9, 26.0, 19.2, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{40}H_{55}F_3O_6Si_2Na$ $(M + Na)^+$ 767.3387, found 767.3381.

Bromoacetylene 3a.　To a solution of alcohol **14** (18.6 mg, 64.9 μmol) in CH_2Cl_2 (1.0 mL) and DMSO (0.3 mL) were added Et_3N (45 μL, 0.325 mmol) and SO_3·py. (41.3 mg, 0.260 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding aldehyde **18** (15.1 mg), which was used for the next reaction without further purification.

To a solution of CBr_4 (70.3 mg, 0.212 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (111 mg, 0.425 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and Et_3N (59 μL, 0.425 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, the aldehyde obtained above (15.1 mg) in CH_2Cl_2 (0.6 mL + 0.4 mL) was added at –78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 20:1) gave dibromoalkene **19** (22.4 mg), which was used for the next reaction without further purification.

To a solution of dibromoalkene **19** obtained above (22.4 mg) in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 0.20 mL, 0.20 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. Concentration and column chromatography (hexane/EtOAc = 4:1) gave bromoacetylene **3a** (11.1 mg, 45.3μmol, 70% in three steps) as a colorless amorphous solid: R_f = 0.23 (hexane/EtOAc = 1:1); $[\alpha]^{24}_D$ –89.9 (*c* 0.90, $CHCl_3$); IR (neat) 3354, 3012, 2949, 2225, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 15.6, 5.0 Hz, 1 H), 5.46 (ddt, *J* = 15.6, 7.8, 1.7 Hz, 1 H), 4.20–4.18 (m, 2 H), 3.40 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.38 (d, *J* = 2.0 Hz, 1 H), 3.27 (dd, *J* = 3.4, 2.0 Hz, 1 H), 2.99 (dd, *J* = 3.4, 2.0 Hz, 1 H), 1.55 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 126.5, 75.8, 62.5, 57.0, 56.5, 55.3, 45.4, 43.6; HRMS (ESI–TOF) calcd for $C_9H_9BrO_3Na$ $(M + Na)^+$ 268.9613, found 268.9611.

Acetate 21.

(entry 2)

To a solution of $EtNH_2$ (70% aqueous solution, 0.5 mL) in MeOH (0.5 mL) was added CuCl (2.0 mg, 20.2 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (8.6 mg, 0.124 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **4** (8.8 mg, 45.3 μmol) in MeOH (0.3 mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 20 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **3a** (10.1 mg, 41.2 μmol) in MeOH (0.3

mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave the corresponding triacetylene (4.2 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (4.2 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (1.0 mg, 8.10 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave acetate **21** (3.2 mg, 7.9 μmol, 20% in two steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1) ; $[\alpha]^{25}_D$ –77.7 (*c* 0.30, $CHCl_3$); IR (neat) 2954, 2930, 2216, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.9 Hz, 1 H), 5.48 (ddd, *J* = 15.6, 7.8, 1.2 Hz, 1 H), 4.58 (dd, *J* = 5.9, 1.2 Hz, 2 H), 4.39 (s, 2 H), 3.44 (d, *J* = 2.0 Hz, 1 H), 3.38 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.33 (dd, *J* = 3.2, 2.0 Hz, 1 H), 3.01 (dd, *J* = 3.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.4, 129.3, 77.8, 73.6, 69.5, 69.1, 63.5, 63.1, 62.0, 57.5, 56.2, 55.1, 52.1, 43.1, 25.8, 20.9, 18.3, –5.1; HRMS (ESI–TOF) calcd for $C_{22}H_{28}O_5SiNa$ $(M + Na)^+$ 423.1604, found 423.1613.

(entry 3)

To a solution of $EtNH_2$ (70% aqueous solution, 0.5 mL) in MeOH (0.5 mL) was added CuCl (1.9 mg, 19.3 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (8.0 mg, 0.116 mmol) at room temperature to discharge the blue color. To the resulting mixture was added diacetylene **4** (8.3 mg, 42.5 μmol) in MeOH (0.3 mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 20 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **3a** (9.8 mg, 38.6 μmol) in MeOH (0.3 mL + 0.2 mL) at 0 °C and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave the corresponding triacetylene (6.7 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (6.7 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave acetate **21** (6.2 mg, 15.4 μmol, 40% in two steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1)

(entry 4)

To a solution of $EtNH_2$ (70% aqueous solution, 0.5 mL) in MeOH (0.7 mL) was added CuCl (2.0 mg, 19.9 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (8.3 mg, 0.119 mmol) at room temperature to discharge the blue color. To the resulting mixture was added diacetylene **4** (8.5 mg, 43.7 μmol) in MeOH (0.3 mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 20 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **3a** (10.1 mg, 39.7 μmol) in MeOH (0.3 mL + 0.2 mL) at –78 °C and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave the corresponding triacetylene (9.9 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (9.9 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave acetate **21** (10.6 mg, 26.4 μmol, 67% in two steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1)

Diepoxide 5a. To a solution of TBS ether **21** (1.2 mg, 2.99 μmol) in THF (0.2 mL) was added HF·py (5.0 μL) at 0 °C. After the mixture was stirred at the same temperature for 40 min, HF·py (2.0 μL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was diluted with Et_2O. The mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then

dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave diepoxide **5a** (1.6 mg, 5.59 μmol, quant) as a light yellow amorphous solid: R_f = 0.40 (hexane/EtOAc = 1:1); $[\alpha]^{28}_D$ –62.5 (*c* 0.07, CH_3OH); IR (neat) 3410, 3015, 2925, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.6 Hz, 1 H), 5.49 (ddt, *J* = 15.6, 7.8, 1.4 Hz, 1 H), 4.59 (dd, *J* = 5.6, 1.4 Hz, 2 H), 4.36 (d, *J* = 5.8 Hz, 2 H), 3.44 (d, *J* = 2.0 Hz, 1 H), 3.38 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.34 (dd, *J* = 3.2, 2.0 Hz, 1 H), 3.02 (dd, *J* = 3.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 1.69 (t, *J* = 5.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 130.44, 129.31, 77.21, 73.99, 70.41, 68.99, 63.50, 62.74, 62.60, 57.49, 56.22, 55.11, 51.51, 43.06, 20.90; HRMS (ESI–TOF) calcd for $C_{16}H_{14}O_5Na$ $(M + Na)^+$ 309.0739, found 309.0731.

Epoxy Alcohol 22.　To a suspension of powdered MS4A (20 mg) in CH_2Cl_2 (1.0 mL) were added (–)-DIPT (22 μL, 0.110 mmol), Ti(O*i*-Pr)$_4$ (22 μL, 73.2 μmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 0.23 mL, 1.38 mmol) at –30 °C. The mixture was stirred at the same temperature for 30 min and a solution of allylic alcohol **2** (19.8 mg, 73.2 μmol) in CH_2Cl_2 (0.8 mL + 0.2 mL) was added at –40 °C. After the resulting mixture was stirred at –40 °C for 8 h and at –30 °C for further 8 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. After the concentration, the mixture was diluted with Et_2O and 3 M aqueous NaOH was added to the mixture. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **22** (17.0 mg, 81%) as a colorless oil: R_f = 0.34 (hexane/EtOAc = 1:1); $[\alpha]^{22}_D$ –2.7 (*c* 1.14, $CHCl_3$); IR (neat) 3435, 2954, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (dt, *J* = 15.6, 4.2 Hz, 1 H), 5.43 (ddt, *J* = 15.6, 7.9, 2.0 Hz, 1 H), 4.17 (dd, *J* = 4.2, 2.0 Hz, 2 H), 3.95–3.92 (m, 1 H), 3.67–3.64 (m, 1 H), 3.34 (dd, *J* = 7.9, 2.2 Hz, 1 H), 3.13 (dt, *J* = 4.2, 2.2 Hz, 1 H), 3.04 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.2 Hz, 1 H), 1.76 (brs, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 125.2, 62.7, 60.8, 58.0, 56.5, 56.5, 53.7, 26.0, 18.4, –5.2; HRMS (ESI–TOF) calcd for $C_{14}H_{26}O_4SiNa$ $(M + Na)^+$ 309.1498, found 309.1490.

Bromoacetylene 3b. To a solution of alcohol **22** (16.6 mg, 57.9 μmol) in CH_2Cl_2 (1.0 mL) and DMSO (0.3 mL) were added Et_3N (40 μL, 0.289 mmol) and SO_3·py. (36.7 mg, 0.231 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave the corresponding aldehyde (11.6 mg), which was used for the next reaction without further purification.

To a solution of CBr_4 (51.0 mg, 0.155 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (81 mg, 0.310 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and Et_3N (43 μL, 0.310 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, the aldehyde obtained above (11.6 mg) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at –78 °C. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 20:1) gave the corresponding dibromoalkene (18.0 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (18.0 mg) in THF (0.4 mL) was added TBAF (1.0 M solution in THF, 0.16 mL, 0.160 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Concentration and column chromatography (hexane/EtOAc = 2:1) gave bromoacetylene **3b** (8.1 mg, 32.6 μmol, 57% in three steps) as a colorless amorphous solid: R_f = 0.24 (hexane/EtOAc = 2:1); $[\alpha]^{21}_D$ –9.0 (*c* 0.62, $CHCl_3$); IR (neat) 3354, 3006, 2949, 2224, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 15.6, 5.1 Hz, 1 H), 5.45 (ddt, *J* = 15.6, 7.8, 1.7 Hz, 1 H), 4.19 (dd, *J* = 5.1, 1.7 Hz, 2 H), 3.40–3.34 (m, 2 H), 3.22 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.0 Hz, 1 H), 1.58 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 126.2, 75.5, 62.4, 58.1, 57.2, 56.1, 45.7, 44.1; HRMS (ESI–TOF) calcd for $C_9H_9BrO_3Na$ $(M + Na)^+$ 268.9613, found 268.9617.

Acetate 23. To a solution of $EtNH_2$ (70% aqueous solution, 0.4 mL) in MeOH (0.7 mL) was added CuCl (1.6 mg, 16.3 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (6.8 mg, 97.8 μmol)

at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **4** (6.9 mg, 35.9 μmol) in MeOH (0.2 mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **3b** (8.0 mg, 32.6 μmol) in MeOH (0.2 mL + 0.2 mL) at –78 °C and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding triacetylene (5.5 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (5.5 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave acetate **23** (6.3 mg, 48% in two steps) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ –1.5 (*c* 0.44, $CHCl_3$); IR (neat) 2954, 2929, 2217, 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.8 Hz, 1 H), 5.47 (ddt, *J* = 15.6, 7.6, 1.4 Hz, 1 H), 4.58 (dd, *J* = 5.8, 1.4 Hz, 2 H), 4.39 (s, 2 H), 3.42 (d, *J* = 2.0 Hz, 1 H), 3.35 (dd, *J* = 7.6, 2.0 Hz, 1 H), 3.26 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.92 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.08 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.5, 129.1, 77.8, 73.3, 69.5, 69.4, 63.4, 63.2, 62.0, 58.7, 57.1, 55.8, 52.1, 43.5, 25.8, 20.9, 18.3, –5.1; HRMS (ESI–TOF) calcd for $C_{22}H_{28}O_5SiNa$ $(M + Na)^+$ 423.1604, found 423.1610.

Diepoxide 5b. To a solution of TBS ether **23** (5.0 mg, 12.4 μmol) in THF (2.5 mL) was added HF·py (5.0 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·py (2.0 μL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was diluted with Et_2O. The mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1, 7:1) gave diepoxide **5b** (2.4 mg, 8.39 μmol, 68%) as a light yellow amorphous solid: R_f = 0.43 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ +32.0 (*c* 0.12, CH_3OH); IR (neat) 3448, 2920, 2214,

1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, J = 15.6, 5.8 Hz, 1 H), 5.48 (ddt, J = 15.6, 7.8, 1.5 Hz, 1 H), 4.58 (dd, J = 5.8, 1.5 Hz, 2 H), 4.36 (d, J = 6.1 Hz, 2 H), 3.43 (d, J = 2.0 Hz, 1 H), 3.35 (dd, J = 7.8, 2.0 Hz, 1 H), 3.27 (dd, J = 4.2, 2.0 Hz, 1 H), 2.92 (dd, J = 4.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 1.67 (brt, J = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.39, 130.50, 129.05, 77.20, 73.69, 70.41, 69.20, 63.45, 62.81, 62.55, 58.69, 57.08, 55.86, 51.52, 43.47, 20.90; HRMS (ESI–TOF) calcd for $C_{16}H_{14}O_5Na$ $(M + Na)^+$ 309.0739, found 309.0743.

Epoxy Alcohol 24.　Light yellow oil; $[\alpha]^{29}_D$ +25.7 (*c* 1.21, $CHCl_3$); HRMS (ESI–TOF) calcd for $C_{12}H_{24}O_3SiNa$ $(M + Na)^+$ 267.1393, found 267.1396; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of epoxy alcohol **9**.

Diepoxide 5c.　Light yellow amorphous solid; $[\alpha]^{25}_D$ +76.0 (*c* 0.03, CH_3OH); HRMS (ESI–TOF) calcd for $C_{16}H_{14}O_5Na$ $(M + Na)^+$ 309.0739, found 309.0743; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of diepoxide **5a**.

Diepoxide 5d.　Light yellow amorphous solid; $[\alpha]^{23}_D$ –32.0 (*c* 0.12, CH_3OH); HRMS (ESI–TOF) calcd for $C_{16}H_{14}O_5Na$ $(M + Na)^+$ 309.0739, found 309.0739; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of diepoxide **5b**.

Acetate 25.　To a suspension of NaH (60% dispersion in oil, 9.5 mg, 0.197 mmol, washed with hexane in advance) in THF (1.0 mL) was added alcohol **14** (16.2 mg, 56.4 μmol) in THF (0.7 mL + 0.3 mL) at 0 °C. To the mixture were added PMBCl (23 μL, 0.169 mmol) and TBAI (10.3 mg, 28.0 μmol) at the same temperature. After the mixture was stirred for 12 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was diluted with EtOAc. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 8:1) gave the corresponding PMB ether (19.7 mg), which was used for the next reaction without further purification.

To a solution of the TBS ether obtained above (19.7 mg) in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 97 μL, 97.0 μmol) at 0 °C. The mixture was stirred for 3 h at the same temperature. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography

(hexane/EtOAc = 1:1) gave the corresponding alcohol (12.6 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (12.6 mg) in CH_2Cl_2 (0.8 mL) were added pyridine (4.5 μL, 56.1 μmol), Ac_2O (4.9 μL, 51.8 μmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1, 3:1) gave acetate **25** (13.9 mg, 41.6 μmol, 74% in three steps) as a colorless oil: R_f = 0.36 (hexane/EtOAc = 2:1); $[\alpha]^{31}_D$ –42.7 (*c* 0.66, $CHCl_3$); IR (neat) 3000, 2934, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 6.02 (dt, *J* = 15.6, 5.8 Hz, 1 H), 5.50 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H), 4.58 (dd, *J* = 5.8, 1.5 Hz, 2 H), 4.49 (d, *J* = 4.2 Hz, 2 H), 3.80 (s, 3H), 3.71 (dd, *J* = 11.7, 2.0 Hz, 1 H), 3.52 (dd, *J* = 11.7, 4.0 Hz, 1 H), 3.37 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.18 (dt, *J* = 4.2, 2.0 Hz, 1 H), 2.96 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.3, 130.0, 129.8, 129.7, 129.3, 113.8, 73.1, 68.8, 63.6, 57.9, 55.3, 54.9, 54.6, 53.5, 20.9; HRMS (ESI–TOF) calcd for $C_{18}H_{22}O_6Na$ $(M + Na)^+$ 357.1314, found 357.1312.

Alcohol 26. To a solution of PMB ether **25** (11.0 mg, 32.9 μmol) in CH_2Cl_2 (1.0 mL) and H_2O (30 μL) was added DDQ (14.9 mg, 65.8 μmol) at 0 °C. The mixture was stirred at the same temperature for 2 h and at room temperature for 1 h. The mixture was diluted with EtOAc. The mixture was washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **26** (5.7 mg, 26.6 μmol, 81%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 1:1); $[\alpha]^{28}_D$ –62.0 (*c* 0.25, $CHCl_3$); IR (neat) 3457, 2925, 1736 cm–1; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.9 Hz, 1 H), 5.51 (ddt, *J* = 15.6, 7.6, 1.2 Hz, 1 H), 4.59 (dd, *J* = 5.9, 1.2 Hz, 2 H), 3.97 (dd, *J* = 13.0, 2.2 Hz, 1 H), 3.72 (dd, *J* = 13.0, 3.4 Hz, 1 H), 3.39 (dd, *J* = 7.6, 2.0 Hz, 1 H), 3.18 (dt, *J* = 3.4, 2.2 Hz, 1 H), 3.10 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.94 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 129.9, 129.9, 63.6, 60.5, 57.8, 55.8, 54.9, 53.1, 20.9; HRMS (ESI–TOF) calcd for $C_{10}H_{14}O_5Na$ $(M + Na)^+$ 237.0739, found 237.0734.

Acetate 29. To a solution of CBr_4 (150 mg, 0.451 mmol) in CH_2Cl_2 (1.0 mL) was added PPh_3 (237 mg, 0.902 mmol) at 0 °C. The mixture was stirred at the same temperature for

15 min and Et_3N (0.13 mL, 0.902 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **27** (22.6 mg, 0.113 mmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at –78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1) gave the corresponding dibromoalkene (39.2 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (39.2 mg) in THF (2.0 mL) was added TBAF (1.0 M solution in THF, 0.44 mL, 0.440 mmol) at room temperature. The mixture was stirred at 45 °C for 18 h and diluted with Et_2O. The mixture was washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding TBS-deprotected dibromoalkene and bromoacetylene **24** (36.3 mg). The same procedure was repeated twice to give bromocetylene **28** (17.3 mg), which was used for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 0.9 mL) in MeOH (1.5 mL) was added CuCl (5.3 mg, 54.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (22.5 mg, 0.324 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **4** (73.4 mg, 0.378 mmol) in MeOH (0.4 mL + 0.4 mL) at room temperature and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **28** (17.3 mg, 0.108 mmol) in MeOH (0.4 mL + 0.4 mL) at –78 °C and the mixture was stirred at the same temperature for 30 min. The mixture was allowed to warm to room temperature for 3 h. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave the corresponding triacetylene (20.5 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (20.5 mg) in CH_2Cl_2 (3.0 mL) were added pyridine (45 μL, 0.335 mmol), Ac_2O (40 μL, 0.424 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture

was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave acetate **29** (22.5 mg, 63% in four steps) as a yellow oil: R_f = 0.69 (hexane/EtOAc = 2:1); IR (neat) 2953, 2929, 2860, 2173, 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dt, J = 16.1, 5.4 Hz, 1 H), 5.78 (dt, J = 16.1, 1.7 Hz, 1 H), 4.63 (dd, J = 5.4, 1.7 Hz, 2 H), 4.40 (s, 2 H), 2.09 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 141.7, 111.0, 79.0, 75.5, 74.5, 69.8, 66.4, 63.4, 62.6, 52.2, 25.8, 20.8, 18.3, 5.1; HRMS (ESI–TOF) calcd for $C_{18}H_{24}O_3SiNa$ $(M + Na)^+$ 339.1393, found 339.1388.

Alcohol 30. To a solution of TBS ether **29** (22.5 mg, 71.1 μmol) in THF (2.0 mL) was added HF·py (0.10 mL) at 0 °C. After the mixture was stirred at the same temperature for 1 h, HF·py (0.10 mL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was diluted with Et_2O. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1, 3:1) gave alcohol **30** (12.6 mg, 88%) as a yellow oil: R_f = 0.37 (hexane/EtOAc = 2:1); IR (neat) 3418, 2925, 2187, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (dt, J = 16.1, 5.6 Hz, 1 H), 5.78 (dt, J = 16.1, 2.0 Hz, 1 H), 4.64 (dd, J = 5.6, 2.0 Hz, 2 H), 4.37 (s, 2 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 141.9, 110.8, 78.1, 75.4, 74.9, 70.7, 66.0, 63.4, 63.2, 51.6, 20.8; HRMS (ESI–TOF) calcd for $C_{12}H_{10}O_3Na$ $(M + Na)^+$ 225.0528, found 225.0519.

Dienal 31. To a solution of dienol **1** (24.2 mg, 0.106 mmol) in CH_2Cl_2 (1.5 mL) and DMSO (0.5 mL) were added Et_3N (80 μL, 0.578 mmol) and SO_3·py. (76.4 mg, 0.481 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave dienal **31** (24.2 mg, 89%) as a colorless oil: R_f = 0.54 (hexane/EtOAc = 4:1); IR (neat) 2954, 2929, 1685, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 8.0 Hz, 1 H), 7.12 (dd, J = 15.3, 11.0 Hz, 1 H), 6.58–6.51 (m, 1 H), 6.31 (dt, J = 15.1, 4.4 Hz, 1 H), 6.08 (dd, J = 15.3, 8.0 Hz, 1 H), 4.33 (dd, J = 4.4, 1.5 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 151.4, 144.2, 131.1, 127.0, 62.9, 25.9, 18.4, –5.3; HRMS (ESI–TOF) calcd for $C_{12}H_{22}O_2SiNa$ $(M + Na)^+$ 249.1287, found 249.1283.

Acetate 32.　To a solution of CBr_4 (142 mg, 0.428 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (225 mg, 0.856 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and Et_3N (0.12 mL, 0.856 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **31** (24.2 mg, 0.107 mmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at –78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1, 30:1) gave the corresponding dibromoalkene (39.7 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (39.7 mg) in THF (2.0 mL) was added TBAF (1.0 M solution in THF, 0.42 mL, 0.420 mmol) at room temperature. The mixture was stirred at 45 °C for 20 h and diluted with Et_2O. The mixture was washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding TBS-deprotected dibromoalkene and TBS-deprotected bromoacetylene (42.3 mg). The same procedure was repeated once to give the corresponding TBS-deprotected bromocetylene (31.3 mg), which was used for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 1.3 mL) in MeOH (3.0 mL) was added CuCl (5.1 mg, 52.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (21.7 mg, 0.312 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **4** (70.7 mg, 0.364 mmol) in MeOH (0.7 mL + 0.3 mL) at room temperature and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added the bromoacetylene obtained above (31.3 mg) in MeOH (0.7 mL + 0.3 mL) at –78 °C and the mixture was stirred at the same temperature for 30 min. The mixture was allowed to warm to room temperature for 3 h. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding triacetylene (18.8 mg), which was used for the next reaction without

further purification.

To a solution of the alcohol obtained above (18.8 mg) in CH_2Cl_2 (2.0 mL) were added pyridine (24 μL, 0.179 mmol), Ac_2O (20 μL, 0.212 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave acetate **32** (20.5 mg, 56% in 4 steps) as a yellow oil: R_f = 0.60 (hexane/EtOAc = 2:1); IR (neat) 2954, 2929, 2173, 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 15.4, 10.8 Hz, 1 H), 6.33 (dd, J = 15.1, 10.8 Hz, 1 H), 5.93 (dt, J = 15.1, 6.0 Hz, 1 H), 5.66 (d, J = 15.4 Hz, 1 H), 4.64 (d, J = 6.0 Hz, 2 H), 4.41 (s, 2 H), 2.09 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.1, 131.9, 131.6, 110.2, 79.5, 76.3, 70.0, 67.4, 64.1, 63.9, 62.9, 52.3, 25.8, 20.9, 18.3, –5.1; HRMS (ESI–TOF) calcd for $C_{20}H_{26}O_3SiNa$ $(M + Na)^+$ 365.1549, found 365.1549.

Alcohol 33.　To a solution of TBS ether **32** (11.2 mg, 32.7 μmol) in THF (1.2 mL), was added HF·py (40 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·py (50 μL) was added. The mixture was stirred at 0 °C for further 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was diluted with Et_2O. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave alcohol **33** (6.4 mg, 28.0 μmol, 86%) as a yellow oil: R_f = 0.52 (hexane/EtOAc = 1:1); IR (neat) 3508, 2912, 2173, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, J = 15.6, 11.0 Hz, 1 H), 6.33 (dd, J = 15.3, 11.0 Hz, 1 H), 5.94 (dt, J = 15.3, 6.1 Hz, 1 H), 5.66 (d, J = 15.6 Hz, 1 H), 4.64 (d, J = 6.1 Hz, 1 H), 4.38 (s, 2 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 145.3, 131.9, 131.8, 110.1, 78.6, 77.2, 70.9, 67.0, 64.1, 63.9, 63.5, 51.6, 20.9; HRMS (ESI–TOF) calcd for $C_{14}H_{12}O_3Na$ $(M + Na)^+$ 251.0684, found 251.0689.

Epoxy Alcohol 34.　To a solution of allylic alcohol **1** (297 mg, 1.30 mmol) in CH_2Cl_2 (17 mL), were added $NaHCO_3$ (179 mg, 2.13 mmol) and *m*CPBA (69–75%, 306 mg, 1.22–1.33 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography

(hexane/EtOAc = 4:1) gave epoxy alcohol **34** (243 mg, 0.996mmol, 78%) as a light yellow oil: HRMS (ESI–TOF) calcd for $C_{12}H_{24}O_3SiNa$ $(M + Na)^+$ 267.1393, found 267.1396; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of epoxy alcohol **16**.

Aldehyde 35. To a solution of alcohol **34** (15.7 mg, 64.1 μmol) in CH_2Cl_2 (0.6 mL) and DMSO (0.2 mL) were added Et_3N (45 μL, 0.321 mmol) and SO_3·py. (40.7 mg, 0.256 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave aldehyde **35** (14.0 mg, 90%) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 1:1); IR (neat) 3439, 2954, 2929, 1730, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 6.1 Hz, 1 H), 6.12 (dt, J = 15.6, 4.2 Hz, 1 H), 5.49 (ddt, J = 15.6, 7.8, 2.0 Hz, 1 H), 4.21 (dd, J = 4.2, 2.0 Hz, 2 H), 3.68 (dd, J = 7.8, 2.0 Hz, 1 H), 3.30 (dd, J = 6.1, 2.0 Hz, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 137.4, 123.3, 62.5, 60.8, 56.2, 25.9, 18.4, –5.3; HRMS (ESI–TOF) calcd for $C_{13}H_{26}O_4SiNa$ $(M + Na)^+$ 297.1498, found 297.1500.

Acetate 36. To a solution of CBr_4 (75.3 mg, 0.227 mmol) in CH_2Cl_2 (0.8 mL) was added PPh_3 (119 mg, 0.454 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min and Et_3N (63 μL, 0.454 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **35** (13.7 mg, 56.7 μmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at –78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave the corresponding dibromoalkene (21.7 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (21.7 mg) in THF (0.7 mL) was added TBAF (1.0 M solution in THF, 0.22 mL, 0.220 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding bromoacetylene (9.7 mg), which was used

for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 0.6 mL) in MeOH (1.0 mL) was added CuCl (2.4 mg, 24.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (10.0 mg, 0.144 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **4** (10.2 mg, 52.7 μmol) in MeOH (0.2 mL + 0.2 mL) at room temperature and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added the bromoacetylene obtained above (9.7 mg) in MeOH (0.2 mL + 0.2 mL) at –78 °C and the mixture was stirred at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding triacetylene (11.1 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (11.1 mg) in CH_2Cl_2 (0.6 mL) were added pyridine (3.7 μL, 45.5 μmol), Ac_2O (4.0 μL, 42.0 μmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave acetate **36** (11.8 mg, 31.2 μM, 58% in four steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1); IR (neat) 2954, 2930, 2216, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, J = 15.6, 5.6 Hz, 1 H), 5.46 (ddt, J = 15.6, 7.3, 1.2 Hz, 1 H), 4.58 (brd, J = 5.6 Hz, 2 H), 4.39 (s, 2 H), 3.58 (dd, J = 7.3, 1.2 Hz, 1 H), 3.33 (d, J = 1.2 Hz, 1 H), 2.09 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 131.1, 128.4, 77.8, 73.9, 69.5, 69.2, 63.3, 63.2, 62.1, 59.5, 52.1, 47.2, 25.8, 20.8, 18.3, –5.1; HRMS (ESI–TOF) calcd for $C_{20}H_{26}O_4SiNa$ $(M + Na)^+$ 381.1498, found 381.1501.

Alcohol 37.　To a solution of TBS ether **36** (11.5 mg, 32.1 μmol) in THF (1.0 mL) was added HF·py (30 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·py (15 μL) was added. After the mixture was stirred at 0 °C for 1 h, HF·py (15 μL) was added. The mixture was stirred at the same temperature for 30 min. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then

dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 4:1) gave alcohol **37** (7.3 mg, 91%) as a yellow oil: R_f = 0.82 (hexane/EtOAc = 1:1); IR (neat) 3436, 2925, 2214, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, J = 15.6, 5.6 Hz, 1 H), 5.46 (ddt, J = 15.6, 7.6, 1.5 Hz, 1 H), 4.59 (dd, J = 5.6, 1.5 Hz, 2 H), 4.36 (brs, 2 H), 3.59 (dd, J = 7.6, 2.0 Hz, 1 H), 3.34 (d, J = 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 131.2, 128.4, 76.9, 74.3, 70.4, 69.1, 63.3, 62.8, 62.7, 59.5, 51.5, 47.1, 20.9; HRMS (ESI–TOF) calcd for $C_{14}H_{12}O_4Na$ $(M + Na)^+$ 267.0633, found 267.0634.

Cell Growth-Inhibitory Activity. HL60 cells were cultured at 37 °C with 5% CO_2 in RPMI (Nissui, Tokyo, Japan) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Sigma-Aldrich Co., St. Louis, MO), 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$. HeLa S_3 cells were cultured at 37 °C with 5% CO_2 in MEM (Nissui) supplemented with 10% heat-inactivated FBS, 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$. HL60 cells were seeded at 1×10^4 cells/well in 96-well plates (Iwaki, Tokyo, Japan). HeLa S_3 cells were seeded at 4×10^3 cells/well in 96-well plates, and cultured overnight. Various concentrations of compounds were then added, and cells were incubated for 72 hours. Cell proliferation was measured by the MTT assay.

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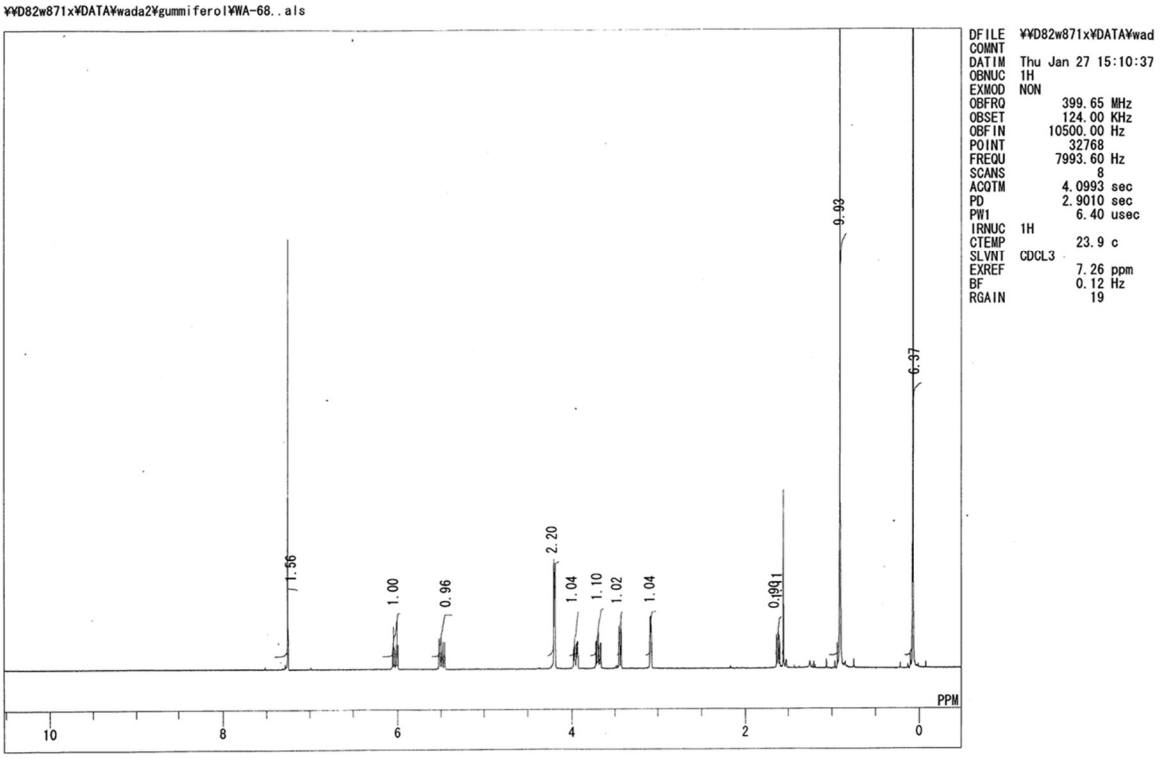
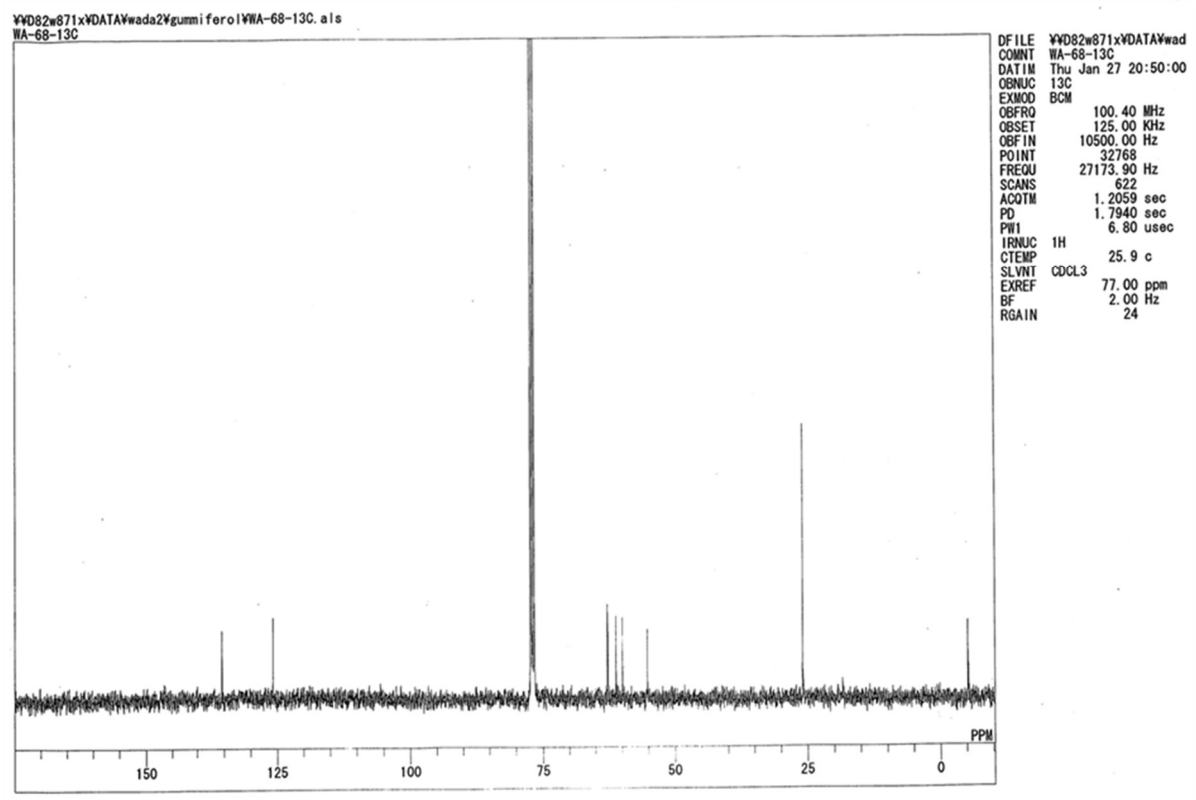
スペクトルデータ (Spectral Data)

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **9**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **9**



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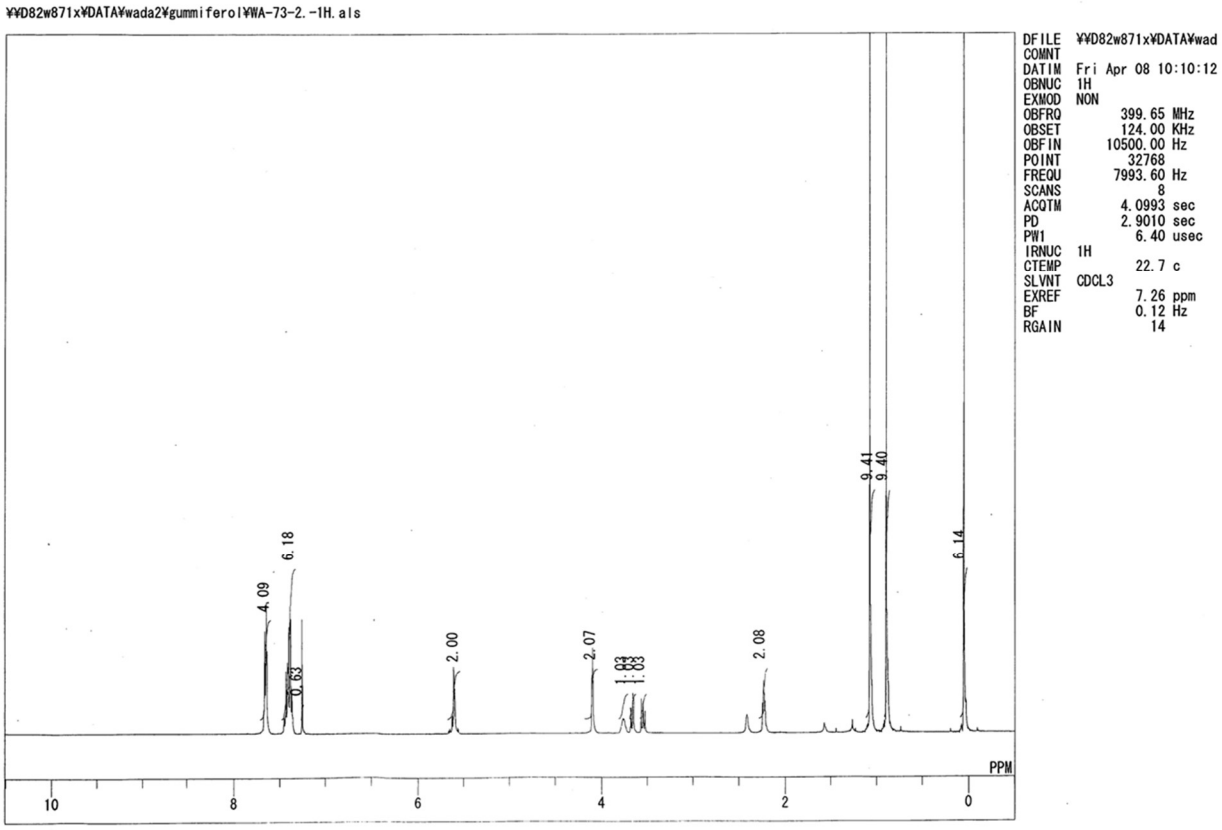

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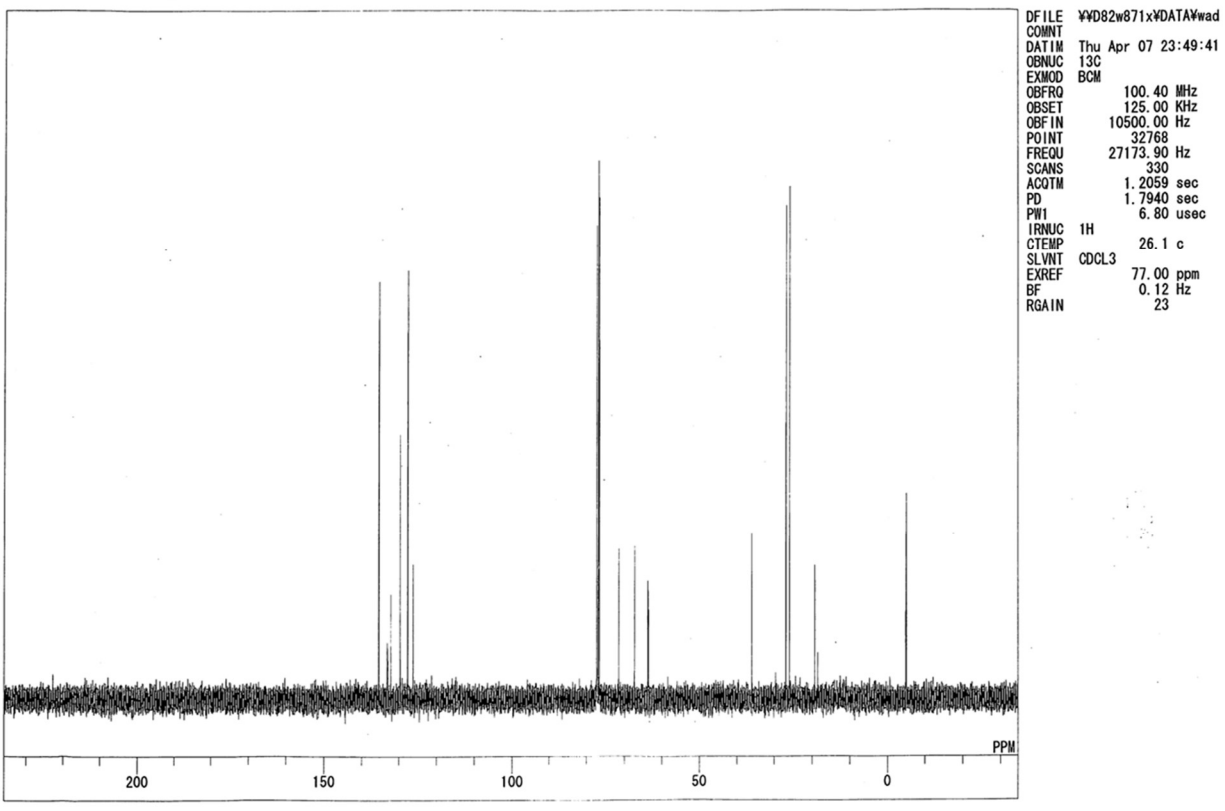
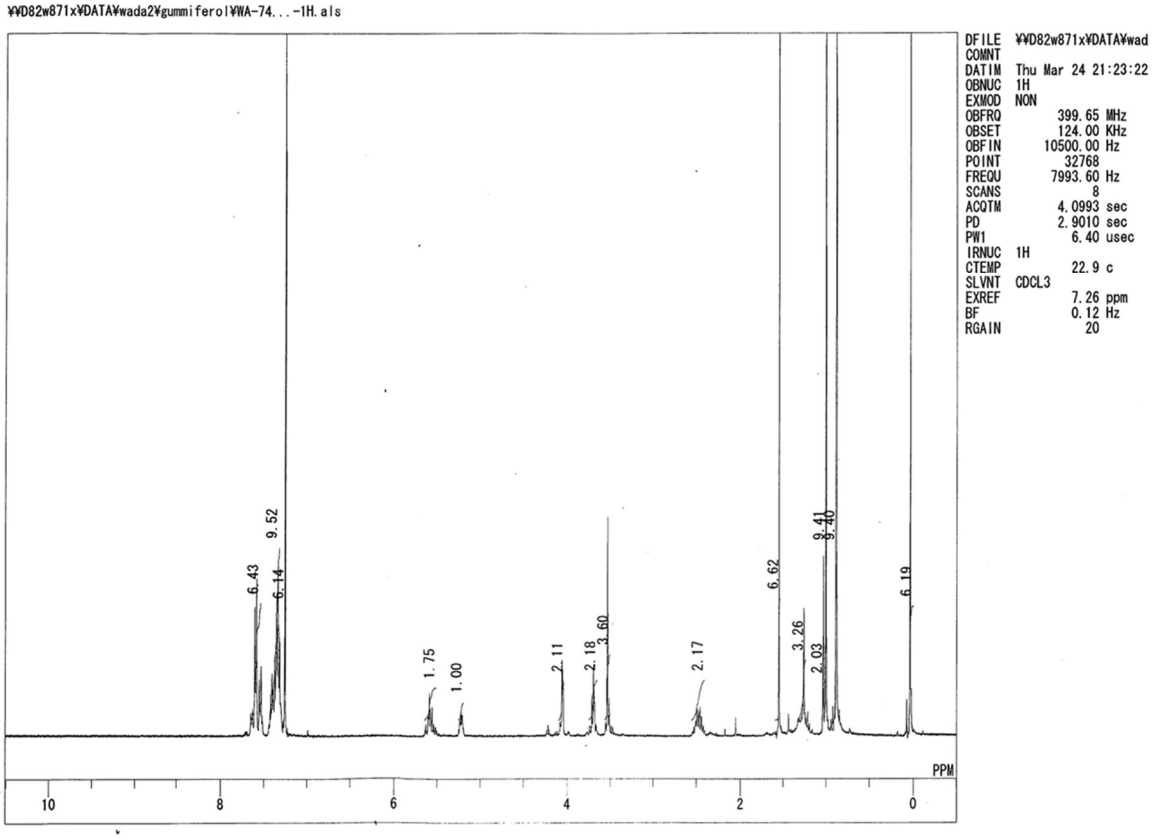
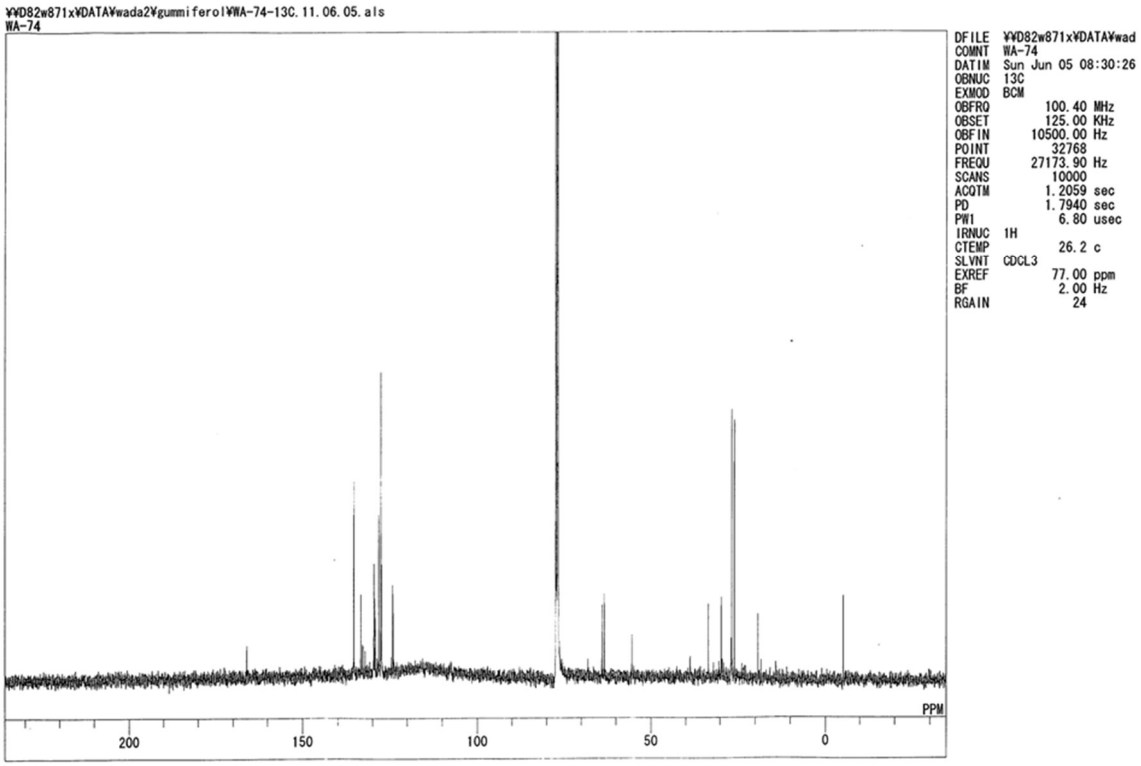


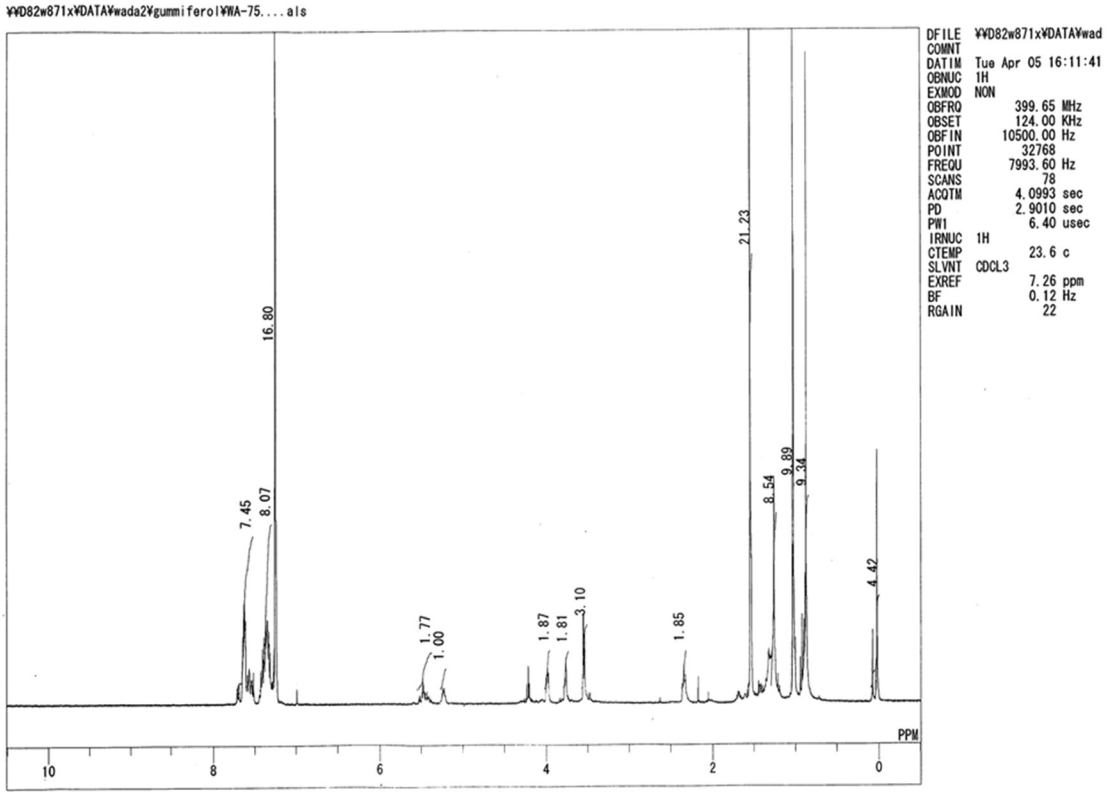
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*S*)-**12**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of (*S*)-**12**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*R*)-**12**



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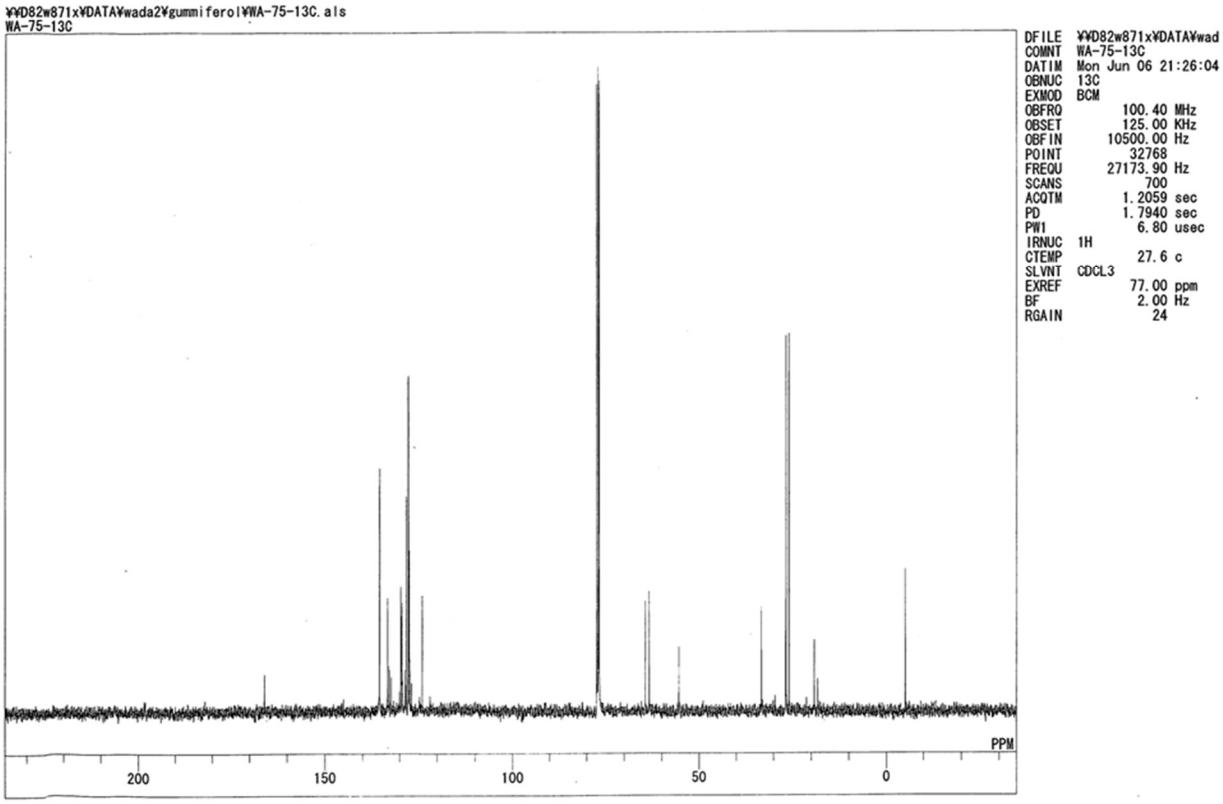
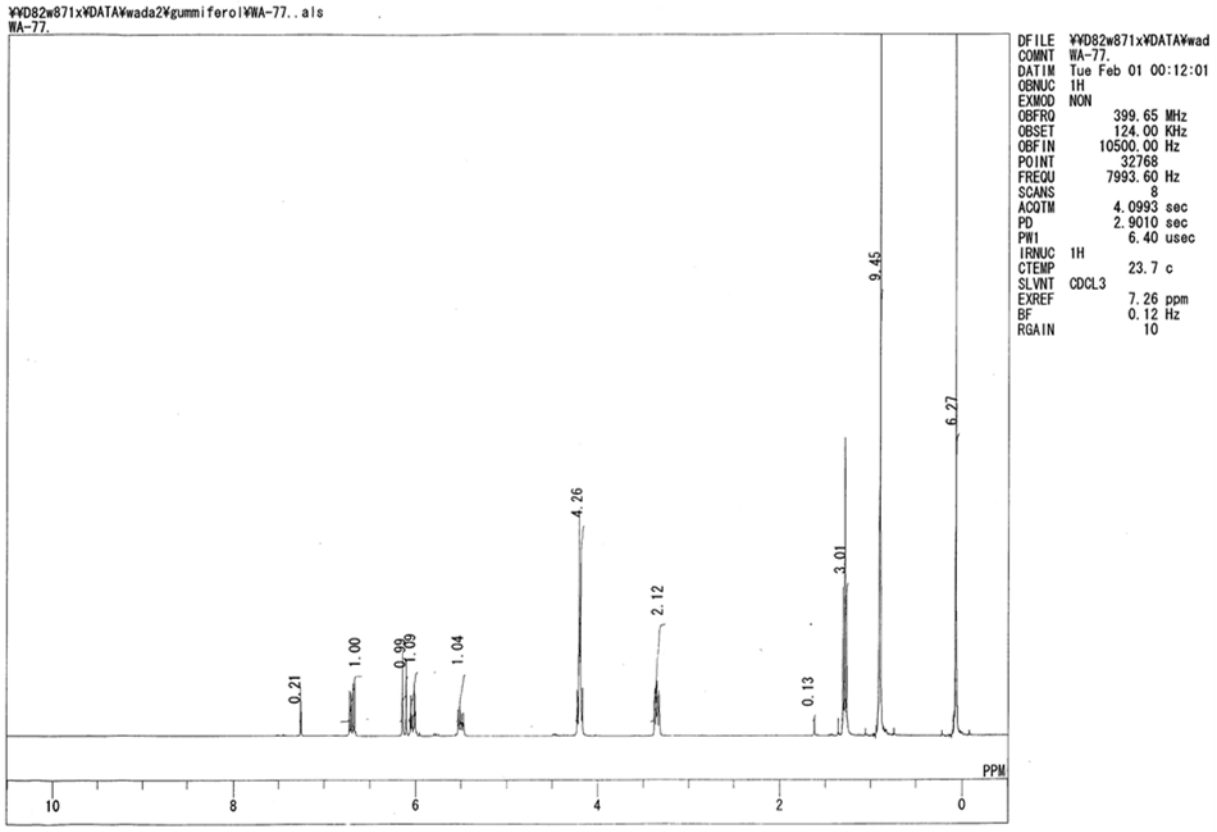
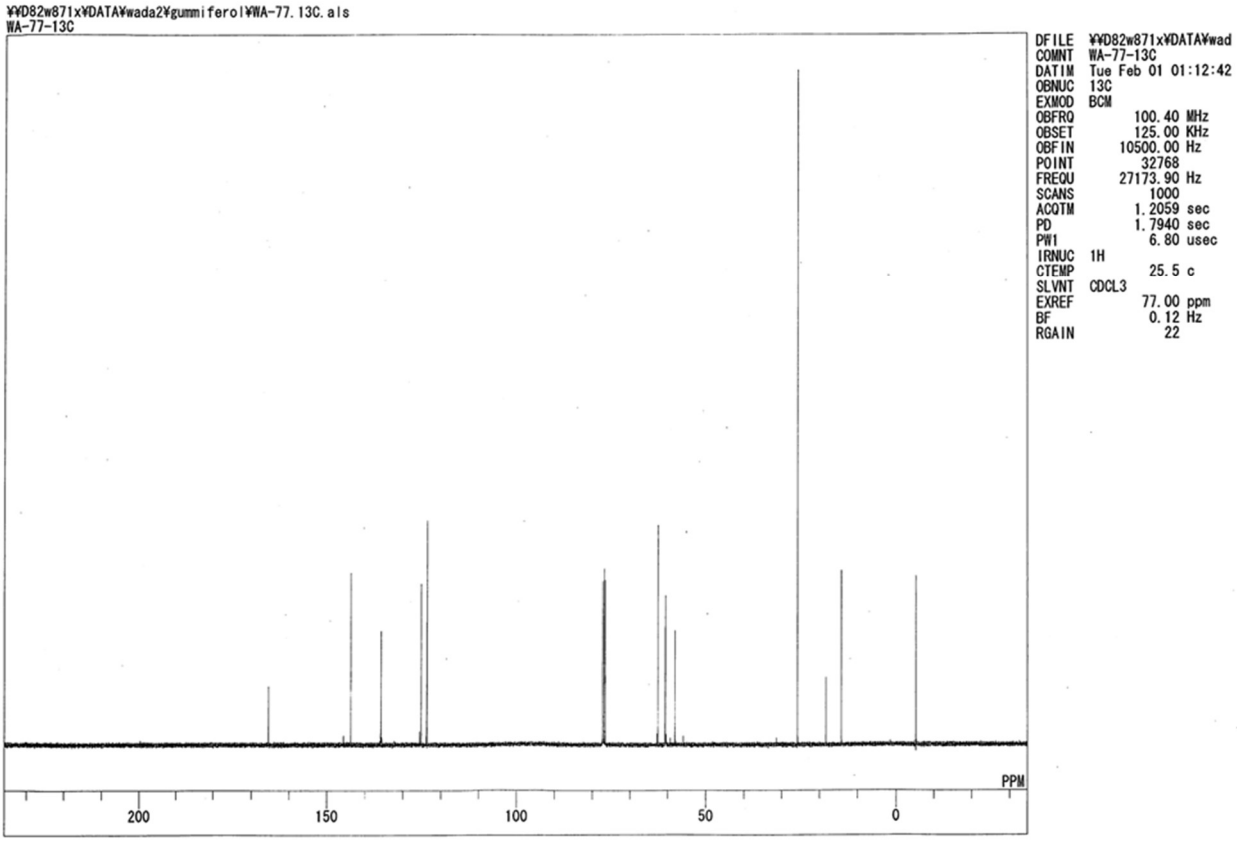


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **13**



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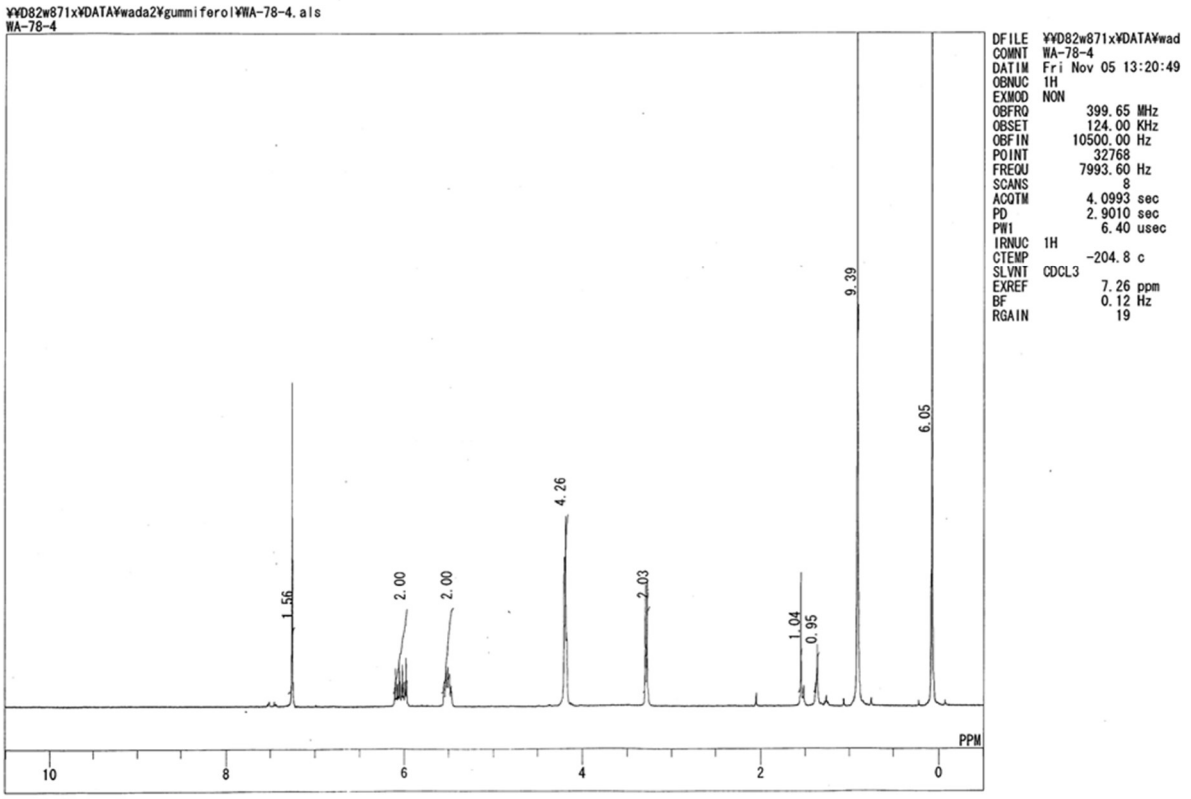
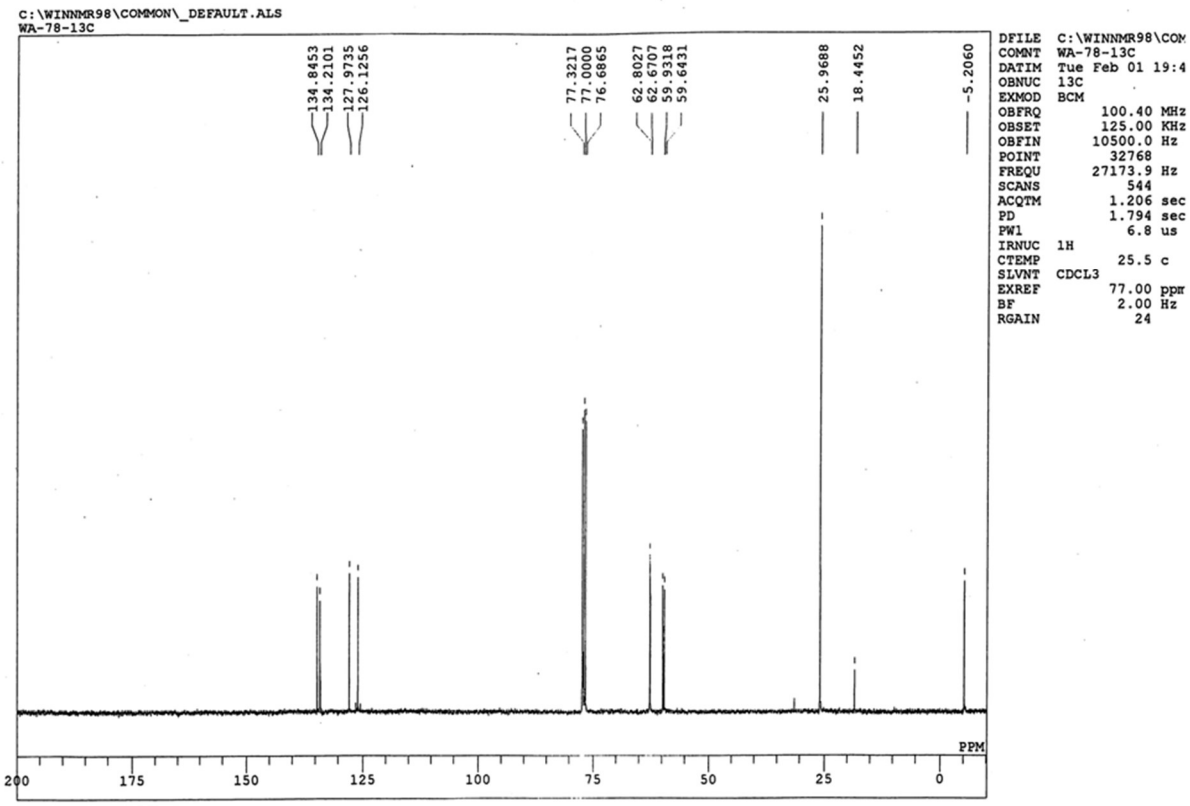


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **2**



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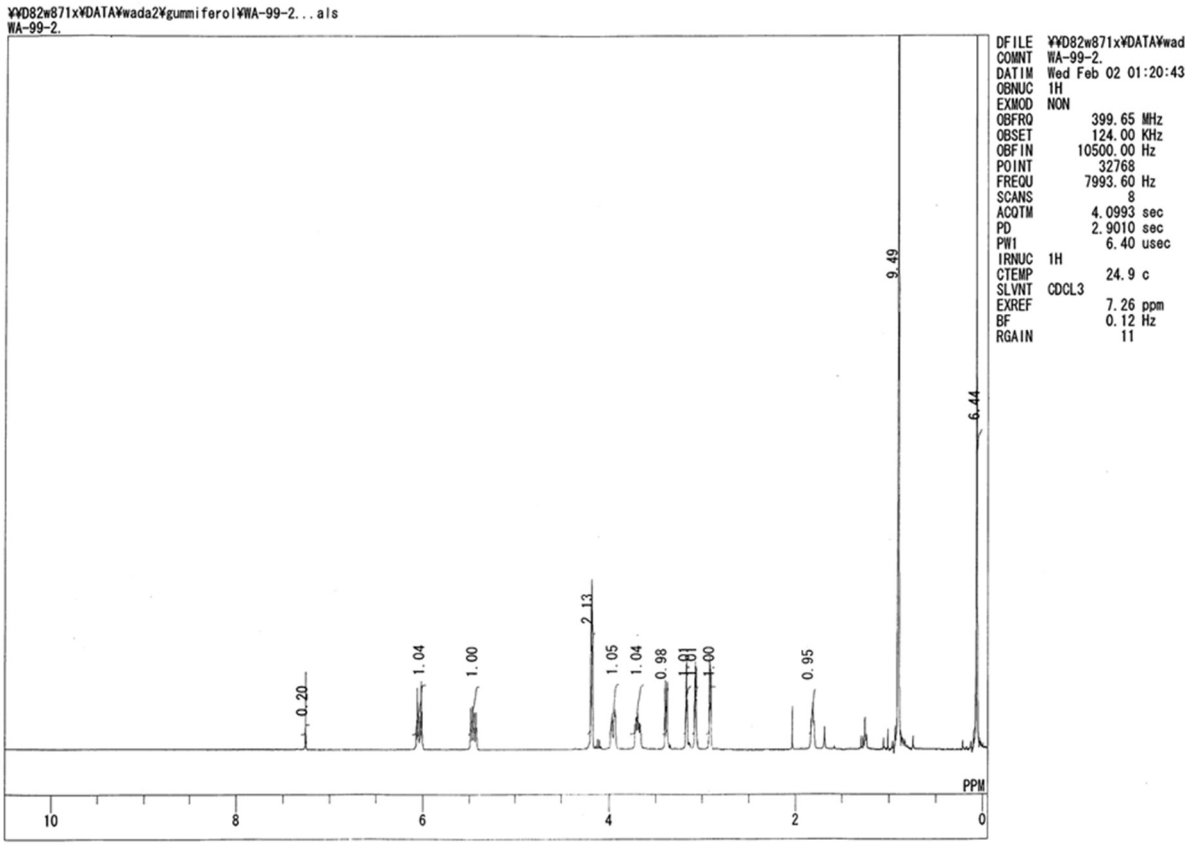

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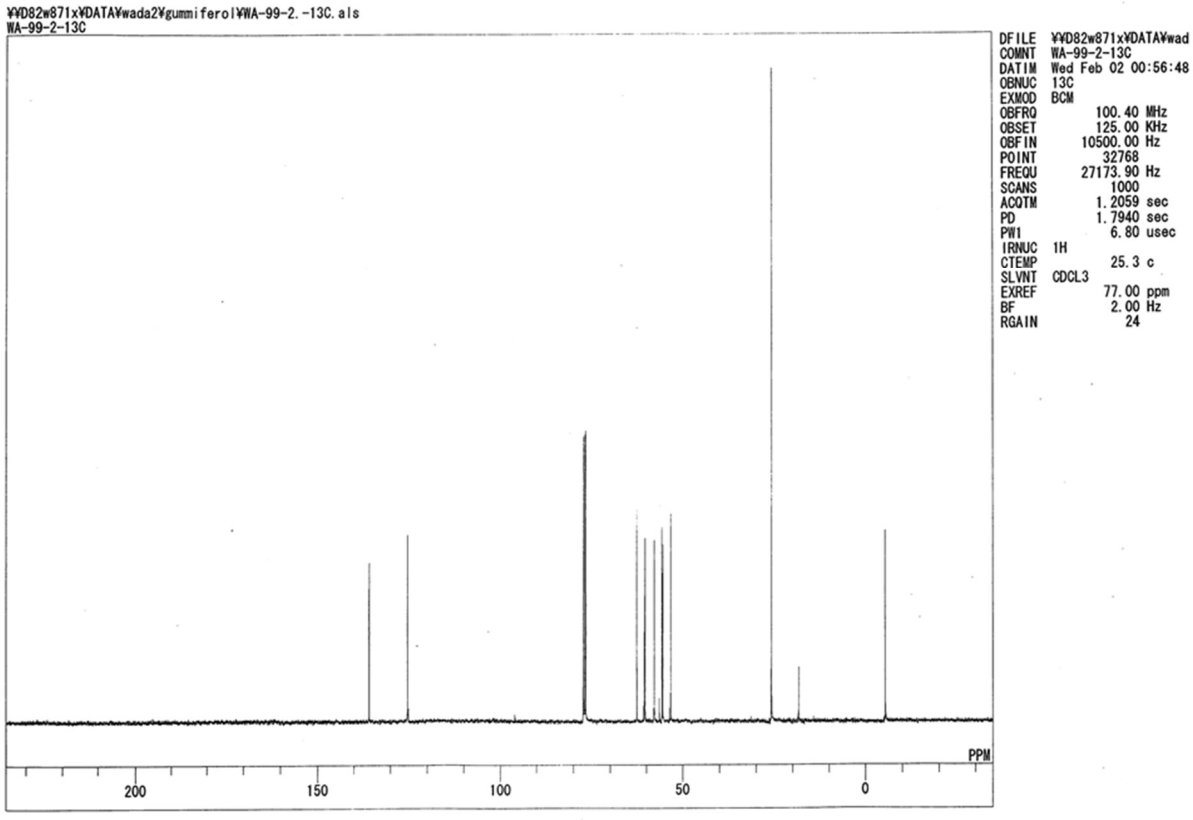
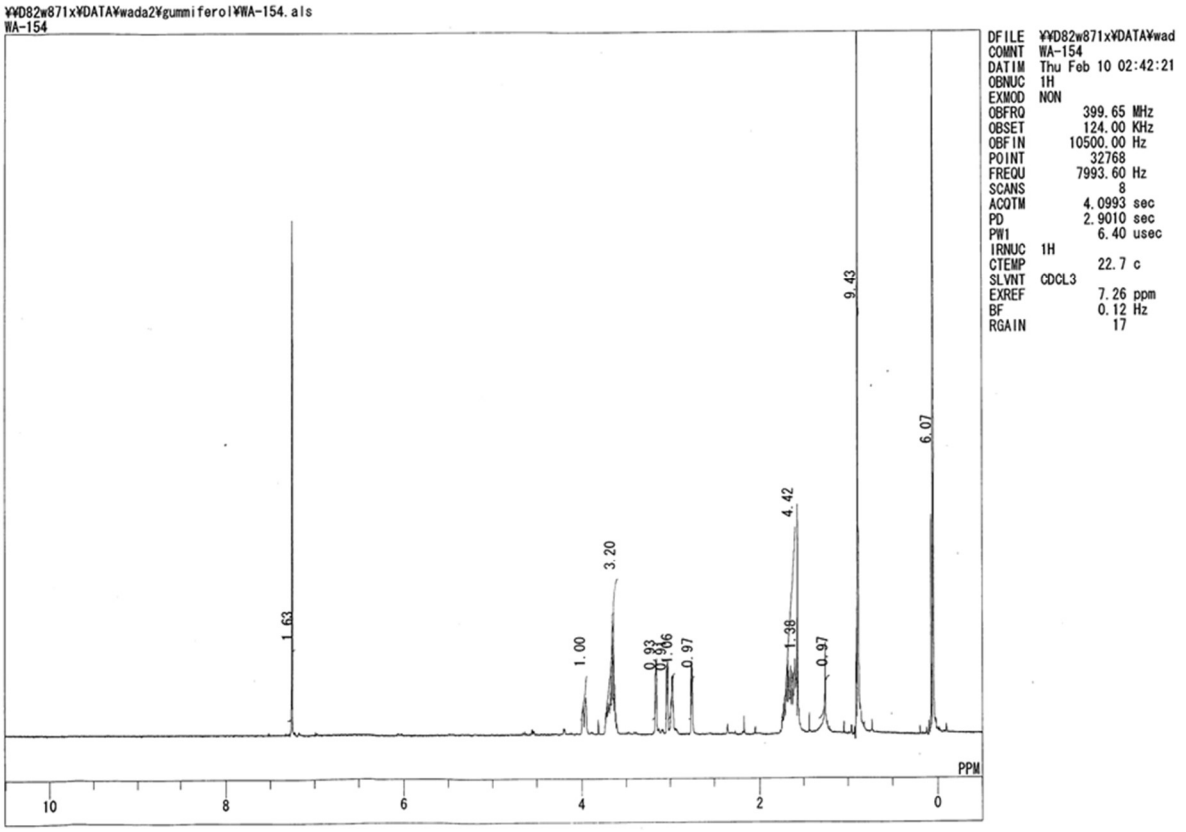


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15**



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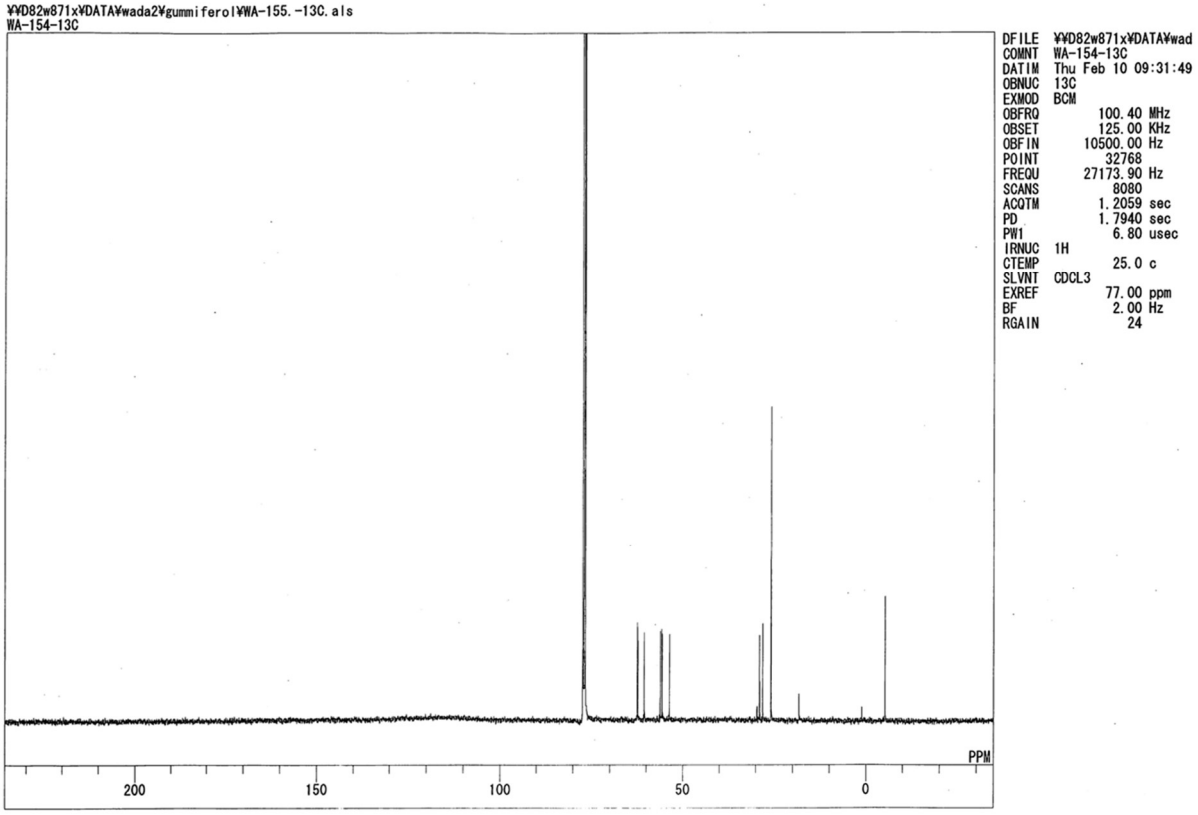
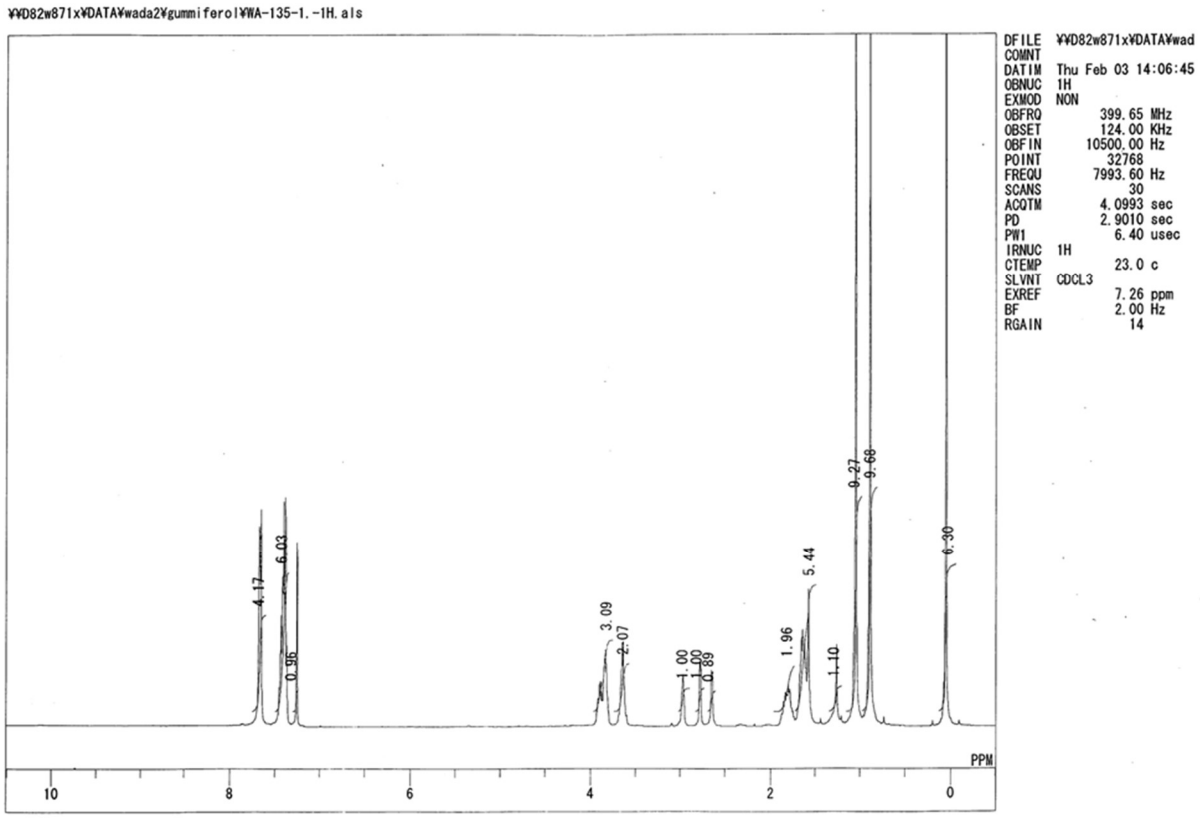


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **16**



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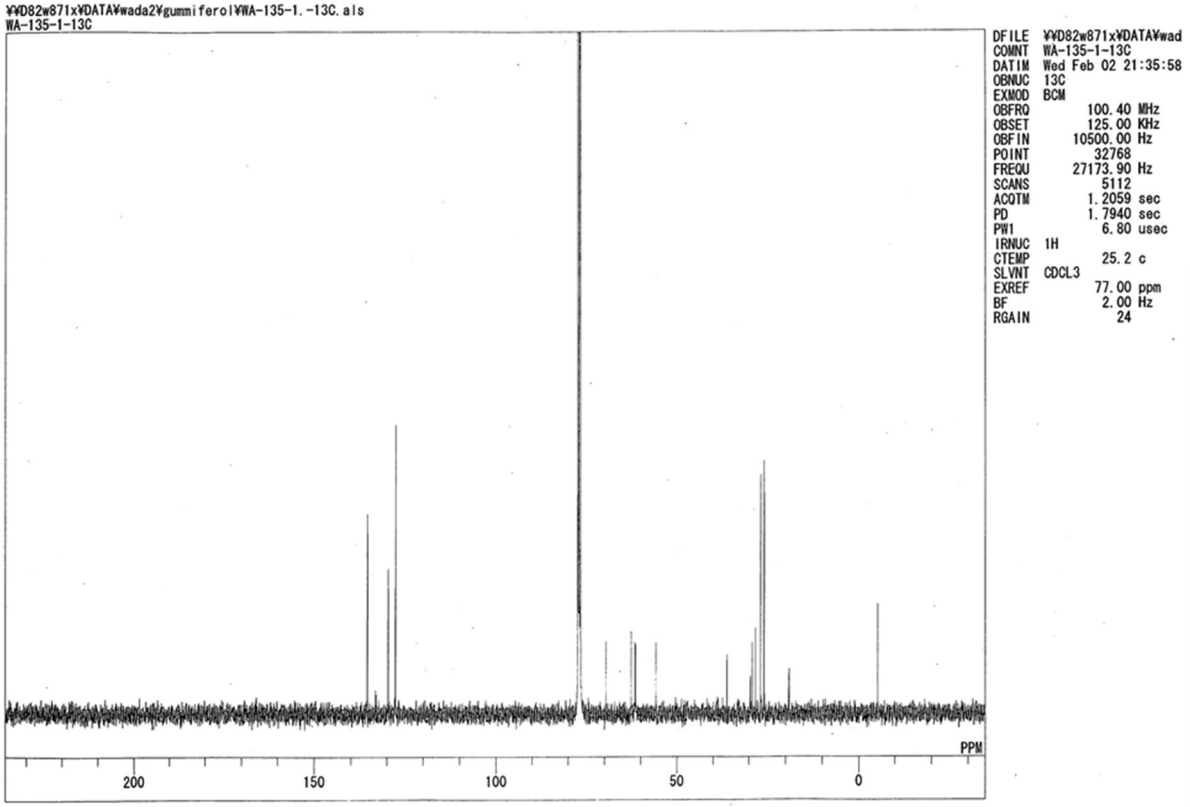
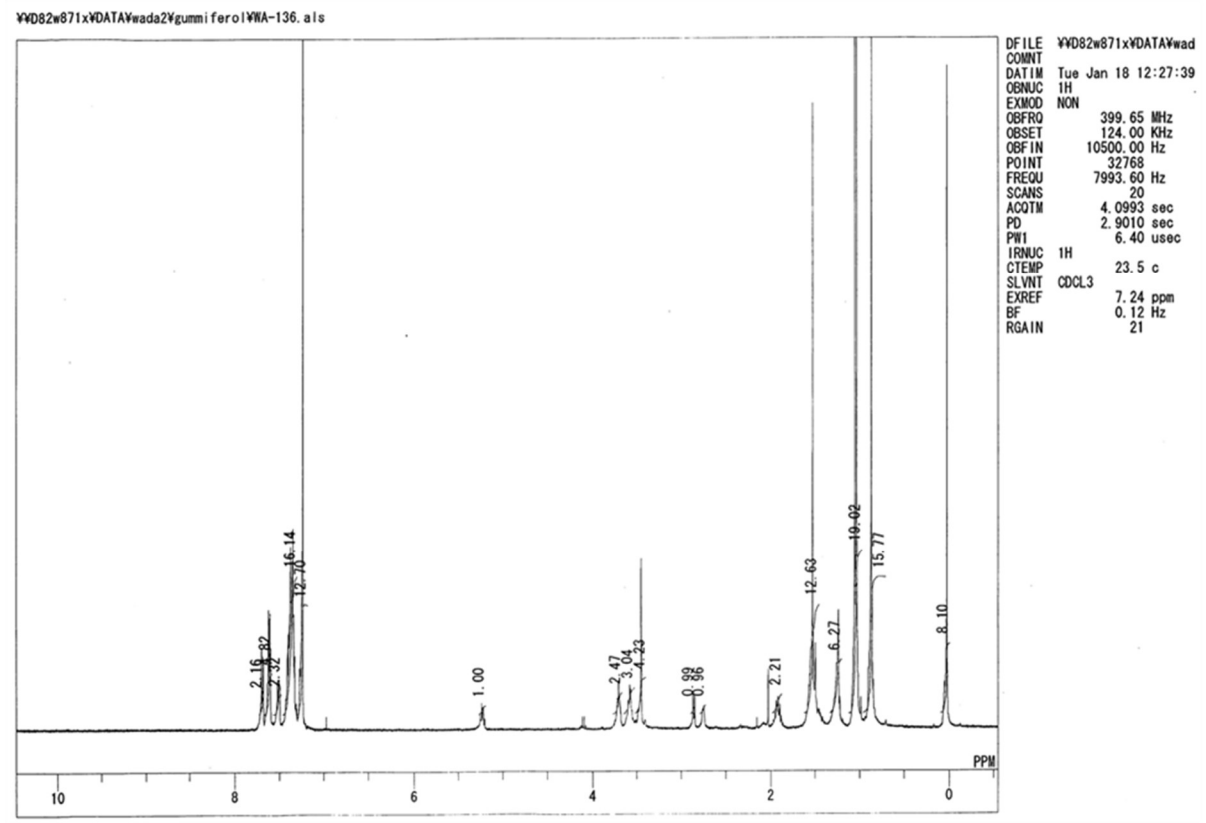
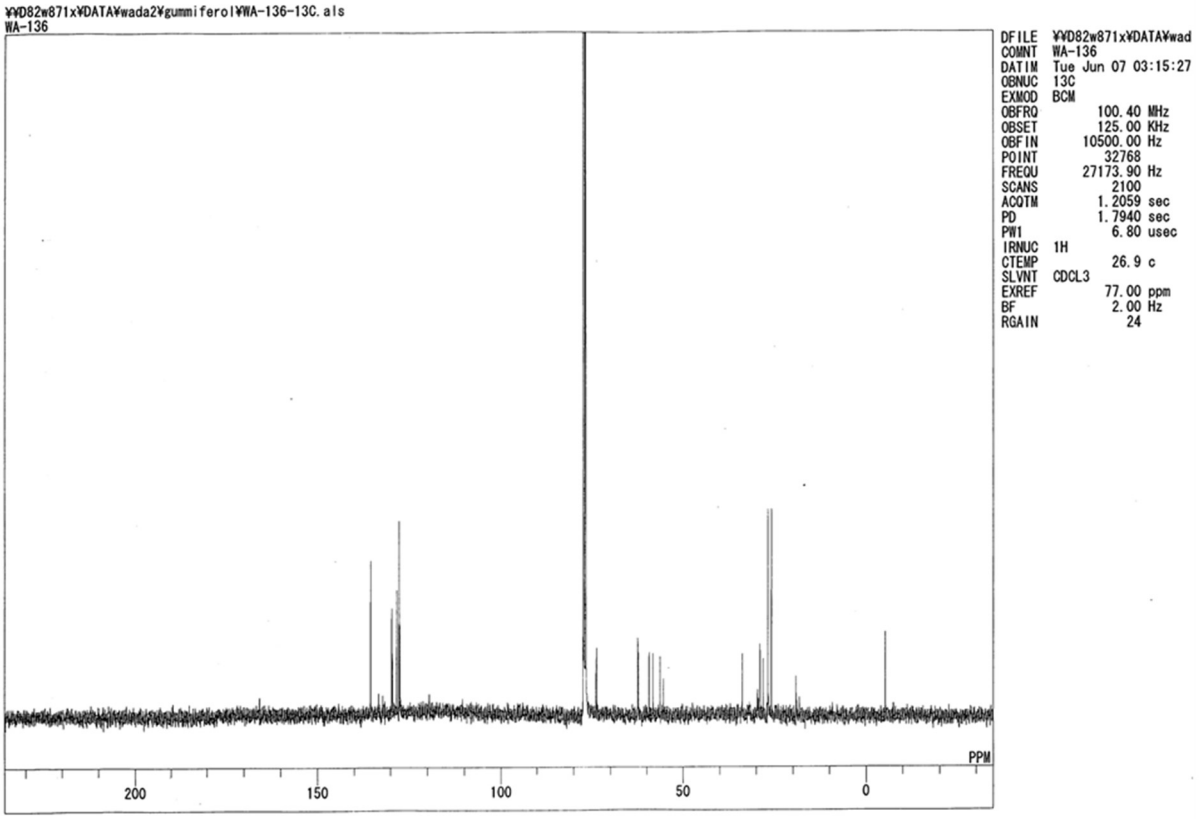


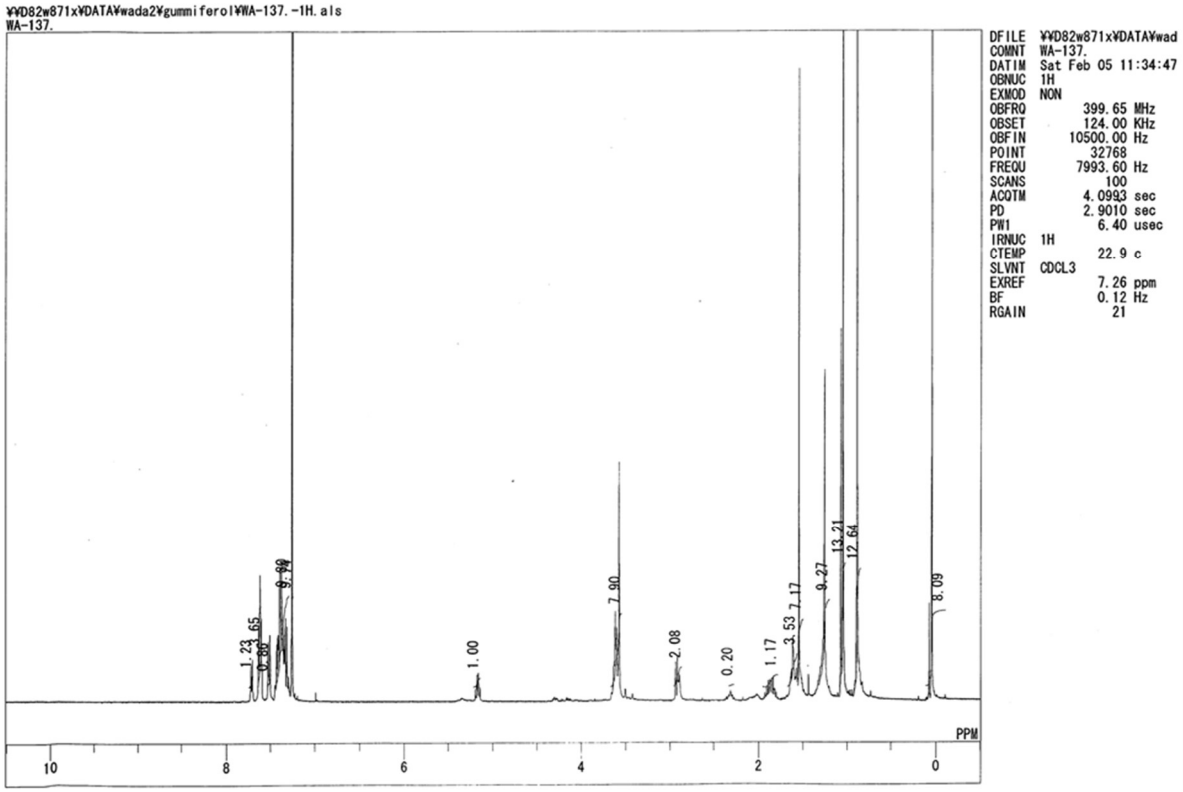
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*S*)-**17**



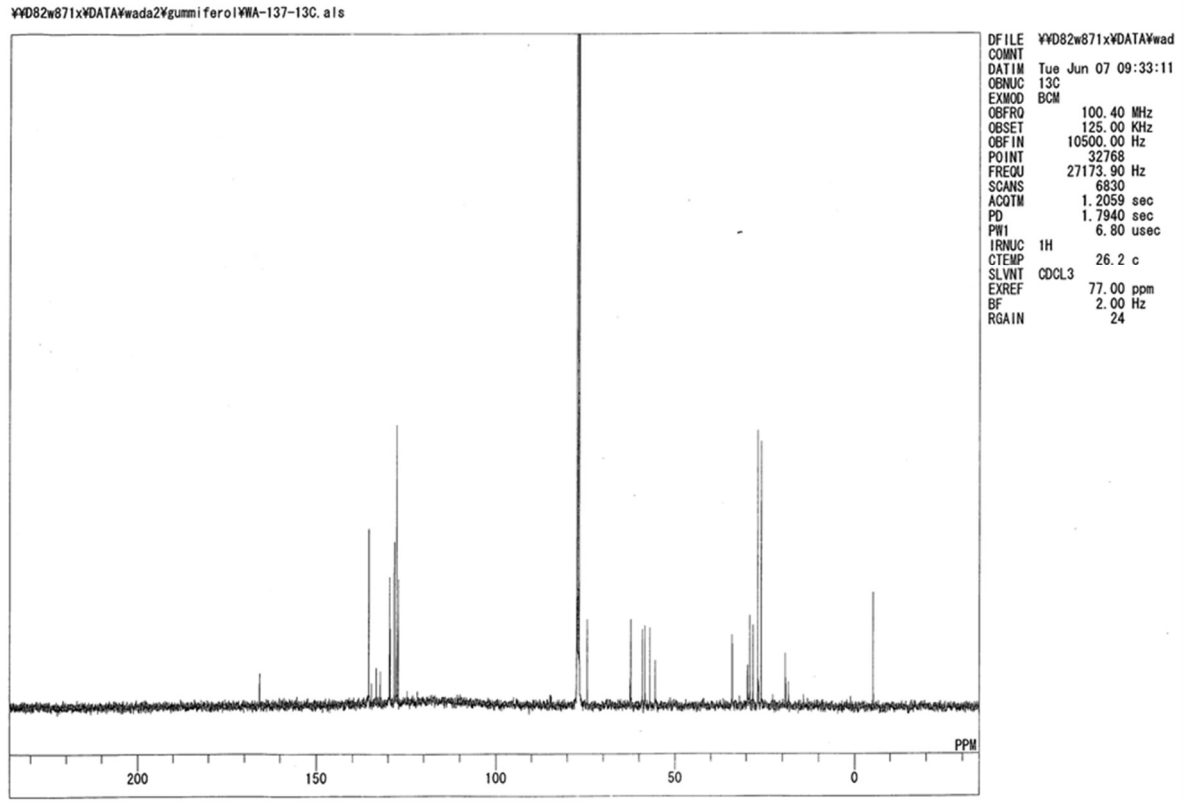
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of (*S*)-**17**



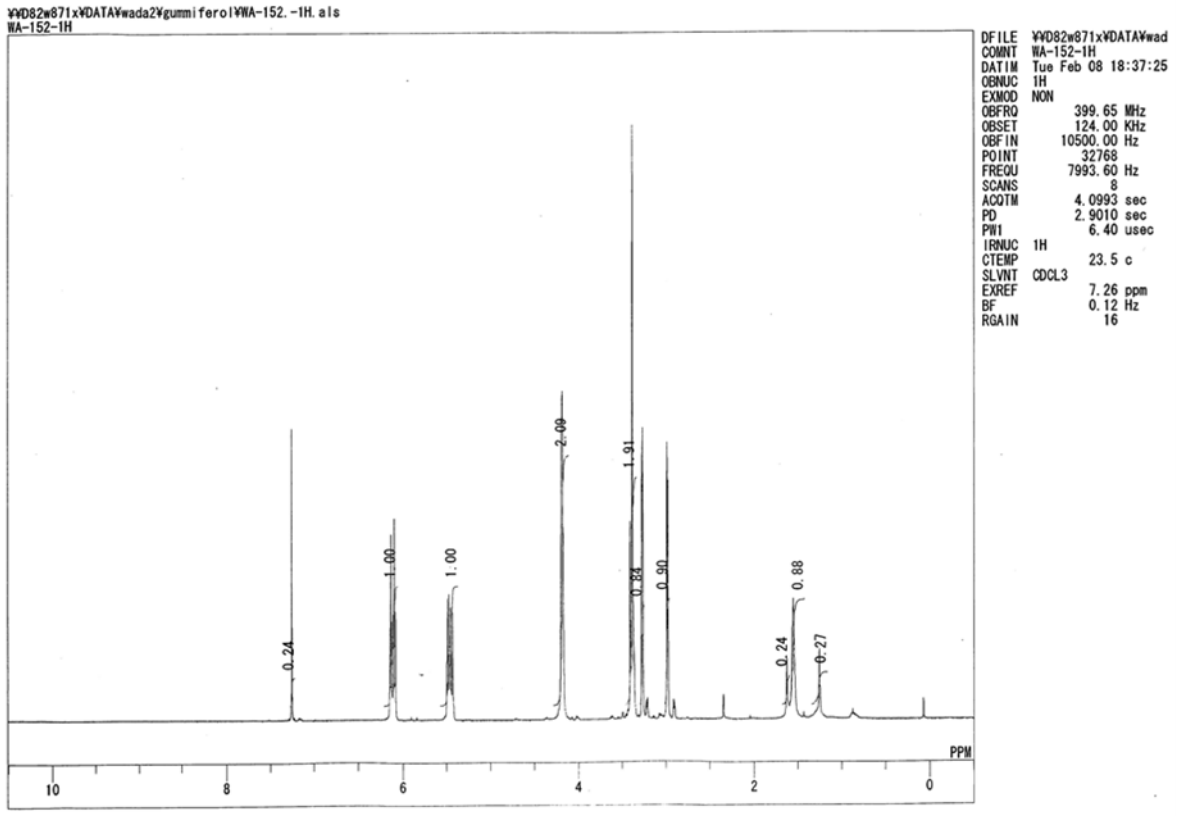
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*R*)-**17**



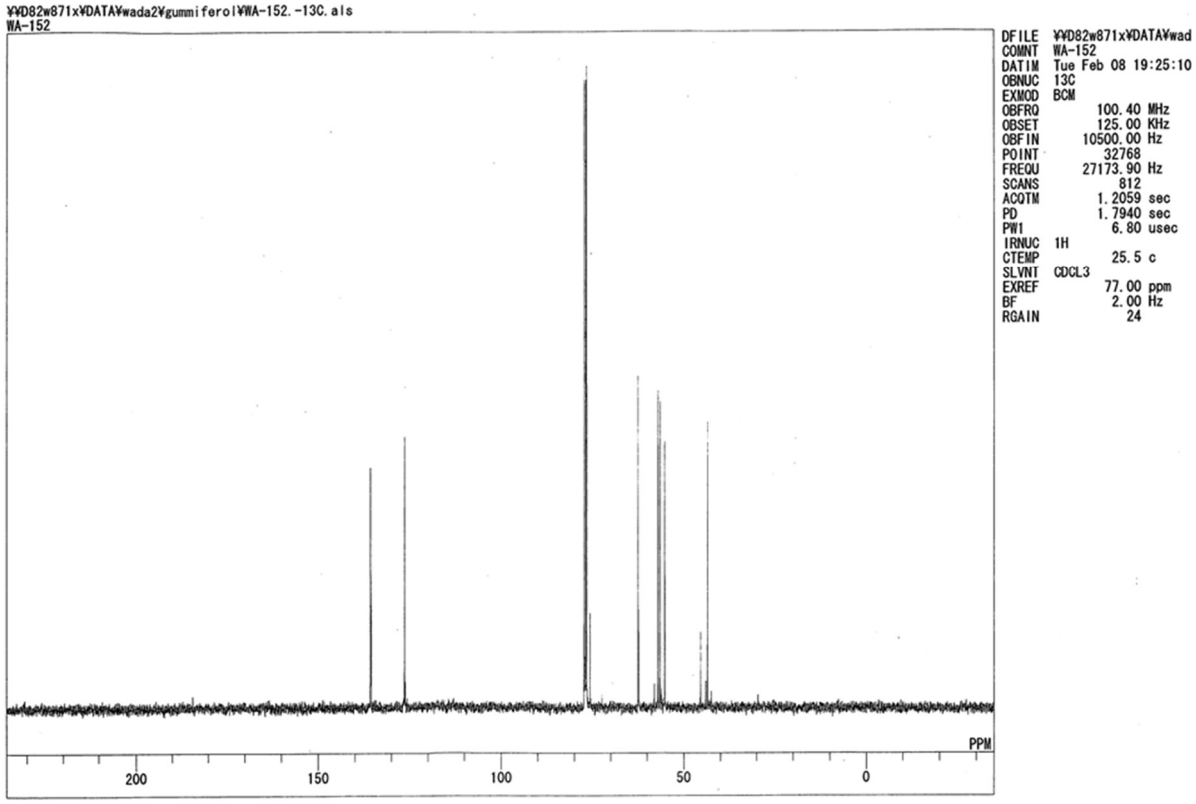
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of (*R*)-**17**



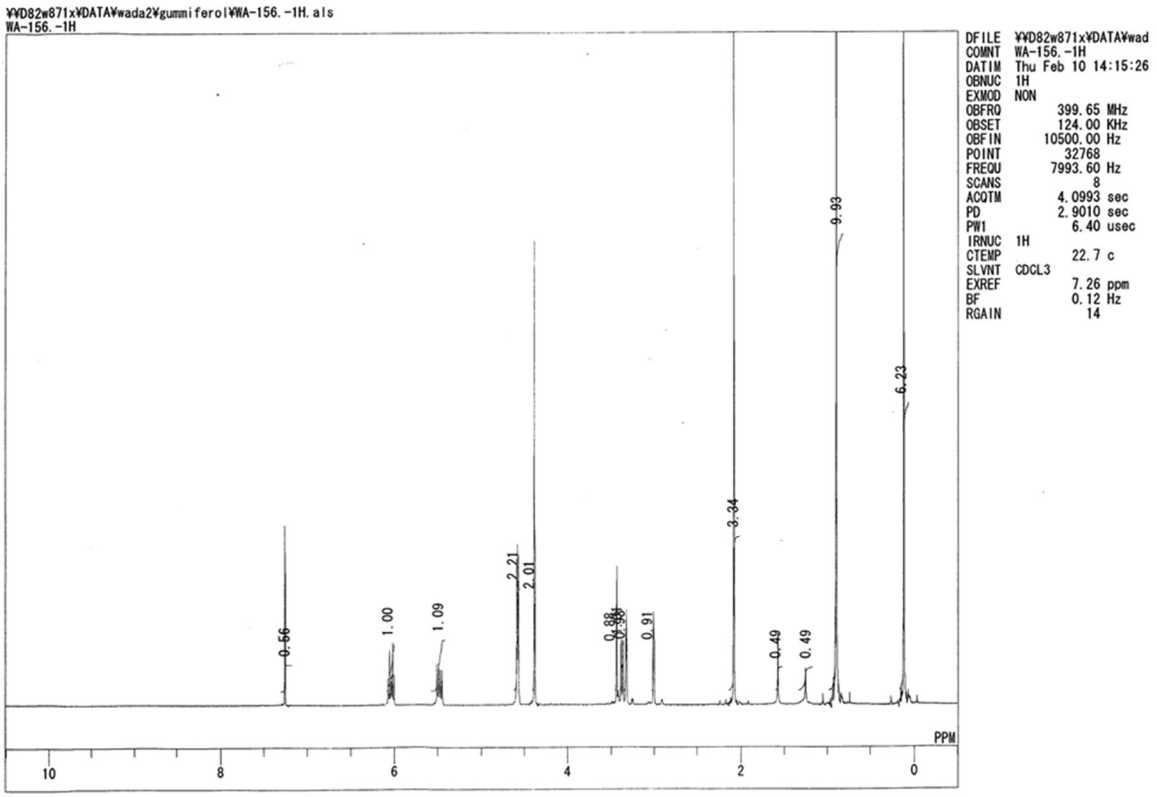
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **3a**



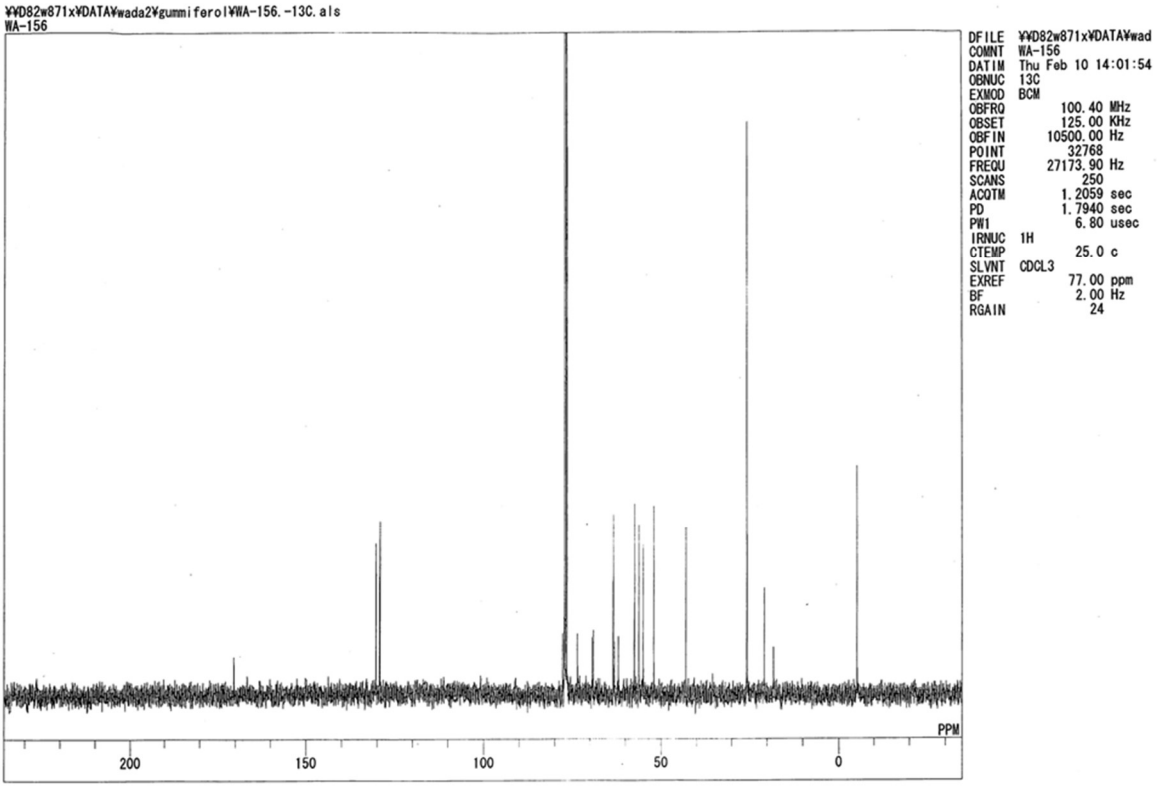
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **3a**



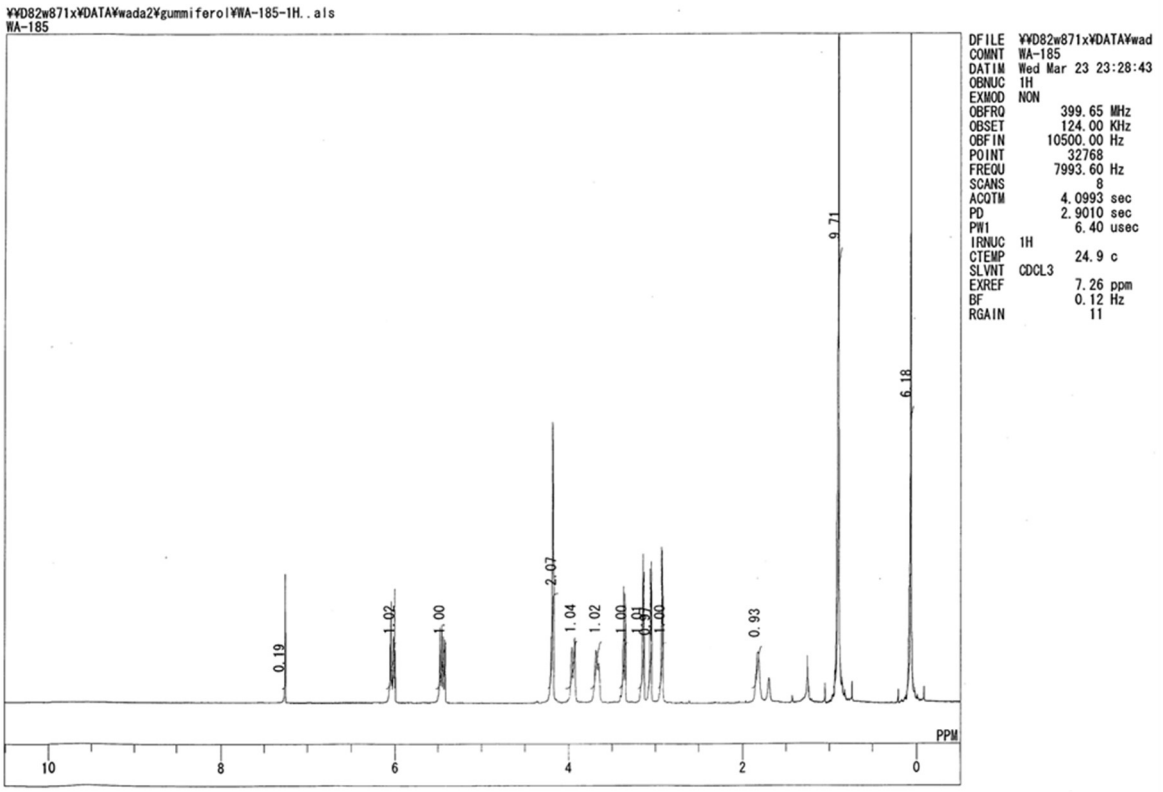
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **21**



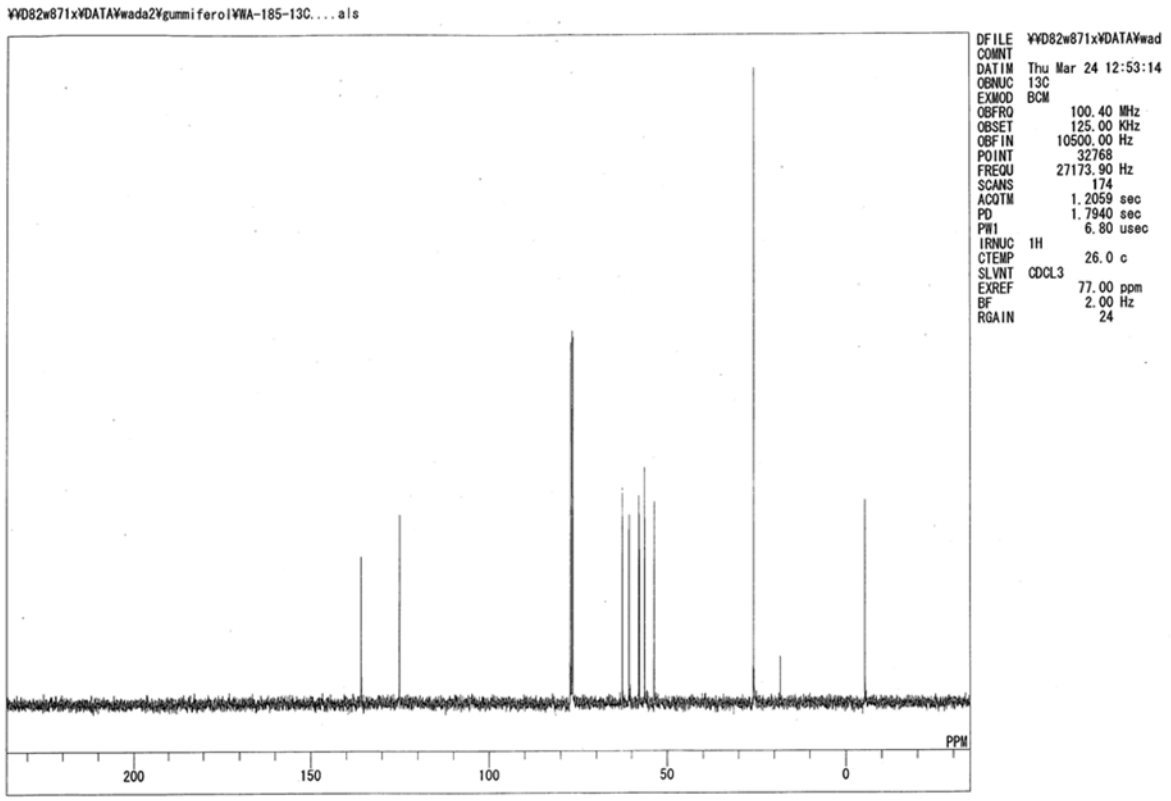
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **21**



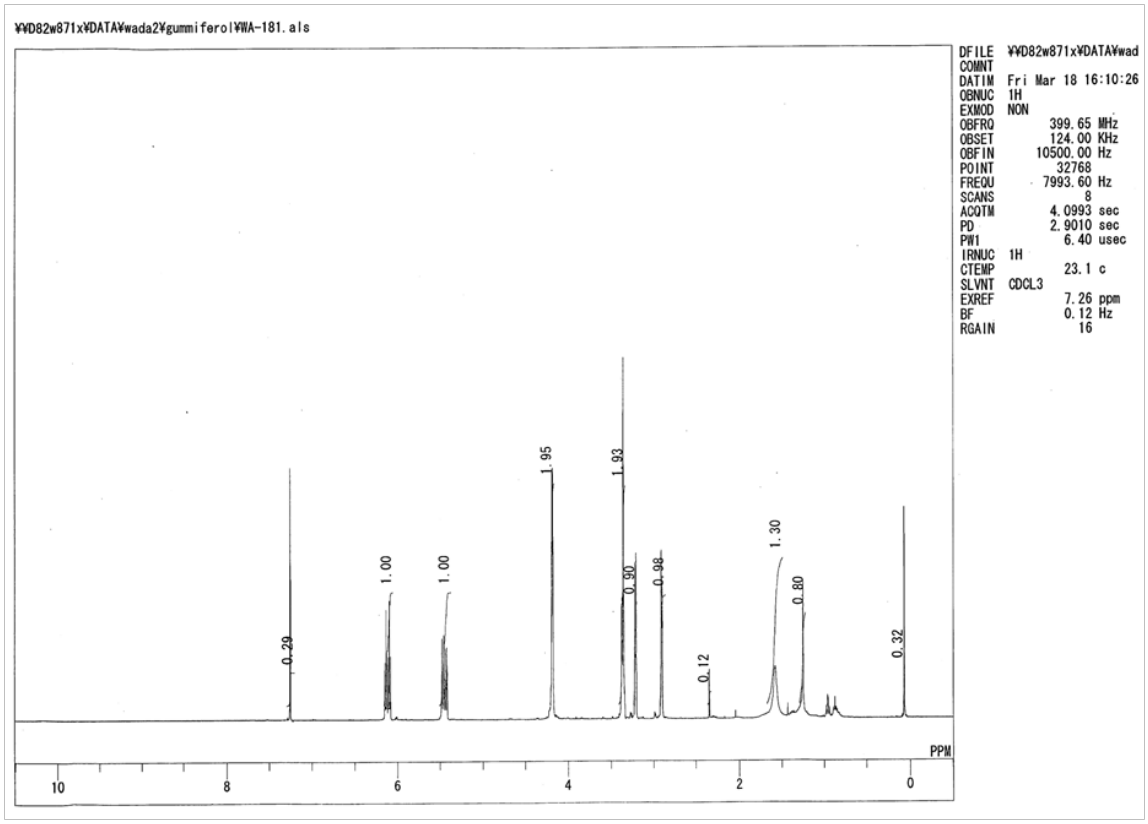
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **22**



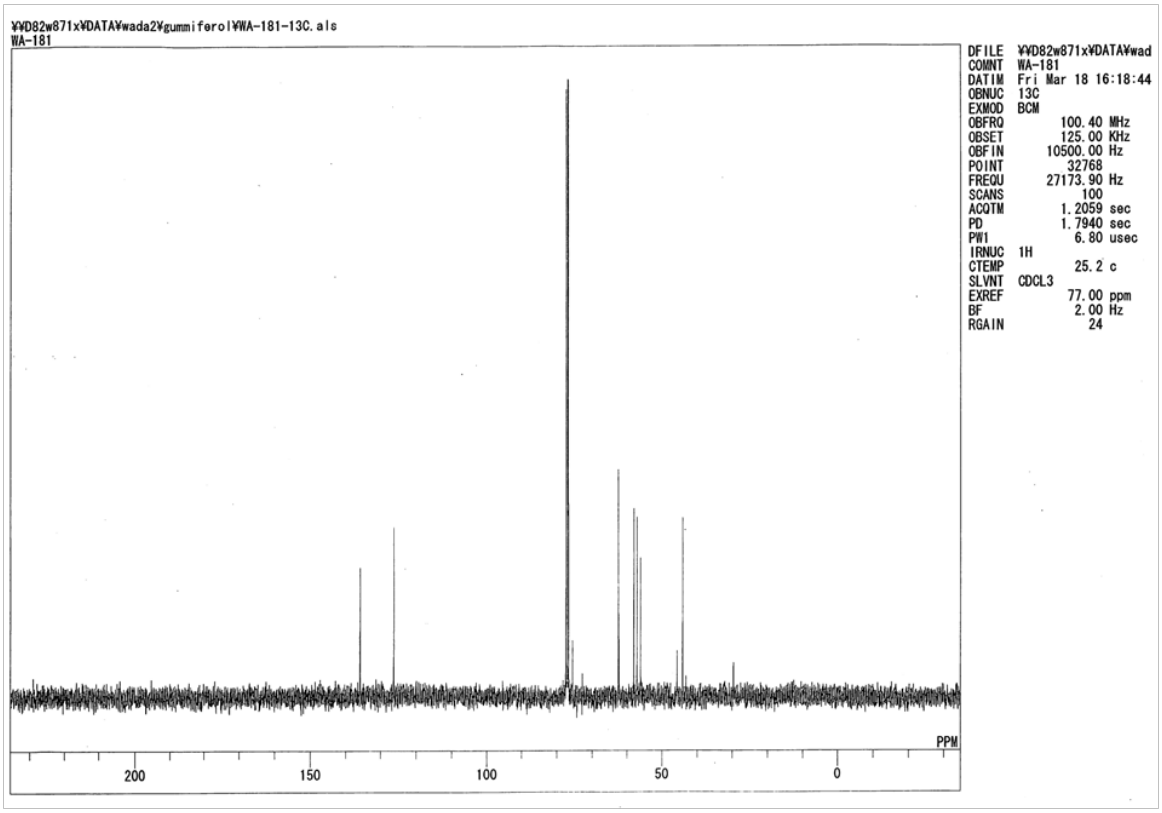
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **22**



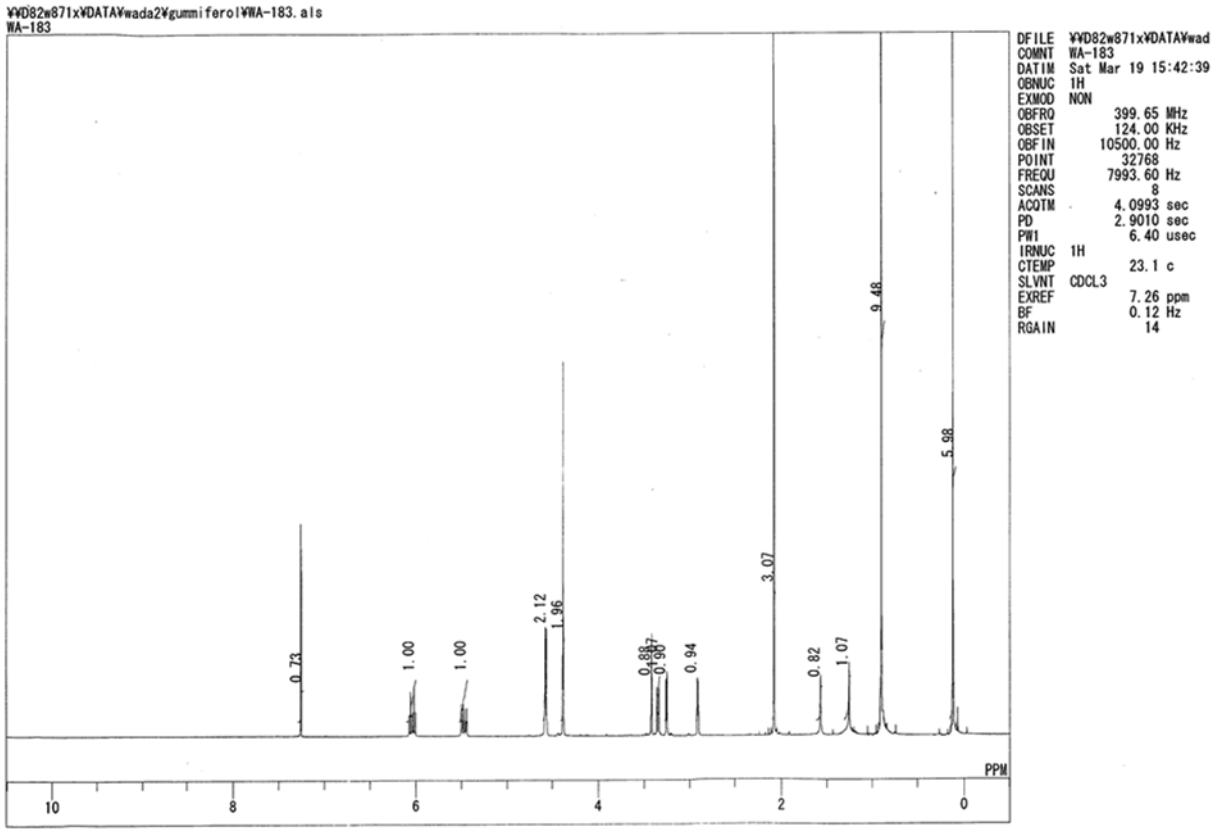
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **3b**



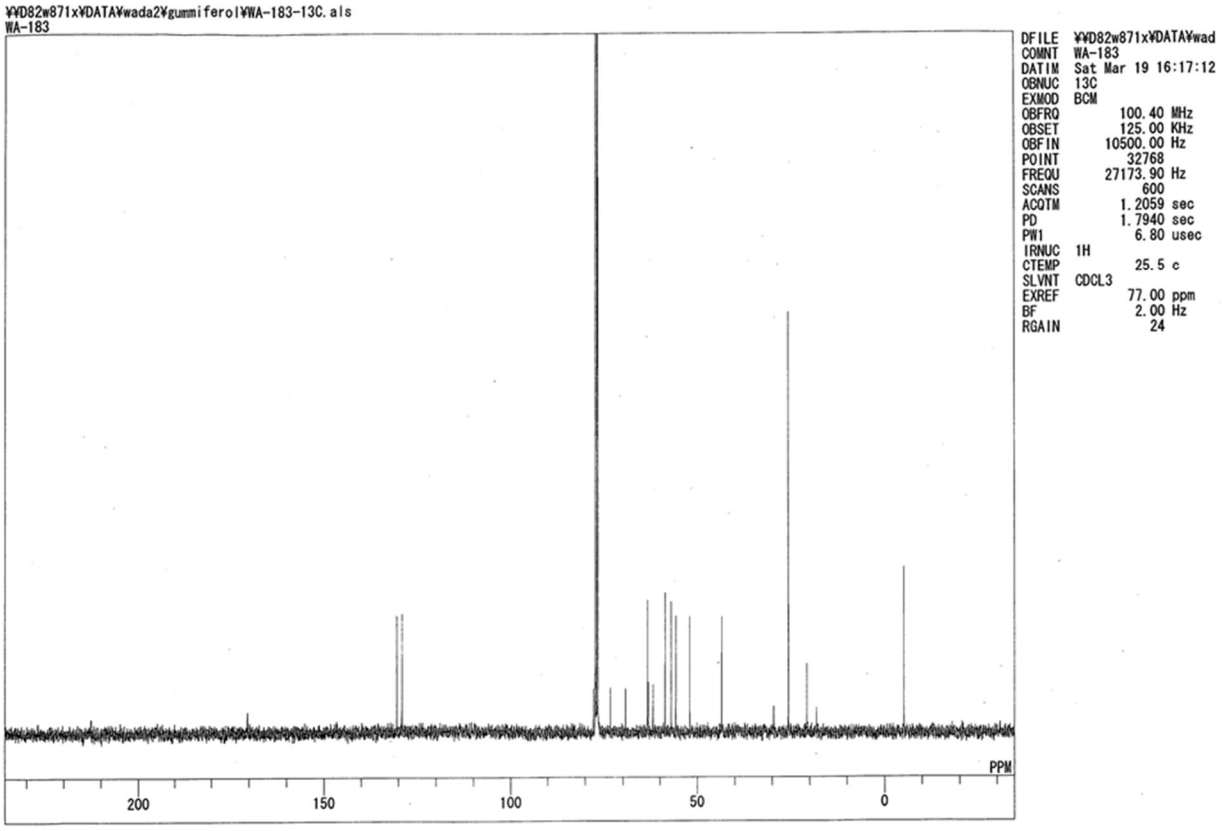
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **3b**



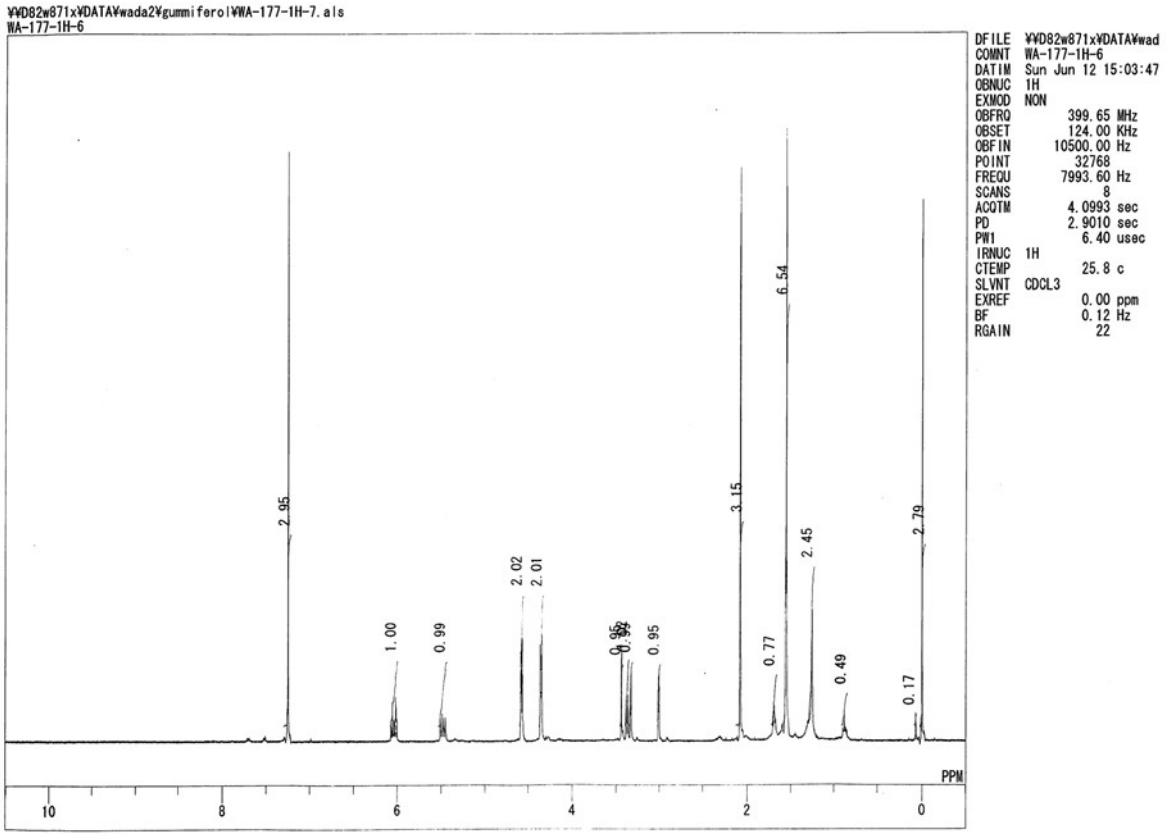
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **23**



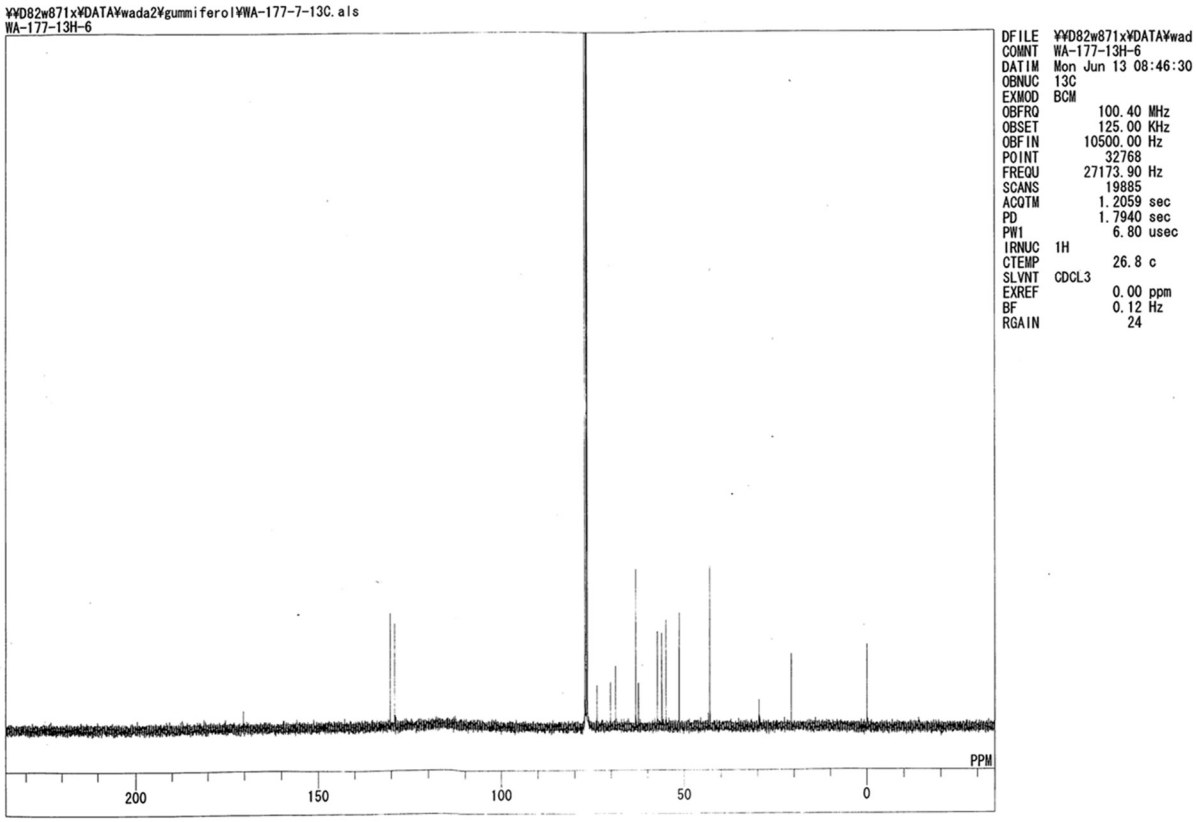
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **23**



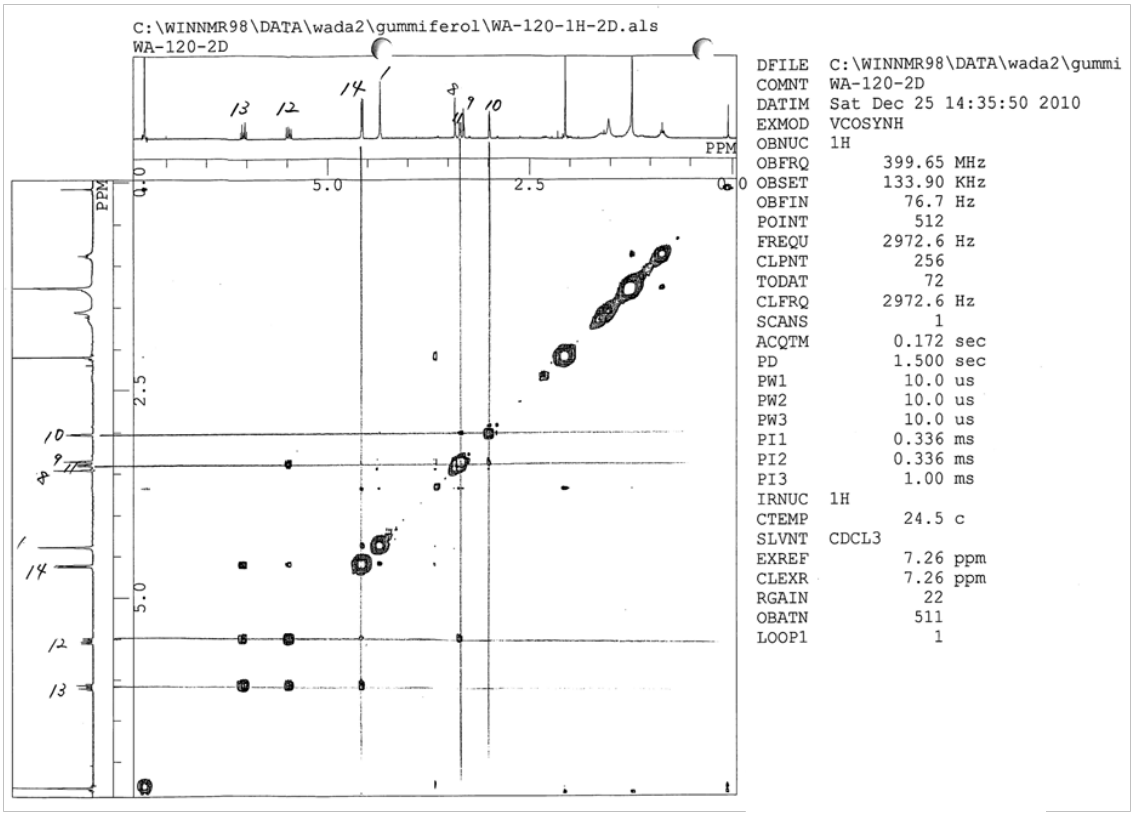
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **5a**



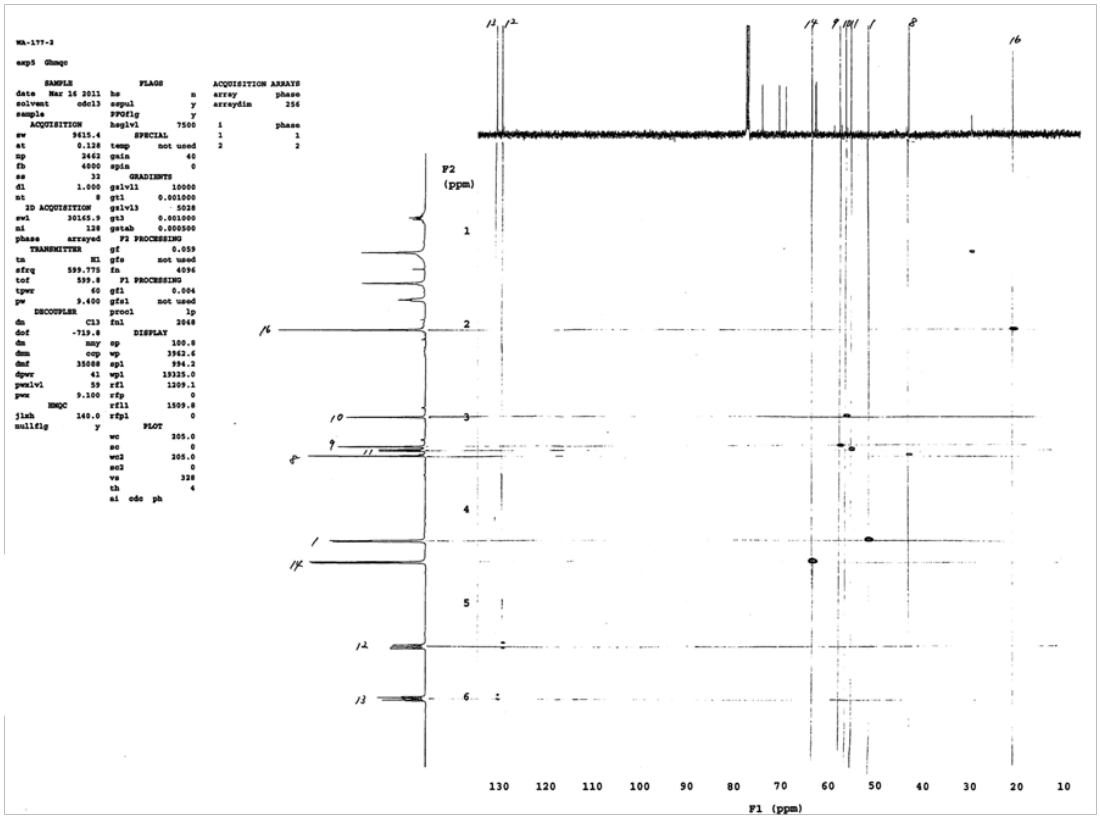
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **5a**



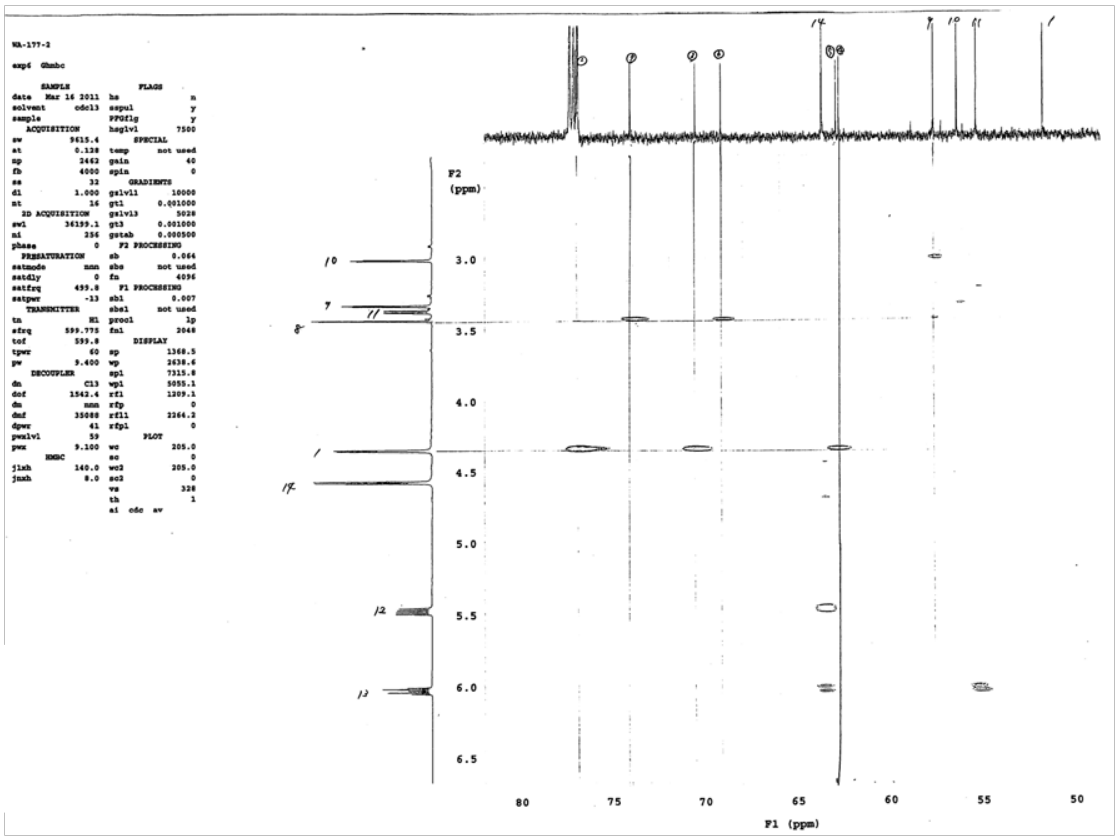
^{1}H–^{1}H COSY (400 MHz, $CDCl_3$) spectrum of **5a**



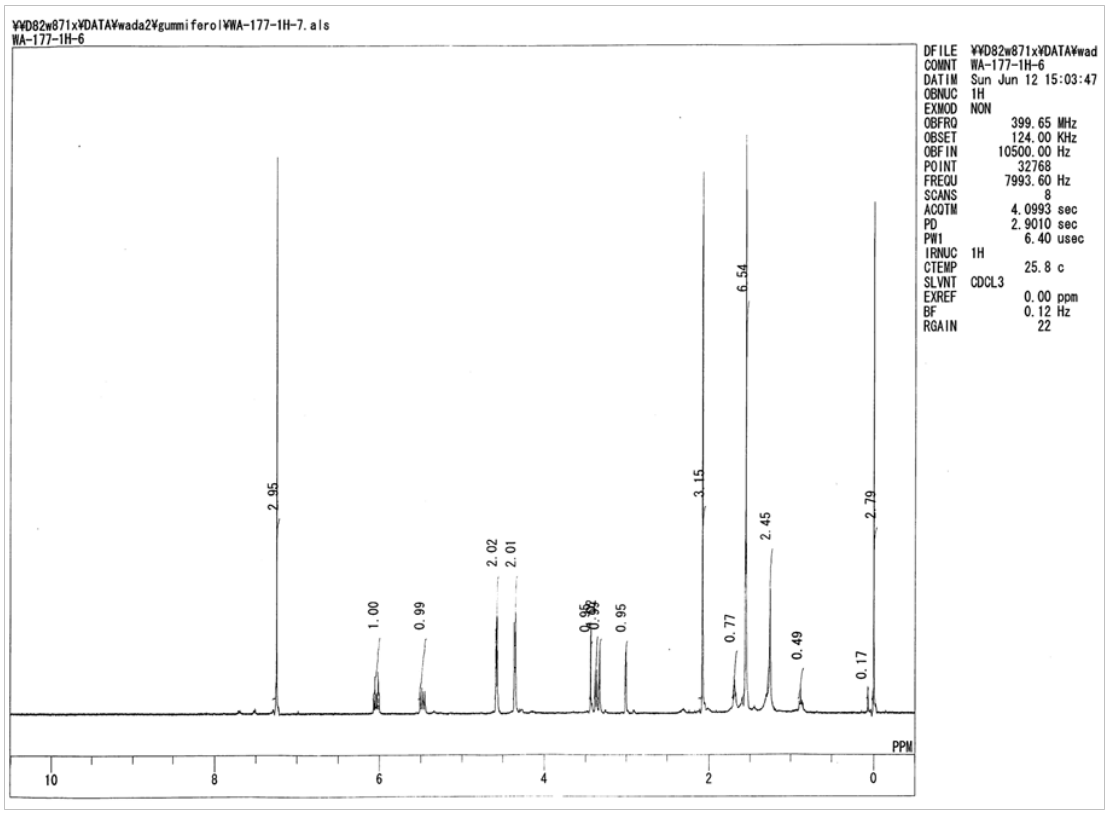
HMQC (600 MHz, $CDCl_3$) spectrum of **5a**



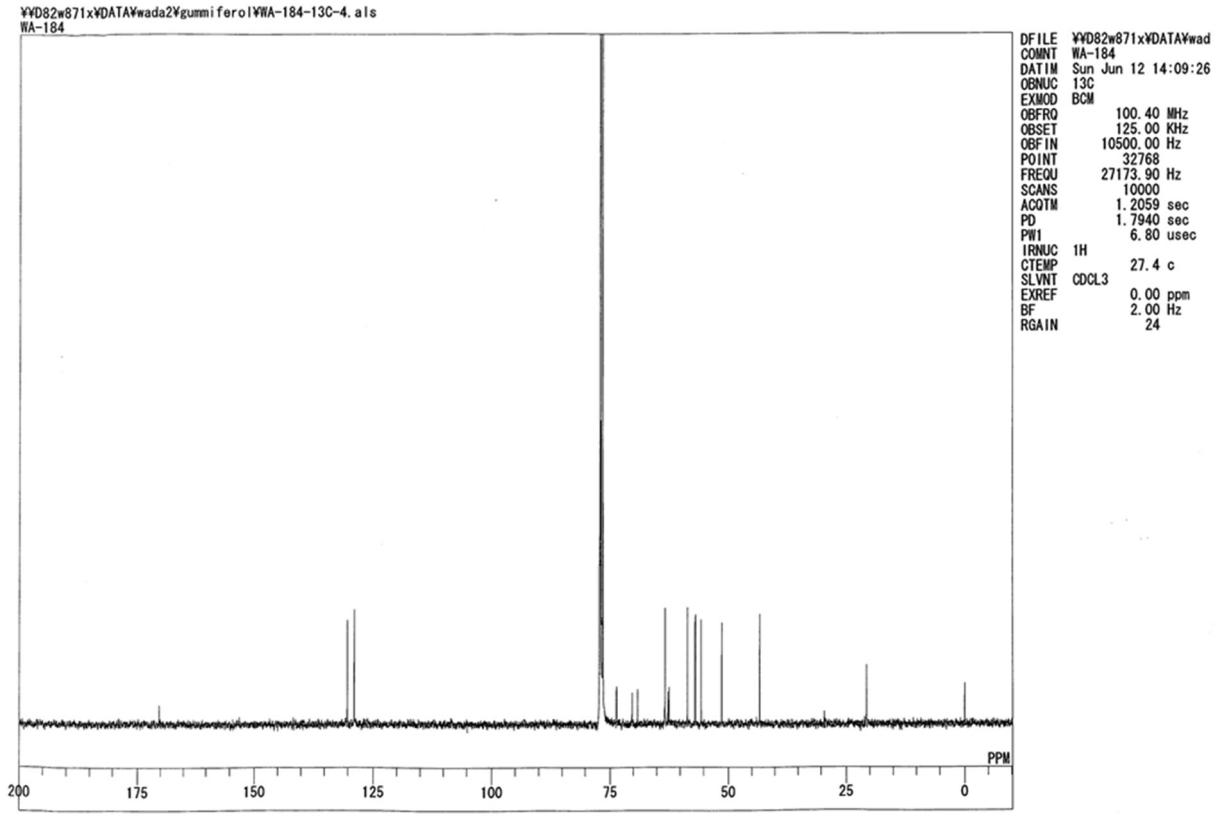
HMBC (600 MHz, $CDCl_3$) spectrum of **5a**



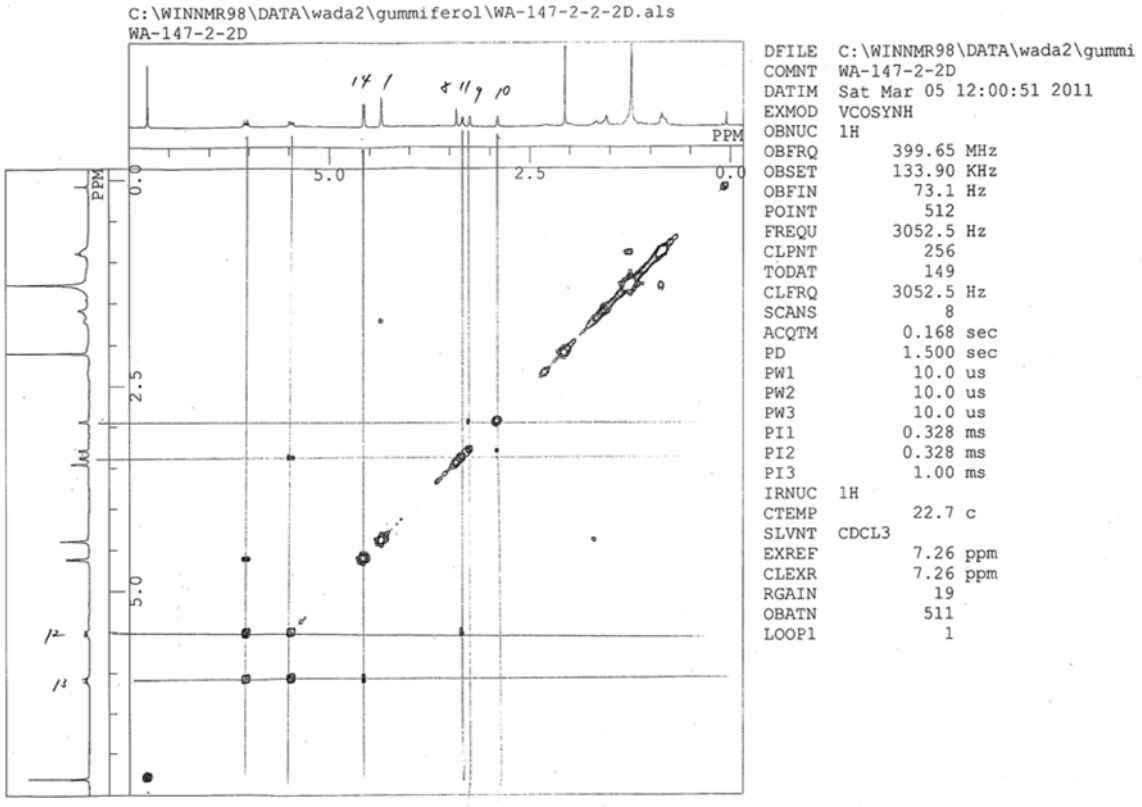
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **5b**



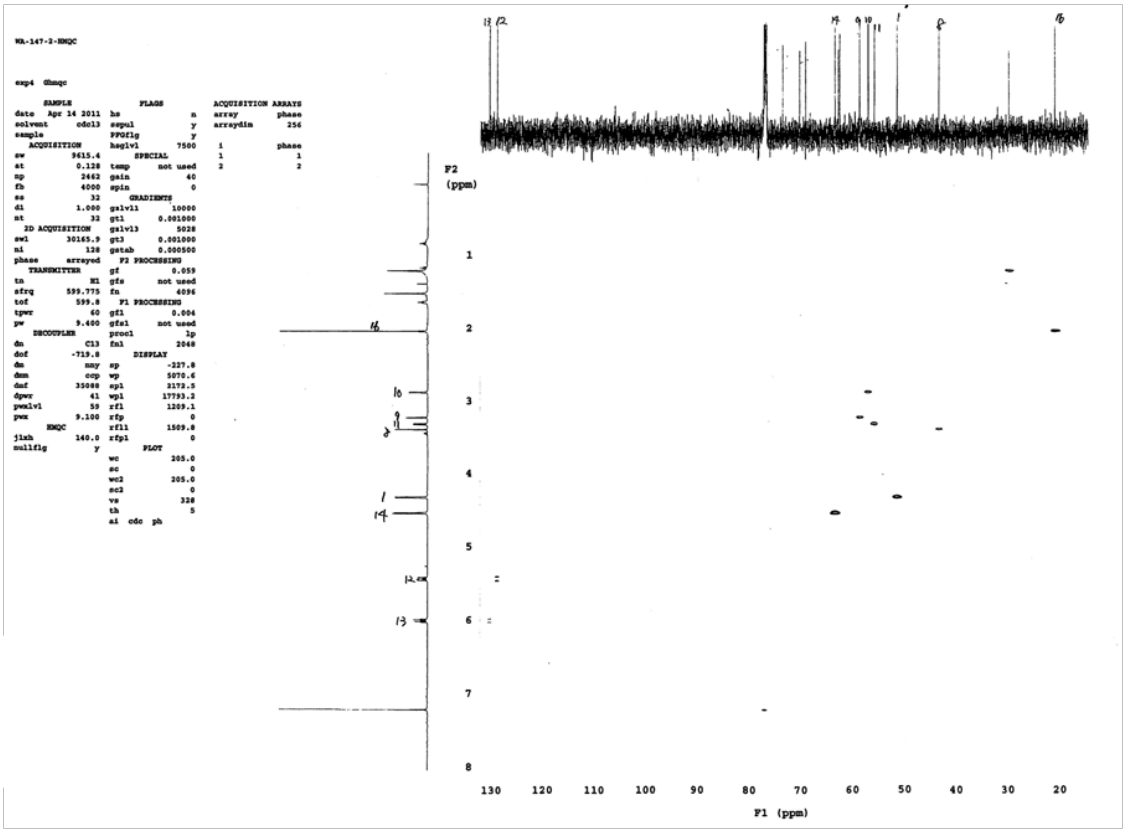
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **5b**



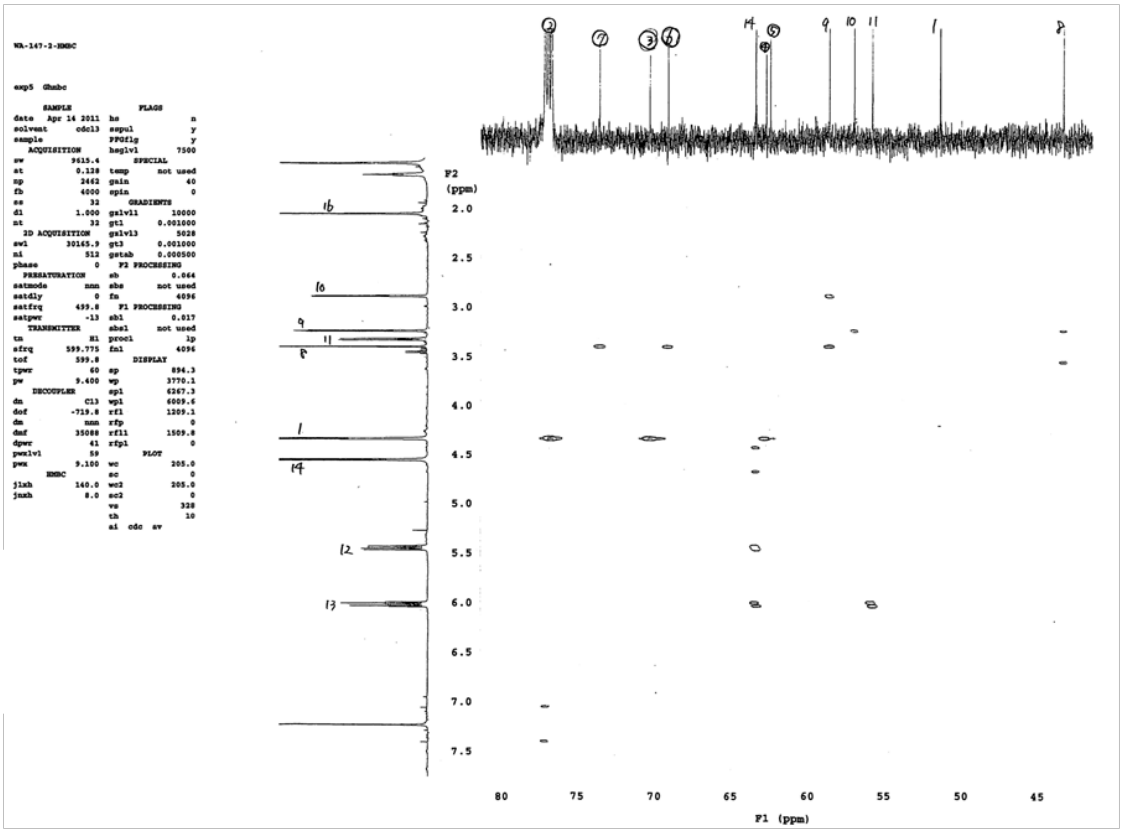
^{1}H–^{1}H COSY (400 MHz, $CDCl_3$) spectrum of **5b**



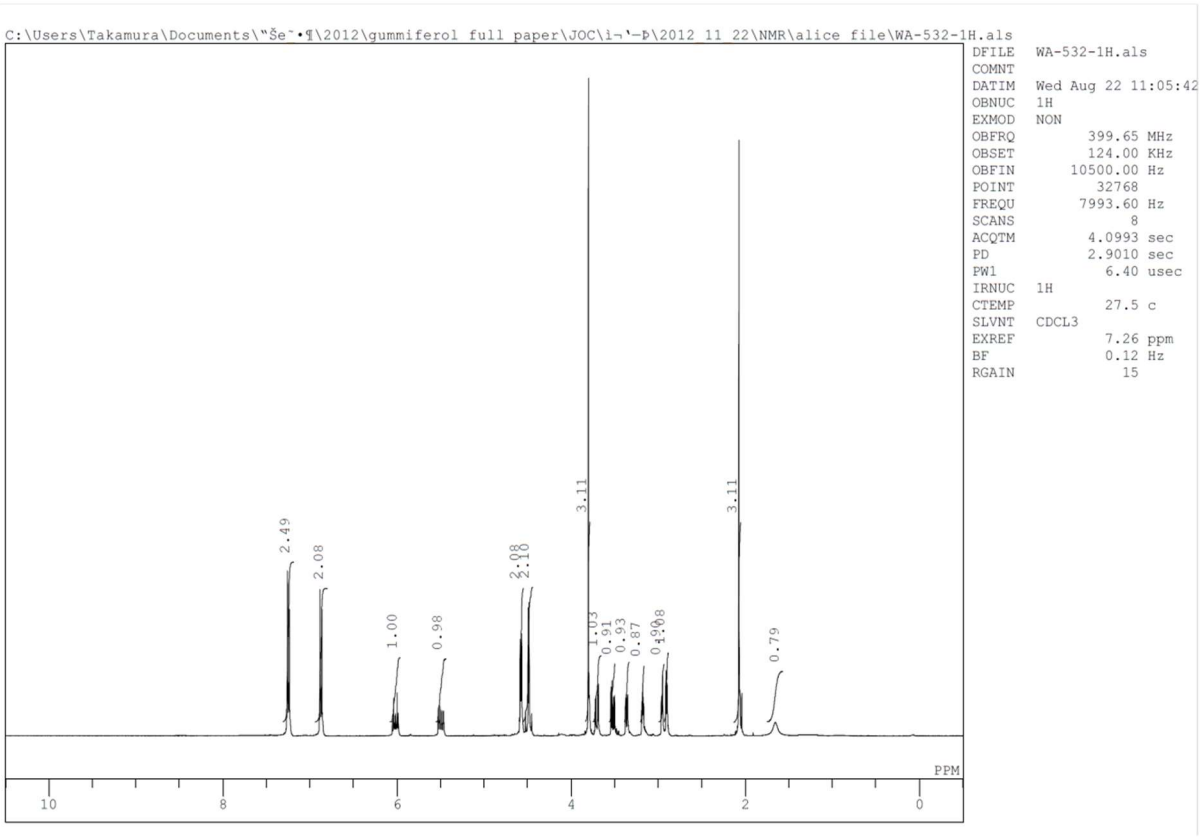
HMQC (600 MHz, $CDCl_3$) spectrum of **5b**



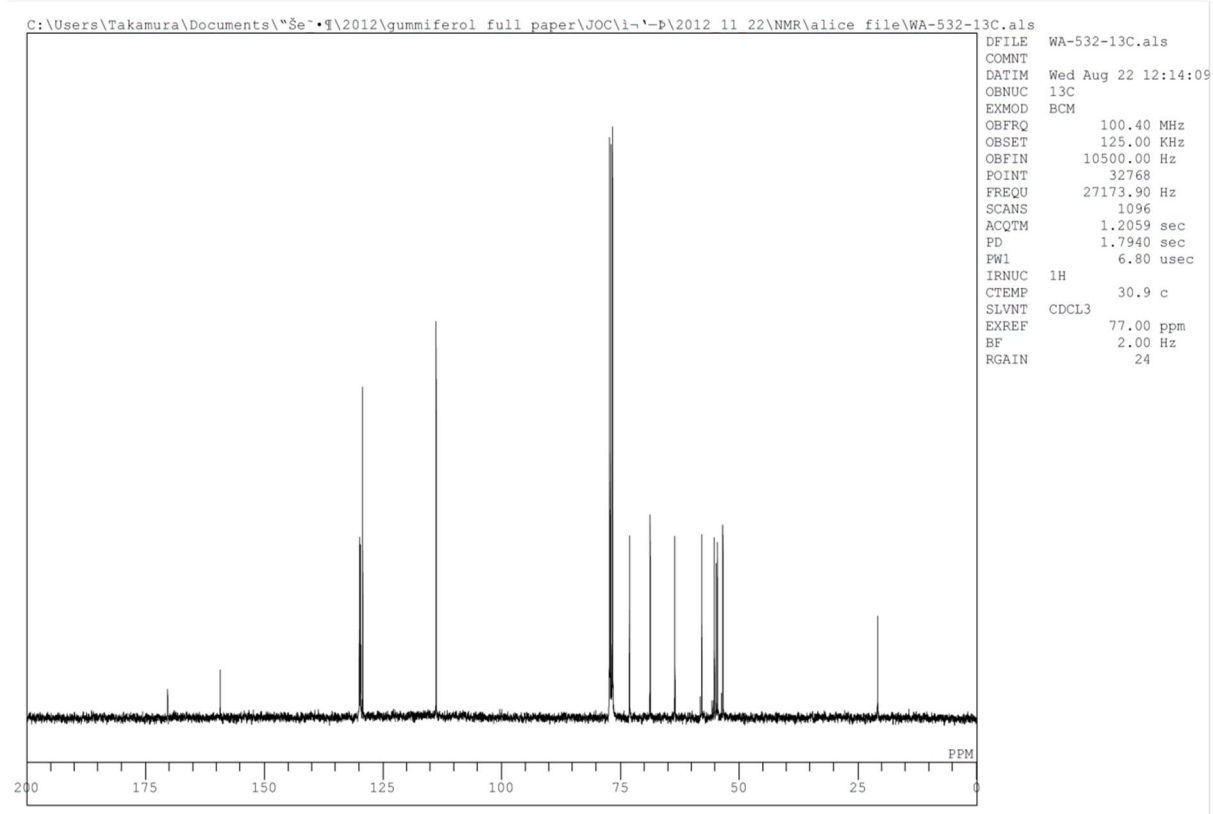
HMBC (600 MHz, $CDCl_3$) spectrum of **5b**



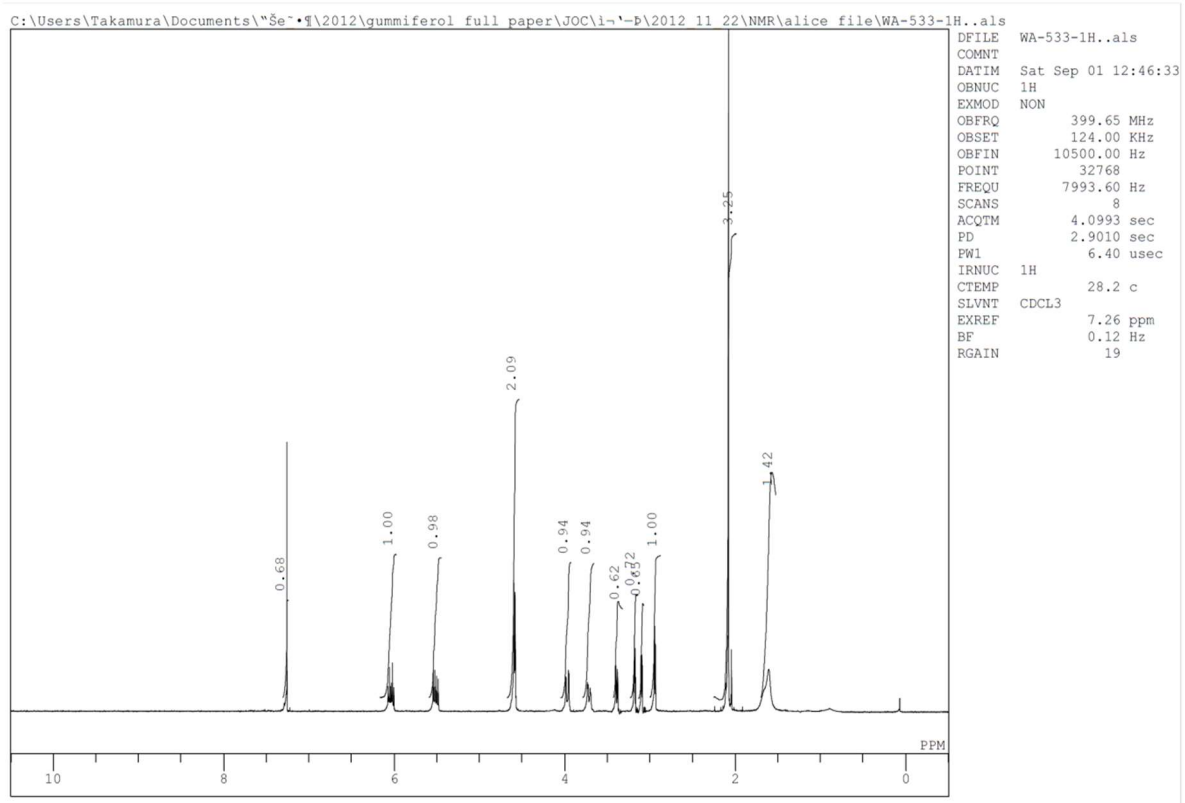
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **25**



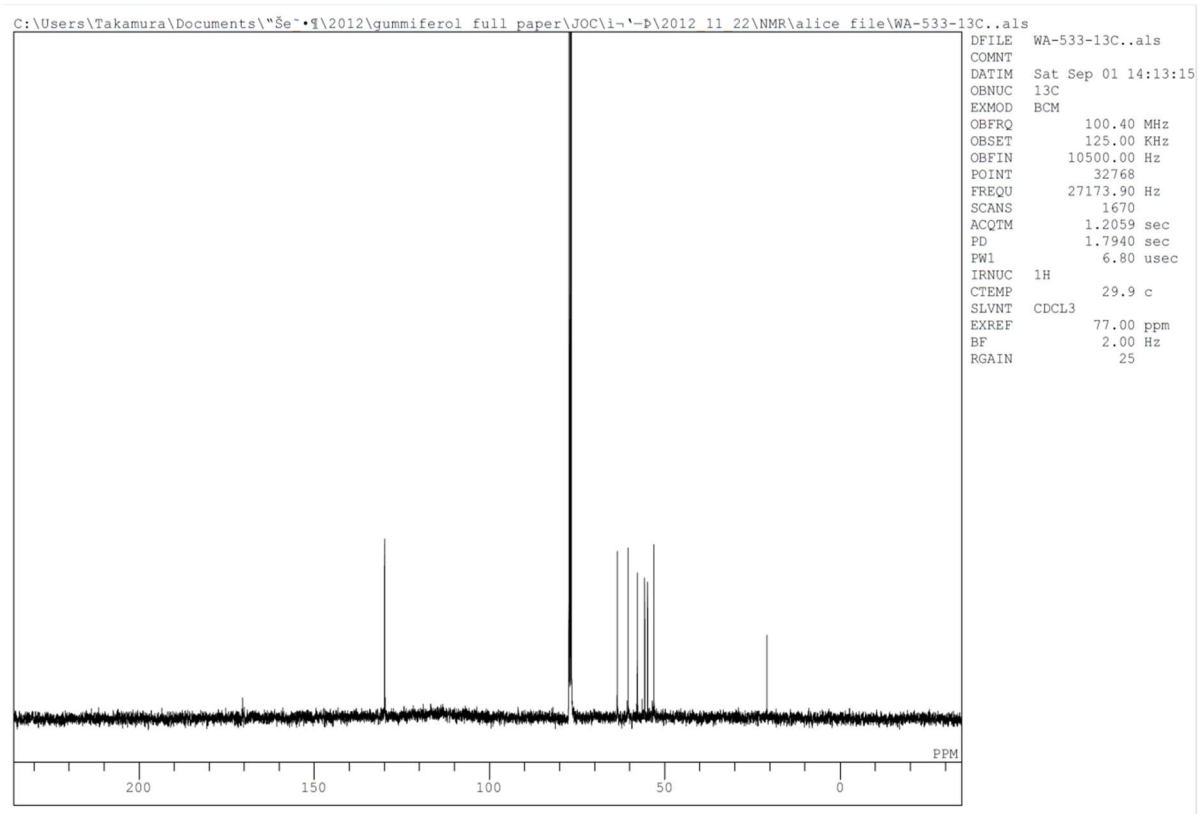
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **25**



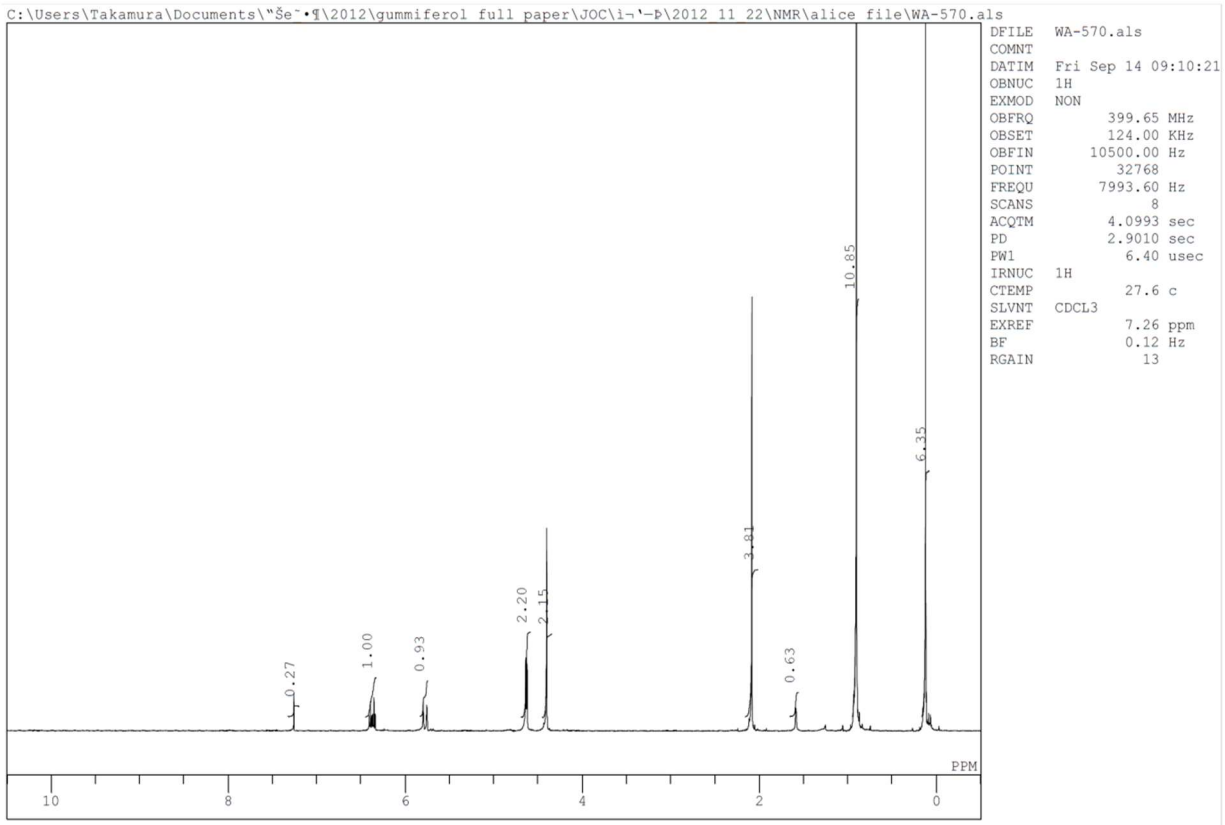
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **26**



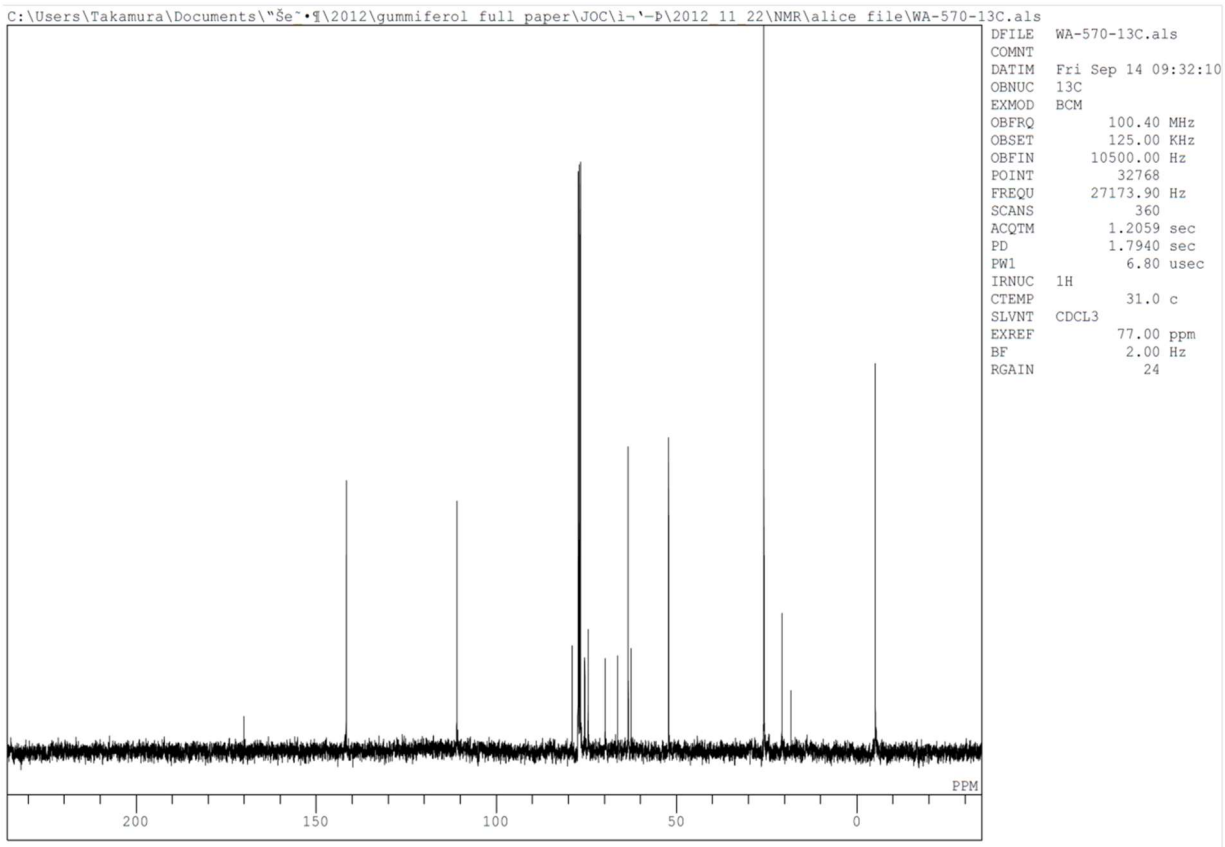
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **26**



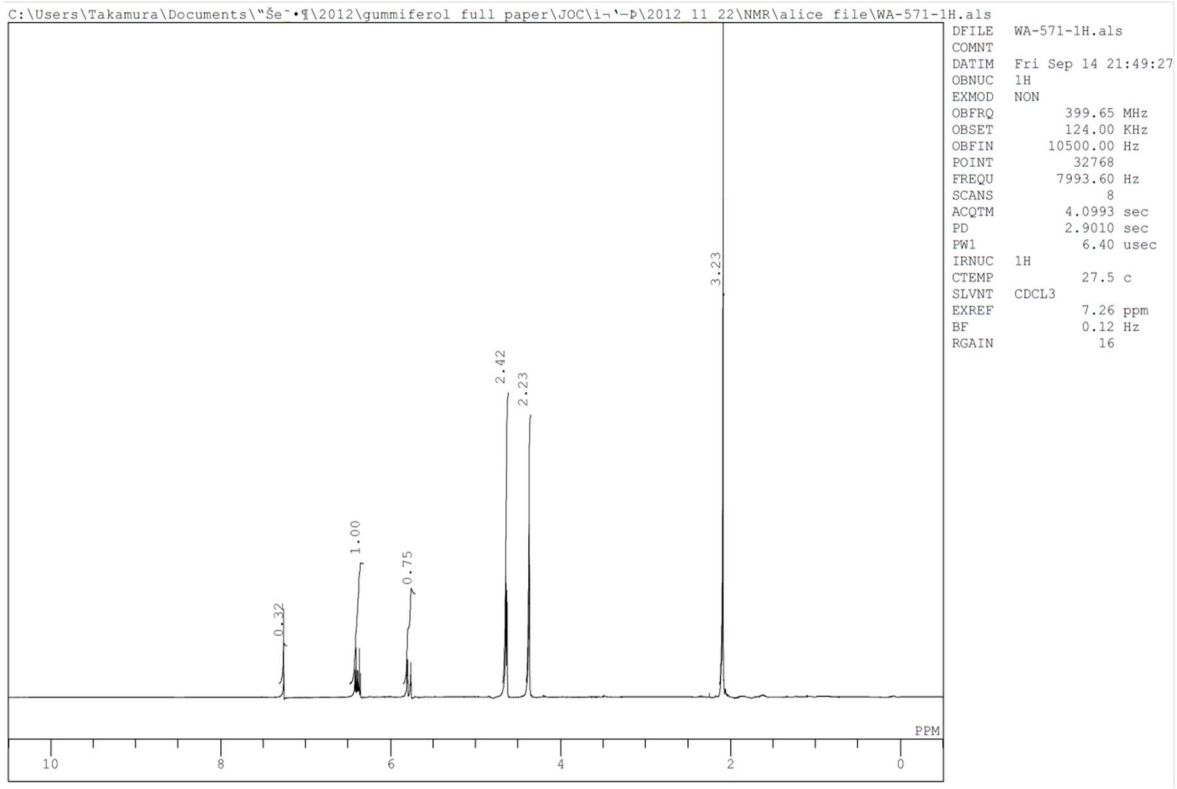
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **29**



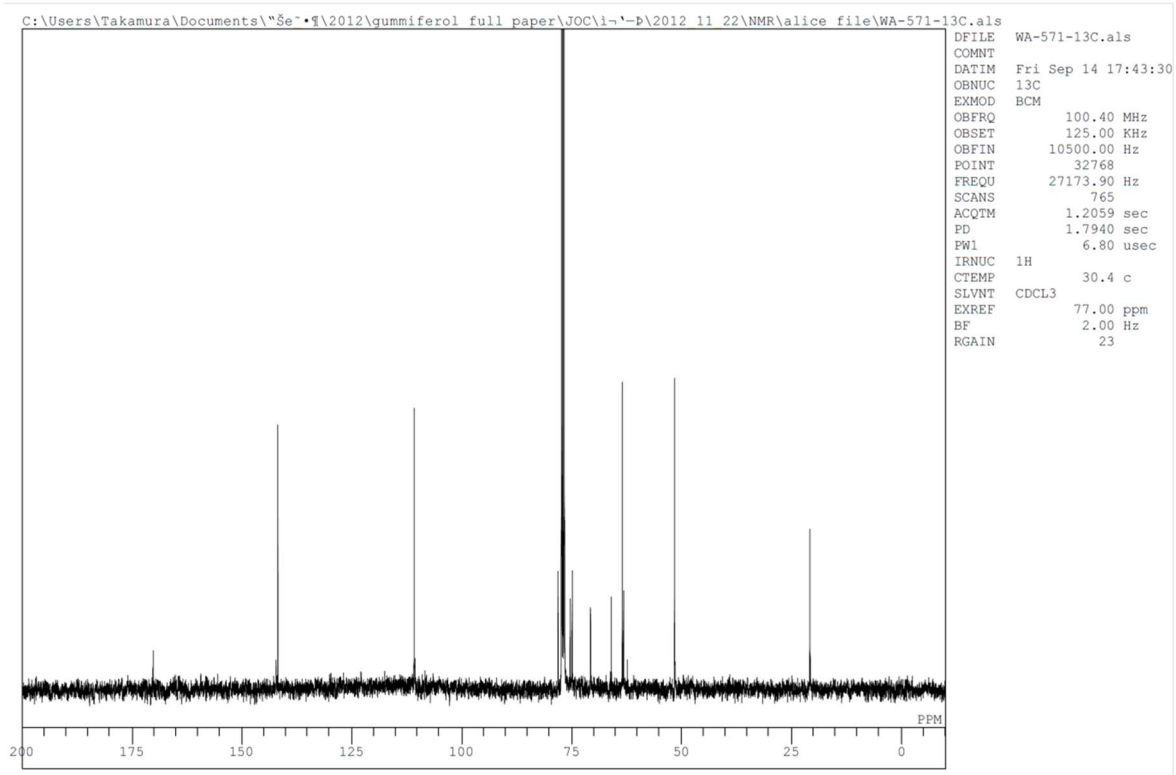
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **29**



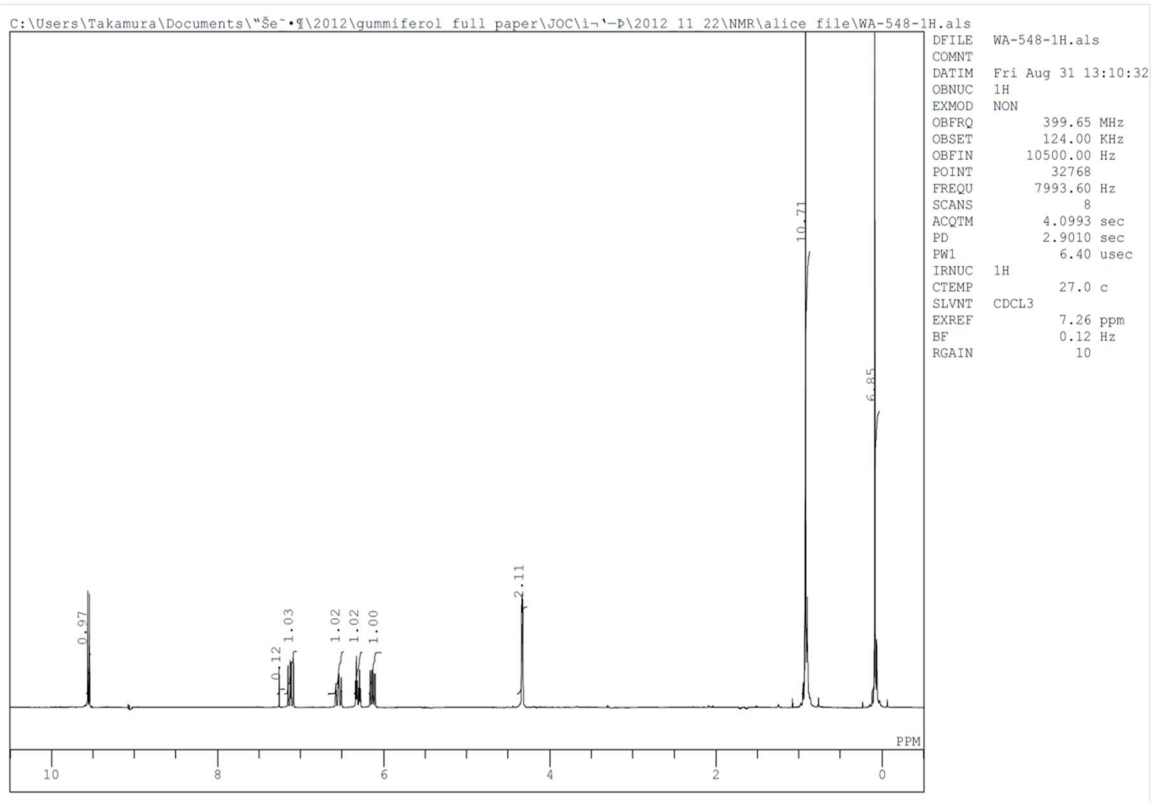
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **30**



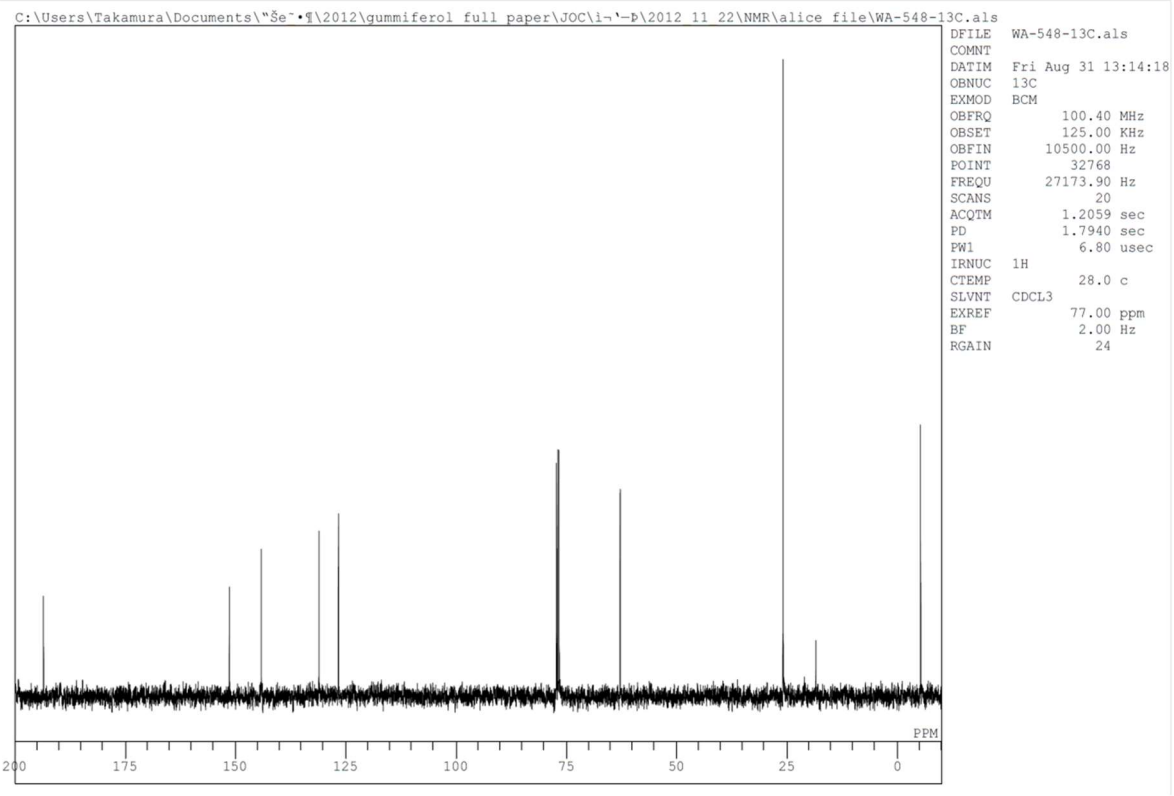
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **30**



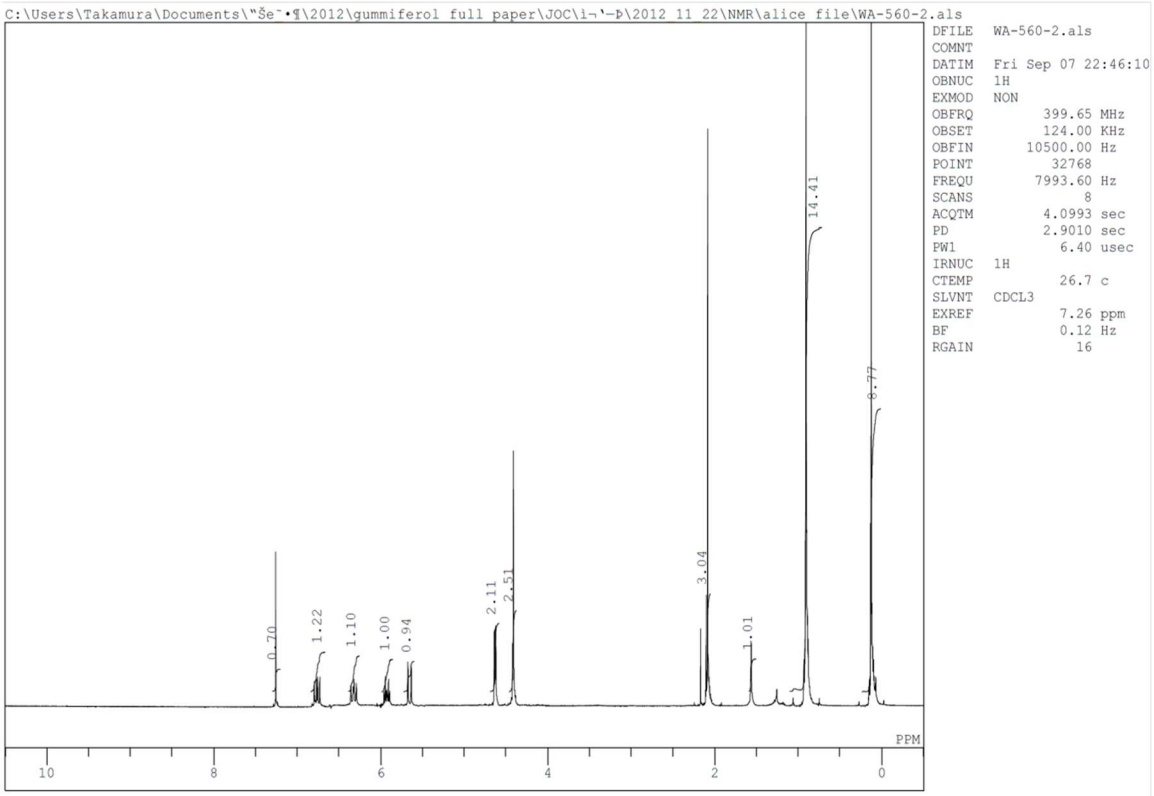
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **31**



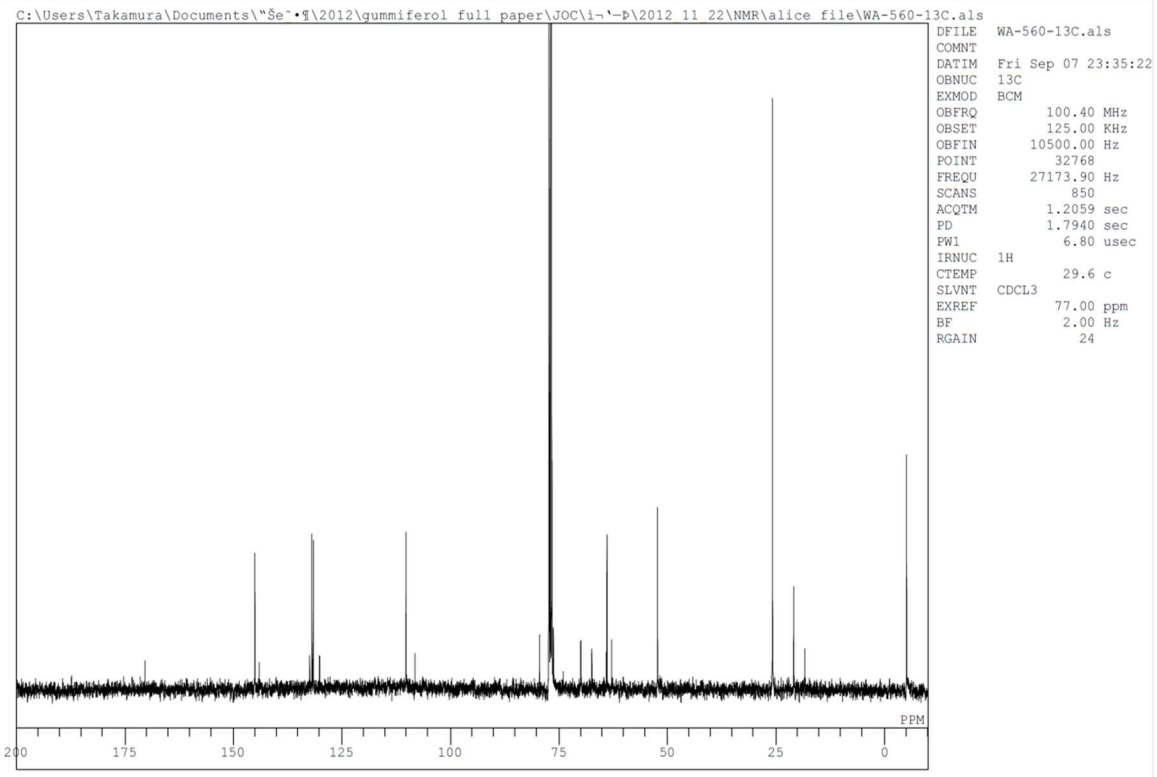
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **31**



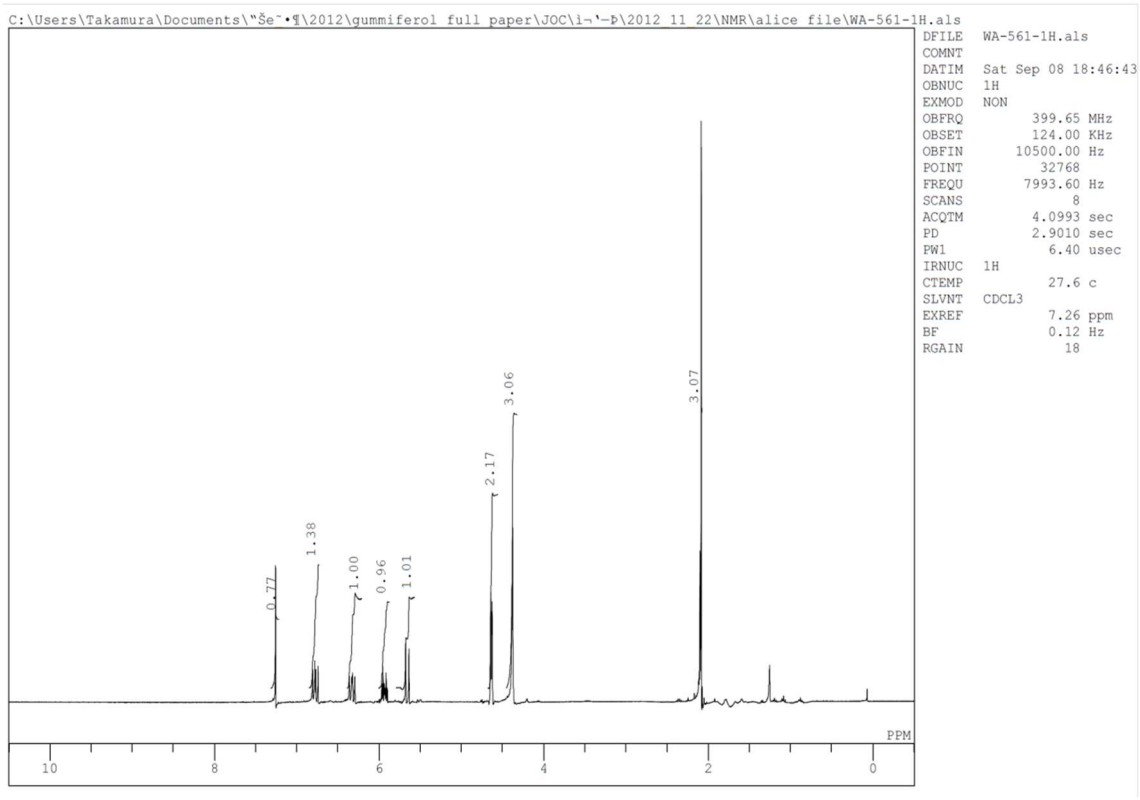
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **32**



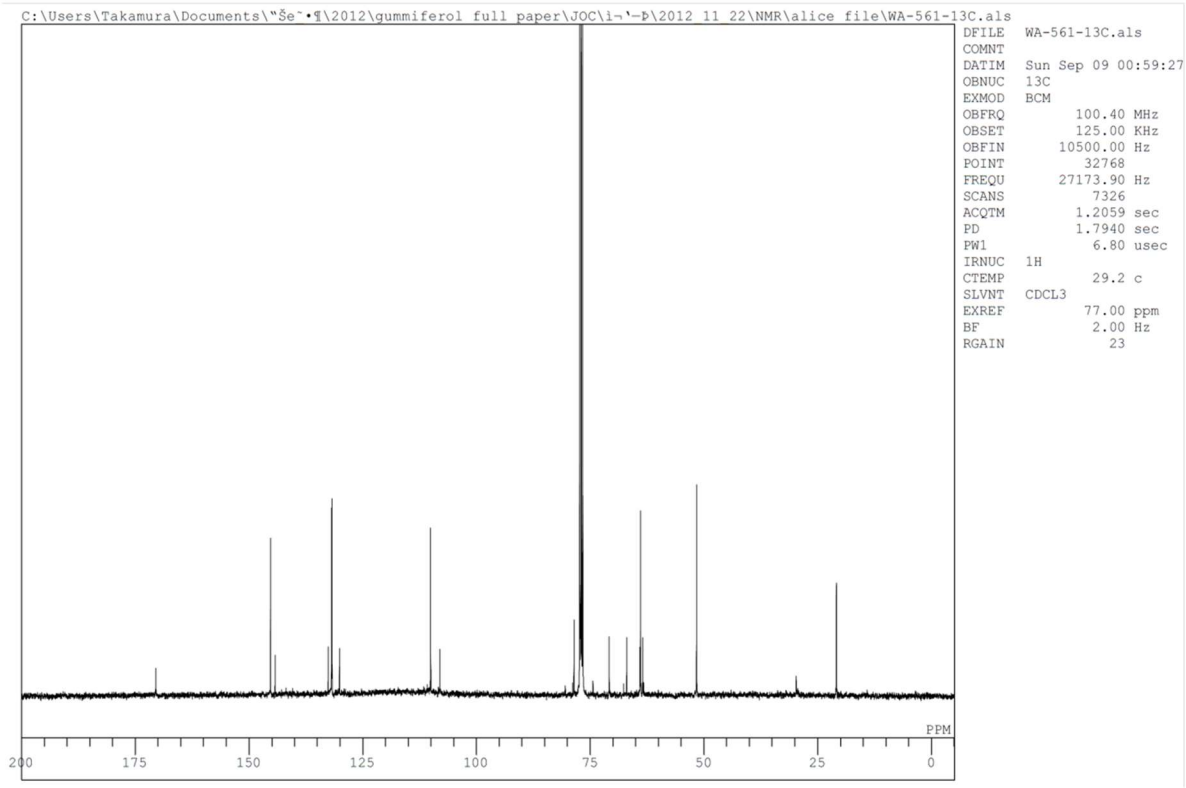
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **32**



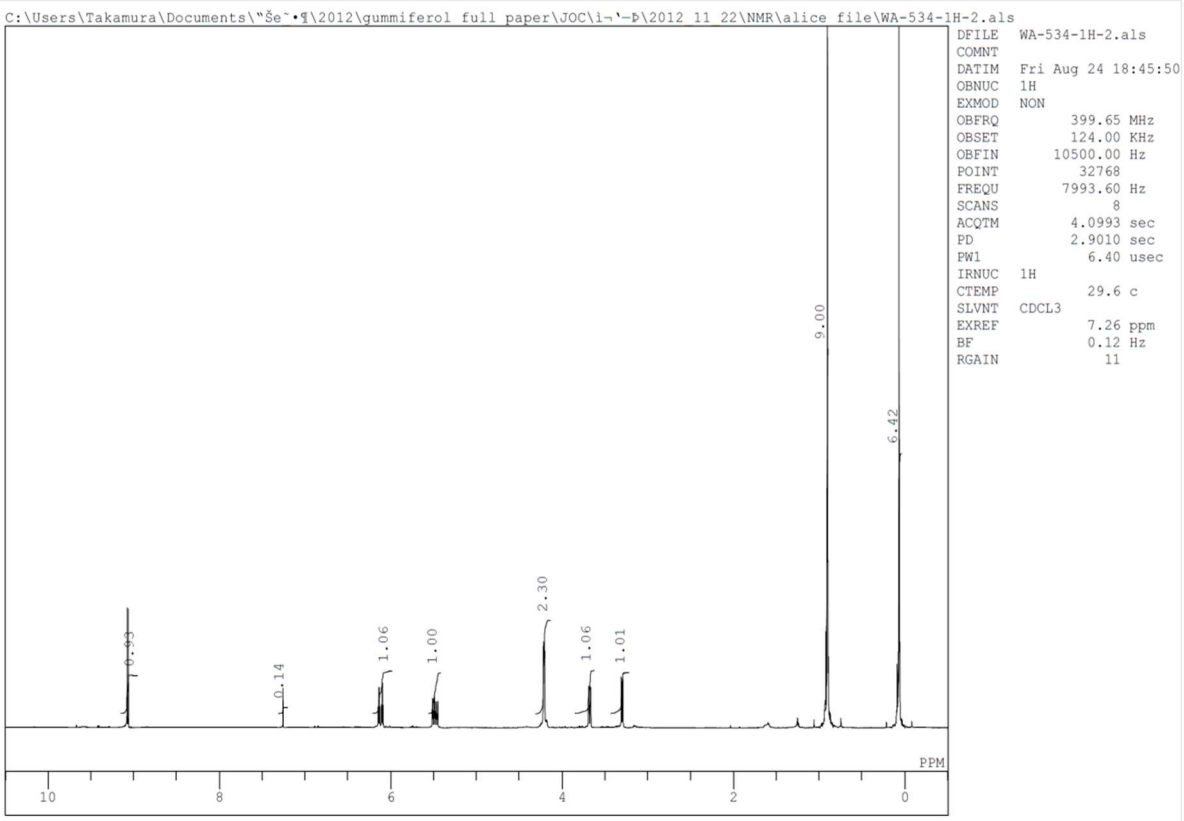
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **33**



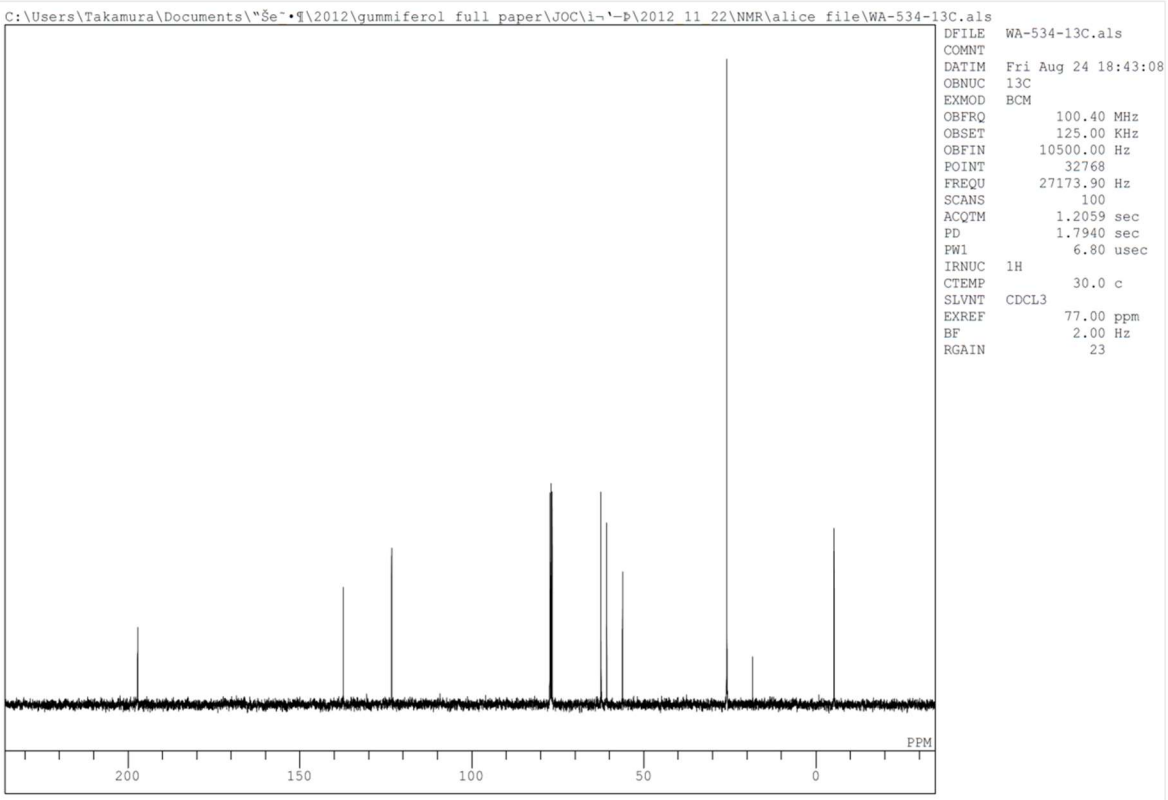
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **33**



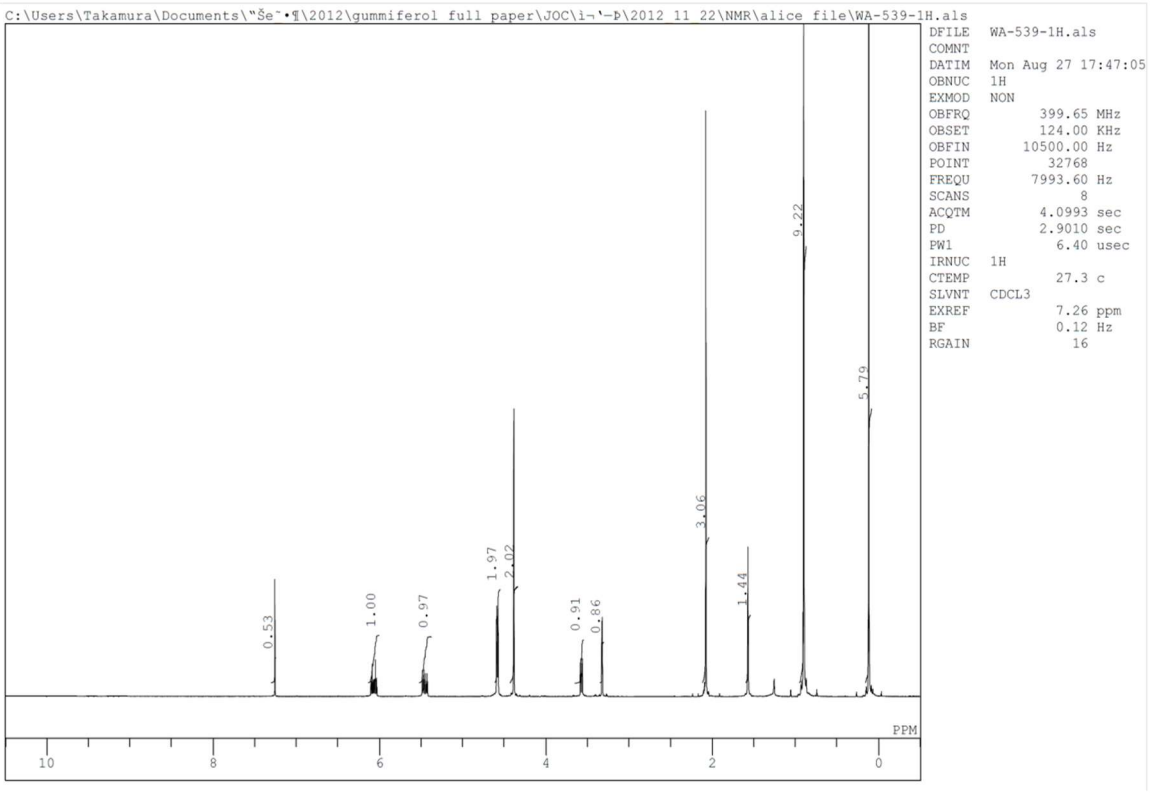
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **35**



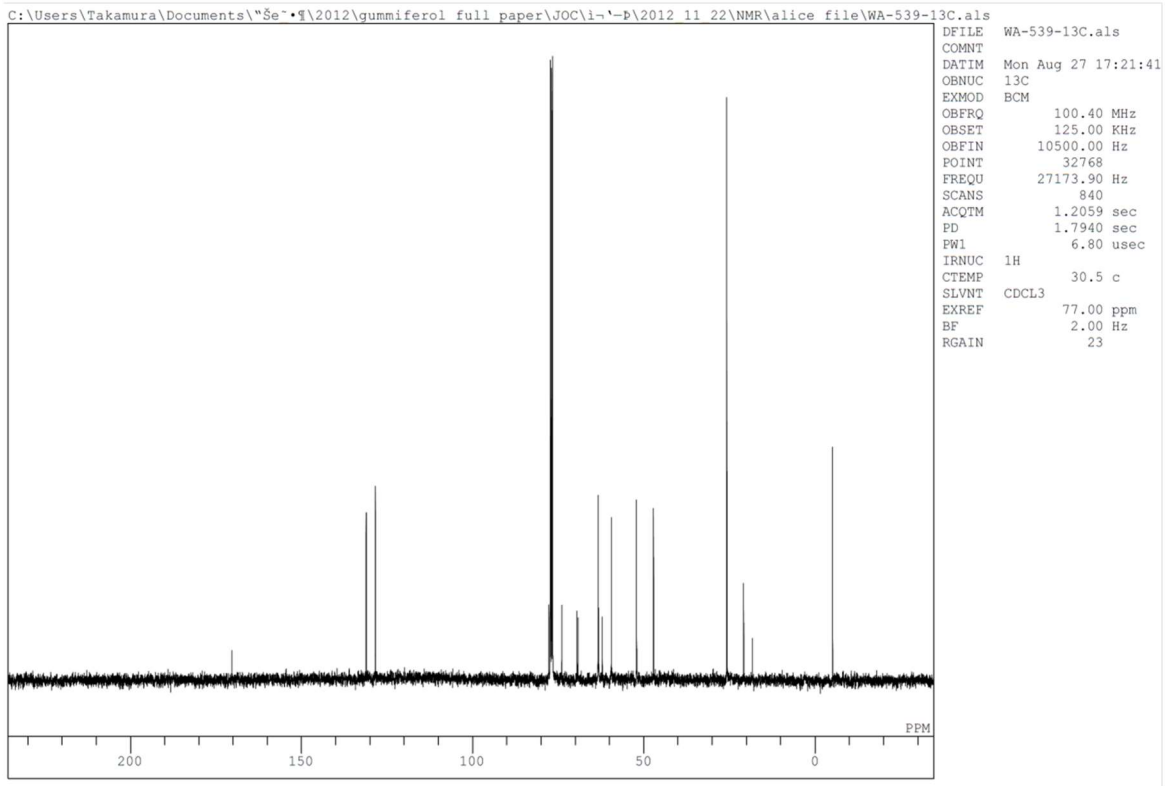
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **35**



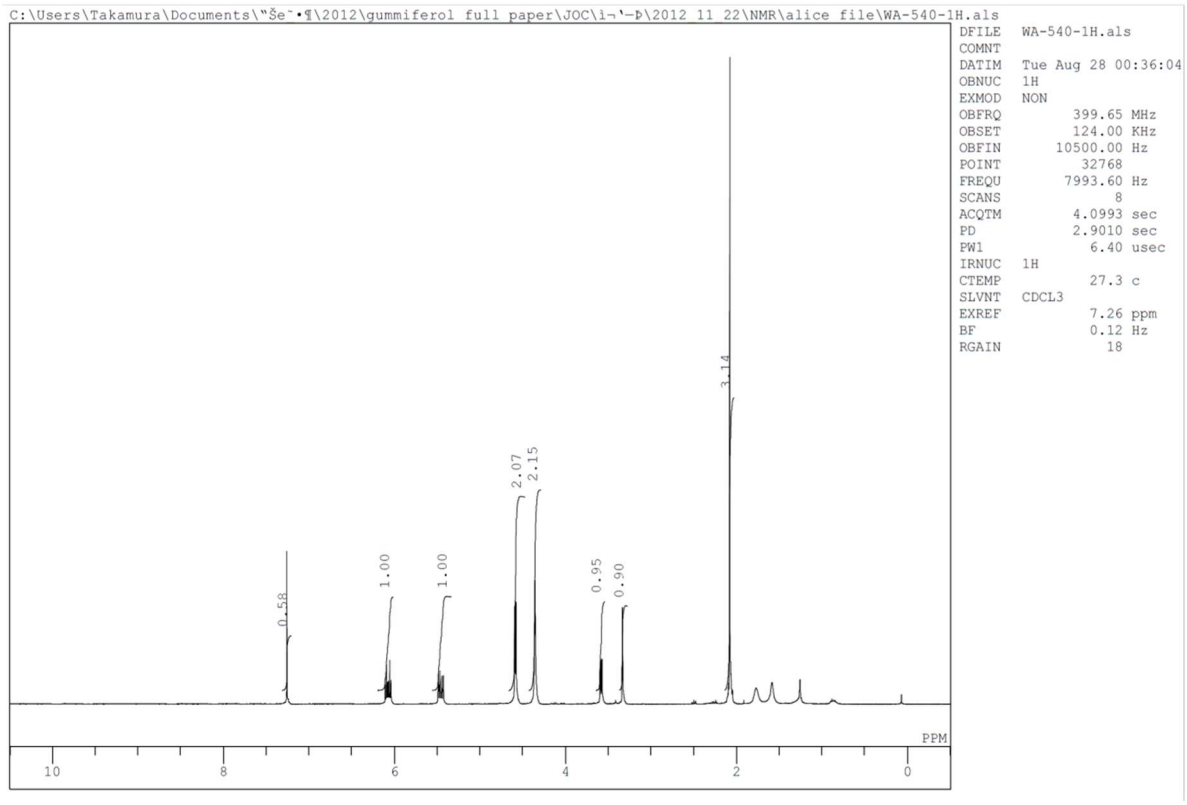
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **36**



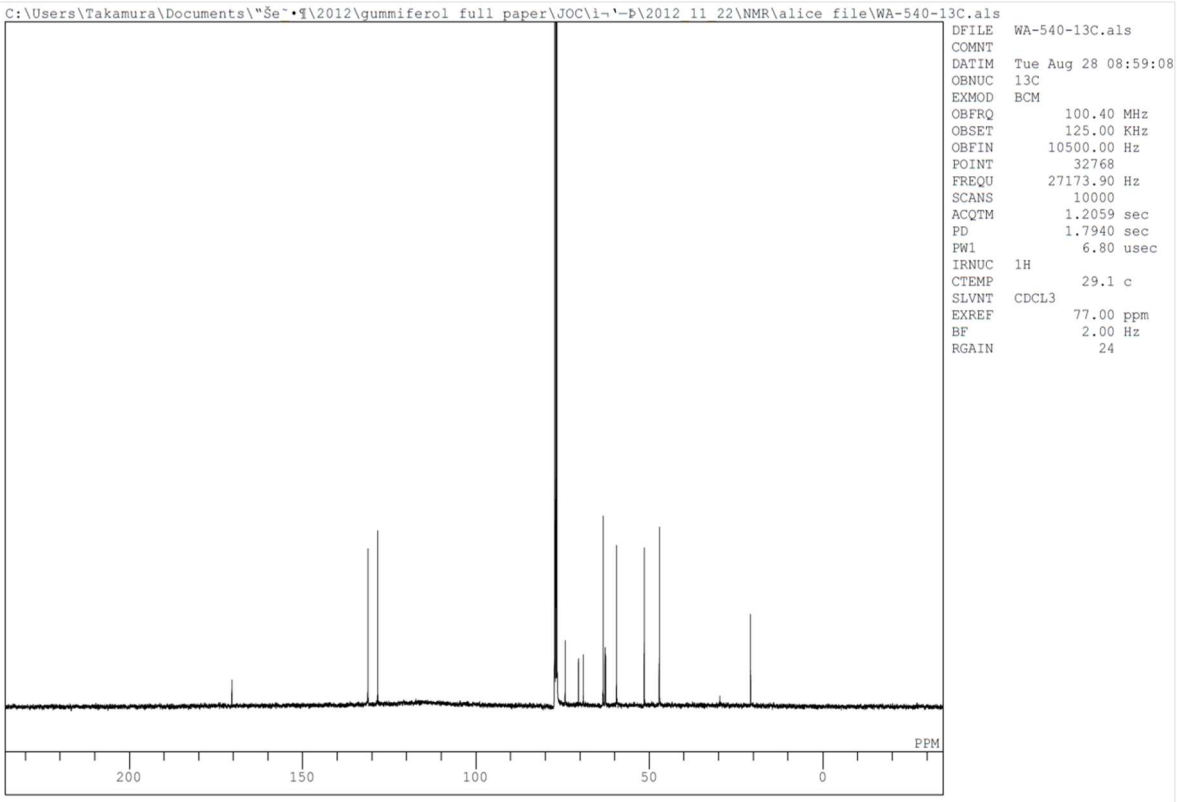
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **36**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **37**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **37**



第3章　　シンビオジノライドC1–C13フラグメントの立体発散的合成と相対立体配置

3 – 1　　序論

シンビオジノライド(**1**) は、扁形動物 *Amphiscolops* sp.に共生する渦鞭毛藻 *Symbiodinium* sp.より単離れされた分子量2860のポリオールマクロライドである[1] (**Figure 3-1**)。この化合物の生物活性作用として、N型カルシウムチャネル開口活性(7 nM)、COX-1 阻害活性(2 μM)、およびMT-4細胞に対する抗HIV活性(EC_{50} 0.18 μM, CC_{50} 0.89 μM)が挙げられる。シンビオジノライド(**1**)の平面構造は、詳細な NMR 解析により解明されている。しかし、61 の立体中心をもち、複雑な分子構造であるため、**1** の立体構造は、いまだ解明されていない。そのため、当研究室ではシンビオジノライドの構造決定を目的とし、分解と合成の両面から研究を進めている。その一環として、筆者は、シンビオジノライドC1–C13フラグメントの合成について検討した。本章では 8 つの可能なジアステレオマーのうち、4つのジアステレオマーの立体発散的かつ立体選択的合成と、本フラグメントの相対立体配置の決定について述べる。

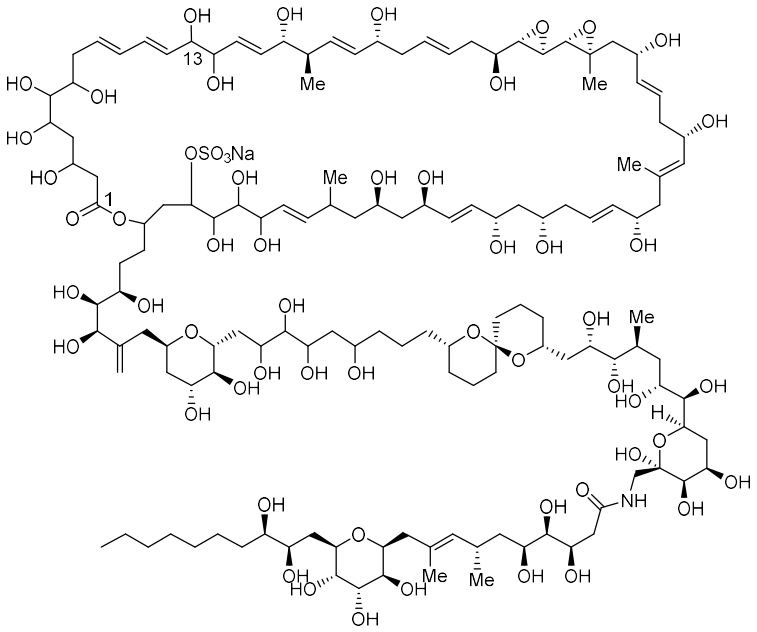
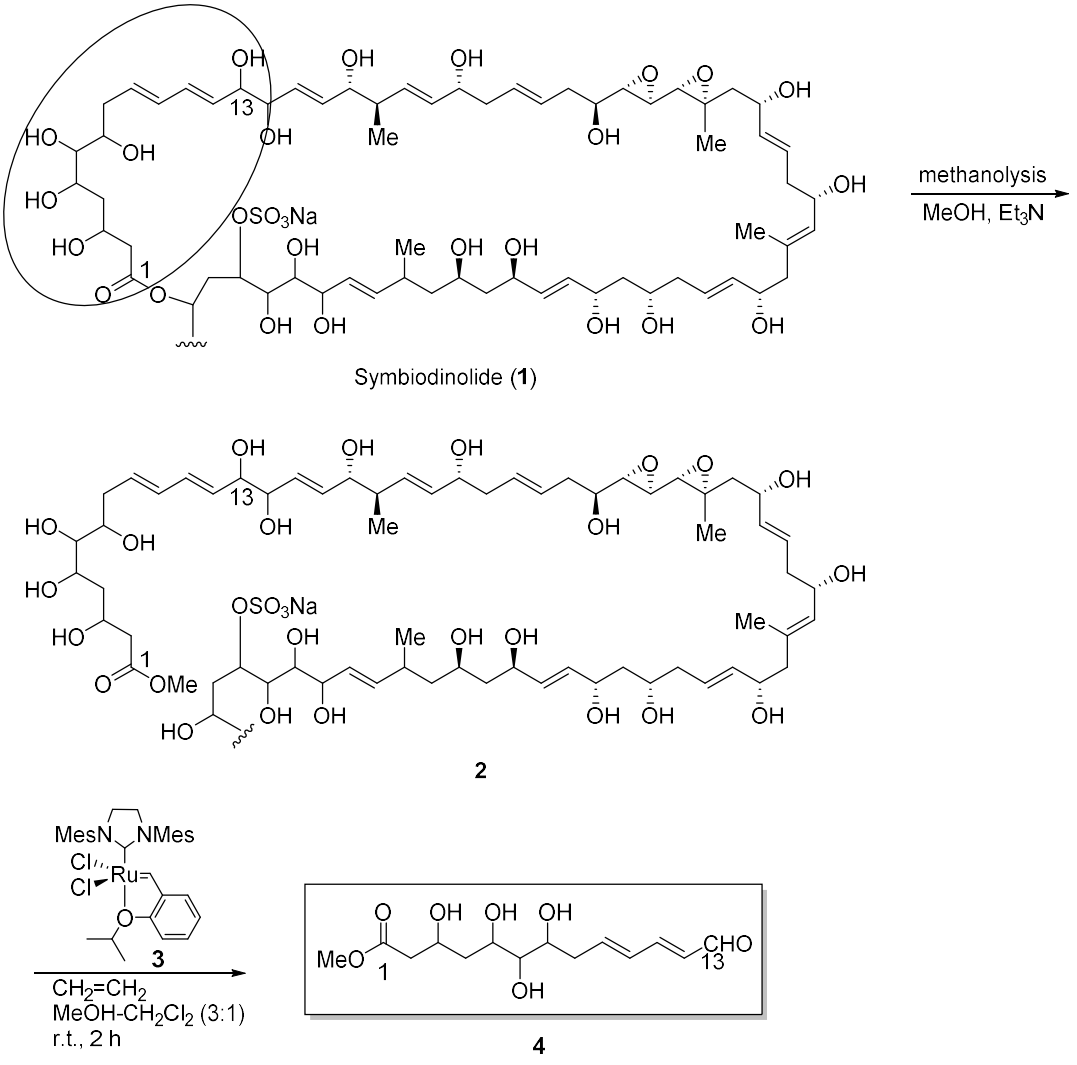


Figure 3-1. Structure of symbiodinolide (**1**).

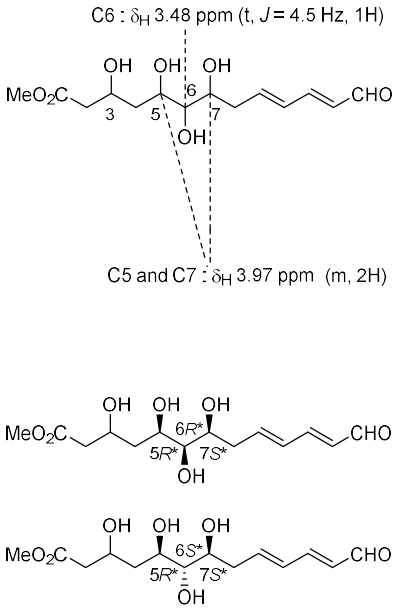
C1–C13 フラグメントの分解反応について説明する[2](**Scheme 3-1**)。シンビオジノライドは、巨大な分子量と高度に酸素官能基化された立体構造により、構造決定が困難な部位が多数存在する。そのため、構造決定を行うにはシンビオジノライドに対し分解反応を行い、より低分子量化させた分解生成物とする必要がある。すなわち、シンビオジノライドに対し、メタノール溶媒中トリエチルアミンを用いてエステル部位を開裂させると **2** が得られ、その後に第二世代 Hoveyda–Grubbs 触媒 **3** 存在下、エチレンガスを用いることにより分解生成物として C1–C13 フラグメント **4** を得ることが出来た。本フラグメントは、62 員環マクロラクトン部位の一部に相当する。分子量は 302 であり、特徴として三つの連続する不斉点を含め、合計四つの不斉炭素を有するため、構造決定が非常に困難な部位である。

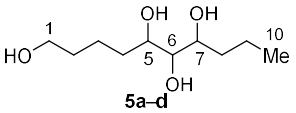


Scheme 3-1. Degradation of Symbiodinolide (**1**)

3 – 2　　ユニバーサル NMR データベース法を用いた候補化合物の選定

ユニバーサルNMRデータベース法を用いた構造の推定について示す[3] (**Figure 3-2**)。C1–C13 フラグメントは、合計 4 つの不斉炭素を有するため候補化合物として 8 種類のジアステレオマーが考えられる。合成によりこれらすべての立体異性体を作り分けるのは非常に困難である。そこで、ユニバーサル NMR データベース法を用いて相対立体配置の推定を行い、その後合成によって構造決定を行うこととした。ユニバーサル NMR データベース法について説明する。この方法は、連続する酸素官能基が存在する鎖状部位の立体配置を、スペクトルデータの比較を行うことにより推定する方法である。すなわち、本フラグメントの C5–C7 位のプロトンのカップリング定数および化学シフト値を読み取った結果、C5 および C7 位は 3.97 ppm、C6 位は 3.48 ppm であった。さらに、C5–C6 位 および C6–C7 位 のビシナルカップリング定数は、共に 4.5 Hz であった。これを、モチーフとなるトリオールのデータに当てはめた。その結果、化学シフト値 (**Table 3-1**)、および、カップリング定数(**Table 3-2**)の一致により(5*R**,6*R**,7*S**) もしくは (5*R**,6*S**,7*S**) の立体構造を有していると推定できた。なお、C3 位に関しては、推定することは出来なかった。





5a–d

NMR Database substrates

Table3-1. ^{1}H NMR chemical shifts of triols **5a–d** in D_2O / ppm

podition	**5a** ααα SS	**5b** αβα AA	**5c** ααβ SA	**5d** αββ AS
1	3.63	3.64	3.63	3.63
5	3.76	3.73	3.83	3.71
6	3.36	3.50	3.36	3.36
7	3.76	3.73	3.72	3.84
10	0.93	0.93	0.93	0.93

Table3-2. ^{1}H NMR $^{3}J_{H,H}$ of triol **5a–d** in D_2O / Hz

podition	**5a** ααα SS	**5b** αβα AA	**5c** ααβ SA	**5d** αββ AS
5,6	4.5	6.0	3.5	7.0
6,7	4.5	6.0	7.0	3.5

α : down　β : up　S : syn　A : anti

$^{3}J_{H,H}$: vicinal coupling

Figure 3-2. ^{1}H NMR analysis of the C1–C13 degraded product.

以上のように C1–C13 フラグメントの分解生成物に対する構造解析を行った結果、本フラグメントの考えられる 8 つのジアステレオマーから、4 つの候補化合物 **6a**–**6d** に絞り込んだ (**Figure 3-3**)。これら 4 つのジアステレオマーを合成し、それらのスペクトルデータと分解生成物のデータとを比較することで、C1–C13 フラグメントの構造決定を行うこととした。

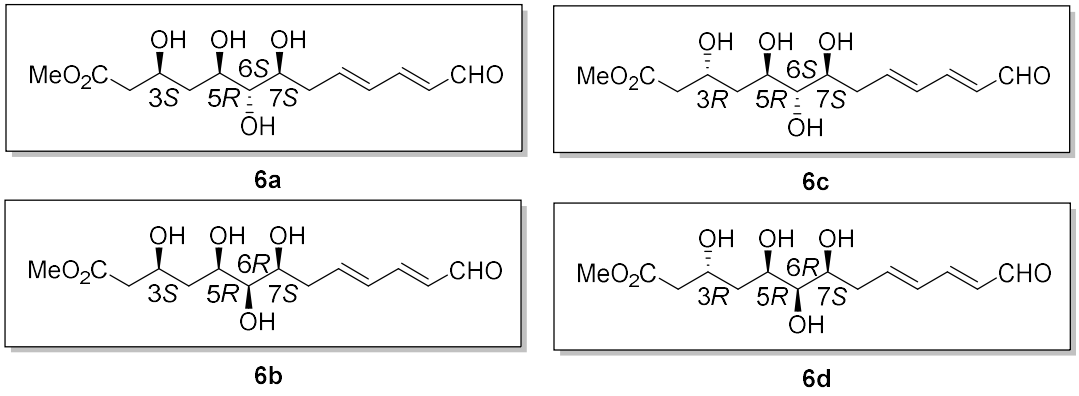
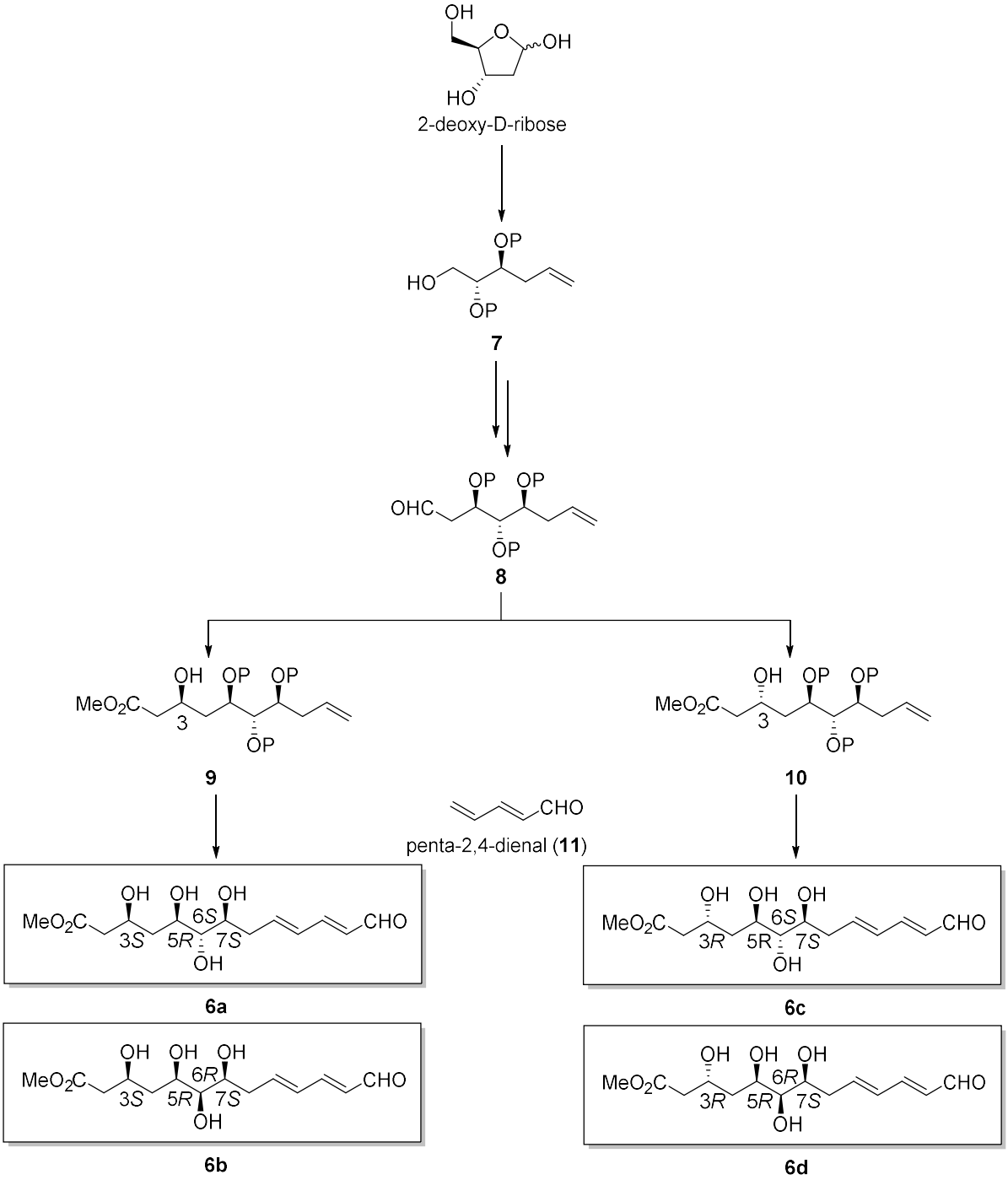


Figure 3-3. Four candidate compounds of the C1–C13 fragment.

3－3　　クロスメタセシスを鍵反応とした合成の検討

3－3－1　合成戦略(1)

C1–C13 フラグメントは求核剤に対して非常に不安定な α,β,γ,δ-共役アルデヒドが存在する。そこで、本フラグメントを合成するにあたり、合成の終盤でα,β,γ,δ-共役アルデヒド部位を導入することで、合成上考えられる種々の問題を克服することにした。そのアプローチとして、クロスメタセシス[4]を鍵反応とした合成を計画した。その合成経路について説明する(**Scheme 3-2**)。出発物質である 2-deoxy-D-ribose より末端オレフィン部位を有するアルコール **7** を合成する。その後、不斉アルドール反応を用いて増炭し **8** を合成することとした[5]。アルデヒド **8** に対し、アルドール反応を用いてアルコール **9**–**10** を作り分けることを想定した。**9** に対し、保護基の除去および penta-2,4-dienal (**11**)[6] とのクロスメタセシスを行い目的のテトラオール **6a** を合成することを想定した。また、**9** に対し、C6 位の立体反転を行った後、保護基の除去および penta-2,4-dienal (**11**)とのクロスメタセシスを行い **6b** を合成出来ると考えた。さらに、**10** に対し、前述と同じ経路で **6c**、**6d** を合成することを想定した。まずは **6a** の合成を検討した。

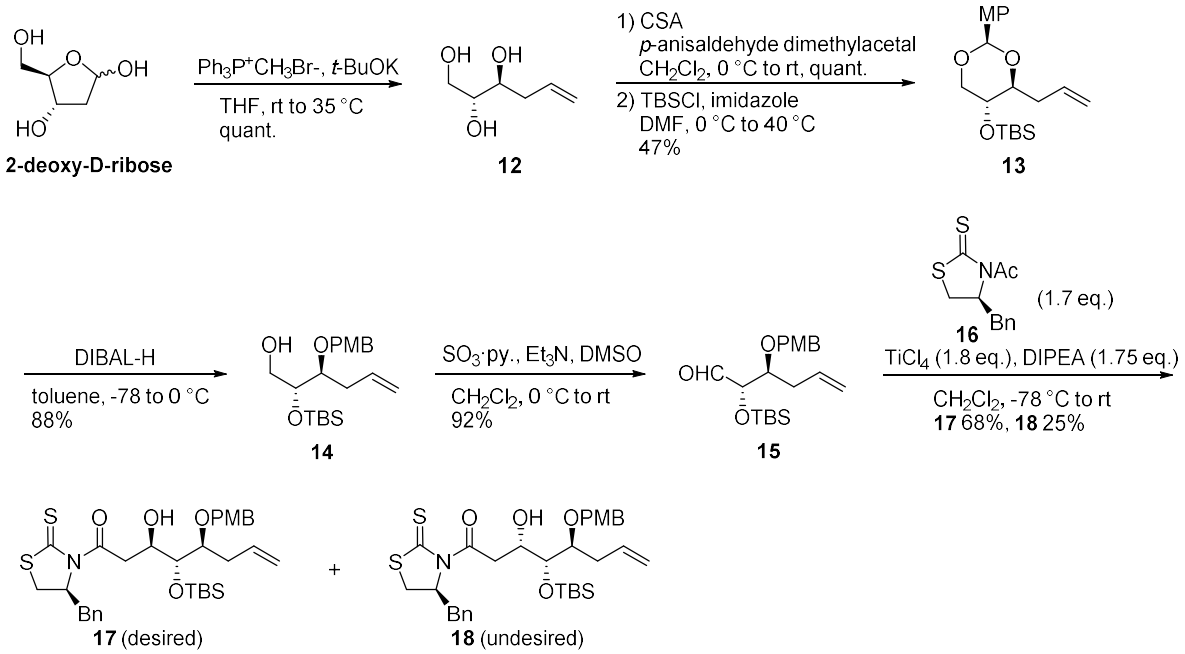


Scheme 3-2. Synthetic Plan of the C1–C13 Fragment

3－3－2　クロスメタセシス前駆体の合成

クロスメタセシスによるジエン部位の導入に先だって、クロスメタセシス前駆体となる末端アルケンの合成を行った。カップリング体 **17** の合成について示す(**Scheme 3-4**)。出発物質である 2-deoxy-D-ribose に対し Wittig 反応により一炭素増炭し、トリオール **12** へ変換した。続いて、アセタール保護を行った後、2級ヒドロキシ基を TBS 保護することで保護体 **13** を得た。保護体 **13** に対し、DIBAL-H を用いた位置選択的なアセタール開裂を行いアルコール **14** とした。アルコールを Parikh–Doering 酸化を行いアルデヒド **15** とした後に、**16** との不斉アルドール反応を行いカップリング体 **17** および **18** をそれぞれ 68%、25%で合成した。

Scheme 3-4



カップリング体 **17** の立体化学の確認について示す(**Figure 3-4**)。**17** の C6 位の立体化学を改良モッシャー法により確認しようと試みた。しかし、^{1}H NMR データが複雑なため、構造確認には至らなかった。そこで、不斉補助基をワインレブアミドへと変換した後に立体化学の確認を行うこととした[7] (**Scheme 3-5**)。その結果、**17** は望みの立体化学を有していることを確認した。

Scheme 3-5

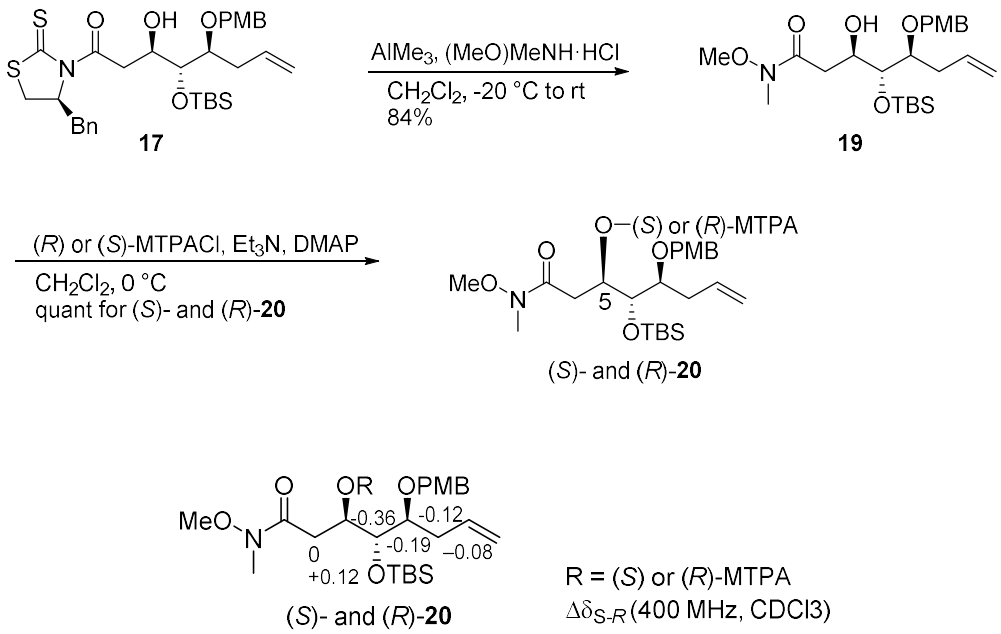
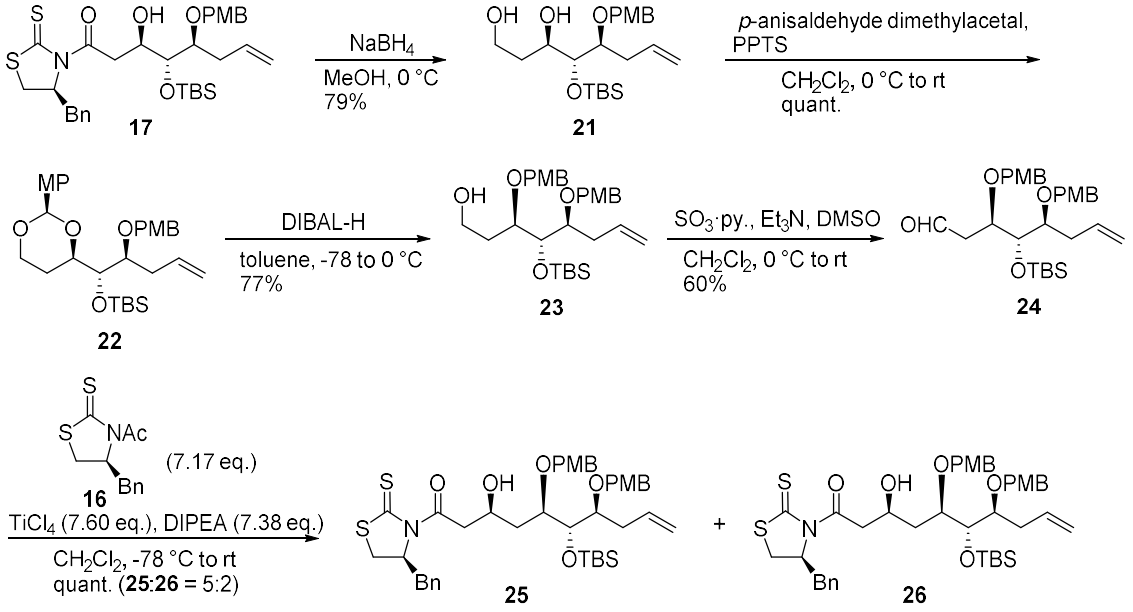


Figure 3-4. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**20**.

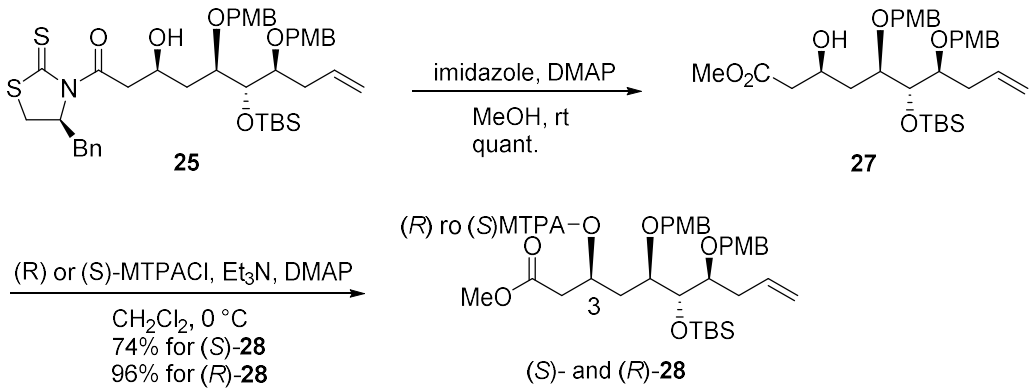
カップリング体 **25** の合成について示す(**Scheme 3-6**)。カップリング体 **17** のヒドロキシ基の立体化学の確認が終わったのでさらなる変換を行った。**17** に対し、$NaBH_4$ を用いて不斉補助基を除去しジオール **21** を得た。得られた **21** に対し、アセタール化を行い保護体 **22** へと変換した。続いて、DIBAL-H を用いてアセタールの位置選択的な開裂を行い[8] アルコール **23** とした。アルコールを Parikh–Doering 酸化によりアルデヒド **24** とした後に、不斉アルドール反応を行いカップリング体 **25** および **26** を定量的に得た。立体選択性は **25**：**26** が 5：2 と課題は残る結果であったが、現段階では立体選択性の改善は行わずに変換を進めることとした。

Scheme 3-6



カップリング体 **25** の C3 位の立体化学の確認について示す。**25** に対し、塩基性条件下メタノールを作用させることでメチルエステル **27** へと変換した。その後前述と同様に改良モッシャー法により立体化学の確認を行った(**Scheme 3-7**)。その結果、**25** は望みの立体化学を有していることを確認した(**Figure 3-5**)。

Scheme 3-7



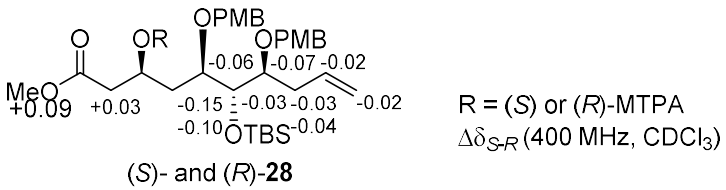


Figure 3-5. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**28**.

3−3−3　クロスメタセシスによるジエン部位導入の検討

クロスメタセシスを用いた C1–C13 フラグメントの基本骨格の構築に先立って、クロスメタセシスに用いる触媒の検討を行った[9]。モデル化合物 **33** と penta-2,4-dienal (**11**)とのクロスメタセシスにおいて、第一世代 Grubbs 触媒や、第一世代 Hoveyda–Grubbs 触媒等、種々条件検討した(**Scheme 3-8**、**Table 3-3**、**entry 3**)。その結果、第二世代 Hoveyda–Grubbs 触媒を用いた際に、低収率ではあるが望みのカップリング体を得ることが出来た。次に第二世代 Hoveyda–Grubbs 触媒を用いた末端オレフィンと penta-2,4-dienal (**11**)とのクロスメタセシスを検討した(**Scheme 3-8**、**Table 3-3**)。末端オレフィンを有する化合物として、立体障害の小さいトリオール **32** を用いて反応を行った。塩化メチレン溶媒下、40 °C で反応を行ったが、反応が汚くなり、望みのカップリング体 **30** は得られなかった(entry 1)。溶媒をトルエンに変え、100 °C まで加熱したが、**32** はほとんどトルエンには溶解せず、カップリング体は得られなかった(entry 2)。保護体 **33** とのクロスメタセシスでは、塩化メチレン溶媒下 40 °C で反応を行ったところ、18%と低収率ではあるが、目的のカップリング体 **30** を合成することが出来た(entry 3)。7 割の原料回収があったため、溶媒をトルエンに変え 100 °C まで加熱したが収率の改善は見られなかった(entry 4)。最終段階でのジエン部位の導入を想定し、末端オレフィンを有する化合物として **34** を用いて反応を行った。トルエン、1,2-ジクロロエタンをそれぞれ溶媒として用い反応を行ったが、原料が回収されるのみであった(entry 5,6)。

Scheme 3-8

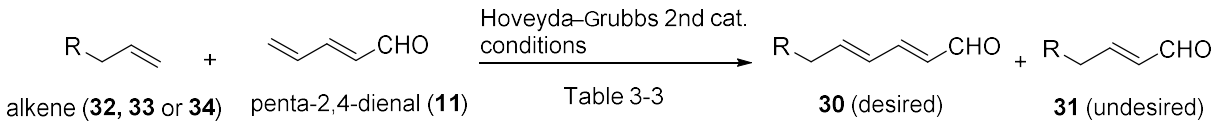
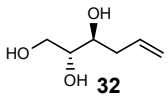
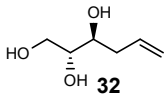
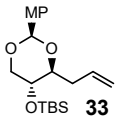
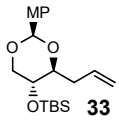
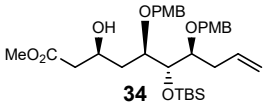
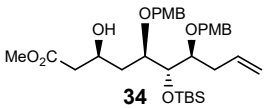


Table 3-3. Cross metathesis of alkene with **11**

entry	alkene	solvent	temp.	results
1	 **32**	CH_2Cl_2	rt to 40 °C	unknown product
2	 **32**	toluene	rt to 100 °C	unknown product
3	 **33**	CH_2Cl_2	rt to 60 °C	recovery of SM (73%) **30** (18%), **31** (9%)
4	 **33**	toluene	rt to 90 °C	recovery of SM (40%) **31** (22%)
5	 **34**	toluene	rt to 90 °C	recovery of SM (67%)
6	 **34**	1,2-dichloroethane	rt to 90 °C	recovery of SM (65%)

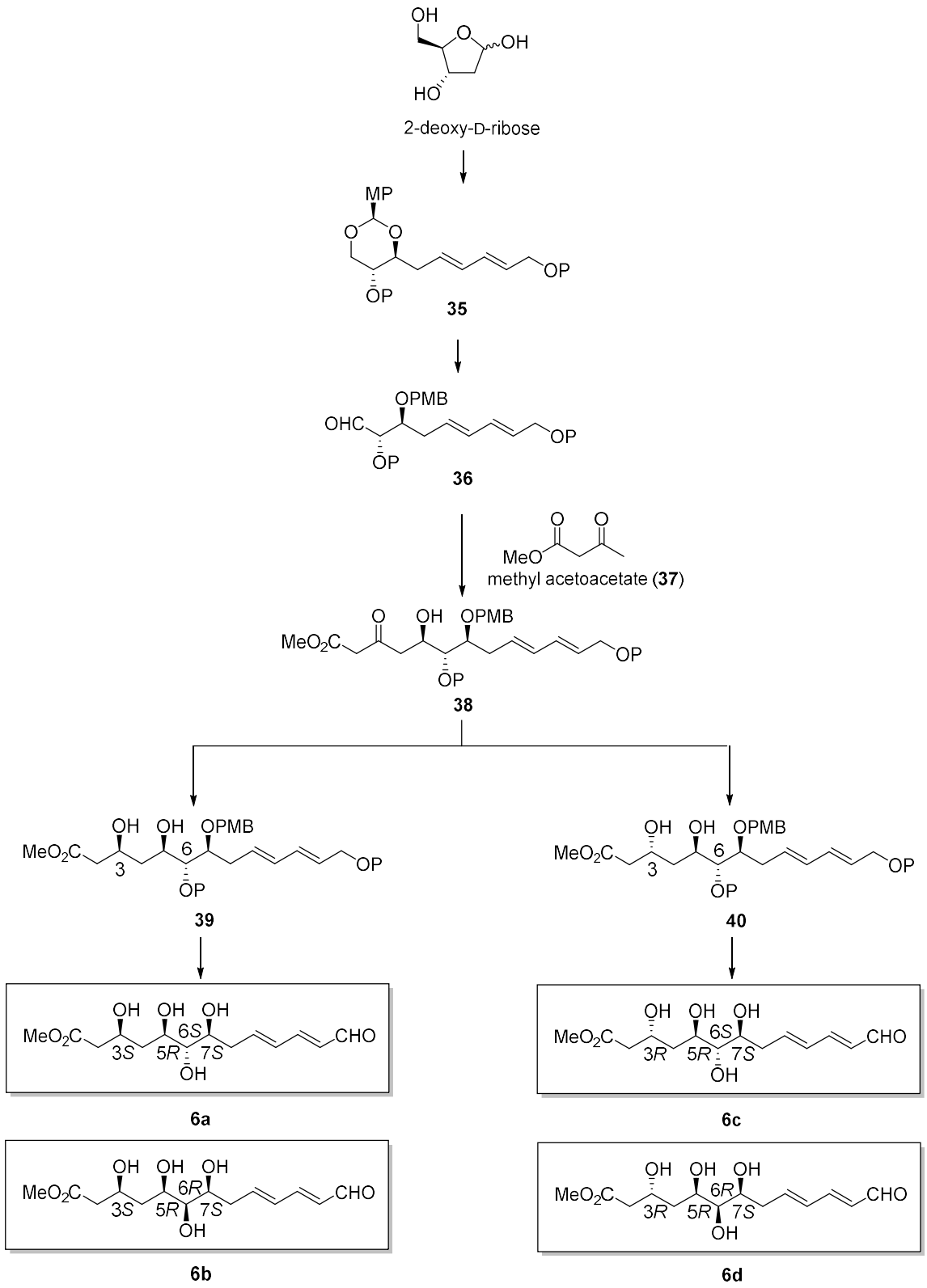
以上の結果より、本フラグメントを合成するにあたって、クロスメタセシスを用いたジエン部位の導入は困難であると判断した。そこで逆合成解析を考え直し、別経路での合成を行うこととした。その際、α,β,γ,δ-共役アルデヒド部位は合成の終盤で導入すること、より効率的に基本骨格を構築することを考慮した。

3－4　　メチルアセトアセテートを用いた基本骨格の構築

3－4－1　合成戦略(2)

C1–C13 フラグメントの新たな合成経路として、メチルアセトアセテートを用いて基本骨格を構築することを計画した [10]。その合成経路について説明する(**Scheme 3-9**)。出発物質である 2-deoxy-D-ribose よりフラグメント右側を構築し **35** を合成する。その後、位置選択的なアセタール開裂と生じたヒドロキシ基の酸化を行い、カップリング前駆体 **36** へと誘導することにした。アルデヒド **36** に対し、methyl acetoacetate(**37**)とアルドール反応を行い C1–C13 フラグメントの基本骨格を構築することとした。得られたカップリング体 **38** に対し、立体選択的な還元 [11] を行い、**39**–**40** を作り分けることとした。**39** に対し、保護基の除去と官能基選択的酸化により目的のテトラオール **6a** を合成することを想定した。また、**39** に対し、C6 位の立体を反転させたのち、保護基の除去および官能基選択的な酸化を行い **6b** を合成することとした。**40** に対し、前述と同様の変換を行いテトラオール **6c** 及び **6d** を合成することを想定した。初めに **6a** の合成を検討した。

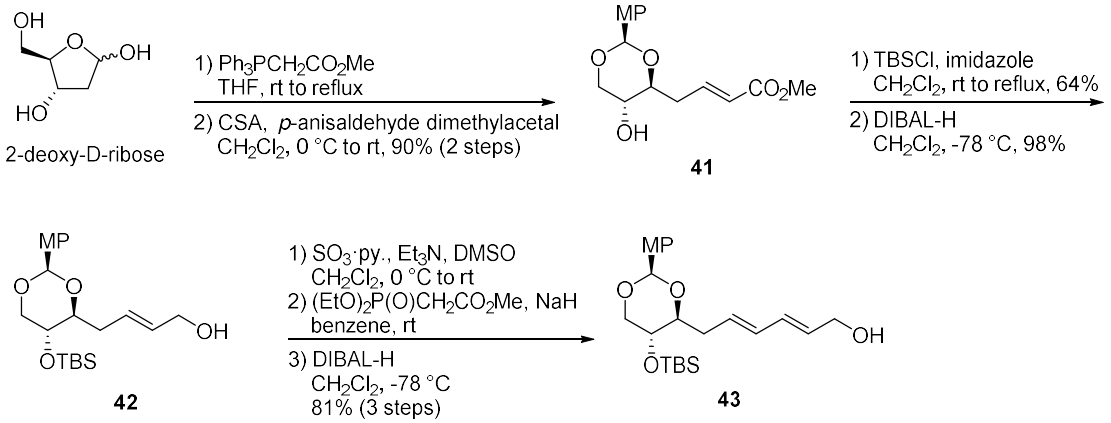
Scheme 3-9. Synthetic Plan of the C1–C13 Fragment



3－4－2　C5–C13 フラグメントの合成

アルコール **43** の合成について示す(**Scheme 3-10**)。出発物質である 2-deoxy-D-ribose より、既知の方法でアリルアルコール **42** を合成した[12]。得られた **42** に対し、Parikh–Doering 酸化を行いアルデヒドとし、次に Horner–Wadsworth–Emmons 反応を行い増炭し、DIBAL-H を用いて、エステル部位の還元を行うことで、アルコール **43** を合成した。

Scheme 3-10



アルコール **43** のヒドロキシ基の保護を行った(**Scheme 3-11**)。アルコール **43** に対する PMB 保護(entry 1)、TBS 保護(entry 2)、TBDPS 保護(entry 3)は問題なく進行した(**Table 3-4**)。

Scheme 3-11

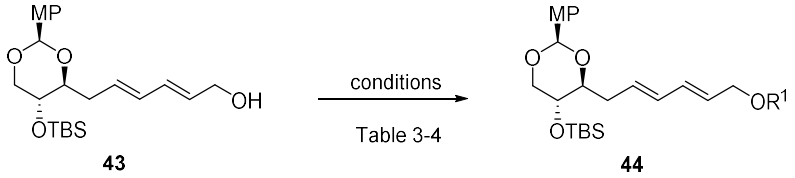


Table 3-4. Protection of alcohol **44**

entry	conditions	yields (%)
1	PMBCl, NaH, THF, 0 °C to reflux	77 (R^1 = PMB)
2	TBSCl, imidazole, CH_2Cl_2, rt	94 (R^1 = TBS)
3	TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt	quant. (R^1 = TBDPS)

保護体 **44** に対し、位置選択的なアセタール開裂を行い **45** を合成すべく検討を行った(**Scheme 3-12**)。まず、PMB 保護体 **44** に対するアセタール開裂を行った(**Table 3-5**)。塩化メチレン溶媒下、–78 °C から–30 °C で反応を行ったが、目的のアルコール **45** は低収率で得られるのみで、副生成物として 2 級 TBS 基が除去された **46** が 13%生じるという結果であった(entry 1)。また、溶媒にトルエンを用い反応温度を 0 °C まで昇温し反応を行ったが収率の改善は見られなかった(entry 2)。次に一級が TBS 基で保護された **44** に対するアセタール開裂を行った。塩化メチレン溶媒下–65 °C から–10 °C で反応を行ったところ、目的のアルコールを 40%とわずかに収率を向上させることが出来た(entry 3)。しかし、一級 TBS 基が除去された **43** が副生成物として得られてきた。トルエン溶媒に変えたところ、反応は促進されたが副生成物が 26%へ増える結果となった(entry 4)。最後に一級が TBDPS 基で保護された **44** に対するアセタール開裂を行った。塩化メチレン溶媒下–65 °C から–10 °C で反応を行ったが収率の改善は見られなかった(entry 5)。溶媒をトルエンに変えたところ、収率は向上し、目的のアルコール **45** を 56%で得ることが出来た(entry 6)。

Scheme 3-12

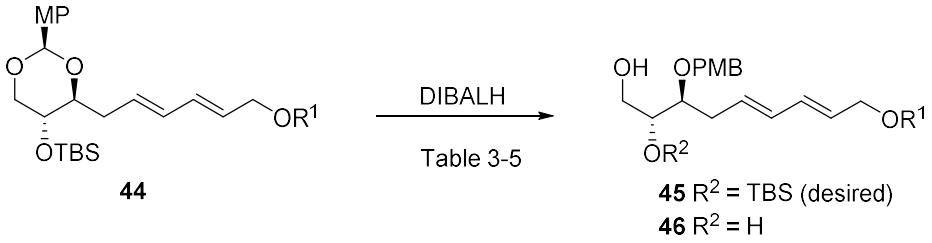


Table 3-5. Cleavage of MP acetal **44**

entry	R^1	solvent	temp.	yields(%) **44** (SM)	**45** (prod)	**46**	**43**
1	PMB	CH_2Cl_2	-78 to -30 °C	49	25	13	-
2	PMB	toluene	-78 to 0 °C	48	22	-	-
3	TBS	CH_2Cl_2	-65 to -10 °C	29	40	-	9
4	TBS	toluene	-65 to -10 °C	16	34	-	26
5	TBDPS	CH_2Cl_2	-65 to -10 °C	63	37	-	-
6	TBDPS	toluene	-65 to -10 °C	31	56	-	-

3－4－3　C1–C13 フラグメントの基本骨格の構築

C1–C13 フラグメントの基本骨格の構築について検討した(**Scheme 3-13**)。一級ヒドロキシ基が TBDPS 保護されたアルコール **45** に対し、Parikh–Doering 酸化を行いアルデヒド **47** を得た。続いてアルデヒド **47** と methyl acetoacetate (**37**)とのアルドール反応について条件検討を行った[10, 13](**Table 3-6**)。この反応は 1.0 当量の methyl acetoacetate (**37**)に対し、2.0 当量以上の塩基を作用させて発生させたジアニオンを求核種としたカップリング反応である。1.0 当量の methyl acetoacetate (**37**)に対し 2.2 当量の LDA を塩基として用い、–60 °C から室温でジアニオンを発生させた後、再び–60 °C へ冷却しアルデヒド **47** を作用させ室温まで昇温させた(entry 1)。その結果、目的のカップリング体 **48** および C5 位の立体異性体 **49** をジアステレオ比 4 : 1 の混合物として 52%の収率で得ることが出来た。選択性の向上を目指し、反応温度を–78 °C に下げたところ反応は完結せず、選択性もほとんど変わらなかった(entry 2)。そこで、塩基を NaH と *n*-BuLi の組み合わせに変え反応を行うこととした(entry 3〜6)。まず、1.2 当量の **37** に対し 2.2 当量の NaH、1.3 当量の *n*-BuLi を 0 °C で段階的に作用させジアニオンを発生させた後、–78 °C へ冷却しアルデヒド **47** を作用させた(entry 3)。しかし、反応は進行せず原料が回収されるのみであった。そこで、1.0 当量のアルデヒド **47** に対し 2.0 当量の methyl acetoacetate (**37**)を用いることとし、それに伴い塩基の当量を NaH(3.0 当量)、*n*-BuLi(2.2 当量)に増やした(entry 4)。すると、94%、ジアステレオ比 6 : 1 でカップリング体 **48** を得ることに成功した。さらなる選択性の向上を目指し、反応温度を–90 °C へ下げたが、反応は完結せず、選択性の改善にも至らなかった(entry 5)。塩基を NaH のみ(5.0 当量)に変え、–78 °C でジアニオンを発生させた後、–95 °C で反応を行なったが原料が回収されるのみであった(entry 6)。塩基を LiHMDS のみ(4.4 当量)、0 °C から室温でジアニオンを発生させた後、–78 °C から室温まで昇温させ反応を行なったが、原料が回収されるのみであった(entry 7)。選択性に課題は残るものの、現段階での最適条件を entry 4 とし、続きの変換を行うこととした。なお、この段階での C5 位の立体化学の確認および、C5 位に関するジアステレオマーの分離は出来なかった。

Scheme 3-13

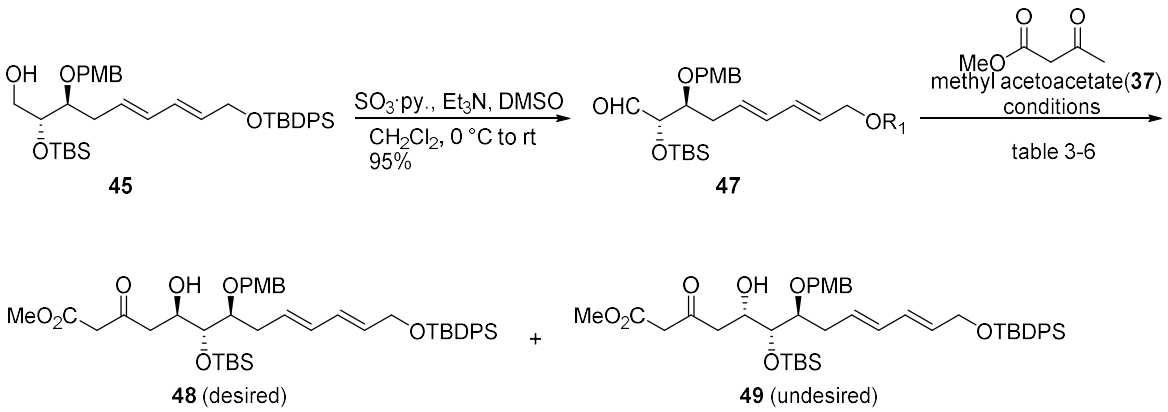


Table 3-6. Optimization of aldol reaction

entry	**37** (eq.)	base	Preparation of dianion temp.	reaction temp.	results (%) **47** (SM)	**48** +**49**
1	1.0	LDA (2.2 eq.)	-60 °C to rt	-60 °C to rt	-	52 (4:1)
2	1.0	LDA (2.2 eq.)	-60 °C to rt	-78 °C	50	29 (4.5:1)
3	1.2	NaH (2.0 eq.) *n*-BuLi (1.3 eq.)	0 °C	-78 °C	92	trace
4	2.0	NaH (3.0 eq.) *n*-BuLi (2.2 eq.)	0 °C	-78 °C	-	94 (6:1)
5	2.0	NaH (3.0 eq.) *n*-BuLi (2.2 eq.)	0 °C	-90 °C	53	39 (5:1)
6	2.0	NaH (5.0 eq.)	0 °C	-95 °C	70	-
7	2.0	LiHMDS (4.4 eq.)	0 °C to rt	-78 °C to rt	43	-

アルドール反応の選択性の発現について説明する。この選択性は polar Felkin-Anh model および cornforth　model にて予想されるものであった[14](**Figure 3-6**)。すなわち、α-alkoxy aldehyde に対する求核攻撃は a に示すように、アルデヒド C=O の π 平面に対し、アルコキシ(OP)が平行に配置された配座が安定であり、図に示すような遷移状態を経て 1,2-*anti* 生成物を与える。この安定化は、形成される σ_{C-C} と σ^*_{C-O} との相互作用によるものである。また、b に示すように、C=O と C－OP との双極子相互作用が最も少なくなるような Cornforth model を適応した場合でも、同様に 1,2-*anti* 生成物を与える。つまり今回の場合は polar Felkin-Anh model および cornforth mode のいずれかも、1,2-*anti* 生成物が立体選択的に得られてくると考えられる。

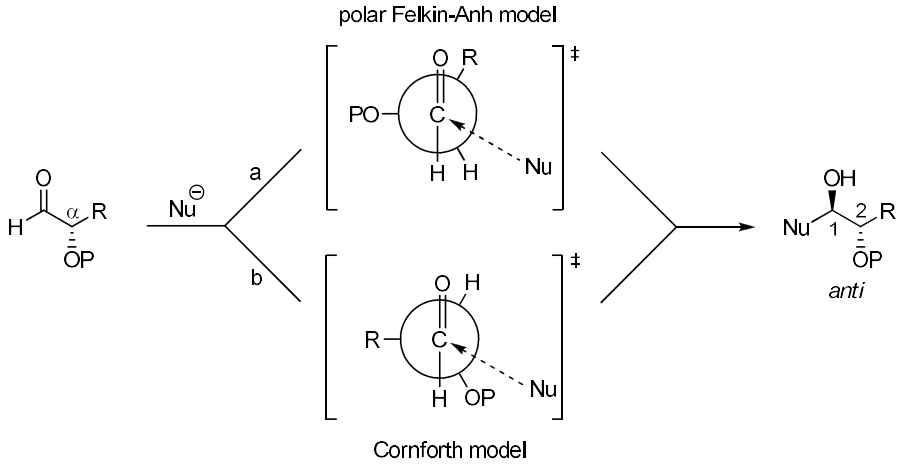
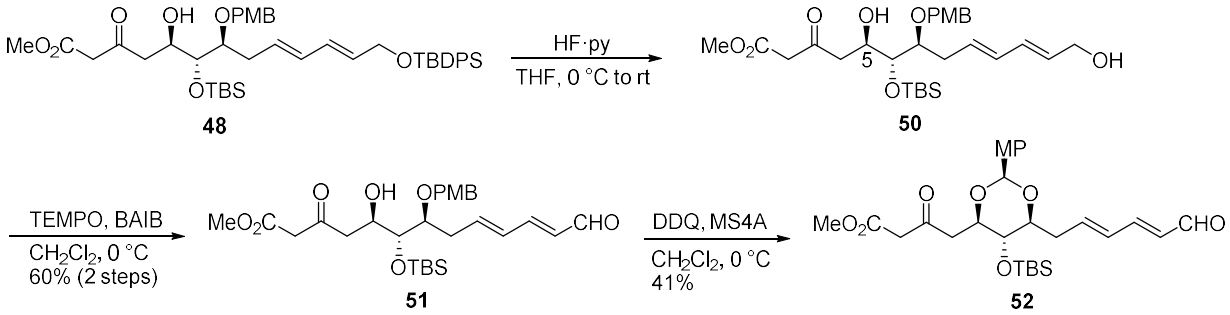


Figure 3-6. Nucleophilic addition model for α-alkoxy aldehydes.

3－4－4　立体化学の確認および立体選択的還元

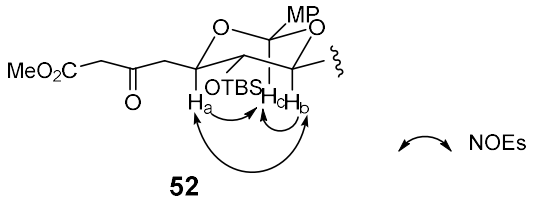
C5 位の立体化学の確認を行うための変換を行った(**Scheme 3-14**)。**48** に対し HF·py.を作用させ、一級 TBDPS 基を選択的に除去しアルコール **50** を得た。生じた一級アルコールを TEMPO 酸化によりアルデヒド **51** へ変換した。なお、この段階でアルドール反応の際に生じた C5 位のジアステレオマーを分離した。続いて MS4A を脱水剤として用い、DDQ を作用させることで MP アセタール **52** を得ることが出来た。

Scheme 3-14



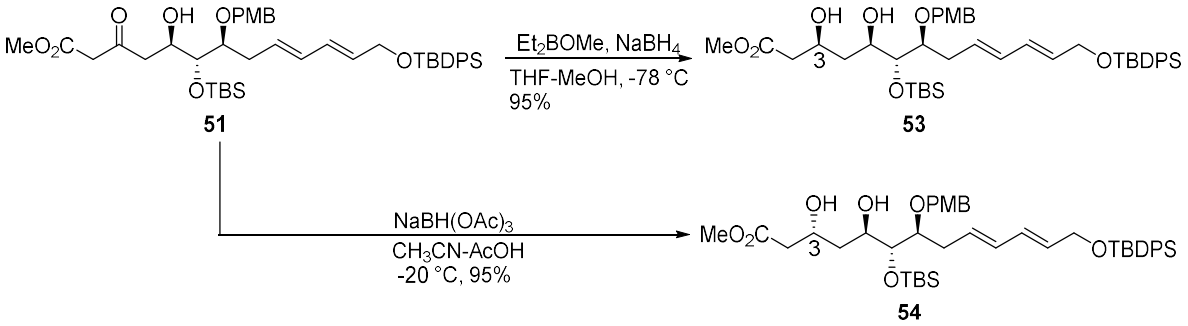
52 に対し、NOE 実験を行った。その結果、H_a−H_b、H_a−H_c、H_b −H_c の間で NOE が観測されたことにより、C5 位のヒドロキシ基は望みの立体化学を有していることを確認した(**Figure 3-7**)。

Figure 3-7



続いて *β*-ヒドロキシケトンの立体選択的な還元を行った。カップリング体 **51** に対し、Et_2BOMe、$NaBH_4$ を作用させることで、単一の立体異性体としてジオール **53** を合成することが出来た[15](**Scheme 3-15**)。また、**51** に対し、$NaBH(OAc)_3$ を作用させ単一の立体異性体としてジオール **54** を合成した。**53** と **54** の ^1H NMR データは異なることを確認した。

Scheme 3-15



C3 位の立体化学の確認を行うための変換を行った(**Scheme 3-16**)。ジオール **53** を MP アセタール **55** へ変換し、先ほどと同様に NOE 実験を行うことで、C3 位の立体化学の確認を行うこととした。その結果、**55** の H_a–H_b、H_a–H_c、H_b–H_c の間で図に示すような NOE が観測されたことにより、C3 位のヒドロキシ基は望みの立体化学を有していることを確認した(**Figure 3-8**)。

Scheme 3-16

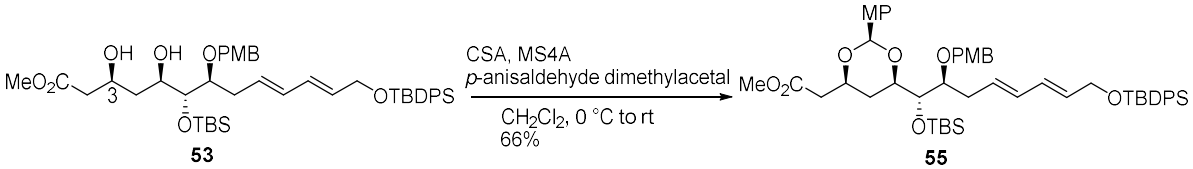
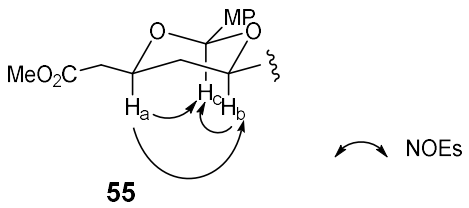


Figure 3-8



3－4－5　(3*S*, 5*R*, 6*S*, 7*S*)-テトラオールの合成

C3、C5位の立体化学の確認が完了したので、さらなる変換を行なった(**Scheme 3-17**)。ジオール **53** に対し、PMB基の除去を行い、**56** を合成すべく条件検討を行なった(**Table 3-7**)。一般的な条件であるDDQを用いたPMB基の除去を試みた[16]。溶媒として塩化メチレン–水の混合溶媒を用い、0 °Cから室温の条件で反応を行った(entry 1)。その結果、目的のアルコール **56** は得られず、C5位のヒドロキシ基との間でMPアセタール化されたアルデヒド **57** が28～78%の収率で得られるのみであった(**Figure 3-9**)。溶媒を塩化メチレン–pH = 7.0のリン酸緩衝液の混合溶媒に変えたがアルデヒド **58** が低収率で得られるという結果であった(entry 2)。次にCANを用い、0 °Cから室温の条件で反応を行ったが[17]、反応が汚くなり、目的化合物は得られなかった(entry 3)。よりマイルドな条件とされる$Ph_3C^+BF_4^-$による酸化的なPMB基の除去を試みたがC5位のヒドロキシ基からジエン部位への6-exo環化が起こりシリルエーテルが脱離した **59** が低収率で得られるのみであった[18](entry 4)。次にTFA酸性条件下での除去を試みたが、同様に **59** が得られるのみであった[19](entry 5)。酸化、および酸性条件でのPMB基の除去は難しいと考え、ルイス酸と求核種との組み合わせを試みることとした。まず、ルイス酸として$MgBr_2 \cdot OEt_2$、求核種として1,3-propanedithiolを用い45 °Cで反応を行ったが、反応は進行しなかった[20](entry 6)。求核種をEt_3SiHに変えたが、構造不明の副生成物が得られるのみであった[21](entry 7)。以上の結果から、この段階でのPMB基の除去は困難であると判断し、数段階の変換後にPMB基の除去を試みることにした。

Scheme 3-17

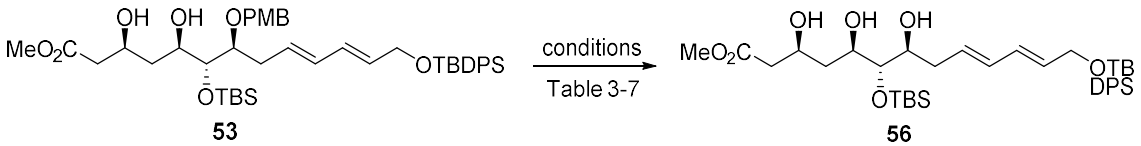
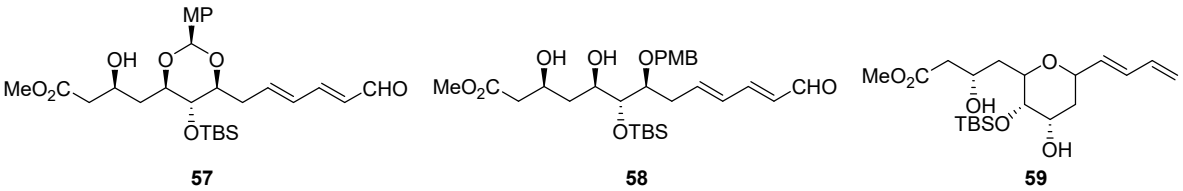


Table 3-7. Deprotection of PMB group

entry	conditions	yields (%)
1	DDQ, CH_2Cl_2/H_2O, 0 °C to rt	**57** (22-78)
2	DDQ, CH_2Cl_2/pH=7 buffer, 0 °C	**58** (19)
3	CAN, CH_3CN/H_2O, 0 °C to rt	unknown product
4	$Ph_3C^+BF_4^-$, CH_2Cl_2, 0 °C	**59** (16)
5	TFA, CH_2Cl_2, rt,	**59** (49)
6	$BF_3{\cdot}OEt_2$, 1,3-propanedithiol, $ClCH_2CH_2Cl$, 50 °C	**53** (76)
7	$BF_3{\cdot}OEt_2$, PhSH, $ClCH_2CH_2Cl$, 50 °C	unknown product

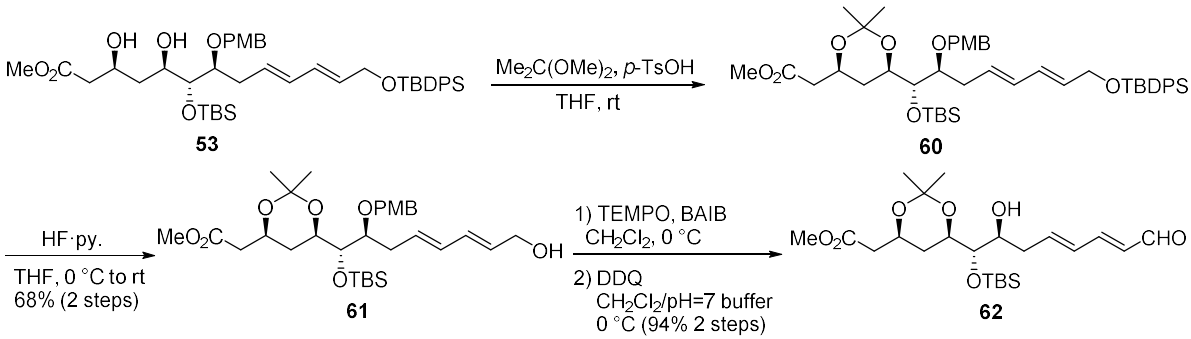
Figure 3-9. Structures of the products 57, 58, and59



ジオール **53** に対する PMB 基の除去が上手くいかない原因として、ジエン部位の反応性が高く、酸化反応や求核反応に耐えられないことが考えられた。そこで、末端をアルデヒドへと変換することでジエン部位の電子密度を下げることにした。また、DDQ を用いた際に C5 位のヒドロキシ基との間で MP アセタールを形成するという知見が得られていたため(entry 1)、まずは C3 と C5 位のヒドロキシ基を保護することにした。

ジオール **53** に対し、アセトナイド保護を行い保護体 **60** へ変換し、続いて HF·py.を作用させ一級 TBDPS 基を選択的に除去しアルコール **61** を得た(**Scheme 3-18**)。なお、この段階でアルドール反応の際に生じた C5 位のジアステレオマーを分離した。**61** のヒドロキシ基を TEMPO 酸化によりアルデヒドへ変換し[22]、続いて DDQ を作用させ PMB 基の除去を行なったところ、反応は問題なく進行し、アルコール **62** を得ることが出来た。

Scheme 3-18



次にアセトナイドの除去の条件検討を行なった(**Scheme 3-19**、**Table 3-8**)。まず、TFA酸性条件下でのアセトナイドの除去を試みた[23](entry 1)。しかし、反応が汚くなり、目的化合物は得られなかった。次に、$MgBr_2$をルイス酸として用いたところ、低収率ではあるが脱保護体 **63** を得ることが出来た[24](entry 2)。なお、この際にアセトナイドが内部に移動した副生成物 **63a** も得られた。より強いルイス酸である$TiCl_4$に変え、0 °C で反応させたところ、**63** のみを中程度の収率で合成することに成功した[25](entry 3)。さらに、反応温度を–30 °C に下げたところ、目的化合物 **63** を 98%の高収率で得ることが出来た(entry 4)。なお、さらに温度を下げると、アセトナイドが内部に移動した **63a** が副生してくるが、再び$TiCl_4$を作用させることで、**63** への変換が可能であることを見出した(entry 5)。

Scheme 3-19

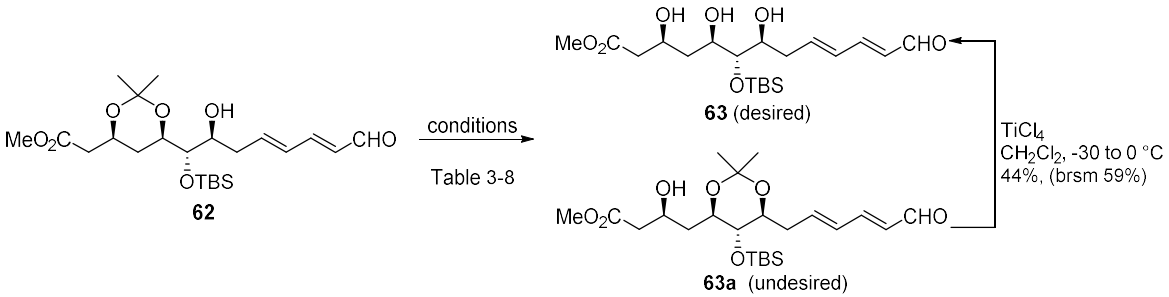


Table 3-8. Deprotection of acetonide group

entry	conditions	results
1	TFA, THF : H_2O = 4 : 1, 0 to 60°C	decomp.
2	$MgBr_2$, benzene, reflux	**63** (14%), **63a** (33%)
3	$TiCl_4$, CH_2Cl_2, 0 °C	**63** (67%)
4	$TiCl_4$, CH_2Cl_2, -30 °C	**63** (98%)
5	$TiCl_4$, CH_2Cl_2, -50 °C	**63** (50%), **63a** (46%)

トリオール **63** を得ることができたので、(3*S*, 5*R*, 6*S*, 7*S*)-テトラオール **51** の合成に向け、最終段階である TBS 基の除去の条件検討を行なった(**Scheme 3-20**、**Table 3-9**)。まず、TBAF による TBS 基の除去を検討したが、反応が汚くなり目的化合物は得られなかった(entry 1)。次に HF·py.を用い、THF 溶媒下 0 ℃ で反応を行ったところ、18%と低収率ではあるが、候補化合物 **6a** を合成することに成功した(entry 2)。また、反応促進を図り、溶媒をアセトニトリルに変えたが、decomp.という結果に終わった(entry 3)。

Scheme 3-20

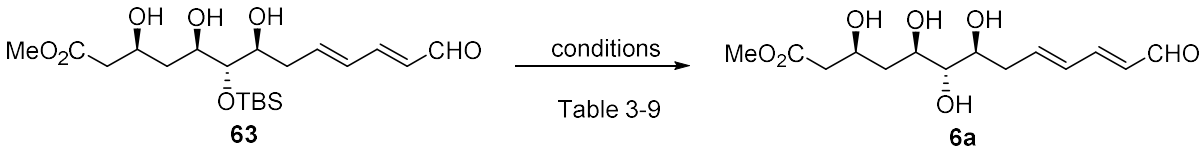


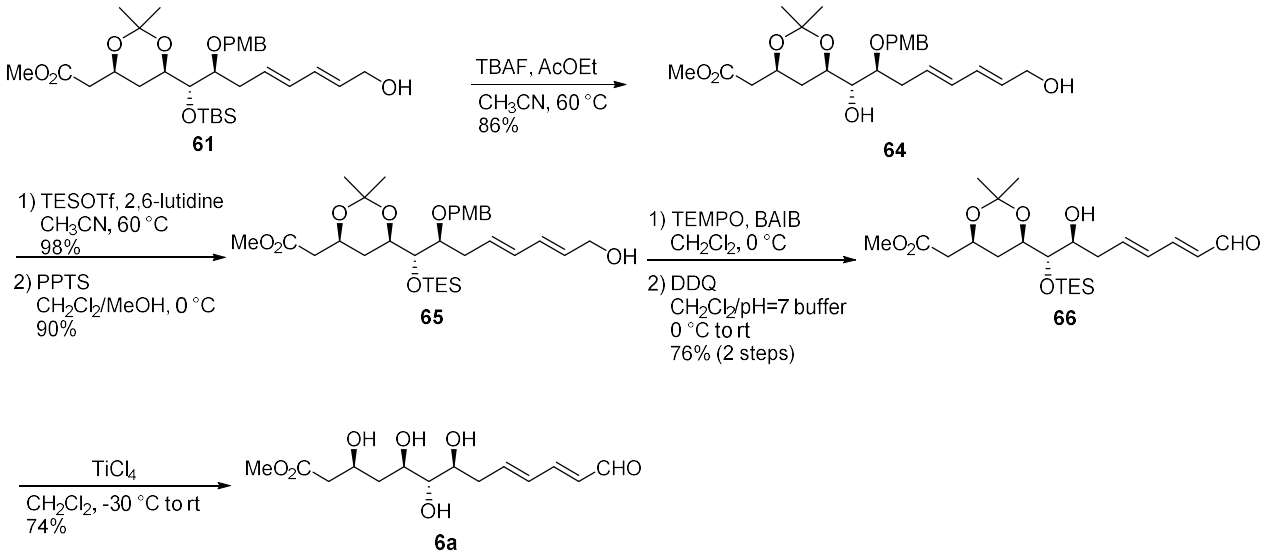
Table 3-9. Deprotection of TBS group

entry	conditions	results
1	TBAF, THF , 0 °C to rt	decomp.
2	HF·pyridine, THF, 0 °C	**6a** 18% (brsm 38%)
3	HF·pyridine, CH_3CN, 0 °C to rt	decomp.

63 から **6a** への反応は非常に遅く、出発物質 **63** が 52%の収率で回収された。反応時間が長くなると、複数の副生成物の生成が観察された。さらに、この変換は再現性がなかった。最終工程の TBS 基の除去は **6b**~**6d** の合成でも課題となるため、最終工程の保護基の除去をより穏やかな条件で行うために、TBS 基を TES 基へ変更することとした。

61 の TBS 基の除去を、MeCN 中 60 ℃で TBAF/AcOH を用いて行い、ジオール **64** を 86%の収率で得た(**Scheme 3-21**)。**64** のヒドロキシ基を TESOTf/2,6-lutidine で処理し、シリルエーテルとした後に、1 級 TES 基を選択的に除去することで、TES エーテル **65** を得た。アリルアルコール **65** を TEMPO 酸化し、PMB 基の除去を行い、不飽和アルデヒド **66** を合成した。最後に、**66** を $TiCl_4$ で-30℃~室温で処理すると、アセトナイドとそれに続く TES 基の除去がワンポットで進行し、目的の(3*S*, 5*R*, 6*S*, 7*S*)-テトラオール **6a** を 74%の収率で合成することに成功した。最終工程の脱保護が問題なく進行することが分かったので、他の候補化合物の合成に着手した。

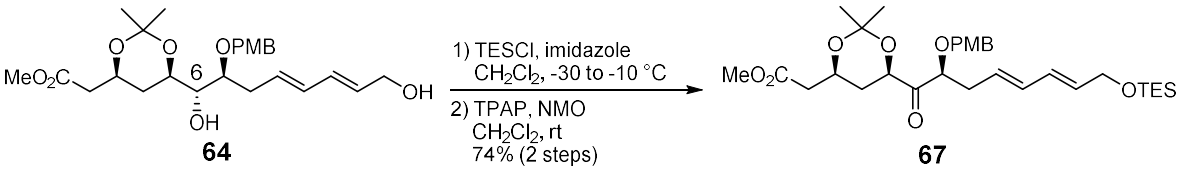
Scheme 3-21



3－4－6　(3*S*, 5*R*, 6*R*, 7*S*)-テトラオールの合成

(3*S*, 5*R*, 6*R*, 7*S*)-テトラオールの合成に着手した。アルコール **64** に対し、C6 位のヒドロキシ基の立体を反転させ、その後、(3*S*, 5*R*, 6*S*, 7*S*)-テトラオールの合成と同様の変換することで、(3*S*, 5*R*, 6*R*, 7*S*)-テトラオールを合成出来ると考えた。すなわち、C6 位のヒドロキシ基を酸化し、続く立体選択的な還元を行うことにより(6*R*)-の立体化学を有するアルコールを合成することとした。ケトン **67** の合成について説明する(**Scheme 3-22**)。アルコール **64** に対し一級ヒドロキシ基を TES 基で保護し、続いて二級ヒドロキシ基を TPAP 酸化[26]によりケトン **67** へ変換した。

Scheme 3-22



続いてケトン **67** に対する立体選択的還元について条件検討を行った(**Scheme 3-23**、**Figure 3-10**)。まず、還元剤として DIBAL-H を用いたところ、エステル部位の還元が起こりアルコール **69** が得られた (entry 1) 。次に Luche 還元を試みたが、一級 TES 基が除去されたジオール **70** が得られるのみであった(entry 2)。そこで、還元剤を $NaBH_4$ に変えたところ、目的の立体化学を有するアルコール **68** を単一の立体異性体として合成することに成功した(entry 3)。

Scheme 3-23

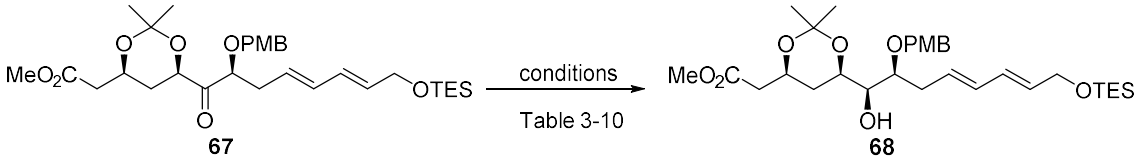
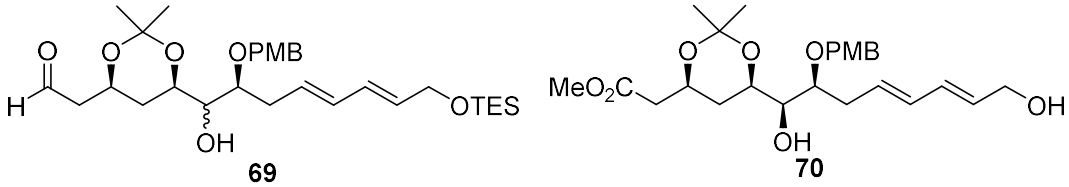


Table 3-10. Stereoselective reduction

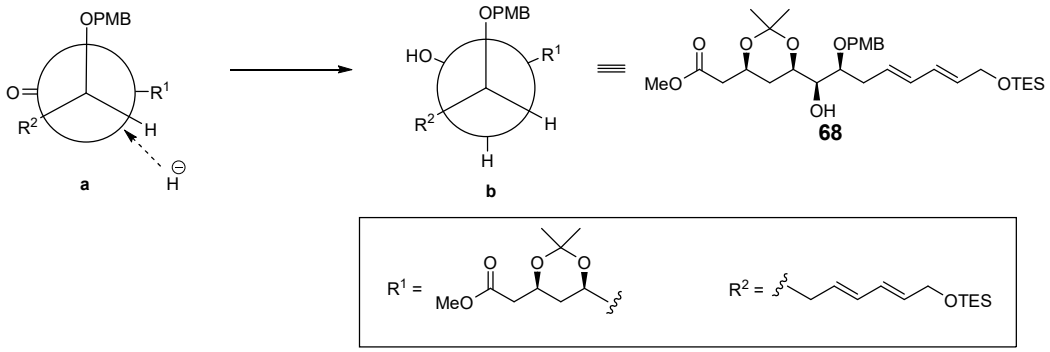
entry	conditions	results
1	DIBAL-H, CH_2Cl_2, -78°C	**69** (84%)
2	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78°C	**70** (98%)
3	$NaBH_4$, MeOH, -78 to 0°C	**68** (98%)

Figure 3-10. Structures of the undesired products 69 and 70



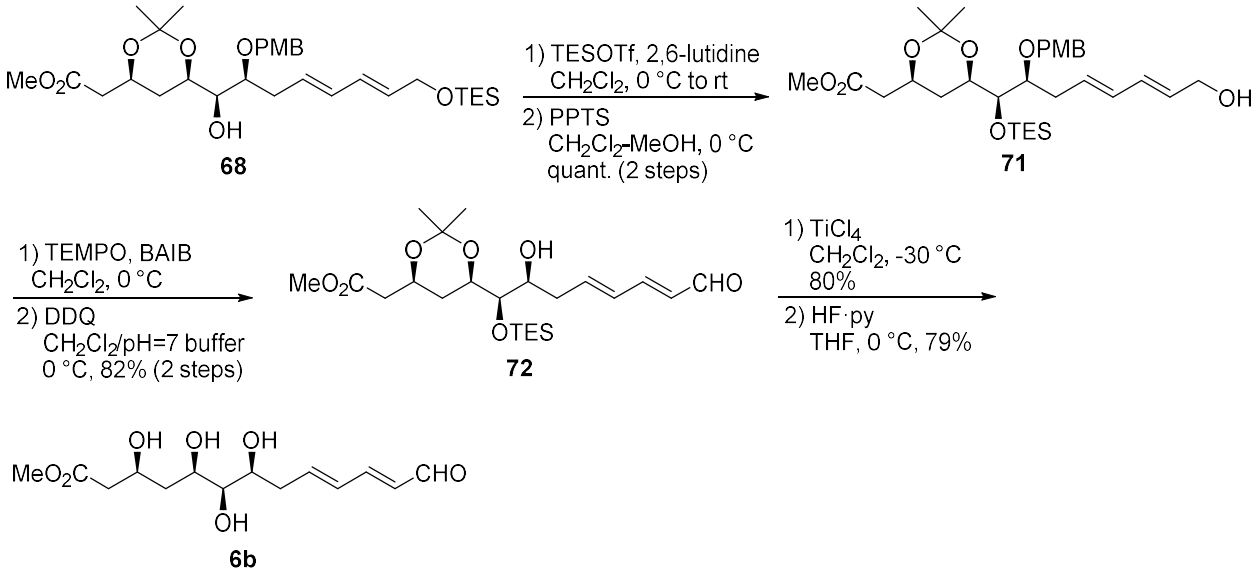
67 から **68** への立体選択的還元の選択性について説明する。この選択性は polar Felkin-Anh model にて予想されるものであった(**Figure 3-11**)。すなわち、**a** に示すような配座で、ヒドリドが Burg-Dunitz 角から接近することで立体選択的に **b** が生成するためアルコール **68** が立体選択的に得られてくると考えられている。

Figure 3-11



目的の立体化学を有するアルコール **68** を合成することが出来たので、(3*S*, 5*R*, 6*R*, 7*S*) -テトラオールの合成に向けてさらなる変換を行った(**Scheme 3-24**)。アルコール **68** を TES 基で保護した後、PPTS を作用させ一級 TES 基を選択的に除去しアルコール **71** を得た。生じたヒドロキシ基を TEMPO 酸化によりアルデヒドへと誘導後、PMB 基の除去を行いアルコール **72** を合成した。次に $TiCl_4$ を用いてアセトナイドの除去した後、最後に HF·py を用いて TES 基の除去を行うことで(3*S*, 5*R*, 6*R*, 7*S*)-テトラオール **6b** の合成を達成した。

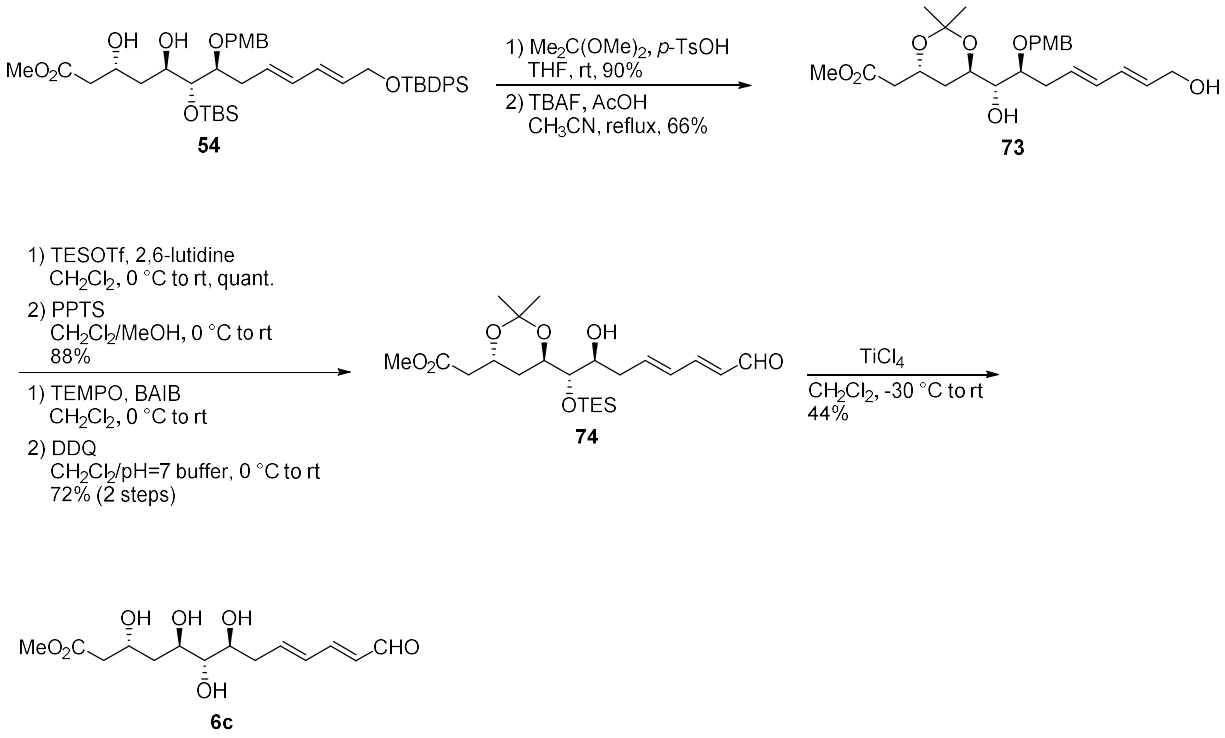
Scheme 3-24



3－4－7　(3*R*, 5*R*, 6*S*, 7*S*)-テトラオールの合成

(3*R*, 5*R*, 6*S*, 7*S*)-テトラオールの合成について説明する(**Scheme 3-25**)。ジオール **54** に対し、アセトナイド保護を行い、続いてシリル基を除去しジオール **73** を得た。**73** のヒドロキシ基を TES 基で保護した後、PPTS を作用させ一級 TES 基を選択的に除去し一級アルコールを得た。ヒドロキシ基を TEMPO 酸化によりアルデヒドへ変換し、続いて DDQ を作用させ PMB 基の除去を行い、アルコール **74** を得ることが出来た。最後に $TiCl_4$ を用いてアセトナイドと TES 基の除去を行い候補化合物 **6c** を合成することに成功した。

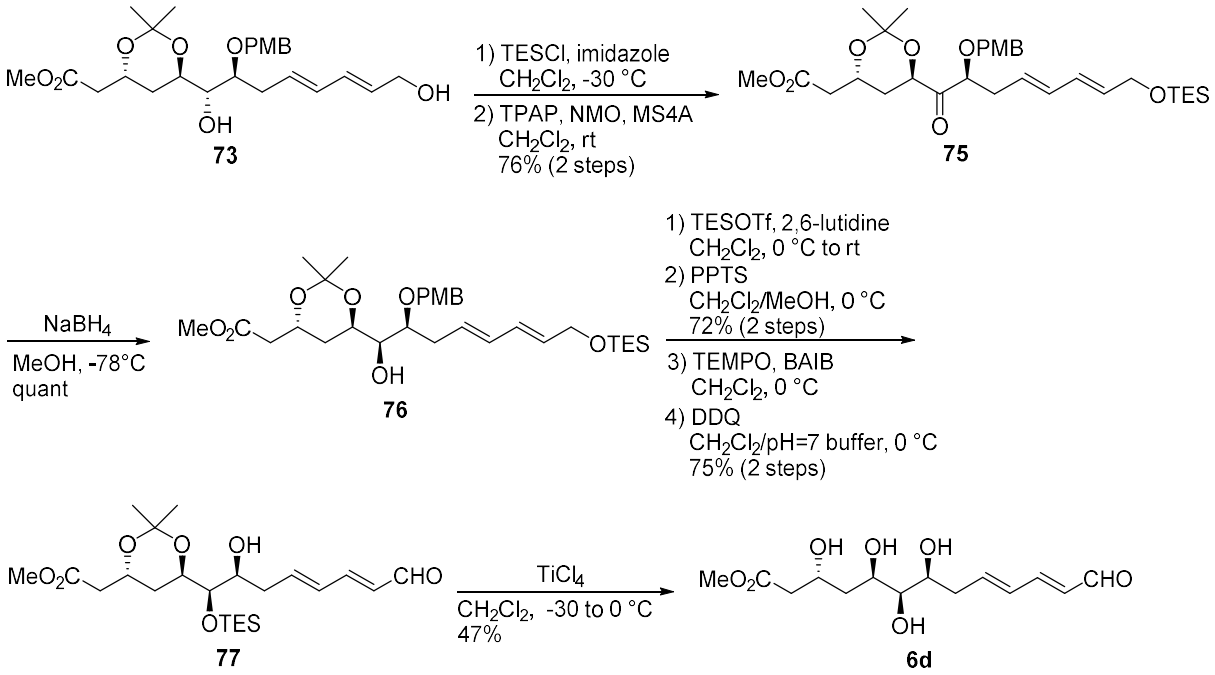
Scheme 3-25



3－4－8　(3*R*, 5*R*, 6*R*, 7*S*)-テトラオールの合成

(3*R*, 5*R*, 6*R*, 7*S*)-テトラオールの合成に着手した(**Scheme 3-26**)。ジオール **73** の一級ヒドロキシ基を TES 基で保護した後、二級アルコールを TPAP 酸化によりケトン **75** へ変換した。$NaBH_4$ を用いた立体選択的還元により、目的の立体化学を有するアルコール **76** を単一の立体異性体として合成することに成功した。続いて二級ヒドロキシ基を TES 基で保護した後、一級 TES 基の除去を行いアルコールを得た。ヒドロキシ基を TEMPO 酸化によりアルデヒドへと誘導後、PMB 基の除去を行いアルコール **77** を合成した。最後に $TiCl_4$ を用いてアセトナイド及び TES 基の除去を行うことで(3*S*, 5*R*, 6*R*, 7*S*)-テトラオール **6d** の合成を達成した。

Scheme 3-26



3 – 5　　相対立体配置の決定

4つのジアステレオマー**6a-6d**が合成できたので、これらの^{1}H NMRスペクトルデータを分解生成物**4**のデータと比較した。その結果、Table 3-11に示したように、**6b**の^{1}H NMRデータは分解生成物**4**と完全に一致することが判明した。一方、**6a**、**6c**、及び**6d**の^{1}H NMRデータはそれぞれ分解生成物**4**と明らかに異なっていた。特に、 **6a**、**6c**、及び**6d**のC4位の2つのプロトンの化学シフトはそれぞれ互いに異なっていたが、**4**及び**6b**のこれらのプロトンの化学シフトは同じであることが分かった。したがって、シンビオジノライド（**1**）のC1–C13フラグメントの相対立体構造は、**6b**に記載したものであることが明らかになった。

Table 3-11. ^{1}H NMR Chemical Shifts of the Degraded Product **4** and the Synthetic Products **6a**−**6d**[a]

position	**4**[b]	**6a**[c]	**6b**[d]	**6c**[b]	**6d**[b]
1-CO_2Me	3.67	3.67	3.67	3.67	3.67
2	2.56	2.56	2.56	2.49	2.48
	2.44	2.44	2.44	2.49	2.48
3	4.21	4.31	4.22	4.31	4.27
4	1.75	1.85	1.75	1.78	1.70
	1.75	1.70	1.75	1.60	1.59
5	3.88	3.85	3.89	3.91	3.93
6	3.33	3.39	3.32	3.39	3.23
7	3.81	3.72	3.80	3.73	3.82
8	2.52	2.61	2.52	2.62	2.52
	2.48	2.40	2.47	2.42	2.48
9	6.47	6.48	6.47	6.50	6.49
10	6.47	6.48	6.47	6.50	6.49
11	7.29	7.29	7.29	7.30	7.29
12	6.09	6.08	6.09	6.08	6.09
13-CHO	9.49	9.49	9.49	9.49	9.49

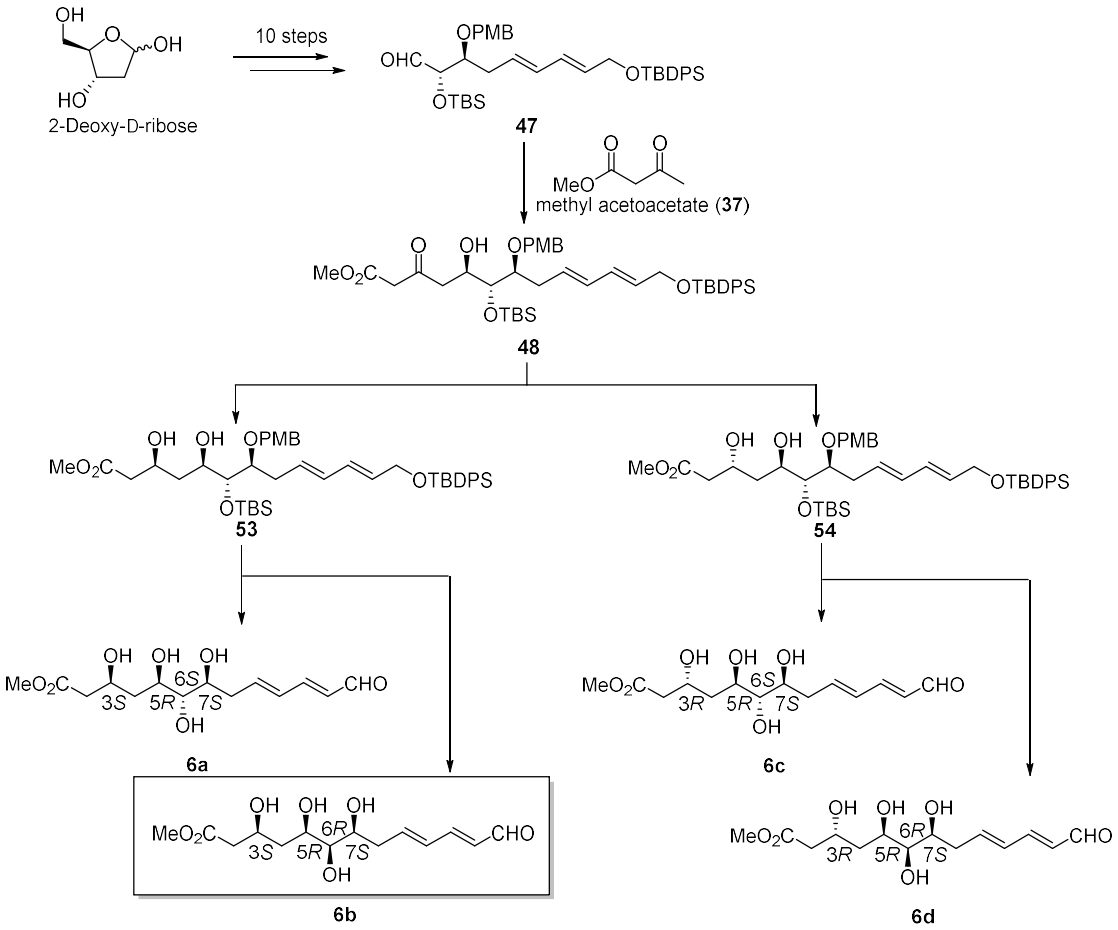
[a]Chemical shifts are reported in ppm with reference to the solvent signal (CD_3OD, 3.30 ppm). [b]Recorded at 800 MHz. [c]Recorded at 600 MHz.

3 – 6　　まとめ

C1–C13 フラグメントのまとめについて示す(**Scheme 3-27**)。分解生成物として得られた C1–C13 フラグメントの相対立体配置を推定し、それを元に立体構造の決定を行うべく合成を行った。2-Deoxy-D-ribose を出発物質とし、10 ステップでアルドール前駆体となるアルデヒド **47** へ変換した。得られたアルデヒドに対し、アルドール反応による炭素骨格の構築により **48** を得た。*β*-ヒドロキシケトンの立体選択的還元を行い、C3 位に関する立体異性体を作り分け、ジオール **53**、**54** を得た。ジオール **53** に対し、保護基の除去、官能基選択的酸化を行い、(3*S*, 5*R*, 6*S*, 7*S*)-テトラオール **6a** を合成する経路を確立した。また、**53** に対し C6 位のヒドロキシ基の立体反転と続く除去、官能基選択的酸化により(3*S*, 5*R*, 6*R*, 7*S*)-テトラオール **6b** の合成を達成した。さらに、ジオール **54** に対し、前述と同様の手法により、候補化合物 **6c** の合成を達成した。**54** に対し、C6 位のヒドロキシ基の立体反転と続く保護基の除去、官能基選択的酸化により **6d** の合成を達成した。

合成した 4 つのジアステレオマー候補 **6a-6d** のそれぞれの ^{1}H NMR スペクトルデータと分解生成物 **4** のデータと比較することにより、シンビオジノライド（**1**）の C1–C13 フラグメントの相対立体構造は、**6b** で示されるものであることを明らかにした。

Scheme 3-27


2-Deoxy-D-ribose
10 steps
47
methyl acetoacetate (37)
48
53
54
6a
6b
6c
6d

実験項 (Experimental Section)

General Methods. Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of argon. Reaction solvents were purchased as dehydrated solvents and stored with active molecular sieves 4A under argon prior to use for reactions. All solvents for work-up procedure were used as received. Analytical thin-layer chromatography (TLC) was performed with aluminium TLC plates (Merck TLC silica gel 60F254). Column chromatography was performed with Fuji Silysia silica gel BW-300 or Kanto Chemical silica gel 60N. Optical rotations were recorded on a JASCO DIP-1000. IR spectra were recorded on a JASCO FT/IR-460 plus. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 or Varian 600 MHz or Varian 800 MHz spectrometer. Chemical shifts are reported in ppm with reference to the internal residual solvent (^{1}H NMR, $CHCl_3$ 7.26 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm) or tetramethylsilane. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br =broad. Coupling constants (*J*) are in hertz. High resolution mass spectra were recorded on a Micromass LCT (ESI-TOF-MS) spectrometer.

Triol 12. To a solution of 2-deoxy-D-ribose (2.0 g, 14.9 mmol) in THF (152 mL) was added *t*-BuOK (4.24 g, 35.8 mmol) at 0 °C. After stirring for 30 min, the mixture was added $Ph_3P^+CH_3Br^-$ (13.6 g, 37.3 mmol) at the same temperature. The mixture was stirred at 35 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C and stirred for 10 h at the same temperature. The resulting solid was filtrated and concentrated. Column chromatography (CH_2Cl_2/MeOH = 15:1, 5:1) gave triol **12** (2.09 g, 15.8 mmol, quant.) as a white solid: R_f = 0.70 (CH_2Cl_2/MeOH = 5:1)

***p*-Methoxybenzyl Ether 13.** To a solution of triol **12** (1.0 g, 7.57 mmol) in CH_2Cl_2 (30 mL) was added *p*-anisaldehyde dimethylacetal (1.94 mL, 11.4 mmol) at room temperature. After the mixture was cooled to 0 °C, CSA (0.53 g, 2.27 mmol) was added. The mixture was stirred at room temperature for 18 h, CSA (0.53 g, 2.27 mmol) was added. The mixture was stirred at 40 °C for 3 days. The reaction was quenched with Et_3N at room temperature. Concentration and column chromatography (hexane/EtOAc = 4:1) gave the corresponding alchole (3.5 g, 50.9 mmol, quant.) as a colorless oil: R_f = 0.25 (hexane/EtOAc = 2:1)

To a solution of the alcohol obtained above (1.88 g, 7.51mmol) in DMF (5.0 mL) were added imidazole (0.77 g, 11.2 mmol), TBSCl (1.47 g, 9.76 mmol) at room temperature. The mixture was stirred at 40 °C for 21 h. After the mixture was cooled to room temperature, imidazole (0.31 g, 4.5 mmol), TBSCl (0.56 g, 3.8 mmol) was added. The mixture was stirred at 40 °C for 21 h. After the mixture was cooled to room temperature, resulting mixture was quenched with MeOH, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 12:1) gave *p*-methoxybenzyl ether **13** (1.29 g, 3.53 mmol, 47%) as a colorless oil: R_f = 0.74 (hexane/EtOAc = 2:1)

Alcohol 14. To a solution of *p*-methoxybenzyl ether **13** (50.0 mg, 137 μmol) in toluene (1.4 ml) was added DIBAL-H (1.02 M solution in hexane, 0.27 mL, 274 μmol) at –78 °C. After the mixture was warm to –30 °C for 2 h, the mixture was added DIBAL-H (1.02 M solution in hexane, 0.27 mL, 274 μmol) at –78 °C. After the mixture was warm to –30 °C for 3 h, quenched with MeOH. The mixture was filtered through a celite pad washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 13:1) gave alcohol **14** (44.0 mg, 117 μmol, 88%) as a colorless oil: R_f = 0.75 (hexane/EtOAc = 2:1)

Aldehyde 15. To a solution of alcohol **14** (44.0 mg, 117 μmol) in CH_2Cl_2 (0.75 mL) and DMSO (0.25 mL) were added Et_3N (48.7 μL, 351μmol) and SO_3·py. (37.2 mg, 234μmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave aldehyde **15** (38.9 mg, 106 μmol, 92%) as a colorless oil: R_f = 0.70 (hexane/EtOAc = 4:1)

Alcohol 17. To a solution of acethyl thiazolidinethione **16** (50.0 mg, 137 μmol) in CH_2Cl_2 (1.0 mL) were added $TiCl_4$ (27.1 μL, 233 μmol) and DIPEA (40.8 μL, 240 μmol) at –40 °C. The mixture was stirred for 2 h at –78 °C. To the mixture was added aldehyde **15** (50.0 mg, 137 μmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) at –78 °C. After the mixture was stirred for 13 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and

brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1) gave alchole **17** (57.7 mg, 93.2 μmol, 68%): yellow oil; R_f = 0.24 (hexane/EtOAc = 4:1)

Weinreb Amide 19. To a solution of (MeO)MeNH·HCl (2.4 mg, 24.3 μmol) in CH_2Cl_2 (0.5 mL) was added $AlMe_3$ (22.5 μL, 24.3 μmol) at –0 °C. The mixture was stirred for 30 min at room temperature. To the mixture was added thiazolidine **17** (5.0 mg, 8.11 μmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) at –20 °C. After the mixture was stirred for 1 h at the room temperature, the reaction was quenched with MeOH. The mixture was filtered through a celite pad washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 4:1) gave weinreb amide **19** (3.2 mg, 6.84 μmol, 84%) as a colorless oil: R_f = 0.47 (hexane/EtOAc = 2:1)

MTPA Ester (*S*)-20. To a solution of alcohol **19** (1.6 mg, 3.42 μmol) in CH_2Cl_2 (0.4 mL) were added DMAP (0.8 mg, 6.42 μmol), Et_3N (1.34 μL, 9.57 μmol), and (*R*)-MTPACl (1.6 μL, 8.2 μmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave MTPA ester (*S*)-**20** (2.6 mg, quant.) as a colorless oil: R_f = 0.34 (hexane/EtOAc = 3:1)

MTPA Ester (*R*)-20. To a solution of alcohol **19** (1.8 mg, 3.84 μmol) in CH_2Cl_2 (0.4 mL) were added DMAP (0.6 mg, 4.90 μmol), Et_3N (1.5 μL, 10.8 μmol), and (*S*)-MTPACl (1.8 μL, 9.22 μmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave MTPA ester (*R*)-**20** (2.7 mg, quant.) as a colorless oil: R_f = 0.34 (hexane/EtOAc = 3:1)

Diol 21. To a solution of thiazolidine **17** (51.0 mg, 82.8 μmol) in MeoH (1.0 mL) was added $NaBH_4$ (4.7 mg, 124 μmol) at 0 °C. The mixture was stirred for 1 h at the same temperature. To the mixture was added $NaBH_4$ (7.8 mg, 206 μmol). After the mixture

was stirred for 30 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 3:1) gave diol **21** (26.8 mg, 65.4 μmol 79%) as a yellow oil: R_f = 0.38 (hexane/EtOAc = 1:1)

***p*-Methoxybenzyl Ether 22.** To a solution of diol **21** (26.2 mg, 63.8 μmol) in CH_2Cl_2 (1.5 mL) was added *p*-anisaldehyde dimethylacetal (33.4 mL, 11.4 μmol) at room temperature. The mixture was added PPTS (4.933 mg, 19.6 μmol) and stirred at room temperature for 40 min. The reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc = 20:1) gave *p*-methoxybenzyl ether **22** (33.8 mg, quant.) as a colorless oil: R_f = 0.63 (hexane/EtOAc = 2:1)

Alcohol 23. To a solution of *p*-methoxybenzyl ether **22** (16.5 mg, 31.2 μmol) in toluene (0.6 mL) was added DIBAL-H (1.03 M solution in hexane, 64.3 μL, 66.2 μmol) at –65 °C. After the mixture was warm to –10 °C for 2 h, the mixture was was added DIBAL-H (1.03 M solution in hexane, 32.2 μL, 33.1 μmol) at –65 °C. After the mixture was warm to –30 °C for 1 h, quenched with MeOH. The mixture was filtered through a celite pad washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 5:1) gave alcohol **23** (11.7 mg, 24.0 μmol, 77%) as a colorless oil: R_f = 0.48 (hexane/EtOAc = 2:1)

Aldehyde 24. To a solution of alcohol **23** (28.9 mg, 54.4 μmol) in CH_2Cl_2 (0.6 mL) and DMSO (0.2 mL) were added Et_3N (22.6 μL, 163 μmol) and SO_3·py. (17.3 mg, 109 μmol) at 0 °C, and stirred at room temperature for 1 h. The mixture were added Et_3N (45.2 μL, 326 μmol) and SO_3·py. (346 mg, 218 μmol) at 0 °C. The mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 18:1, 10:1) gave the corresponding aldehyde **24** (17.2 mg, 33.2 μmol, 60%) as a colorless oil: R_f = 0.61 (hexane/EtOAc = 4:1)

Alcohol 25. To a solution of acethyl thiazolidinethione **16** (56.0 mg, 233 μmol) in

CH_2Cl_2 (0.6 mL) were added $TiCl_4$ (27.1 μL, 247 μmol) and DIPEA (40.8 μL, 240 μmol) at –40 °C. The mixture was stirred for 2 h at –78 °C. To the mixture was added aldehyde **25** (17.2 mg, 32.5 μmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) at –78 °C. After the mixture was stirred for 17 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave alchole **26** (18.1 mg, 165 μmol, 71%): yellow oil; R_f = 0.73 (hexane/EtOAc = 2:1)

Ester 27. To a solution of thiazolidine **25** (5.6 mg, 7.18 μmol) in MeOH (1.0 mL) were added imidazole (0.5 mg, 7.18 μmol) and DMAP (0.9 mg, 7.18 μmol) at room temperature. After stirring for 12 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave diol **27** (4.6 mg, quant.) as a colorless oil: R_f = 0.58 (hexane/EtOAc = 2:1)

MTPA Ester (*S*)-28. To a solution of alcohol **27** (2.3 mg, 3.82 μmol) in CH_2Cl_2 (0.4 mL) were added DMAP (0.8 mg, 6.42 μmol), Et_3N (1.05 μL, 7.64 μmol), and (*R*)-MTPACl (1.0 μL, 5.35 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*S*)-**28** (2.3 mg, 2.83 μmol, 74%) as a white solid: R_f = 0.61 (hexane/EtOAc = 2:1)

MTPA Ester (*R*)-28. To a solution of alcohol **27** (2.3 mg, 3.82 μmol) in CH_2Cl_2 (0.4 mL) were added DMAP (0.8 mg, 6.42 μmol), Et_3N (1.05 μL, 7.64 μmol), and (*S*)-MTPACl (1.0 μL, 5.35 μmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*R*)-**28** (3.0 mg, 3.67 μmol, 96%) as a white solid: R_f = 0.61 (hexane/EtOAc = 2:1)

Dienal 30.

(entry 3)

To a solution of olefin **29** (61.9 mg, 0.17 mmol) in CH_2Cl_2 (3.3 mL) were added penta-2,4-dienal (34.4 mg, 0.42 mmol) and catalytic amount of Hoveyda−Gurbbs 2nd cat. at toom temperature. After the mixture was stirred at 60 °C for 2 days, the mixture was quenched with Et_3N. Short column (hexane/EtOAc = 4:1) gave crude dienal. Purification by column chromatography (hexane/EtOAc = 30:1, 20:1) gave dienal **30** (19.2 mg, 18%) as a light yellow oil: R_f = 0.67 (hexane/EtOAc = 2:1) and olefin **29** (45.4 mg, 73%) as a colorless oil: R_f = 0.82 (hexane/EtOAc = 4:1) and aldehyde **31** (6.4 mg, 0.016 μmol,　9%) as a colorless oil: R_f = 0.67 (hexane/EtOAc = 4:1)

Alcohol 43.　To a solution of allylic alcohol **42** (5.04 g, 12.8 mmol) in CH_2Cl_2 (51.0 mL) and DMSO (13.0 mL) were added Et_3N (7.8 mL, 56.3 mmol) and SO_3·py. (4.07 g, 25.6 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave the corresponding aldehyde (4.53 g), which was used in the next reaction without further purification.

To a stirred solution of sodium hydride (1.11 g, 27.8 mmol) in benzene (35.0 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (6.0 mL, 30.2 mmol) at 0 °C. The mixture was added the aldehyde (4.53 g) in benzene (5.0 mL + 2.5 mL+ 2.5 mL) at room temperature and stirred for 1 h at the same temperature. The mixture was quenched with H_2O at 0 °C, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 20:1) gave corresponding ester (4.85 g), which was used in the next reaction without further purification.

To a solution of ester (4.85 g) in CH_2Cl_2 (50.0 mL) was added DIBAL-H (1.04 M solution in hexane, 20.0 mL, 20.8 mmol) at –78 °C. After the mixture was stirred for 30 min at the same temperature, quenched with MeOH. The mixture was filtered through a celite pad washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 4:1) gave alcohol **43** (4.11 g, 10.4 mmol 81% in three steps) as a colorless oil: R_f = 0.19 (hexane/EtOAc = 4:1); $[\alpha]^{25}_D$ –60.6 (*c* 0.92, $CHCl_3$); IR (neat) 3427, 2856, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.85 (dt, *J* = 15.0, 6.6 Hz, 1 H), 5.75 (dt, *J* = 15.0, 6.6 Hz, 1 H), 5.43 (s,

1 H), 4.18 (t, *J* = 3.6 Hz, 2 H), 3.80 (s, 3 H), 3.58 (t, *J* = 3.6 Hz, 2 H), 2.64 (dd, *J* = 14.4, 6.6 Hz, 1 H), 2.36 (dd, *J* = 14.4, 6.6 Hz, 1 H), 0.91 (s, 9 H), 0.09 (d, *J* = 8.3 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 131.7, 130.5, 130.4, 127.6, 127.3, 114.0, 113.5, 100.7, 81.9, 71.7, 66.2, 63.5, 55.3, 34.8, 25.8, 18.0, –4.0, –4.6 ; HRMS (ESI–TOF) calcd for $C_{14}H_{26}O_3SiNa$ $(M + Na)^+$ 443.2230, found 443.2236.

***p*-Methoxybenzyl Ether 44.** To a stirred solution of sodium hydride (34.3 mg, 714 μmol) in THF (4.0 mL) was added alcohol **43** (200 mg, 476 μmol) in THF (0.7 mL + 0.3 mL) at 0 °C. After being stirred for 30 min at 0 °C conditions, the mixture was added PMBCl (77.6 μL, 571 μmol) and TBAI (17.6 mg, 47.6μmol) at the same temperature. The mixture was stirred for 6 h at reflux conditions. After the mixture was cooled at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc, 40:1, 30:1) gave *p*-methoxybenzyl ether **44** (194 mg, 366 mmol 77%): colorless oil; R_f = 0.47 (hexane/EtOAc, 4:1)

TBS Ether 44. To a solution of alcohol **43** (150 mg, 356 μmol) in CH_2Cl_2 (1.0 mL) were added imidazole (33.9 mg, 498 μmol), and TBSCl (64.4 mg, 472 μmol) at 0 °C. After the mixture was stirred at room temperature for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1, 10:1) gave TBS ether **44** (178 mg, 335 mmol, 94%) as a colorless oil: R_f = 0.76 (hexane/EtOAc = 2:1)

TBDPS Ether 44. To a solution of alcohol **43** (48.8 mg, 116 μmol) in CH_2Cl_2 (1.0 mL) were added DMAP (21.2 mg, 174 μmol), imidazole (11.8 mg, 174 μmol), and TBDPSCl (36.1 μL, 139 μmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1, 10:1) gave TBDPS ether **44** (79.1 mg, quant.) as a colorless oil: R_f = 0.76 (hexane/EtOAc = 2:1); $[\alpha]^{24}_D$ –33.7 (*c* 0.95, $CHCl_3$); IR (neat) 3060, 2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.0, 1.8 Hz, 4 H), 7.45–7.37 (m, 8 H), 6.01 (dd, *J* = 8.6, 1.8 Hz, 2 H),

6.32–6.14 (m, 2 H), 5.87 (dt, *J* = 14.9, 7.8 Hz, 1 H), 5.71 (dt, *J* = 14.9, 4.9 Hz, 1 H), 5.47 (d, *J* = 1.8 Hz, 1 H), 4.26 (d, *J* = 4.9 Hz, 2 H), 4.19 (dt, *J* = 8.6, 2.0 Hz, 1 H), 3.82 (s, 3 H), 3.64–3.60 (m, 1 H), 3.56 (d, *J* = 2.0 Hz, 1 H), 2.67 (dd, *J* = 14.9, 6.9 Hz, 1 H), 2.39 (dd, *J* = 14.9, 6.9 Hz, 1 H), 1.10 (s, 9 H), 0.94 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 135.5, 135.5, 135.4, 133.7, 132.1, 130.4, 129.9, 129.3, 127.6, 127.6, 127.5, 127.3, 113.5, 100.7, 82.0, 71.7, 66.2, 64.2, 55.3, 34.9, 26.9, 26.8, 25.8, 19.3, 18.0, –4.0, –4.6; HRMS (ESI–TOF) calcd for $C_{39}H_{54}O_5Si_2Na$ $(M + Na)^+$ 681.3408, found 681.3398.

Alcohol 45.

(entry 1)

To a solution of *p*-methoxybenzyl ether **44** (212.4 mg, 392.8 μmol) in CH_2Cl_2 (3.0 mL), was added DIBALH (1.02 M in hexane, 0.77 ml, 785.6 μmol) at –78 °C. The mixture was warmed to –30 °C. After the mixture was stirred for 3 h at the same temperature, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 30:1, 10:1, 6:1, 4:1) gave alcohol **45** (54.1 mg, 98.2 μmol, 25%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1) and *p*-methoxybenzyl ether **44** (104.7 mg, 192.5 μmol 49% recovery) as a colorless oil; R_f = 0.25 (hexane/EtOAc, 3:1).

(entry 2)

To a solution of *p*-methoxybenzyl ether **44** (99.5 mg, 184 μmol) in toluene (1.8 mL) was added DIBALH (1.02 M in hexane, 0.36 mL, 368 μmol) at –78 °C. The mixture was warmed to –10 °C and stirred for 2 h at the same temperature. The mixture was added DIBALH (1.02 M in hexane, 0.36 mL, 368 μmol) at –78 °C. After the mixture was stirred for 5 h at –10 °C, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 15:1, 10:1, 7:1) gave alcohol **45** (22.3 mg, 22%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1) and *p*-methoxybenzyl ether **44** (47.8 mg, 48% recovery) as a colorless oil; R_f = 0.25 (hexane/EtOAc, 3:1)

(entry 3)

To a solution of TBS ether **44** (60.0 mg, 112 μmol) in CH_2Cl_2 (1.8 mL) was added DIBALH (1.05 M in hexane, 128 μL, 134 μmol) at –65 °C. The mixture was warmed to

–10 °C and stirred for 2 h at the same temperature. The mixture was added DIBALH (1.05 M in hexane, 128 μL, 134 μmol) at –65 °C. After the mixture was stirred for 2 h at –10 °C, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 40:1 15:1, 10:1, 7:1) gave alcohol **45** (23.6 mg, 44.8 μmol, 40%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1) and TBS ether **44** (19.0 mg, 32.5 μmol, 29% recovery) as a colorless oil; R_f = 0.25 (hexane/EtOAc, 3:1) and alcohol **43** (3.9 mg, 10.1 μmol, 9%) as a colorless oil: R_f = 0.19 (hexane/EtOAc = 4:1)

(entry 4)

To a solution of TBS ether **44** (178 mg, 333 μmol) in toluene (3.0 mL) was added DIBALH (1.05 M in hexane, 0.63 mL, 666 μmol) at –65 °C. The mixture was warmed to –10 °C and stirred for 2 h at the same temperature. The mixture was added DIBALH (1.05 M in hexane, 0.32 mL, 333 μmol) at –65 °C. After the mixture was stirred for 2 h at –10 °C, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 40:1 15:1, 10:1, 7:1) gave alcohol **45** (61.1 mg, , 113.2 μmol, 34%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1) and TBS ether **44** (28.1 mg, 53.3 μmol, 16%, recovery) as a colorless oil; R_f = 0.76 (hexane/EtOAc, 3:1) and alcohol **43** (36.4 mg, 86.6 μmol, 26%) as a colorless oil: R_f = 0.19 (hexane/EtOAc = 4:1)

(entry 5)

To a solution of TBDPS ether **44** (76.4 mg, 116 μmol) in toluene (3.7 mL) was added DIBALH (1.02 M in hexane, 0.64 mL, 656 μmol) at –65 °C. The mixture was warmed to –10 °C and stirred for 2 h at the same temperature. The mixture was added DIBALH (1.02 M in hexane, 0.64 mL, 656 μmol) at –65 °C. After the mixture was stirred for 1 h at –10 °C, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 40:1, 10:1, 7:1) gave alcohol **45** (42.4 mg, 42.9 μmol, 37%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1) and TBDPS ether **44** (48.2 mg, 77.7 μmol, 67% recovery) as a colorless oil; R_f = 0.19 (hexane/EtOAc = 4:1)

(entry 6)

To a solution of TBDPS ether **44** (176 mg, 267 μmol) in toluene (5.3 mL) was added DIBALH (1.02 M in hexane, 0.5 mL, 535 μmol) at –65 °C. The mixture was warmed to

–10 °C and stirred for 2 h at the same temperature. The mixture was added DIBALH (1.02 M in hexane, 0.5 mL, 535 μmol) at –65 °C. After the mixture was stirred for 2 h at –10 °C, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad washed with EtOAc. Concentration and short column chromatography (hexane/EtOAc, 40:1, 15:1, 7:1) gave TBDPS ether **44** (54.0 mg, 82.8 μmol, 31% recovery) as a colorless oil; R_f = 0.76 (hexane/EtOAc = 2:1) and alcohol **45** (98.0 mg, 149.5 μmol, 56%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 2:1); $[\alpha]^{23}_{D}$ –14.1 (*c* 1.00, $CHCl_3$); IR (neat) 3476, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.5 Hz, 4 H), 7.43–7.37 (m, 6 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.27 (dd, *J* = 15.0, 10.6 Hz, 1 H), 4.14 (dd, *J* = 15.0, 10.6 Hz, 1 H), 5.73–5.68 (m, 2 H), 4.55 (s, 2 H), 4.26 (d, *J* = 4.2 Hz, 2 H), 3.79 (s, 3 H), 3.72–3.67 (m, 1 H), 3.59–3.55 (m, 1 H), 2.52–2.46 (m, 1 H), 2.39–2.33 (m, 1 H), 1.08 (s, 9 H), 0.93 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.4, 133.7, 132.3, 130.4, 130.3, 129.9, 129.5, 127.6, 113.8, 80.4, 74.0, 72.5, 64.2, 55.3, 34.5, 26.9, 25.9, 19.3, 18.1, 14.3, –4.3, –4.5; HRMS (ESI–TOF) calcd for $C_{39}H_{56}O_5Si_2Na$ $(M + Na)^+$ 683.3564, found 683.3555.

Aldehyde 47. To a solution of alcohol **45** (79.3 mg, 148 μmol) in CH_2Cl_2 (1.0 mL) and DMSO (0.3 mL) were added Et_3N (103 μL, 740 μmol) and SO_3·py. (94.2 mg, 592 μmol) at 0 °C. The mixture was stirred at room temperature for 2.5 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave the aldehyde **47** (75.4 mg, 140.6 μmol, 95%) as a colorless oil: R_f = 0.70 (hexane/EtOAc = 2:1) $[\alpha]^{23}_{D}$ –14.1 (*c* 1.06, $CHCl_3$); IR (neat) 2931, 2860, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, *1* H), 7.73–7.68 (m, 4 H), 7.44–7.36 (m, 6 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 6.27–6.10 (m, 2 H), 5.70 (dt, *J* = 14.4, 4.6 Hz, 1 H), 5.55 (dt, *J* = 14.4, 6.8 Hz, 1 H), 4.58–4.49 (m, 2 H), 4.25 (d, *J* = 4.6 Hz, 2 H), 4.13 (m, 1 H), 3.80 (s, 3 H), 3.73–3.69 (m, 1 H), 2.43 (t, *J* = 6.8 Hz, 1 H), 1.08 (s, 9 H), 1.00 (s, 9 H), 0.50 (d, *J* = 4.4 Hz, 6 H); ^{13}C NMR (1 00 MHz, $CDCl_3$) δ 203.2, 159.1, 135.4, 133.6, 133.2, 131.0, 130.03, 129.5, 129.4, 129.0, 128.6, 127.6, 113.7, 80.8, 79.0, 71.9, 64.2, 55.3, 33.9, 26.9, 25.8, 19.3, 18.3, –4.6, –4.7; HRMS (ESI–TOF) calcd for $C_{39}H_{54}O_5Si_2Na$ $(M + Na)^+$ 681.3408, found 681.3410.

Alcohol 48.

(entry 1)

Preparation of LDA. To a stirred solution of diisopropyl amine (26.4μL, 186 μmol) in THF (1.3 mL), was added *n*-BuLi (1.57 M in hexane, 108 μL, 170 μmol) at –60 °C. After stiring for 8 min, the mixture was warm to room temperature and stired for 5 min. Then, the mixture was cooled at –60 °C.

To a stirred solution of LDA obtained above was added methyl acetoacetate (**37**) (8.35 μL, 77.4 μmol) at –60 °C. After stiring for 20 min, the mixture was warm to room temperature and stired for 5 min. After stiring for 10 min at –60 °C, the mixture was added aldehyde **47** (51.0 mg, 77.4 μmol) in THF (0.3 mL + 0.2 mL) at –60 °C and gradually warm to room temperature. After stiring for 2 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6.5:1) gave alchole **48** (31.4 mg, 40.2 μmol, dr = 4:1, 52%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 4:1)

(entry 2)

Preparation of LDA. To a stirred solution of diisopropyl amine (37.1μL, 153 μmol) in THF (1.8 mL), was added *n*-BuLi (1.57 M in hexane, 153 μL, 240 μmol) at –60 °C. After stirring for 8 min, the mixture was warm to room temperature and stirred for 5 min. Then, the mixture was cooled at –60 °C.

To a stirred solution of LDA obtained above was added methyl acetoacetate (**37**) (11.8 μL, 109 μmol) at –60 °C. After stirring for 20 min, the mixture was warm to room temperature and stirred for 5 min. After stirring for 10 min at –78 °C, the mixture was added aldehyde **47** (72.0 mg, 109 μmol) in THF (0.3 mL + 0.2 mL) at –78 °C. After stirring for 20 min at the same temperature, the mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6.5:1) gave alchole **48** (21.0 mg, 27.2 μmol, dr = 4.5:1, 25%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 4:1) and aldehyde **47** (36.2 mg, 54.5 μmol, 50% recovery) as a colorless oil: R_f = 0.70 (hexane/EtOAc = 2:1)

(entry 4)

To a stirred solution of sodium hydride (19.7 mg, 411 μmol) in THF (1.0 mL) was

added methyl acetoacetate (**37**) (29.5 μL, 247 μmol) at 0 °C. After stirring for 20 min, the mixture was added *n*-BuLi (1.57 M in hexane, 192 μL, 301 μmol) at 0 °C. After stirring for 10 min at –78 °C, the mixture was added aldehyde **47** (90.3 mg, 137 μmol) in THF (0.3 mL + 0.2 mL) at –78 °C and stirred for 15 min at the same temperature. The mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5.5:1) gave alchole **48** (100 mg, 232.1 μmol, dr = 6:1, 94%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 4:1); $[\alpha]^{22}_D$ +2.2 (*c* 1.00, $CHCl_3$); IR (neat) 3517, 2930, 1748 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.81 (dd, *J* = 6.1, 2.4 Hz, 4 H), 7.23–7,22 (m, 8 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.42 (dd, *J* = 15.0, 10.6 Hz, 1 H), 6.22 (dd, *J* = 15.0, 10.6 Hz, 1 H), 5.84 (dt, *J* = 15.0, 7.4 Hz, 1 H), 5.69 (dt, *J* = 15.0, 5.1 Hz, 1 H), 4.41 (d, *J* = 4.6 Hz, 2 H), 4.32 (m, 1 H), 4.24 (d, *J* = 4.6 Hz, 2 H), 3.87 (t, *J* = 4.6 Hz, 1 H), 3.61 (dt, *J* = 6.6, 4.6 Hz, 1 H), 3.32 (s, 3 H), 3.26 (s, 3 H), 3.03 (s, 2 H), 2.80 (dd, *J* = 6.8, 3.7 Hz, 1 H), 2.65 (d, *J* = 9.3 Hz, 1 H), 2.48 (m, 2 H), 1.19 (s, 9 H), 1.01 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 159.8, 135.9, 134.2, 132.6, 130.9, 130.8, 130.5, 129.9, 114.2, 114.1, 79.9, 77.1, 72.1, 69.0, 64.7, 54.9, 51.8, 49.8, 45.6, 34.0, 27.2, 26.5, 26.3, 19.6, 18.7, –3.9, –4.0; HRMS (ESI–TOF) calcd for $C_{44}H_{62}O_8Si_2Na$ $(M + Na)^+$ 797.3881, found 797.3875.

(entry 5)

To a stirred solution of sodium hydride (17.3 mg, 360 μmol) in THF (1.3 mL) was added methyl acetoacetate (**37**) (25.9 μL, 240 μmol) at 0 °C. After stirring for 20 min, the mixture was added *n*-BuLi (1.57 M in hexane, 168 μL, 264 μmol) at 0 °C. After stirring for 10 min at –95 °C, the mixture was added aldehyde **47** (79.4 mg, 120 μmol) in THF (0.4 mL + 0.3 mL) at –95 °C and stirred for 50 min at the same temperature. The mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 5.5:1) gave alchole **48** (36.2 mg, 93.6 μmol, dr = 5:1, 39%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 4:1) and aldehyde **47** (41.5 mg, 127.2 μmol, 53% recovery) as a colorless oil: R_f = 0.70 (hexane/EtOAc = 2:1)

Aldehyde 51. To a solution of TBDPS ether **48** (27.9 mg, 36.0 μmol) in THF (3.6 mL)

was added HF·py. (100 μL) at 0 °C. After the mixture was stirred at room temperature for 6 h, HF·py. (100 μL) was added. After the mixture was stirred at room temperature for 3 h, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 2:1) gave alcohol **50** (15.4 mg) as a colorless oil: R_f = 0.39 (hexane/EtOAc = 1:1), which was used in the next reaction without further purification.

To a solution of alcohol **50** (15.4 mg) in CH_2Cl_2 (3.0 mL) were added BAIB (25.0 mg, 77.8 μmol) and TEMPO (0.48 mg, 3.1 μmol) at 0 °C. After the mixture was stirred for 6 h at the same temperature, quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 3:1) gave aldehyde **51** (11.6 mg, 21.6 μmol, 60% in 2 steps) as a colorless oil: R_f = 0.56 (hexane/EtOAc = 1:1)

***p*-Methoxybenzyl Acetal 52.** To a solution of aldehyde **51** (5.9 mg, 11.0 μmol) and MS4A (10.0 mg) in CH_2Cl_2 (0.5 mL), was added DDQ (3.7 mg, 16.5 μmol) at 0 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was filtered through a Celite pad washed with EtOAc. Then, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave aldehyde **52** (12.4 mg, 4.51 μmol, 41%) as a colorless oil: R_f = 0.73 (hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, C_6D_6) δ 9.38 (d, J = 7.8 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 6.40 (ddd, J = 15.4, 10.0, 4.4 Hz, 1 H), 6.03 (m, 2 H), 5.92 (dd, J = 15.4, 7.8 Hz, 1 H), 5.28 (s, 1 H), 3.86–3.80 (m, 1 H), 3.47 (td, J = 7.8, 2.7 Hz, 1 H), 3.31 (s, 3 H), 3.18 (s, 3 H), 2.61–2.58 (m, 1 H), 2.29–2.22 (m, 1 H), 1.36–1.25 (m, 4 H), 1.00 (s, 9 H), 0.05 (d, J = 27.8 Hz, 1 H).

Diol 53. To a solution of α-hydroxy ketone **51** (310.6 mg, 400 μmol) in THF (8.6 mL) and MeOH (2.1 mL), was added Et_2BOMe (0.48 mL, 481 μmol) at –78 °C. After the mixture was stirred for 15 min at the same temperature, the reaction was added $NaBH_4$ (18.2 mg, 481 μmol). After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with AcOH. The mixture was diluted with EtOAc, washed with

H_2O, and brine, and then dried over Na_2SO_4. Co evaporated with MeOH (10 mL×5) and column chromatography (hexane/EtOAc = 4:1, 3:1) gave diol **53** (304 mg, 392.0 μmol, 98%) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 2:1); $[\alpha]^{25}_D$ –2.5 (*c* 1.00, $CHCl_3$); IR (neat) 3464, 2930, 1738 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.80 (d, *J* = 8.5 Hz, 4 H), 7.25–7,22 (m, 8 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 6.43 (dd, *J* = 15.1, 10.5 Hz, 1 H), 6.28 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.94 (dt, *J* = 15.1, 7.1 Hz, 1 H), 5.74 (dt, *J* = 15.1, 5.1 Hz, 1 H), 4.45 (d, *J* = 4.2 Hz, 2 H), 4.24 (d, *J* = 4.2 Hz, 2 H), 4.07–3.98 (m, 1 H), 3.88–3.75 (m, 2 H), 3.59 (d, *J* = 41.2 Hz, 1 H), 3.31 (s, 3 H), 3.25 (s, 3 H), 2.63–2.60 (m, 1 H), 2.44 (t, *J* = 5.1 Hz, 1 H), 2.25 (dd, *J* = 16.3, 8.5 Hz, 1 H), 2.12 (dd, *J* = 16.3, 3.6 Hz, 1 H), 1.78–1.59 (m, 2 H), 1.20 (s, 9 H), 1.03 (s, 9 H), 0.22 (d, *J* = 20.3 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 172.6, 159.7, 135.9, 134.2, 132.9, 132.4, 131.4, 131.1, 130.7, 130.5, 130.2, 129.9, 114.3, 114.0, 79.9, 77.7, 73.6, 72.1, 69.6, 64.7, 54.8, 41.8, 38.6, 33.9, 27.2, 26.6, 26.3, 19.6, 18.8, –3.7, –3.9; HRMS (ESI–TOF) calcd for $C_{44}H_{64}O_8Si_2Na$ $(M + Na)^+$ 799.4037, found 799.4037.

Diol 54. To a solution of α-hydroxy ketone **51** (595 mg, 0.77 mmol) in CH_3CN (9.0 mL) and AcOH (9.0 mL), was added $NaBH(OAc)_3$ (244 mg, 1.15 mmol) and at –20 °C. After the mixture was stirred for 2 h at –20 °C, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave diol **54** (565 mg, 0.73 μmol, 95%) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 2:1); $[\alpha]^{25}_D$ –9.1 (*c* 1.00, $CHCl_3$); IR (neat) 3476, 2930, 1739 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.73–7,41 (m, 4 H), 7.25–7,09 (m, 8 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.35 (dd, *J* = 15.1, 10.5 Hz, 1 H), 6.18 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.84 (dt, *J* = 15.1, 7.6 Hz, 1 H), 5.61 (dt, *J* = 15.1, 4.9 Hz, 1 H), 4.40 (d, *J* = 1.9 Hz, 2 H), 4.30 (d, *J* = 1.9 Hz, 1 H), 4.16 (d, *J* = 4.6 Hz, 2 H),, 4.07 (m, 1 H), 3.84–3.81 (m, 1 H), 3.68 (m, 1 H), 3.25 (s, 3 H), 3.21 (s, 3 H), 2.52 (t, *J* = 6.4 Hz, 2 H), 2.34–2.29 (m, 1 H), 2.17 (dd, *J* = 15.1, 3.4 Hz, 1 H), 1.71–1.66 (m, 2 H), 1.12 (s, 9 H), 0.94 (s, 9 H), 0.14 (d, *J* = 15.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 159.7, 135.9, 134.2, 132.4, 131.4, 131.1, 130.7, 130.5,　129.9, 114.2, 114.0, 80.3, 77.7, 70.0, 72.1, 66.3, 64.7, 54.8, 51.3, 41.4, 38.4, 34.2, 27.2, 26.5, 26.3, 19.6, 18.8, 14.3, –3.6, –4.1; HRMS (ESI–TOF) calcd for $C_{44}H_{64}O_8Si_2Na$ $(M + Na)^+$ 799.4037, found 799.4036.

***p*-Methoxybenzyl Acetal 55.** To a solution of diol **53** (5.4 mg, 6.82 μmol) in CH_2Cl_2 (0.5 mL) was added MS4A (5.0 mg) and *p*-anisaldehyde dimethylacetal (1.7μL, 10.2 μmol) at room temperature. The mixture was added CSA (0.46 mg, 2.0 μmol) at 0 °C and stirred at room temperature for 4 h. The mixture was added *p*-anisaldehyde dimethylacetal (1.7μL, 10.2 μmol) and CSA (0.46 mg, 2.0 μmol) at 0 °C. After the mixture was stirred at room temperature for 12 h, the reaction was quenched with Et_3N. The reaction was filtered through a Celite pad. Concentration and column chromatography (hexane/EtOAc = 10:1) gave *p*-methoxybenzyl asetal **55** (4.0 mg, 4.50 μmol, 66%) as a colorless oil: R_f = 0.72 (hexane/EtOAc = 2:1); δ 7.85–7.83 (m, 5 H), 7.64 (d, J = 8.5 Hz, 2 H), 7.47–7.44 (m, 5 H), 7.02 (dd, J = 7.4, 4.0 Hz, 5 H), 6.55 (dd, J = 15.1, 10.4 Hz, 1 H), 6.38 (dd, J = 15.1, 10.4 Hz, 1 H), 6.00 (dt, J = 15.1, 7.3 Hz, 1 H), 5.86 (dt, J = 15.1, 4.8 Hz, 1 H), 5.73 (s, 1 H), 4.62 (s, 1 H), 4.54–4.47 (m, 1 H), 4.36 (d, J = 4.8 Hz, 2 H), 4.29–4.24 (m, 1 H), 4.17 (t, J = 4.8 Hz, 1 H), 3.88–3.84 (m, 1 H), 3.68 (s, 3 H), 3.64 (s, 3 H), 3.62 (s, 3 H), 2.89 (dd, J = 15.1, 7.3 Hz, 1 H), 2.76–2.64 (m, 2 H), 1.93–1.80 (m, 2 H), 1.25–1.23 (brs, 1 H), 1.13 (s, 9 H), 1.01 (s, 9 H), 0.24 (s, 6 H).

Alcohol 61. To a solution of diol **53** (202 mg, 260 μmol) in THF (2.6 mL) were added $Me_2C(OMe)_2$ (0.32 mL, 2.26 mmol) and *p*-TsOH·H_2O (4.9mg, 26.0 μmol) at room temperature. The mixture was stirred at room temperature for 25 min, then quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave acetonide **60** (212 mg) as a colorless oil: R_f = 0.62 (hexane/EtOAc = 2:1), which was used in the next reaction without further purification.

To a solution of TBDPS ether **60** (212 mg) in THF (4.5 mL) was added HF·py. (0.5 mL) at 0 °C and. After the mixture was stirred at room temperature for 2 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 2.5:1) gave alcohol **61** (101.8 mg, 176.8 μmol, 68% in 2 steps) as a colorless oil: R_f = 0.33 (hexane/EtOAc = 2:1); $[\alpha]^{23}_D$ –5.5 (c 0.98, $CHCl_3$); IR (neat) 3459, 2952, 2692, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.20 (dd, J = 15.3, 10.6 Hz, 1 H), 6.08 (dd, J = 15.3, 10.6 Hz, 1 H),

5.76–5.70 (m, 2 H), 4.45 (s, 2 H), 4.24–4.20 (m, 2 H), 4.13 (d, *J* = 5.6 Hz, 2 H), 3.94 (ddd, *J* = 12.6, 4.9, 2.4 Hz, 1 H), 3.90 (s, 3 H), 3.48 (dt, *J* = 7.1, 4.4 Hz, 1 H), 2.53 (dd, *J* = 15.3, 7.1 Hz, 1 H), 2.38–2.33 (m, 4 H), 1.47 (dt, *J* = 12.6, 2.4 Hz, 1 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 0.89 (s, 9 H), 0.08 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.0, 131.9, 131.7, 131.3, 130.6, 129.8, 129.6, 113.6, 98.7, 78.7, 76.3, 71.6, 69.3, 65.9, 63.5, 55.3, 51.6, 41.6, 33.4, 31.7, 29.9, 26.2, 19.8, 18.5, –4.0, –4.3; HRMS (ESI–TOF) calcd for $C_{31}H_{50}O_8SiNa$ $(M + Na)^+$ 601.3173, found 601.3169.

Aldehyde 62. To a solution of alcohol **61** (101 mg, 176μmol) in CH_2Cl_2 (2.0 mL) was added BAIB (146 mg, 440 μmol) and TEMPO (5.5 mg, 35.2 μmol) at 0 °C, and stirred for 30 min at the same temperature. After the mixture was stirred for 1.5 h at room temperature, quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 3:1) gave corresponding aldehyde (101.5 mg, 105.6 μmol, 60%) as a colorless oil: R_f = 0.58 (hexane/EtOAc = 2:1)

To a solution of aldehyde (101.5 mg) in CH_2Cl_2 (4.0 mL) and pH=7 phosphate buffer (0.14 mL) was added DDQ (47.9 mg, 211 μmol) and at 0 °C and stirred at the same temperature. After the mixture was stirred for 30 min at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. Then, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave aldehyde **62** (76.0 mg, 165.4 μmol, 94% in 2 steps) as a colorless oil: R_f = 0.52 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ –14.4 (*c* 0.97, $CHCl_3$); IR (neat) 3490, 2953, 1739, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.8 Hz, 1 H), 7.09 (dd, *J* = 15.3, 9.9 Hz, 1 H), 6.43–6.31 (m, 2 H), 6.10 (dd, *J* = 15.3, 7.8 Hz, 1 H), 4.34–4.27 (m, 1 H), 4.03 (ddd, *J* = 8.0, 5.4, 2.4 Hz, 1 H), 3.78 (dt, *J* = 8.0, 3.9 Hz, 1 H), 3.68 (s, 3 H), 3.53 (t, *J* = 5.4 Hz, 1 H), 2.56 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.51 (dd, *J* = 5.4, 3.9 Hz, 1 H), 2.42–2.37 (m, 2 H), 2.30 (d, *J* = 3.9 Hz, 1 H), 1.70 (dt, *J* = 12.7, 2.4 Hz, 1 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 0.90 (s, 9 H), 0.11 (d, *J* = 5.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.1, 151.9, 143.0, 130.8, 130.6, 98.8, 77.3, 72.7, 69.7, 65.9, 51.7, 41.5, 36.5, 32.7, 29.9, 26.0, 19.8, 18.3, –3.8, –4.2; HRMS (ESI–TOF) calcd for $C_{23}H_{40}O_7SiNa$ $(M + Na)^+$ 479.2441, found 479.2440.

Triol 63.

(entry 2)

To a solution of $MgBr_2$ (6.3 mg, 34.2 μmol) in benzene (0.2 mL) was added acetonide **62** (3.9 mg, 8.54 μmol) in benzene (0.3 mL + 0.2 mL) at room temperature, and stirred for 1 h at the same temperature. After the mixture was refluxed for 12 h, quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1, 1:1) gave corresponding triol **63** (0.5 mg, 4.8 μmol, 14%) as a colorless oil: R_f = 0.09 (hexane/EtOAc = 1:1), and acetonide **63a** (1.3 mg, 11.3 μmol, 33%) as a colorless oil: R_f = 0.53 (hexane/EtOAc = 1:1)

(entry 3)

To a solution of acetonide **62** (3.1 mg, 6.79 μmol) in CH_2Cl_2 (0.5 mL) was added $TiCl_4$ (1.1 μL, 10.2 μmol) and at 0 °C. After the mixture was stirred for 10 min stirred at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. Then, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave triol **63** (1.9 mg, 4.55 μmol,　67%) as a colorless oil: R_f = 0.09 (hexane/EtOAc = 1:1)

(entry 4)

To a solution of acetonide **62** (4.8 mg, 10.5 μmol) in CH_2Cl_2 (0.75 mL) was added $TiCl_4$ (1.7 μL, 15.7 μmol) and at –30 °C. After the mixture was stirred for 5 min stirred at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. Then, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1, 1:1) gave triol **63** (4.3 mg, 10.3 μmol, 98%) as a colorless oil: R_f = 0.09 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ –5.1 (*c* 0.73, $CHCl_3$); IR (neat) 3449, 2928, 1736, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 8.1 Hz, 1 H), 7.09 (dd, J = 15.3, 9.8 Hz, 1 H), 6.41–6.33 (m, 2 H), 6.10 (dd, J = 15.3, 8.0 Hz, 1 H), 4.30–4.28 (m, 1 H), 3.99–3.95 (m, 1H), 3.72 (s, 3 H), 3.69 (d, J = 2.2 Hz, 1 H), 3.54 (t, J = 14.4 Hz, 1 H), 2.63–2.35 (m, 4 H), 1.85 (t, J = 14.4 Hz, 1 H), 1.56 (m, 1 H), 0.91 (s, 9 H), 0.12 (d, J = 2.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 172.8, 152.0, 143.2, 131.9, 130.8, 130.5, 77.9, 73.7, 72.6, 69.2, 51.9, 41.6, 41.4, 38.4, 36.7, 26.1, 18.3, –4.0; HRMS (ESI–TOF) calcd for $C_{20}H_{36}O_7SiNa$ $(M + Na)^+$ 439.2128, found 439.2126..

(entry 5)

To a solution of acetonide **62** (13.8 mg, 30.2 μmol) in CH_2Cl_2 (2.3 mL) was added $TiCl_4$ (3.79 μL, 36.2 μmol) and at –50 °C. After the mixture was stirred for 10 min stirred at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. Then, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1, 1:1) gave triol **63** (6.3 mg, 50%) as a colorless oil: R_f = 0.09 (hexane/EtOAc = 1:1) and acetonide **63a** (6.3 mg, 46%) as a colorless oil: R_f = 0.53 (hexane/EtOAc = 1:1)

(3*S*, 5*R*, 6*S*, 7*S*)-Tetraol 6a. To a solution of TBS ether **63** (12.4 mg, 29.8 μmol) in THF (1.5 mL) was added HF·py. (60 μL) at 0 °C and stirred for 2 h at the same temperature. After the mixture was stirred at room temperature for 2 h, HF·py. (70 μL) was added at 0 °C and stirred for 30 min at the same temperature. After the mixture was stirred at room temperature for 5 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine. Back extract with AcOEt and then dried over Na_2SO_4. Concentration and flash column chromatography (CH_2Cl_2/MeOH = 20:1) gave (3*S*, 5*R*, 6*S*, 7*S*)-tetraol **6a** (1.6 mg, 5.36 μmol, 18%, 33% brsm) as a colorless oil: R_f = 0.33 (CH_2Cl_2/MeOH = 10:1); $[\alpha]^{23}_D$ –32.1 (*c* 0.15, $CHCl_3$); IR (neat) 3417, 2924, 1731, 1679 cm^{-1}; ^1H NMR (400 MHz, CO_3OD) δ 9.48 (d, *J* = 8.1 Hz, 1 H), 7.33 (ddd, *J* = 15.3, 10.0, 2.7 Hz, 1 H), 6.48 (dd, *J* = 15.3, 2.7 Hz, 2 H), 6.08 (dd, *J* = 15.3, 8.1 Hz, 1 H), 4.33–4.26 (m, 1 H), 3.85 (ddd, *J* = 9.0, 5.9, 2.7 Hz, 1 H), 3.74–3.69 (m, 1H), 3.67 (s, 3 H), 3.38 (t, *J* = 6.3 Hz, 1 H), 2.57 (dd, *J* = 15.3, 4.4 Hz, 2 H), 2.43 (dd, *J* = 15.3, 8.6 Hz, 2 H), 1.85 (t, *J* = 14.4 Hz, 1 H), 1.85 (ddd, *J* = 14.3, 5.9, 3.1 Hz, 1 H), 0.91 (s, 9 H), 0.12 (d, *J* = 2.2 Hz, 6 H); ^{13}C NMR (100 MHz, CO_3OD) δ196.0, 152.0, 143.2, 131.9, 130.8, 130.5, 77.9, 73.7, 72.6, 69.2, 51.9, 41.6, 41.4, 38.4, 36.7, 26.1, 18.3, –4.0; HRMS (ESI–TOF) calcd for $C_{20}H_{36}O_7SiNa$ $(M + Na)^+$ 439.2128, found 439.2126.

Diol 64. To a solution of TBS ether 17 (160 mg, 0.277 mmol) in MeCN (2.8 mL) was added a mixed solution of TBAF (1.0 M solution in THF, 2.8 mL, 2.80 mmol) and AcOH (0.16 mL, 2.77 mmol) at room temperature. After the mixture was stirred at 60 °C for 6 days, the reaction was quenched with saturated aqueous NH4Cl. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was washed with EtOAc three times. The combined organic layer was dried over

Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1, EtOAc) gave diol **64** (111 mg, 0.238 mmol, 86%) as a colorless oil: R_f = 0.09 (hexane/EtOAc = 1:1); $[\alpha]^{22}_D$ +10.5 (*c* 0.71, $CHCl_3$); IR (neat) 3420, 2928, 2858, 1738, 1613 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.17 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.26−6.16 (m, 2 H), 5.91−5.86 (m, 1 H), 5.62 (dt, *J* = 14.0, 5.6 Hz, 1 H), 4.51−4.47 (m, 1 H), 4.43 (d, *J* = 11.2 Hz, 1 H), 4.33−4.29 (m, 1 H), 4.22 (d, *J* = 11.2 Hz, 1 H), 4.11−4.06 (m, 1 H), 3.92−3.84 (m, 3 H), 3.60−3.56 (m, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 2.62−2.48 (m, 3 H), 2.18 (dd, *J* = 15.6, 5.2 Hz, 1 H), 1.46−1.40 (m, 2 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 0.92 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.9, 159.9, 132.7, 131.2, 130.9, 130.7, 130.0, 114.2, 99.0, 77.6, 73.8, 71.2, 69.7, 66.3, 63.3, 54.9, 51.2, 41.6, 32.9, 31.4, 30.3, 19.9; HRMS (ESI−TOF) calcd for $C_{25}H_{36}O_8Na$ $[M + Na]^+$ 487.2308, found 487.2306.

Allylic Alcohol 65. To a solution of diol **64** (94.4 mg, 0.163 mmol) in CH_2Cl_2 (1.6 mL) was added 2,6-lutidine (67 μL, 0.456 mmol) and TESOTf (88 μL, 0.391 mmol) at 0 °C. After the mixture was stirred at room temperature for 40 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1, 10:1) gave the corresponding bis-TES ether (111 mg, 0.160 mmol, 98%) as a colorless oil: R_f = 0.71 (hexane/EtOAc = 2:1); $[\alpha]^{26}_D$ +4.2 (*c* 0.49, $CHCl_3$); IR (neat) 2953, 2871, 1742, 1612 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.24 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.41 (dd, *J* = 15.0, 10.6 Hz, 1 H), 6.30 (dd, J = 15.0, 10.6 Hz, 1 H), 5.95−5.87 (m, 1 H), 5.73 (dt, *J* = 15.0, 5.3 Hz, 1 H), 4.48 (d, *J* = 11.2 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 4.35−4.27 (m, 1 H), 4.15 (d, *J* = 5.3 Hz, 2 H), 4.12−4.07 (m, 1 H), 3.95 (t, *J* = 5.0 Hz, 1 H), 3.61 (q, *J* = 5.4 Hz, 1 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 2.60−2.53 (m, 3 H), 2.22 (dd, *J* = 15.4, 5.4 Hz, 1 H), 1.50−1.44 (m, 2 H), 1.46 (s, 3 H), 1.33 (s, 3 H), 1.09 (t, *J* = 8.2 Hz, 9 H), 1.02 (t, *J* = 7.4 Hz, 9 H), 0.80 (q, *J* = 8.2 Hz, 6 H), 0.62 (q, *J* = 7.4 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 159.8, 132.5, 131.3, 131.1, 131.0, 130.4, 130.0, 114.1, 99.0, 78.8, 76.9, 71.9, 69.8, 66.4, 63.5, 54.9, 51.1, 41.8, 33.7, 31.8, 30.2, 19.9, 7.5, 7.2, 5.9, 5.2; HRMS (ESI−TOF) calcd for $C_{37}H_{64}O_8Si_2Na$ $[M + Na]^+$ 715.4037, found 715.4031.

To a solution of the corresponding TES ether (99.7 mg, 0.144 mmol) in CH2Cl2 (7.0 mL) and MeOH (0.7 mL) was added PPTS (11.0 mg, 43.0 μmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with Et3N.

The mixture was diluted with EtOAc, washed with H2O and brine, and then dried over Na2SO4. Concentration and column chromatography (hexane/EtOAc = 10:1, 2:1) gave allylic alcohol 65 (75.1 mg, 0.130 mmol 90%) as a colorless oil: R_f = 0.53 (hexane/EtOAc = 1:1); $[\alpha]^{21}_D$ +2.5 (c 1.53, $CHCl_3$); IR (neat) 3460, 2952, 2875, 1739, 1612 cm−1; 1H NMR (400 MHz, C6D6) δ 7.23 (d, J = 8.0 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 2 H), 6.26−6.16 (m, 2 H), 5.90−5.83 (m, 1 H), 5.64−5.57 (m, 1 H), 4.48 (d, J = 11.5 Hz, 1 H), 4.36 (d, J = 11.5 Hz, 1 H), 4.32−4.31 (m, 1 H), 4.11−4.07 (m, 1 H), 3.96−3.93 (m, 1 H), 3.90 (brs, 2 H), 3.62−3.58 (m, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 2.59−2.54 (m, 3 H), 2.24 (dd, J = 15.5, 5.1 Hz, 1 H), 1.49−1.46 (m, 2 H), 1.46 (s, 3 H), 1.33 (s, 3 H), 1.08 (t, J = 7.9 Hz, 9 H), 0.79 (q, J = 7.9 Hz, 6 H); 13C NMR (100 MHz, C6D6) δ 170.9, 159.8, 132.4, 131.3, 131.2, 131.1, 131.0, 130.0, 114.1, 99.0, 78.7, 76.8, 71.8, 69.8, 66.4, 63.2, 54.9, 51.2, 41.8, 33.7, 31.7, 30.2, 19.9, 7.5, 5.9; HRMS (ESI−TOF) calcd for C31H50O8SiNa [M + Na]+ 601.3173, found 601.3171.

Alcohol 66. To a solution of alcohol **65** (45.6 mg, 78.8 μmol) in CH_2Cl_2 (1.6 mL) were added $PhI(OAc)_2$ (65.0 mg, 0.197 mmol) and TEMPO (2.5 mg, 15.8 μmol) at 0 °C. After the mixture was stirred at room temperature for 5 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding unsaturated aldehyde (44.5 mg), which was used for the next reaction without further purification.

To a solution of the PMB ether obtained above (44.5 mg) in CH_2Cl_2 (1.7 mL) and phosphate pH standard solution (0.1 mL) was added DDQ (26.0 mg, 0.116 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **66** (27.5 mg, 34.7 μmol 76% in two steps) as a colorless oil: R_f = 0.23 (hexane/EtOAc = 2:1); $[\alpha]^{23}_D$ −15.2 (*c* 1.00, $CHCl_3$); IR (neat) 3479, 2953, 2876, 1739, 1682, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 7.8 Hz, 1 H), 7.09 (dd, J = 15.4, 10.0 Hz, 1 H), 6.44−6.30 (m, 2 H), 6.10 (dd, J = 15.4, 7.8 Hz, 1 H), 4.35−4.28 (m, 1 H), 4.05−4.01 (m, 1 H), 3.78−3.75 (m, 1 H), 3.68 (s, 3 H), 3.54 (d, J = 5.5 Hz, 1 H), 2.60−2.51 (m, 2 H), 2.43−2.32 (m, 2 H), 1.72−1.64 (m, 2 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 0.97 (t, J = 8.0 Hz, 9 H), 0.65 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.1, 151.9, 143.0, 130.8, 130.6, 98.8, 72.8, 70.0, 65.9, 51.7, 41.5, 36.6, 32.5, 29.9, 19.8, 7.0, 5.3; HRMS (ESI−TOF) calcd for $C_{23}H_{40}O_7SiNa$ $[M + Na]^+$ 479.2441, found 479.2446.

Tetraol 6a from 66. To a solution of acetonide **66** (4.1 mg, 8.99 μmol) in CH_2Cl_2 (0.5 mL) was added $TiCl_4$ (2.0 μL, 18.2 μmol) at −30 °C. The mixture was gradually warmed up to room temperature for 1 h. After the mixture was stirred at room temperature for 27 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was washed with EtOAc four times. The combined organic layer was dried over Na_2SO_4. Concentration and column chromatography (CH_2Cl_2/MeOH = 10:1) gave tetraol **6a** (2.0 mg, 6.65 μmol 74%).

Ketone 67. To a solution of diol **64** (59.5 mg, 0.128 mmol) in CH_2Cl_2 (1.2 mL) were added imidazole (12.2 mg, 0.179 mmol) and TESCl (26 μL, 0.154 mmol) at −30 °C. After the mixture was gradually warmed up to −10 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding mono-TES ether (60.8 mg), which was used for the next reaction without further purification.

To a suspension of the alcohol obtained above (60.8 mg) and MS4 Å (50.0 mg) in CH_2Cl_2 (1.3 mL) were added NMO (64.0 mg, 0.546 mmol) and TPAP (1.8 mg, 5.30 μmol) at room temperature. After the mixture was stirred at room temperature for 8 h, the mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 4:1) gave ketone **67** (54.8 mg, 0.094 mmol 74% in two steps) as a colorless oil: R_f = 0.56 (hexane/EtOAc = 2:1); $[\alpha]^{22}_D$ +15.6 (*c* 0.50, $CHCl_3$); IR (neat) 2953, 2871, 1738, 1613 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.31 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.31 (dd, *J* = 14.0, 10.6 Hz, 1 H), 6.17 (dd, *J* = 15.0, 10.6 Hz, 1 H), 5.86 (dt, *J* = 15.0, 7.6 Hz, 1 H), 5.72 (dt, *J* = 14.0, 5.0 Hz, 1 H), 4.59−4.51 (m, 2 H), 4.37−4.16 (m, 3 H), 4.10 (d, *J* = 4.7 Hz, 2 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 2.66−2.55 (m, 2 H), 2.43 (dd, *J* = 15.8, 7.6 Hz, 1 H), 2.09 (dd, *J* = 15.8, 5.0 Hz, 1 H), 1.65 (dt, *J* = 12.9, 2.7 Hz, 1 H), 1.42−1.35 (m, 1 H), 1.40 (s, 3 H), 1.20 (s, 3 H), 1.00 (t, *J* = 7.9 Hz, 9 H), 0.60 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 206.8, 170.5, 159.8, 132.9, 132.1, 130.6, 130.0, 129.7, 129.1, 114.1, 99.4, 80.4, 73.4, 72.3, 66.1, 63.4, 54.8, 51.2, 41.2, 35.7, 32.2, 30.1, 19.3, 7.2, 5.1; HRMS (ESI−TOF) calcd for $C_{31}H_{48}O_8SiNa$ $[M + Na]^+$ 599.3016, found 599.3012.

Alcohol 68. To a solution of ketone **67** (8.5 mg, 14.7 μmol) in MeOH (0.5 mL) was added $NaBH_4$ (0.6 mg, 14.7 μmol) at –78 °C. After the mixture was stirred for 20 min at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2.5:1) gave alcohol **68** (8.3 mg, 14.4 μmol 98%) as a colorless oil: R_f = 0.30 (hexane/EtOAc = 2:1); $[\alpha]^{23}_D$ +20.8 (*c* 0.44, $CHCl_3$); IR (neat) 3518, 2953, 2885, 1740 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.40 (dd, *J* = 15.1, 10.5 Hz, 1 H), 6.25 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.74 (m, 2 H), 4.49 (d, *J* = 11.2 Hz, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 4.15 (d, *J* = 4.9 Hz, 2 H), 3.98 (m, 2 H), 3.52 (t, *J* = 4.7 Hz, 2 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 2.66 (m, 2 H), 2.50 (m, 3 H), 2.12 (dd, *J* = 15.6, 4.9 Hz, 1 H), 1.41 (s, 3 H), 1.30 (s, 3 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 0.62 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 159.8, 132.8, 131.6, 131.1, 130.2, 130.2, 129.9, 114.1, 99.1, 78.4, 74.7, 71.7, 70.0, 66.2, 63.4, 54.9, 51.1, 41.4, 34.2, 32.4, 30.3, 19.8, 7.2, 5.1; HRMS (ESI–TOF) calcd for $C_{31}H_{50}O_8SiNa$ $(M + Na)^+$ 601.3173, found 601.3183.

Allylic Alcohol 71. To a solution of alcohol **68** (8.3 mg, 14.4 μmol) in CH_2Cl_2 (0.5 mL) were added 2,6-lutidine (17 μL, 0.113 mmol) and TESOTf (24 μL, 0.107 mmol) at 0 °C. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave the corresponding bis-TES ether (10.1 mg), which was used for the next reaction without further purification.

To a solution of TES ether obtained above (10.1 mg) in CH_2Cl_2 (0.5 mL) and MeOH (0.1 mL) was added PPTS (1.8 mg, 7.30 μmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, the reaction was quenched with Et_3N. Concentration and column chromatography (hexane/EtOAc = 3:1) gave allylic alcohol **71** (8.5 mg, 14.4 μmol quant. in 2 steps) as a colorless oil: R_f = 0.22 (hexane/EtOAc = 2:1); $[\alpha]^{21}_D$ +11.2 (*c* 1.15, $CHCl_3$); IR (neat) 3463, 2952, 2871, 1739, 1612 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.22 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.25−6.21 (m, 2 H), 5.81−5.74(m, 1 H), 5.64−5.57 (m, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.35 (d, *J* = 11.5 Hz, 1 H), 4.33−4.30

(m, 1 H), 4.16−4.10 (m, 1 H), 3.89 (d, *J* = 2.9 Hz, 2 H), 3.73 (dd, *J* = 7.1, 3.2 Hz, 1 H), 3.54−5.49 (m, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.75−2.68 (m, 1 H), 2.57−2.48 (m, 2 H), 2.16 (dd, *J* = 15.6, 4.9 Hz, 1 H), 1.48−1.42 (m, 2 H), 1.41 (s, 3 H), 1.10 (t, *J* = 7.8 Hz, 9 H), 0.76 (t, *q* = 7.8 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.9, 159.8, 132.4, 131.5, 131.2, 130.9, 129.8, 129.6, 114.1, 99.1, 79.6, 76.4, 71.4, 66.1, 63.2, 54.9, 51.2, 41.6, 33.5, 32.9, 30.4, 19.8, 7.6, 5.9; HRMS (ESI–TOF) calcd for $C_{31}H_{50}O_8SiNa$ $(M + Na)^+$ 601.3173, found 601.3170.

Alcohol 72. To a solution of alcohol **71** (8.5 mg, 14.6 μmol) in CH_2Cl_2 (0.5 mL) were added BAIB (12.1 mg, 36.5 μmol) and TEMPO (1.0 mg, 6.40 μmol) at 0 °C.

After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave corresponding aldehyde (7.6 mg), which was used in the next reaction without further purification.

To a solution of aldehyde (7.6 mg) in CH_2Cl_2 (0.4 mL) and phosphate pH standard solution (40 μL) was added DDQ (3.6 mg, 16.0 μmol) and at 0 °C and stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. Then, washed with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **72** (5.5 mg, 11.8 μmol 82% in 2 steps) as a colorless oil: R_f = 0.16 (hexane/EtOAc = 2:1); $[\alpha]^{21}_D$ –35.7 (*c* 0.47, $CHCl_3$); IR (neat) 3490, 2954, 2871, 1739 , 1682, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.55 (d, *J* = 8.1 Hz, 1 H), 7.08 (dd, *J* = 15.2, 10.4 Hz, 1 H), 6.42−6.26 (m, 2 H), 6.09 (dd, *J* = 15.2, 7.8 Hz, 1 H), 4.32−4.26 (m, 1 H), 3.98−3.94 (m, 1 H), 3.71−3.69 (m, 1 H), 3.69 (s, 3 H), 3.45 (d, *J* = 6.6 Hz, 1 H), 2.57−2.30 (m, 4 H), 1.65−1.60 (m, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.26−1.17 (m, 1 H), 0.97 (t, *J* = 7.9 Hz, 9 H), 0.69−0.61 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.0, 151.9, 142.6, 130.7, 130.6, 98.9, 77.1, 71.0, 69.3, 65.5, 51.7, 41.4, 39.2, 31.9, 29.9, 19.6, 7.1, 5.3; HRMS (ESI–TOF) calcd for $C_{23}H_{40}O_7SiNa$ $(M + Na)^+$ 479.2441, found 479.2442.

(3*S*, 5*R*, 6*R*, 7*S*)-Tetraol 6b. To a solution of TES ether **72** (9.6 mg, 23.0 μmol) in THF (1.0 mL) was added HF·py. (50 μL) at 0 °C and stirred for 2.5 h at the same temperature. After the mixture was stirred at room temperature for 2 h. After the mixture was stirred at room temperature for 5 h, the mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine. Back extract with AcOEt and then dried over Na_2SO_4. Concentration and flash column chromatography (CH_2Cl_2e/MeOH = 20:1) gave (3*S*, 5*R*, 6*R*, 7*S*)-tetraol **6b** (5.5 mg, 18.2 μmol, 79%) as a colorless oil: R_f = 0.35 (CH_2Cl_2/MeOH = 10:1); $[\alpha]^{21}_D$ –6.1 (*c* 0.10, $CHCl_3$); IR (neat) 3367, 2924, 2858, 1727 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 9.49 (d, *J* = 7.8 Hz, 1 H), 7.29 (dd, *J* = 15.6, 9.9 Hz, 1 H), 6.51−6.41 (m, 2 H), 6.09 (dd, *J* = 15.6, 7.8 Hz, 1 H), 4.25−4.20 (m, 1 H), 3.90−3.86 (m, 1 H), 3.83−3.79 (m, 1 H), 3.67 (s, 3 H), 3.33−3.31 (m, 1 H), 2.56 (dd, *J* = 15.0, 4.2 Hz, 1 H), 2.53−2.43 (m, 2 H), 2.44 (dd, *J* = 15.0, 8.7 Hz, 1 H), 1.76−1.72 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 196.0, 173.7, 154.8, 145.0, 131.9, 131.2, 76.1, 72.9, 71.7, 67.7, 52.0, 43.1, 41.1, 38.7; HRMS (ESI–TOF) calcd for $C_{14}H_{22}O_7Na$ $(M + Na)^+$ 325.1263, found 325.1266.

Diol 73. To a solution of diol **54** (871 mg, 1.12 mmol) in THF (11 mL) were added $Me_2C(OMe)_2$ (1.4 mL, 11.2 mmol) and *p*-TsOH· H_2O (21.0 mg, 0.112 mmol) at room temperature. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave the corresponding acetonide (822 mg, 1.00 mmol 90%) as a colorless oil: R_f = 0.62 (hexane/EtOAc = 2:1); $[\alpha]^{21}_D$ −0.4 (*c* 0.99, $CHCl_3$); IR (neat) 2929, 2856, 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.8, 1.5 Hz, 4 H), 7.44−7.36 (m, 6 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.26 (dd, *J* = 15.0, 10.5 Hz, 1 H), 6.11 (dd, *J* = 15.0, 10.5 Hz, 1 H), 5.73−5.65 (m, 2 H), 4.47 (s, 2 H), 4.25−4.16 (m, 3 H), 3.99−3.94 (m, 1 H), 3.81−3.78 (m, 1 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.42−3.38 (m, 1 H), 2.52 (dd, J = 15.6, 8.3 Hz, 1 H), 2.44−2.33 (m, 3 H), 2.08−2.01 (m, 1 H), 1.59 (brs, 1 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 1.08 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 159.1, 135.5, 133.7, 131.9, 130.5, 130.2, 130.0, 129.5, 129.3, 127.6, 113.7, 100.6, 79.3, 75.9, 71.8, 66.8, 64.3, 63.8, 55.3, 51.6, 40.7, 33.8, 32.8, 26.9, 26.2, 24.6, 24.5, 19.3, 18.4, −4.0,

−4.3; HRMS (ESI−TOF) calcd for $C_{47}H_{68}O_8Si_2Na$ $[M + Na]^+$ 839.4351, found 839.4348.

To a solution of the corresponding bis-silyl ether (409 mg, 0.501 mmol) in MeCN (5.0 mL) was added a mixed solution of TBAF (1.0 M solution in THF, 2.0 mL, 2.00 mmol) and AcOH (0.10 mL, 2.00 mmol) at room temperature. After the mixture was stirred at reflux for 3 days, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was washed with EtOAc twice. The combined organic layer was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 1:1) gave diol **73** (154 mg, 0.330 mmol 66%) as a colorless oil: R_f = 0.19 (hexane/EtOAc = 1:1); $[\alpha]^{20}_D$ +43.1 (*c* 0.68, $CHCl_3$); IR (neat) 3459, 2925, 1739, 1612 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.19−7.16 (m, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.25−6.15 (m, 2 H), 5.92−5.85 (m, 1 H), 5.63−5.57 (m, 1 H), 4.43 (d, *J* = 11.5 Hz, 1 H), 4.37−4.30 (m, 1 H), 4.23 (d, *J* = 11.5 Hz, 1 H), 4.18−4.13 (m, 1 H), 3.96 (d, *J* = 5.7 Hz, 1 H), 3.89 (d, *J* = 5.4 Hz, 2 H), 3.54−3.50 (m, 1 H), 3.33 (s, 3 H), 3.33 (s, 3 H), 2.61−2.55 (m, 2 H), 2.48 (dd, *J* = 15.6, 8.8 Hz, 1 H), 2.23−2.18 (m, 2 H), 2.08−2.01 (m, 1 H), 1.37 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 159.8, 132.8, 131.2, 131.2, 130.9, 130.6, 129.8, 114.2, 100.8, 77.8, 73.8, 71.3, 67.1, 64.2, 63.3, 54.9, 51.1, 40.9, 32.9, 32.5, 25.1, 25.0; HRMS (ESI−TOF) calcd for $C_{25}H_{36}O_8Na$ $[M + Na]^+$ 487.2308, found 487.2302.

Alcohol 74. To a solution of diol **73** (22.4 mg, 48.2 μmol) in CH_2Cl_2 (1.0 mL) were added 2,6-lutidine (40 μL, 0.270 mmol) and TESOTf (52 μL, 0.232 mmol) at 0 °C. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 4:1) gave the corresponding bis-TES ether (34.1 mg, 48.2 μmol, quant.) as a colorless oil: R_f = 0.50 (hexane/EtOAc = 4:1); $[\alpha]^{25}_D$ +16.4 (*c* 0.23, $CHCl_3$); IR (neat) 2953, 2871, 1743, 1612 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.23 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.46−6.35 (m, 1 H), 6.34−6.24 (m, 1 H), 5.95−5.86 (m, 1 H), 5.73 (dt, *J* = 15.1, 5.4 Hz, 1 H), 4.47 (d, *J* = 11.2 Hz, 1 H), 4.46−4.38 (m, 1 H), 4.34 (d, *J* = 11.2 Hz, 1 H), 4.22−4.13 (m, 3 H), 4.05 (dd, *J* = 5.9, 4.1 Hz, 1 H), 3.50 (q, *J* = 5.3 Hz, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 2.62−2.45 (m, 3 H), 2.25 (dd, *J* = 15.5, 5.1

Hz, 1 H), 2.21−2.12 (m, 1 H), 1.44 (s, 3 H), 1.43−1.34 (m, 1 H), 1.32 (s, 3 H), 1.10 (t, *J* = 7.9 Hz, 9 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 0.84−0.76 (q, *J* = 7.9 Hz, 6 H), 0.62 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 159.8, 132.6, 131.3, 130.7, 130.4, 129.9, 114.1, 100.9, 79.2, 76.4, 71.9, 67.3, 64.2, 63.5, 54.9, 51.1, 41.0, 33.9, 32.9, 24.9, 24.8, 7.5, 7.2, 5.9, 5.2; HRMS (ESI−TOF) calcd for $C_{37}H_{64}O_8Si_2Na$ $[M + Na]^+$ 715.4037, found 715.4037.

To a solution of the corresponding TES ether (15.0 mg, 21.6 μmol) in CH_2Cl_2 (0.7 mL) and MeOH (70 μL) was added PPTS (1.6 mg, 6.32 μmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. After the mixture was stirred at room temperature for 30 min, the reaction was quenched with Et3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 2:1) gave the corresponding allylic alcohol (10.7 mg, 19.0 μmol, 88%) as a colorless oil: R_f = 0.66 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ +12.8 (*c* 0.74, $CHCl_3$); IR (neat) 3462, 2952, 2875, 1742, 1612 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.23 (d, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 6.24−6.15 (m, 2 H), 5.88−5.81 (m, 1 H), 5.63−5.57 (m, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H), 4.44−4.39 (m, 1 H), 4.35 (d, *J* = 11.5 Hz, 1 H), 4.20−4.15 (m, 1 H), 4.04 (t, *J* = 4.9 Hz, 1 H), 3.89 (d, *J* = 5.4 Hz, 2 H), 3.51−3.47 (m, 1 H), 3.33 (s, 3 H), 3.33 (s, 3 H), 2.59−2.49 (m, 4 H), 2.25 (dd, *J* = 15.5, 4.9 Hz, 1 H), 2.19−2.12 (m, 1 H), 1.44 (s, 3 H), 1.40−1.30 (m, 1 H), 1.32 (s, 3 H), 1.10 (t, *J* = 8.0 Hz, 9 H), 0.79 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 159.8, 132.5, 131.2, 131.1, 131.0, 129.9, 114.1, 100.9, 79.1, 76.3, 71.9, 67.3, 64.2, 63.2, 54.9, 51.1, 41.0, 33.8, 32.8, 24.9, 24.8, 7.5, 5.9; HRMS (ESI−TOF) calcd for $C_{31}H_{50}O_8SiNa$ $[M + Na]^+$ 601.3173, found 601.3168.

To a solution of the corresponding allylic alcohol (52.8 mg, 91.3 μmol) in CH_2Cl_2 (1.8 mL) were added BAIB (76.0 mg, 0.228 mmol) and TEMPO (2.9 mg, 18.3 μmol) at 0 °C. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding unsaturated aldehyde (48.8 mg), which was used for the next reaction without further purification.

To a solution of the PMB ether obtained above (48.8 mg) in CH_2Cl_2 (1.7 mL) and phosphate pH standard solution (0.1 mL) was added DDQ (26.0 mg, 0.115 mmol) at

0 °C. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **74** (29.9 mg, 65.7 μmol 72% in two steps) as a colorless oil: R_f = 0.61 (hexane/EtOAc = 1:1); $[\alpha]^{23}_D$ +5.8 (*c* 0.88, $CHCl_3$); IR (neat) 3472, 2953, 2876, 1741, 1682, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.8 Hz, 1 H), 7.09 (dd, *J* = 15.2, 10.2 Hz, 1 H), 6.44−6.29 (m, 2 H), 6.10 (dd, *J* = 15.2, 7.8 Hz, 1 H), 4.26−4.19 (m, 1 H), 4.00−3.95 (m, 1 H), 3.68 (s, 3 H), 3.67−3.63 (m, 2 H), 2.59−2.51 (m, 2 H), 2.46 (dd, *J* = 15.6, 5.2 Hz, 1 H), 2.39−2.31 (m, 2 H), 2.07− 2.00 (m, 1 H), 1.63−1.56 (m, 1 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 0.65 (q, *J* = 7.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.2, 151.8, 142.9, 131.0, 130.7, 100.8, 72.8, 67.3, 63.7, 51.7, 40.7, 36.8, 33.5, 24.6, 24.5, 7.0, 5.4; HRMS (ESI−TOF) calcd for $C_{23}H_{40}O_7SiNa$ $[M + Na]^+$ 479.2441, found 479.2446.

(3*R*, 5*R*, 6*S*, 7*S*)-Tetraol 6c. To a solution of acetonide **74** (20.7 mg, 45.4 μmol) in CH_2Cl_2 (2.3 mL) was added $TiCl_4$ (10 μL, 90.8 μmol) at −30 °C. The mixture was gradually warmed up to room temperature for 2 h. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was washed with EtOAc four times. The combined organic layer was dried over Na_2SO_4. Concentration and column chromatography (CH_2Cl_2/ MeOH = 10:1) gave tetraol **6c** (6.1 mg, 20.0 μmol 44%) as a colorless oil: R_f = 0.35 (CH_2Cl_2/MeOH = 10:1); $[\alpha]^{24}_D$ −8.9 (c 0.10, $CHCl_3$); IR (neat) 3388, 2925, 2853, 1730, 1674, 1636 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 9.49 (d, *J* = 7.8 Hz, 1 H), 7.33−7.28 (m, 1 H), 6.50−6.47 (m, 2 H), 6.08 (dd, *J* = 15.0, 7.8 Hz, 1 H), 4.32−4.27 (m, 1 H), 3.93−3.89 (m, 1 H), 3.75−3.71 (m, 1 H), 3.67 (s, 3 H), 3.39 (t, *J* = 6.6 Hz, 1H), 2.65−2.61 (m, 1 H), 2.54−2.47 (m, 2 H), 2.43−2.37 (m, 1 H), 1.78 (ddd, *J* = 14.4, 9.6, 2.4 Hz, 1 H), 1.60 (ddd, *J* = 14.4, 9.6, 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 196.0, 173.8, 155.5, 145.8, 131.8, 131.0, 78.1, 73.1, 70.6, 66.4, 52.0, 43.9, 40.3, 37.8; HRMS (ESI−TOF) calcd for $C_{14}H_{22}O_7Na$ $[M + Na]^+$ 325.1263, found 325.1271.

Ketone 75. To a solution of diol **73** (10.8 mg, 23.4 μmol) in CH_2Cl_2 (0.3 mL) were

added imidazole (2.2 mg, 32.8 μmol) and TESCl (4.7 μL, 28.1 μmol) at −30 °C. After the mixture was stirred at −30 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave the corresponding mono-TES ether (12.9 mg), which was used for the next reaction without further purification.

To a suspension of the alcohol obtained above (12.9 mg) and MS4Å (15.0 mg) in CH_2Cl_2 (0.3 mL) were added NMO (13.4 mg, 0.115 mmol) and TPAP (1.0 mg, 2.85 μmol) at room temperature. After the mixture was stirred at room temperature for 8 h, the mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 4:1) gave ketone **75** (10.3 mg, 17.8 μmol, 76% in two steps) as a colorless oil: R_f = 0.56 (hexane/ EtOAc = 2:1); $[\alpha]^{22}_D$ +28.7 (*c* 0.53, $CHCl_3$); IR (neat) 2953, 2871, 1739, 1613 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.28 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 6.34 (dd, *J* = 13.7, 10.2 Hz, 1 H), 6.15 (dt, *J* = 15.1, 10.2 Hz, 1 H), 5.83−5.76 (m, 1 H), 5.72−5.64 (m, 1 H), 4.56 (dd, *J* = 10.8, 3.3 Hz, 1 H), 4.47 (t, *J* = 5.9 Hz, 1 H), 4.34−4.27 (m, 3 H), 4.10 (t, *J* = 4.6 Hz, 2 H), 3.31 (s, 6 H), 2.64−2.58 (m, 2 H), 2.38 (dd, *J* = 16.0, 8.4 Hz, 1 H), 2.13−2.04 (m, 2 H), 1.60−1.53 (m, 1 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.00 (t, *J* = 8.0 Hz, 9 H), 0.60 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 207.5, 170.4, 159.9, 133.0, 132.1, 130.6, 129.9, 128.8, 114.1, 101.3, 81.2, 72.2, 70.5, 63.8, 63.4, 54.9, 51.2, 40.4, 35.8, 33.1, 25.1, 24.5, 7.2, 5.1; HRMS (ESI−TOF) calcd for $C_{31}H_{48}O_8SiNa$ $[M + Na]^+$ 599.3016, found 599.3013.

Alcohol 76. To a solution of ketone **75** (5.2 mg, 9.02 μmol) in MeOH (0.4 mL) was added $NaBH_4$ (1.0 mg, 26.4 μmol) at −78 °C. After the mixture was stirred at −78 °C for 20 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave alcohol **76** (5.4 mg, 9.02 μmol, quant.) as a colorless oil: R_f = 0.33 (hexane/ EtOAc = 2:1); $[\alpha]^{22}_D$ +32.0 (*c* 1.11, $CHCl_3$); IR (neat) 3518, 2953, 2871, 1739, 1613 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.19 (d, *J* = 7.6 Hz, 2 H), 6.79 (d, *J* = 7.6 Hz, 2 H), 6.39 (dd, *J* = 15.0, 10.5 Hz, 1 H), 6.24 (dd, *J* = 15.0, 10.5 Hz, 1 H), 5.78−5.67 (m, 2 H), 4.47 (d, *J* = 11.2 Hz, 1 H),

4.34−4.25 (m, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 4.14 (d, *J* = 4.9 Hz, 2 H), 4.04−3.98 (m, 1 H), 3.54−3.48 (m, 2 H), 3.32 (s, 3 H), 3.32 (s, 3 H), 2.69−2.62 (m, 1 H), 2.53−2.38 (m, 2 H), 2.12 (dd, *J* = 11.2, 4.4 Hz, 1 H), 1.80−1.73 (m, 1 H), 1.38 (s, 3 H), 1.27 (s, 3 H), 1.22−1.15 (m, 1 H), 1.01 (t, J = 7.8 Hz, 9 H), 0.61 (q, J = 7.8 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.7, 159.8, 132.9, 131.6, 130.1, 130.1, 129.9, 129.8, 114.1, 100.9, 78.3, 74.4, 71.7, 67.7, 63.9, 63.4, 54.9, 51.1, 40.7, 34.1, 33.8, 24.9, 7.2, 5.1; HRMS (ESI−TOF) calcd for $C_{31}H_{50}O_8SiNa$ $[M + Na]^+$ 601.3173, found 601.3165.

Alcohol 77. To a solution of alcohol **76** (23.2 mg, 40.0 μmol) in CH_2Cl_2 (0.4 mL) were added 2,6-lutidine (17 μL, 0.113 mmol) and TESOTf (24 μL, 0.107 mmol) at 0 °C. After the mixture was stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave the corresponding bis-TES ether (28.1 mg), which was used for the next reaction without further purification.

To a solution of the TES ether obtained above (28.1 mg) in CH_2Cl_2 (1.4 mL) and MeOH (0.2 mL) was added PPTS (3.1 mg, 12.5 μmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. After the mixture was stirred at room temperature for 20 min, the reaction was quenched with Et_3N. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 1:1) gave the corresponding allylic alcohol (16.9 mg, 28.8 μmol, 72% in two steps) as a colorless oil: R_f = 0.44 (hexane/EtOAc = 1:1); $[\alpha]^{22}_D$ +27.5 (*c* 0.65, $CHCl_3$); IR (neat) 3465, 2952, 2885, 1739, 1612 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.24 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.27−6.11 (m, 2 H), 5.83− 5.74 (m, 1 H), 5.65−5.54 (m, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 4.40−4.32 (m, 1 H), 4.17−4.08 (m, 1 H), 3.88 (d, *J* = 4.9 Hz, 2 H), 3.78 (dd, *J* = 10.8, 3.7 Hz, 1 H), 3.57−3.48 (m, 1 H), 3.33 (s, 6 H), 2.74−2.65 (m, 1 H), 2.59−2.44 (m, 3 H), 2.20 (dd, *J* = 15.8, 5.0 Hz, 1 H), 1.92−1.83 (m, 1 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.09 (t, *J* = 7.9 Hz, 9 H), 0.80−0.69 (m, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 159.8, 132.3, 131.5, 131.4, 131.2, 131.0, 129.7, 114.1, 100.9, 80.1, 75.6, 71.7, 68.3, 63.9, 63.2, 54.9, 51.1, 40.9, 34.6, 33.8, 25.2, 24.6, 7.5, 5.9; HRMS (ESI−TOF) calcd for $C_{31}H_{50}O_8SiNa$ $[M + Na]^+$ 601.3173, found 601.3170.

To a solution of the corresponding allylic alcohol (16.9 mg, 29.2 μmol) in CH_2Cl_2 (0.7 mL) were added BAIB (24.2 mg, 73.0 μmol) and TEMPO (1.0 mg, 6.40 μmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding unsaturated aldehyde (13.5 mg), which was used for the next reaction without further purification.

To a solution of the PMB ether obtained above (13.5 mg) in CH_2Cl_2 (0.5 mL) and phosphate pH standard solution (25 μL) was added DDQ (6.3 mg, 28.0 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 2:1) gave alcohol **77** (10.0 mg, 21.9 μmol, 75% in two steps) as a colorless oil: R_f = 0.23 (hexane/EtOAc = 2:1); $[\alpha]^{24}_D$ −5.8 (*c* 1.16, $CHCl_3$); IR (neat) 3490, 2952, 2871, 1739, 1681, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.8 Hz, 1 H), 7.08 (dd, *J* = 15.0, 10.0 Hz, 1 H), 6.42−6.26 (m, 2 H), 6.09 (dd, *J* = 15.0, 7.8 Hz, 1 H), 4.27−4.19 (m, 1 H), 3.93−3.87 (m, 1 H), 3.68 (s, 3 H), 3.68−3.65 (m, 1 H), 3.47 (dd, J = 17.1, 7.6 Hz, 1 H), 2.59−2.30 (m, 5 H), 1.76−1.69 (m, 1 H), 1.65−1.57 (m, 1 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 0.69−0.61 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.2, 151.8, 142.5, 130.7, 130.7, 100.9, 69.3, 67.9, 63.3, 51.7, 40.5, 39.4, 34.0, 24.8, 24.3, 7.1, 5.4; HRMS (ESI−TOF) calcd for $C_{23}H_{40}O_7SiNa$ $[M + Na]^+$ 479.2441, found 479.2438.

(3*R*, 5*R*, 6*R*, 7*S*)-Tetraol 6d. To a solution of acetonide **77** (18.2 mg, 39.9 μmol) in CH_2Cl_2 (2.0 mL) was added $TiCl_4$ (8.8 μL, 80.3 μmol) at −30 °C. After the mixture was gradually warmed up to 0 °C for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and washed with H_2O and brine. The aqueous phase was washed with EtOAc four times. The combined organic layer was dried over Na_2SO_4. Concentration and column chromatography (CH_2Cl_2/MeOH = 10:1) gave tetraol **6d** (5.7 mg, 18.8 μmol, 47%) as a colorless oil: R_f = 0.25 (CH_2Cl_2/MeOH = 10:1); $[\alpha]^{26}_D$ −19.1 (*c* 0.03, $CHCl_3$); IR (neat) 3390, 2921,

2852, 1730, 1677, 1637 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 9.49 (d, J = 7.8 Hz, 1 H), 7.29 (dd, J = 15.6, 10.4 Hz, 1 H), 6.51−6.41 (m, 2 H), 6.09 (dd, J = 15.6, 7.8 Hz, 1 H), 4.29−4.24 (m, 1 H), 3.95−3.91 (m, 1 H), 3.82−3.79 (m, 1 H), 3.67 (s, 3 H), 3.23 (t, J = 3.9 Hz, 1 H), 2.56−2.43 (m, 4 H), 1.70 (ddd, J = 14.4, 10.2, 3.0 Hz, 1 H), 1.59 (ddd, J = 14.4, 10.2, 3.0 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 196.0, 173.7, 154.8, 145.0, 131.9, 131.2, 77.1, 72.8, 70.1, 66.4, 52.0, 43.8, 41.9, 38.7; HRMS (ESI−TOF) calcd for $C_{14}H_{22}O_7Na$ $[M + Na]^+$ 325.1263, found 325.1270.

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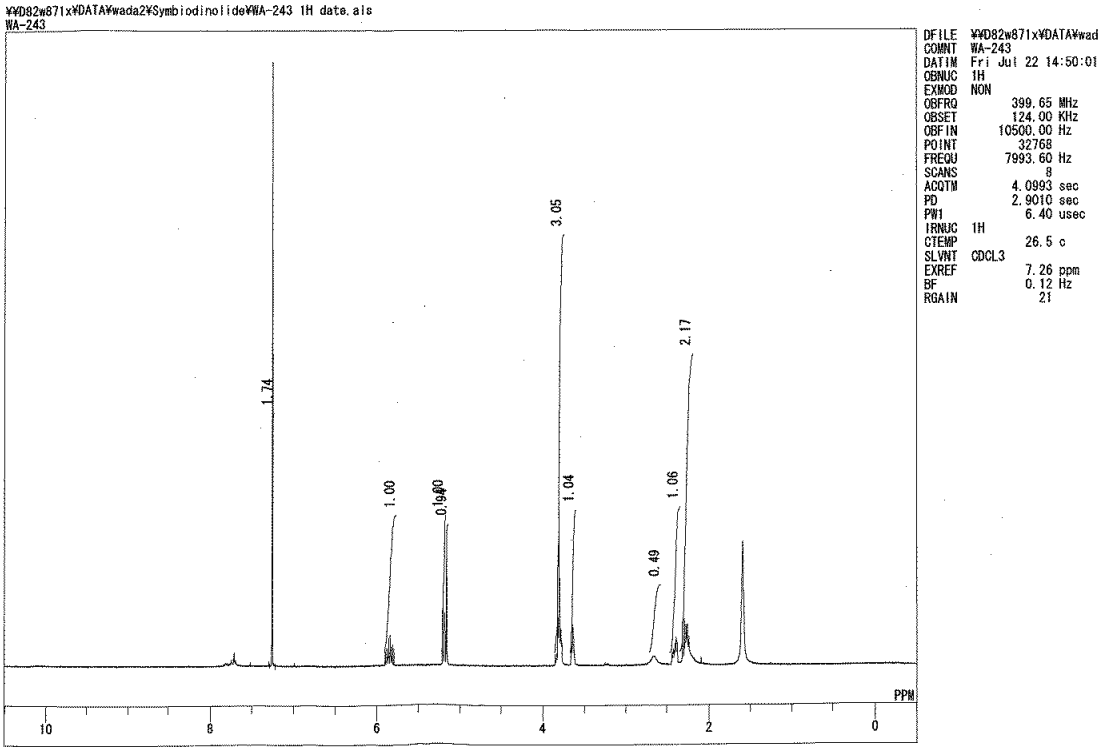
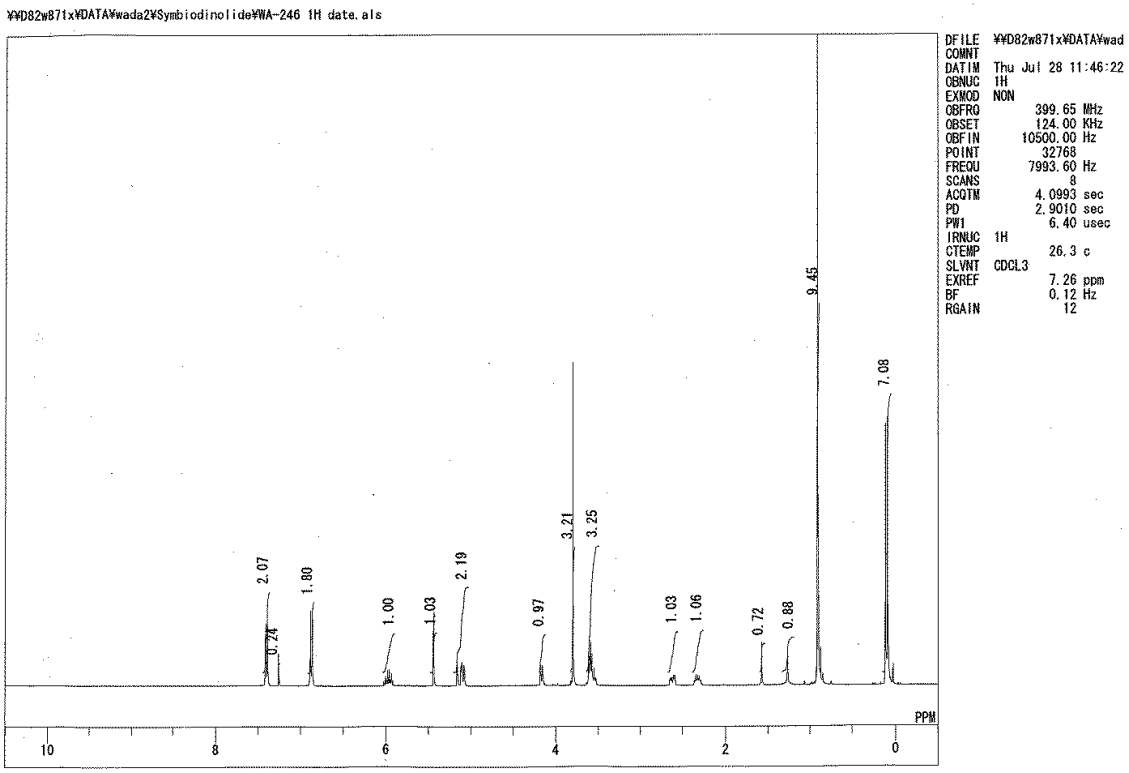
スペクトルデータ (Spectral Data)

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **12**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13**



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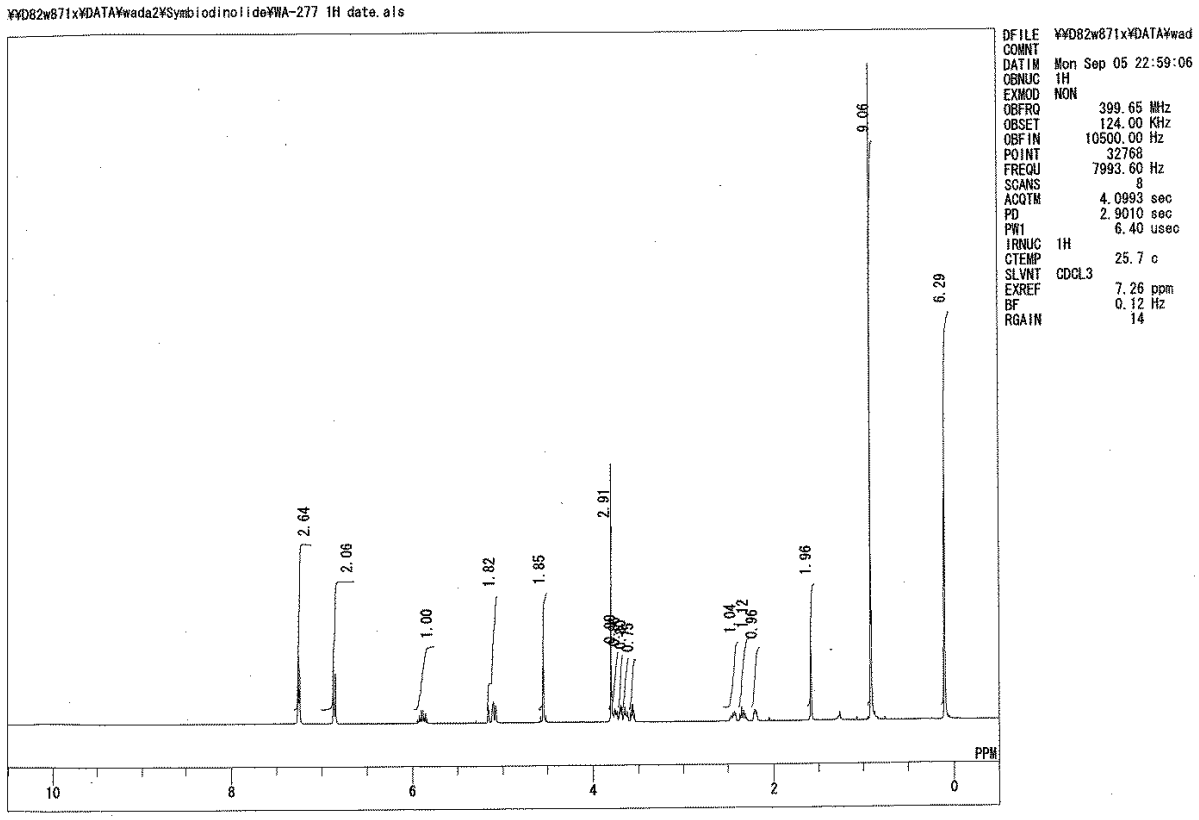

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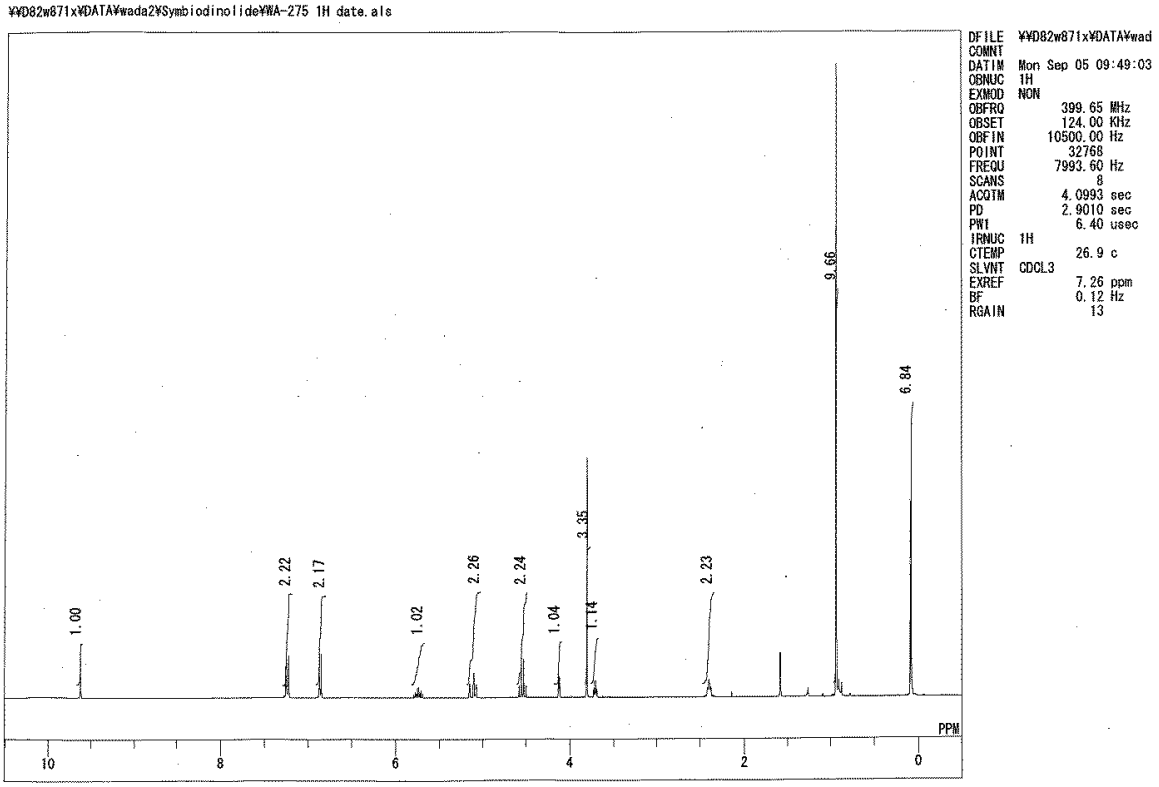
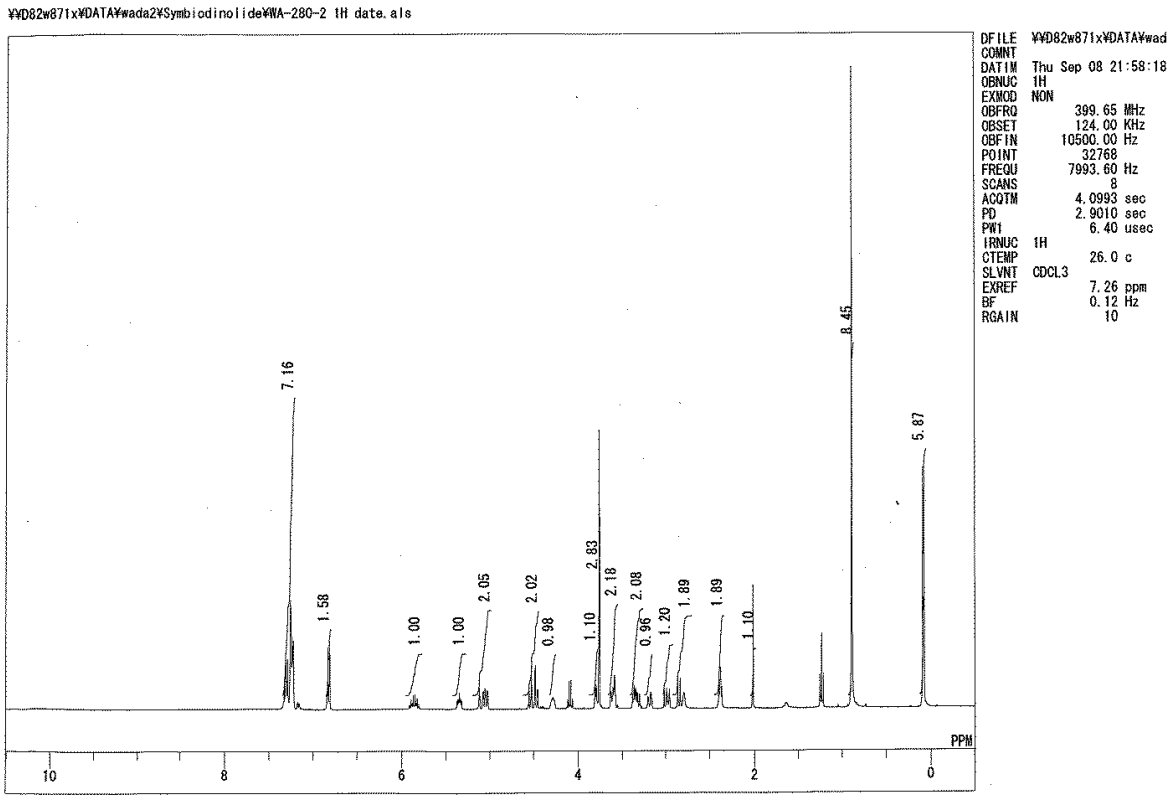


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **17**



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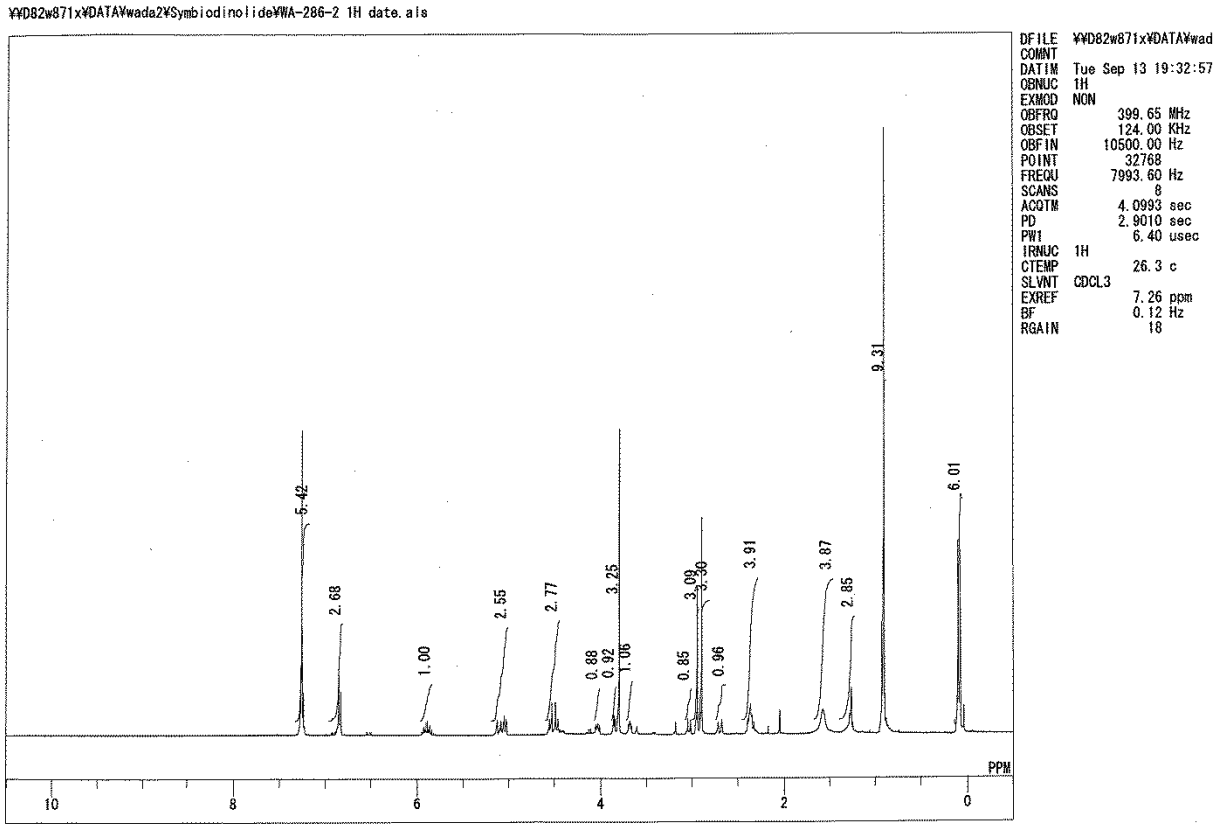
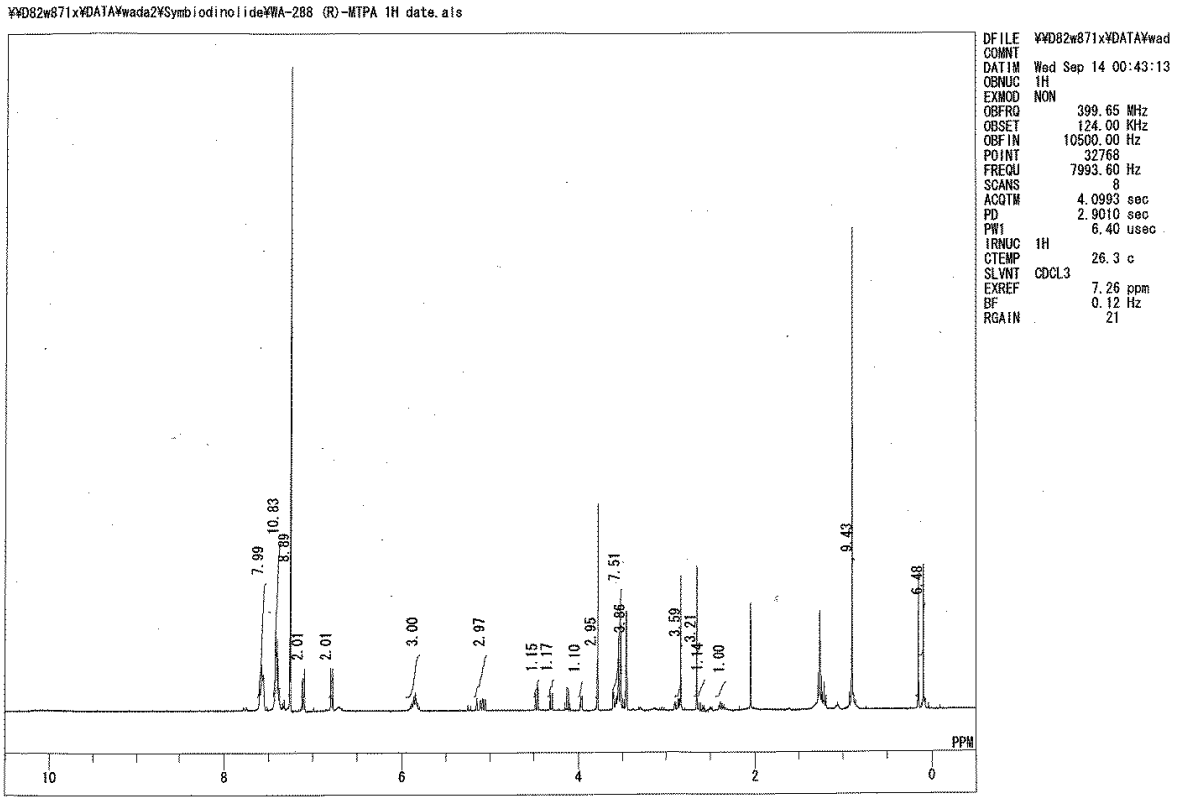


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*S*)-**20**



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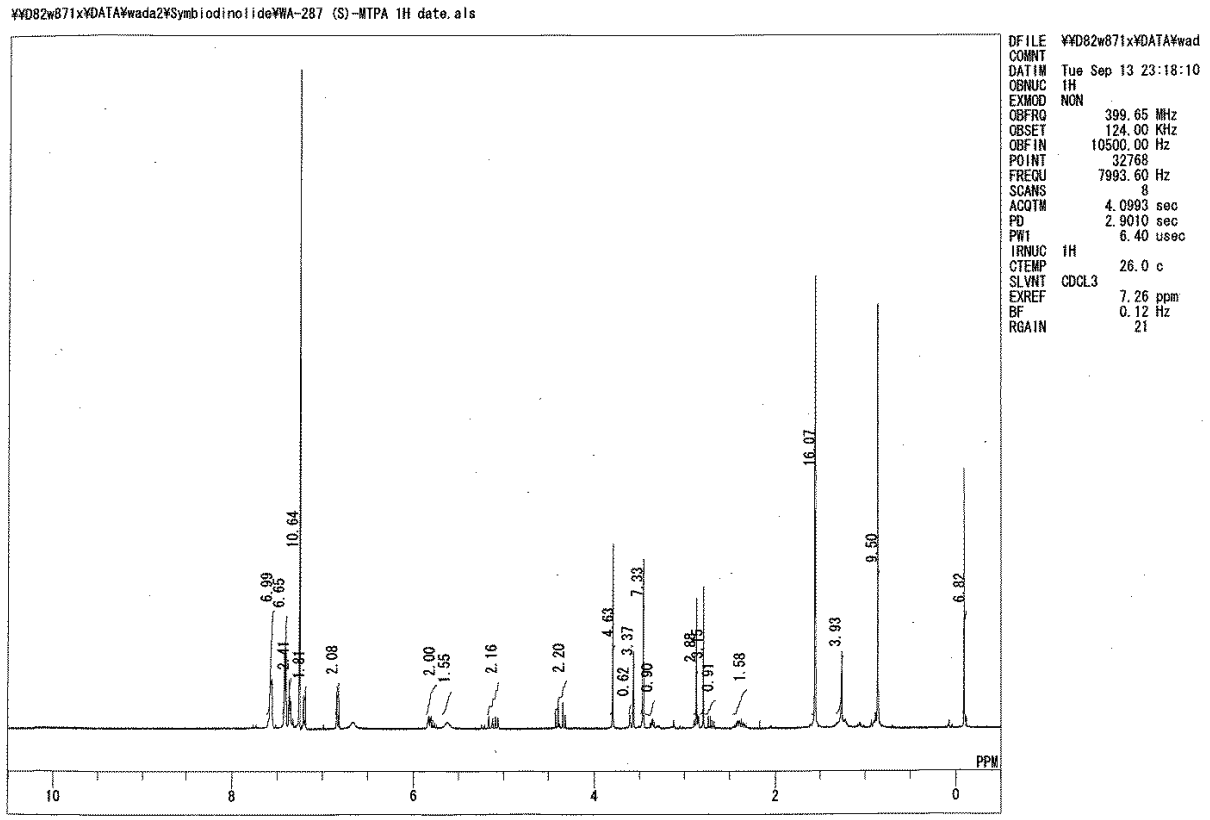
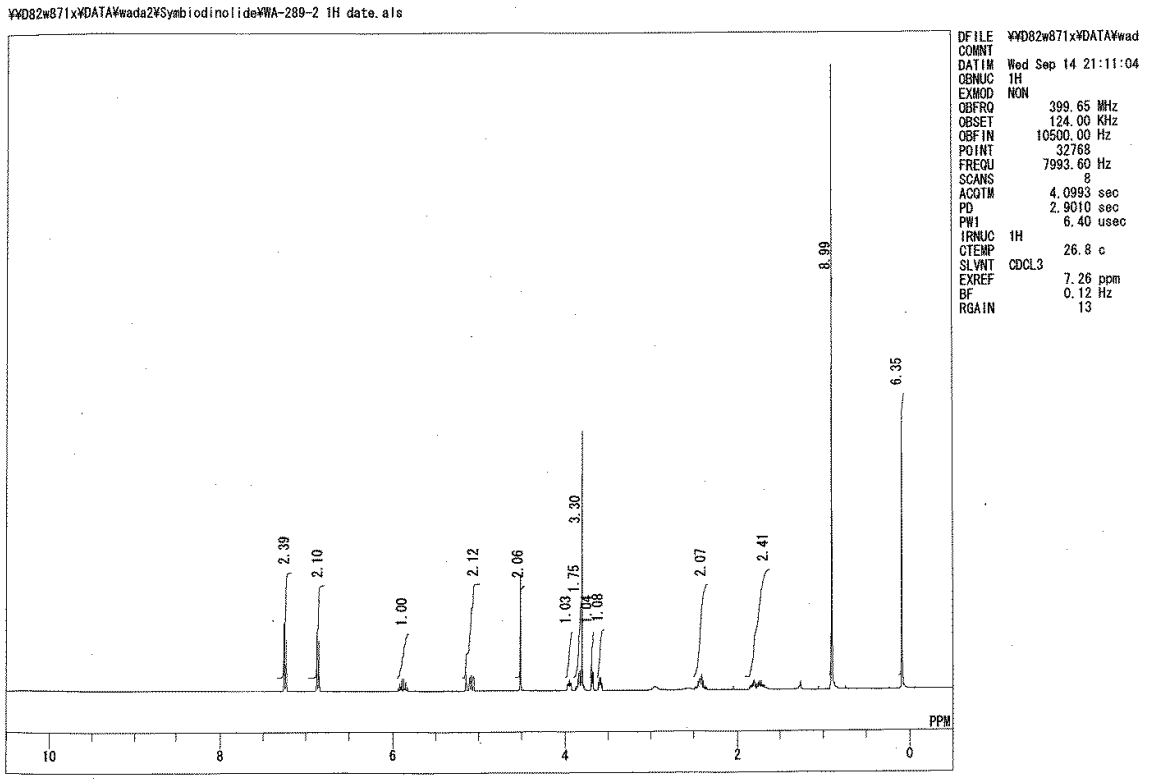


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **21**



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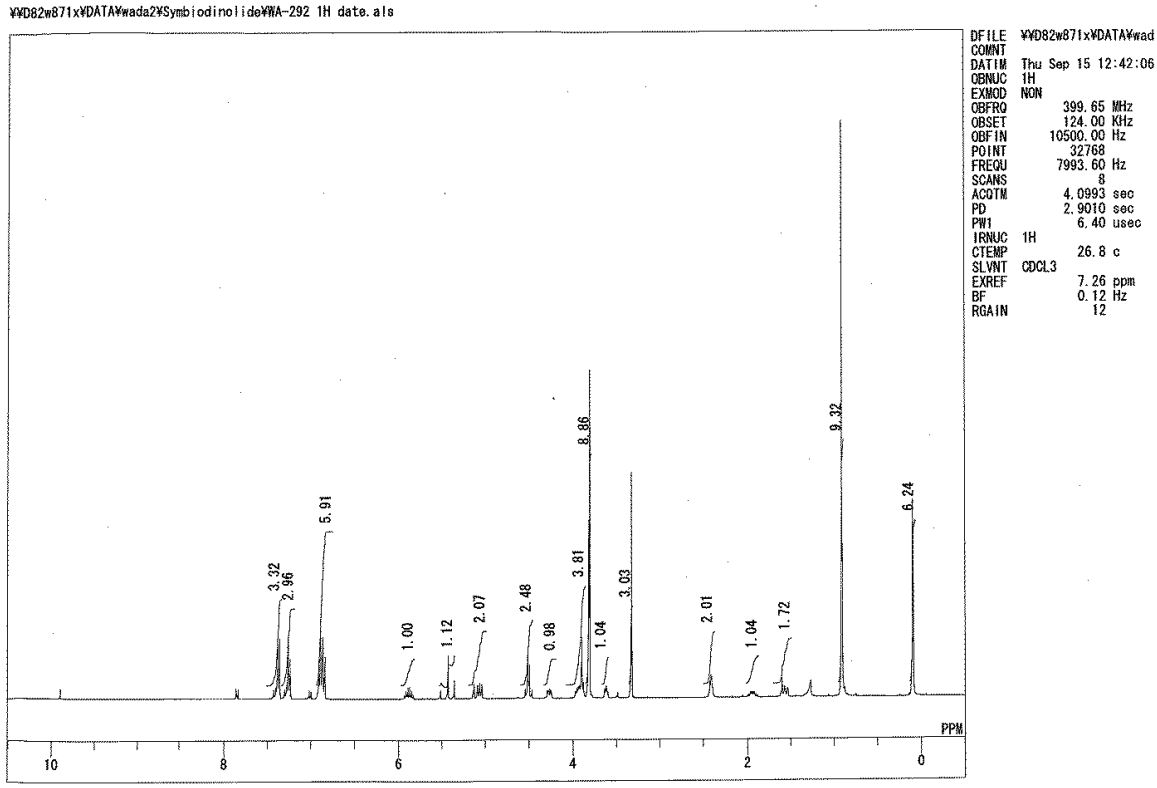

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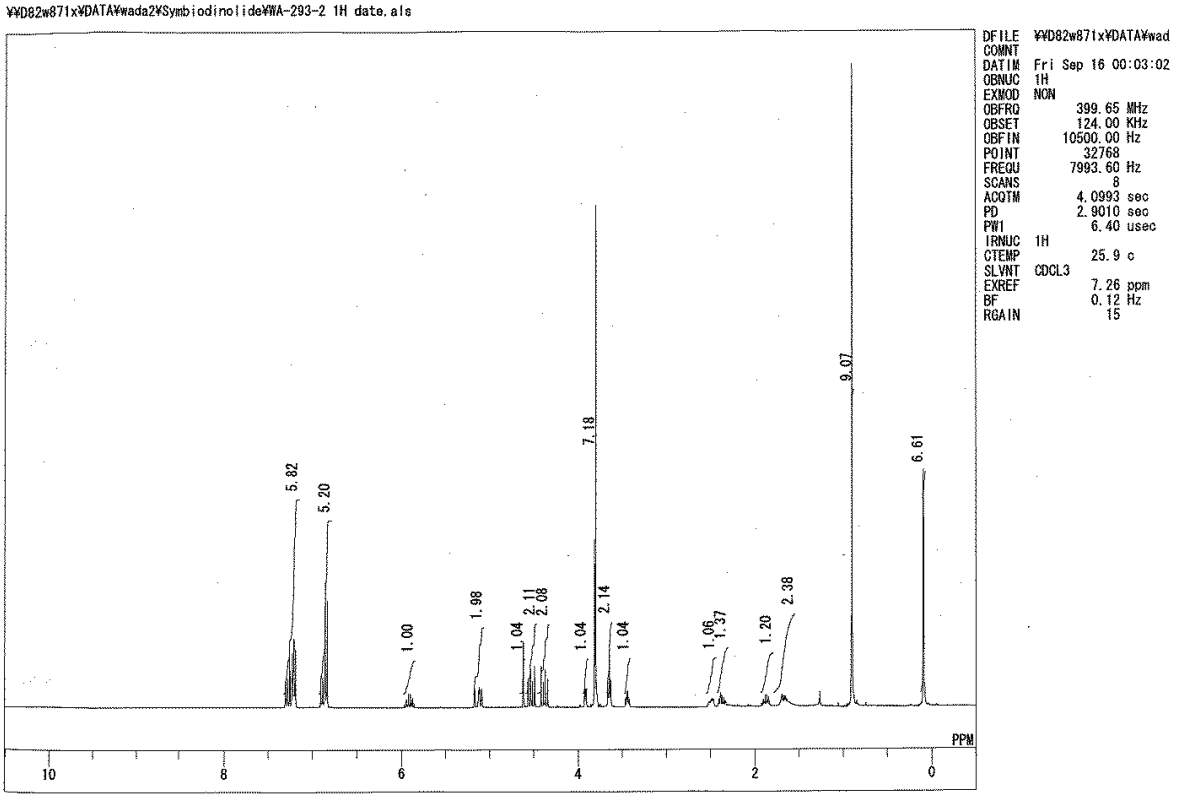
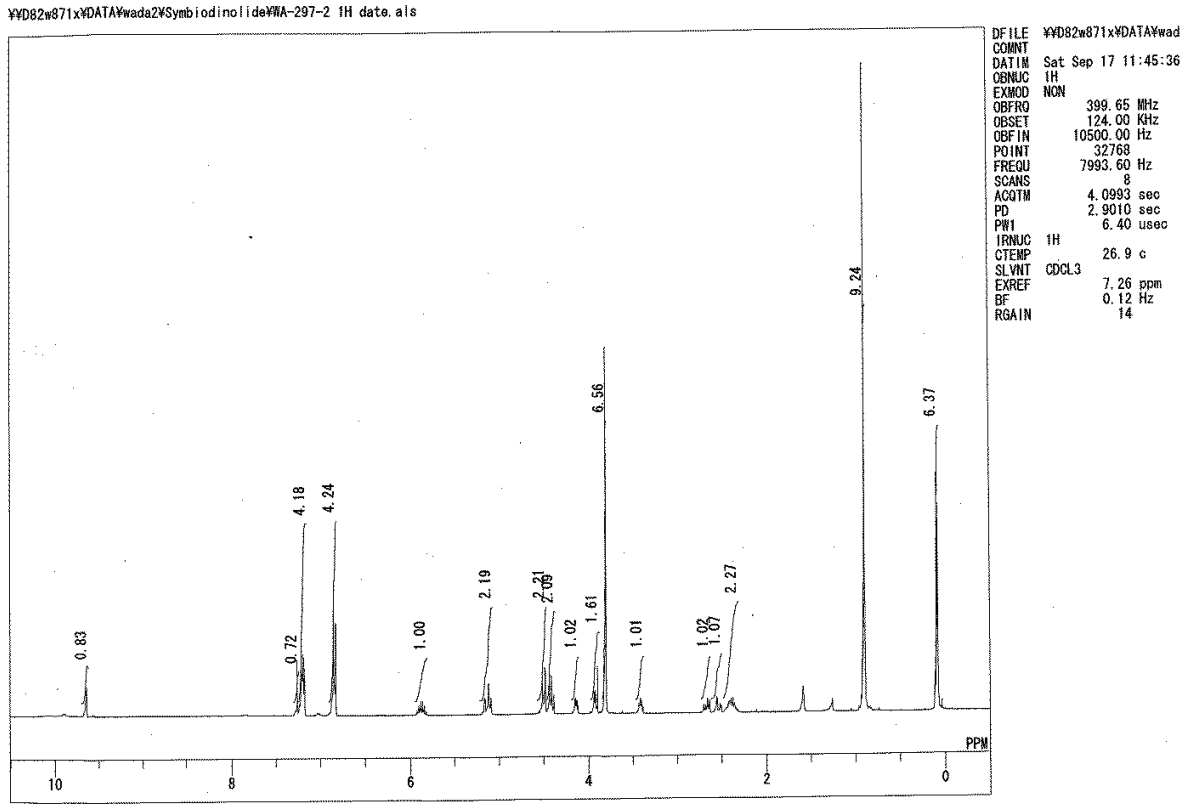
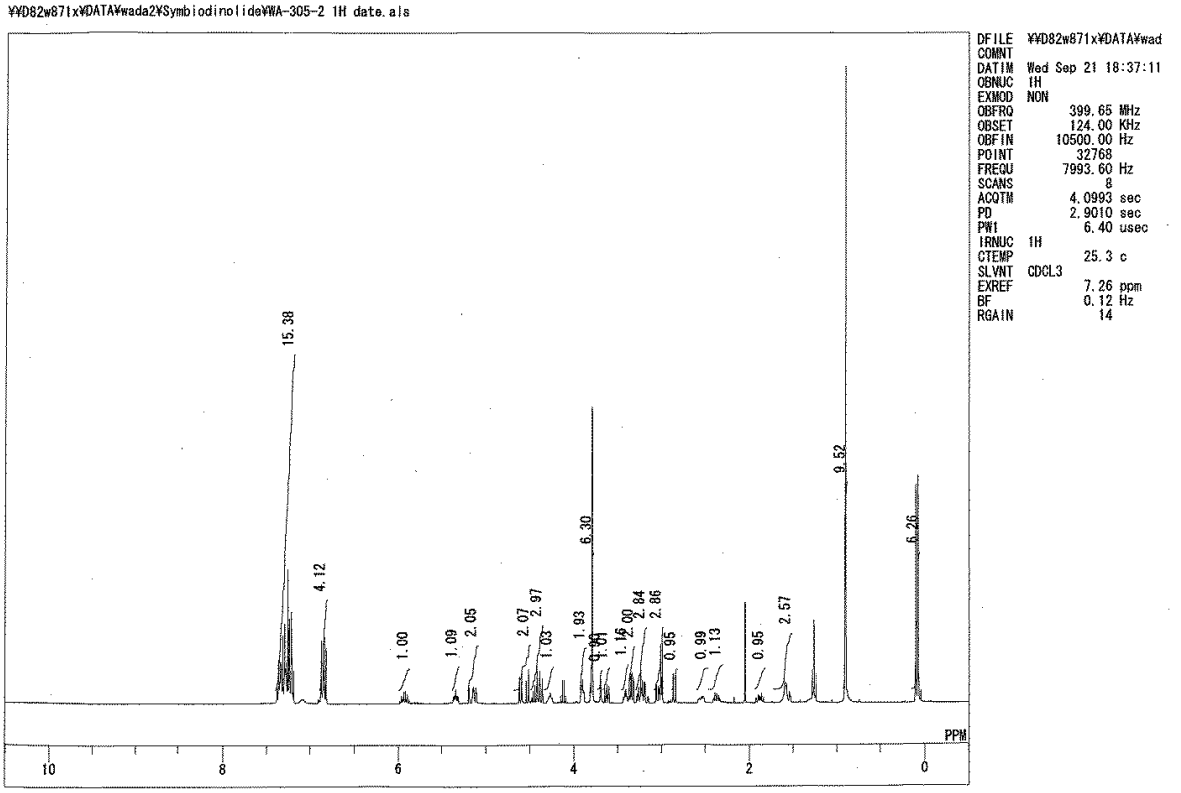


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **24**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **25**



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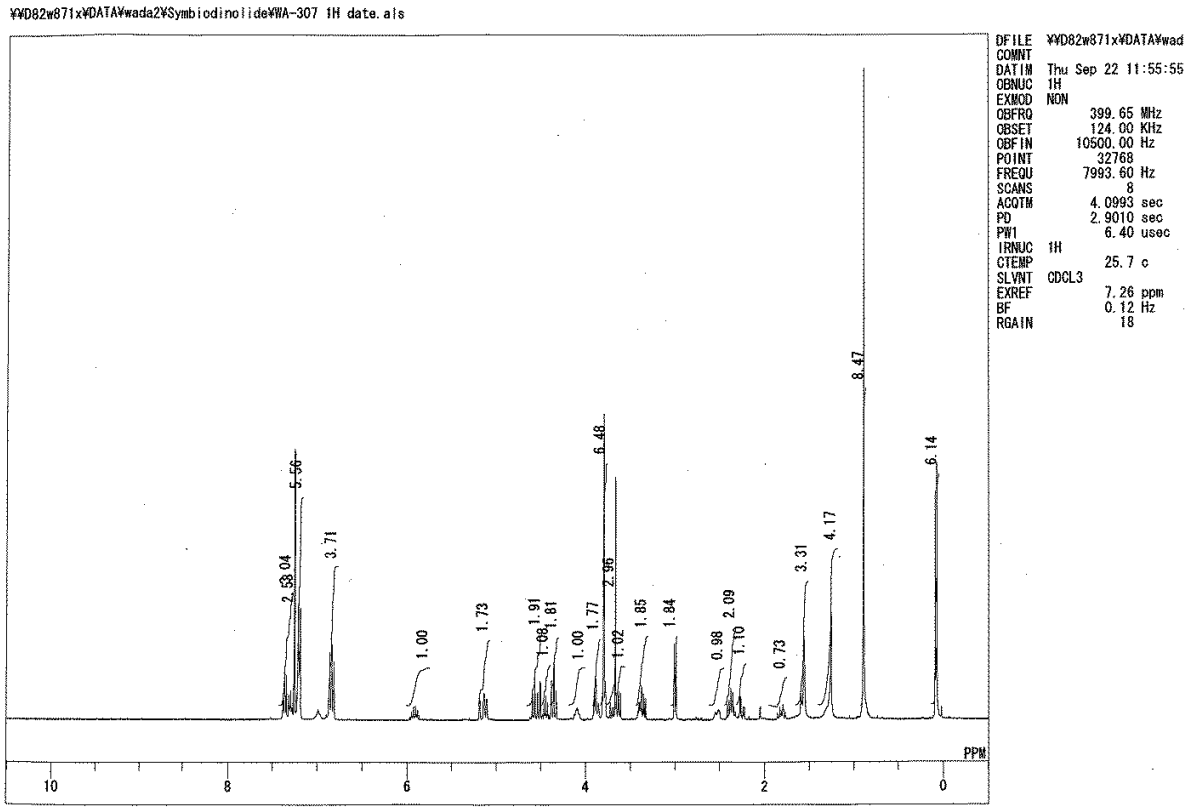
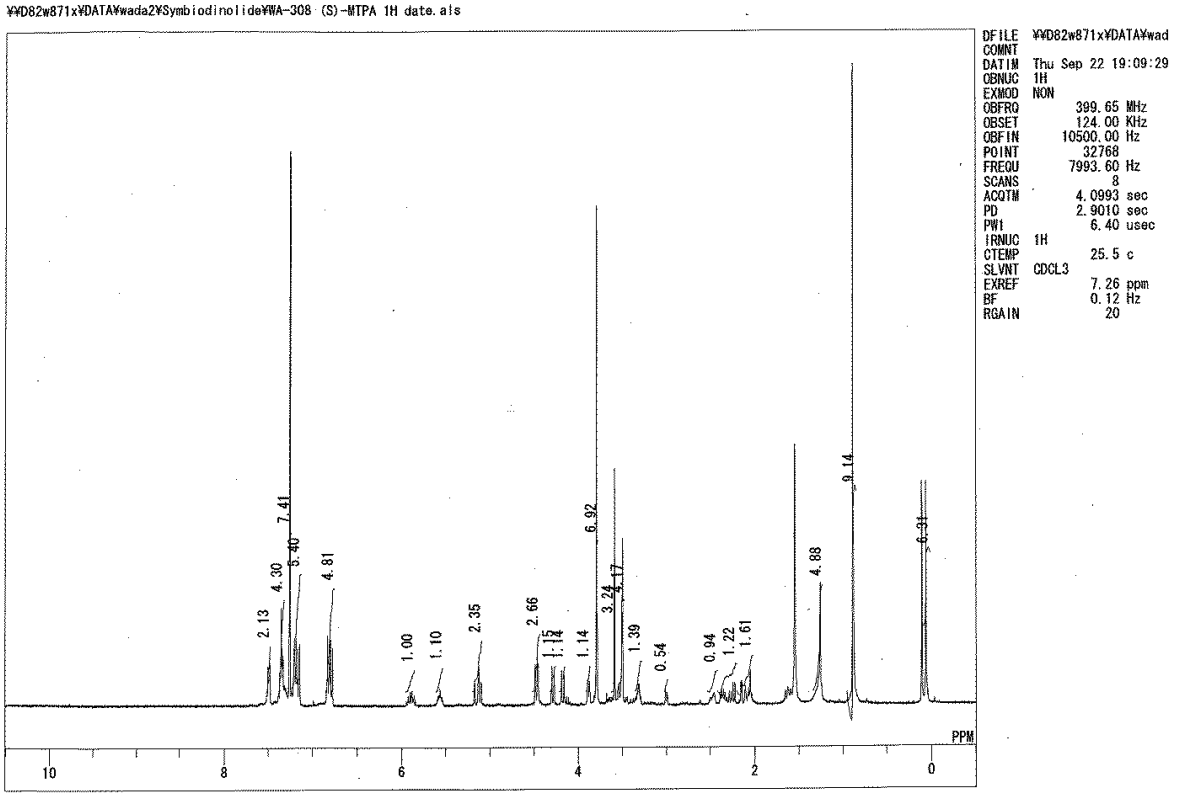


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*S*)-**28**



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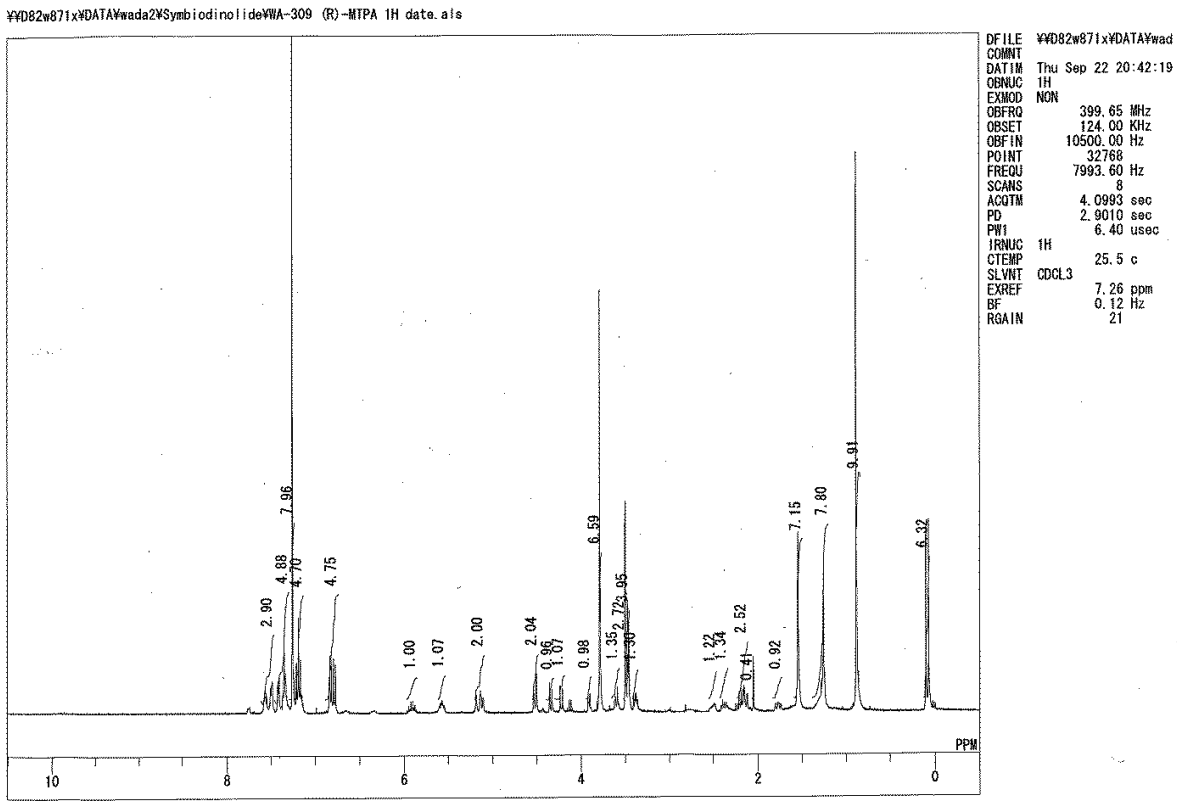
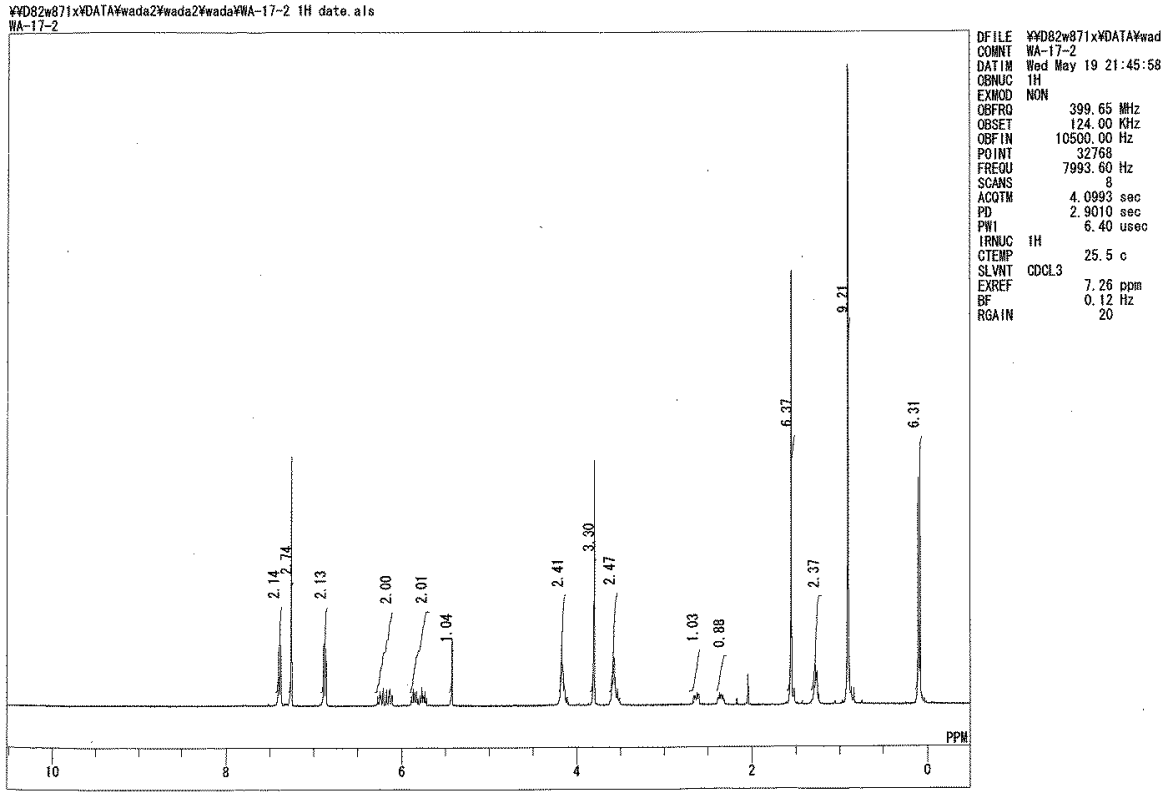


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **43**



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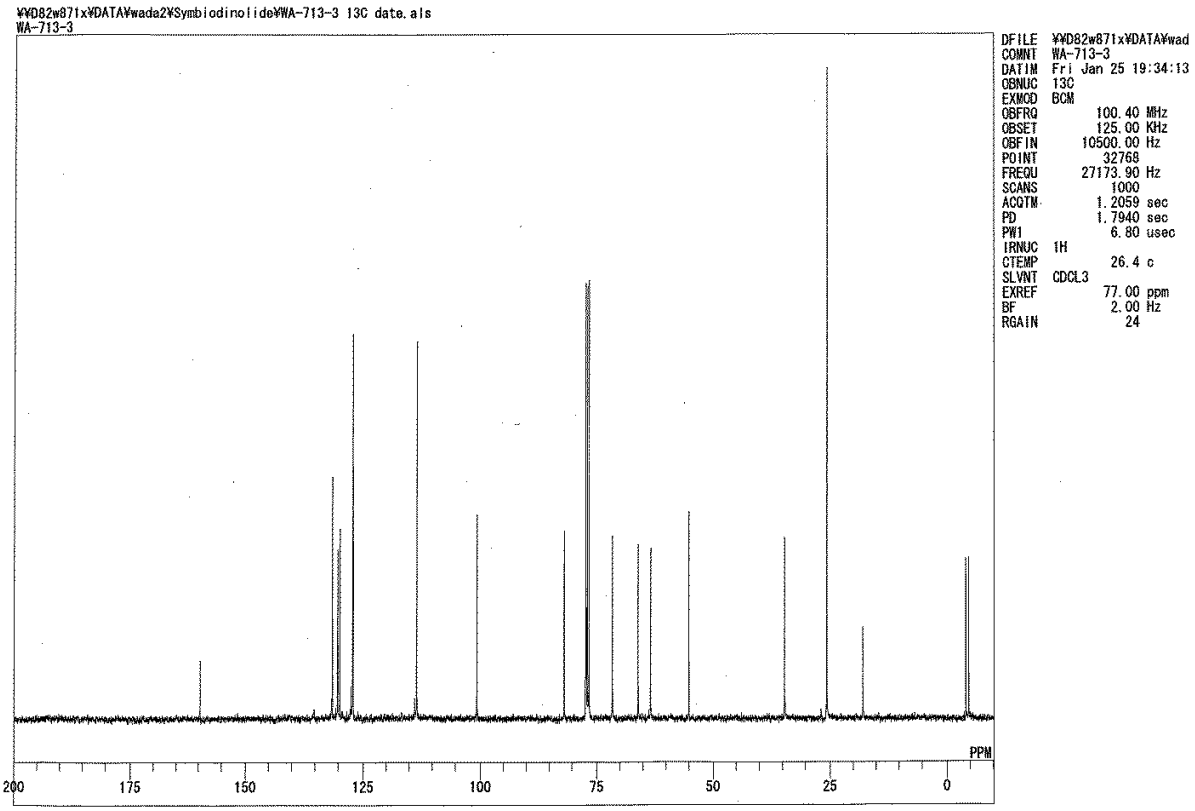

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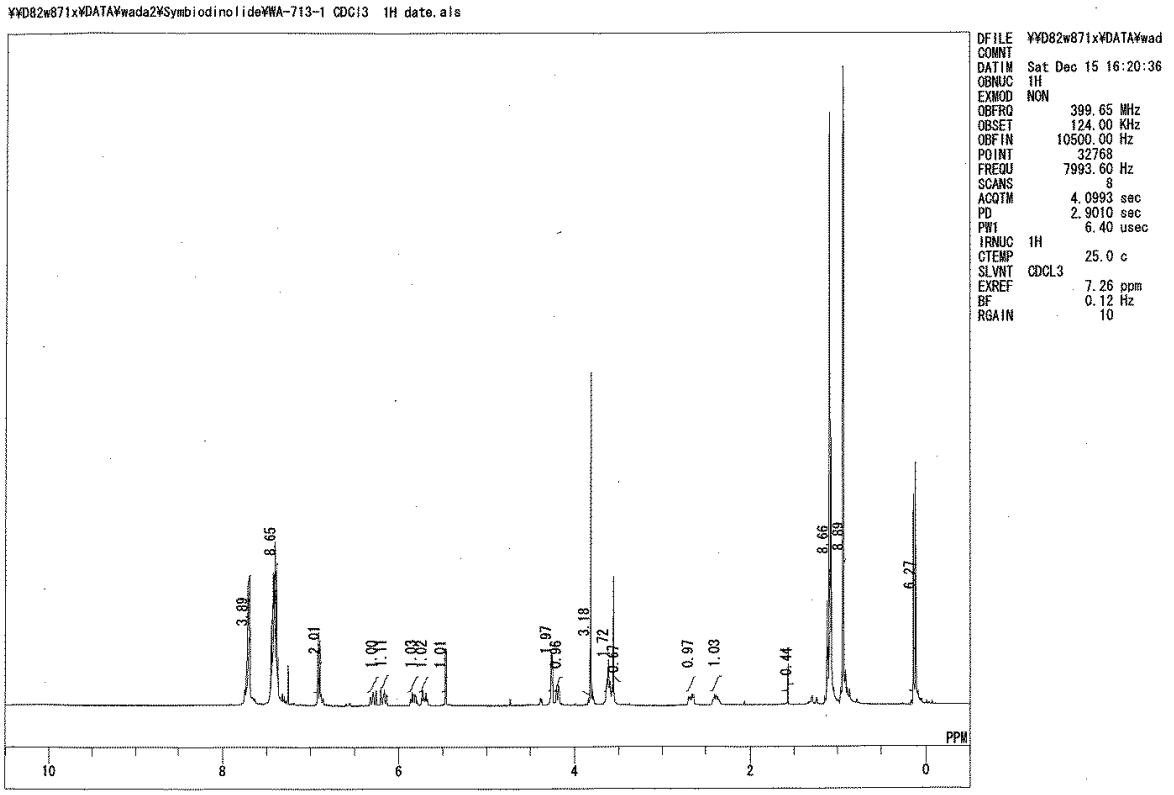

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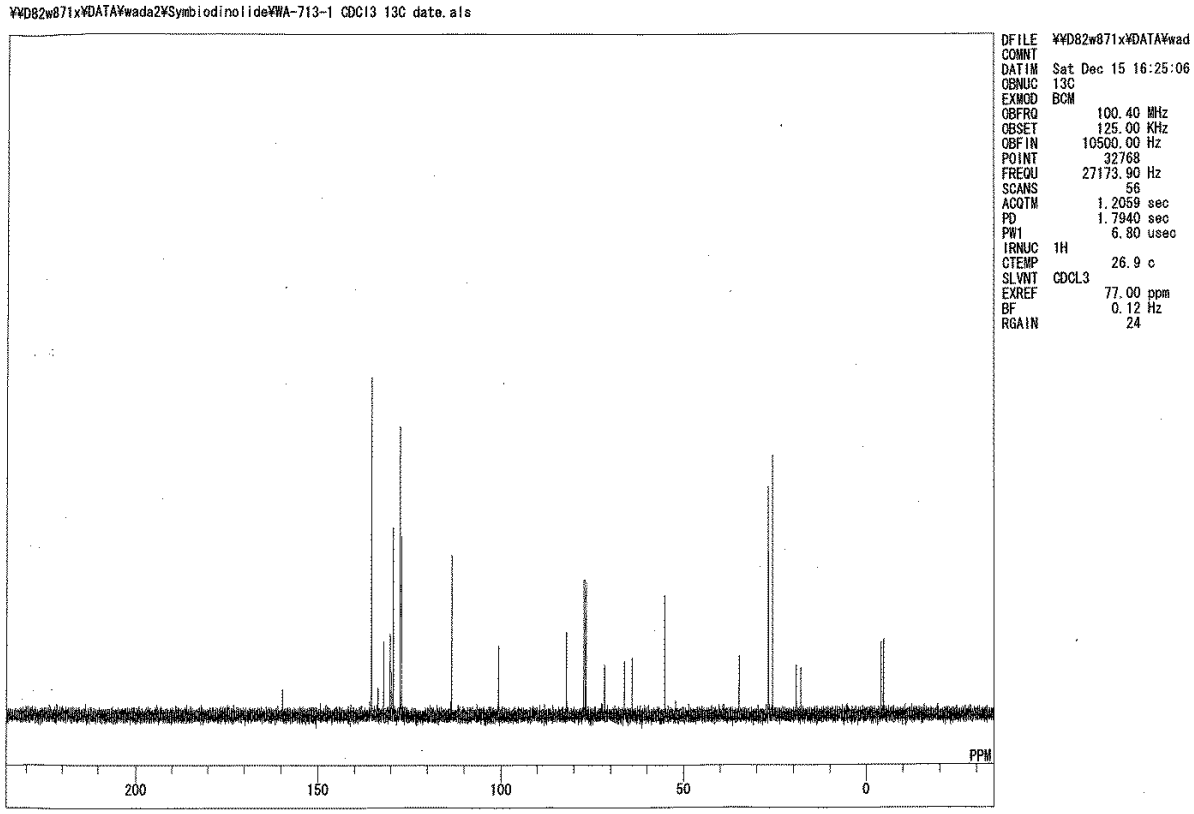
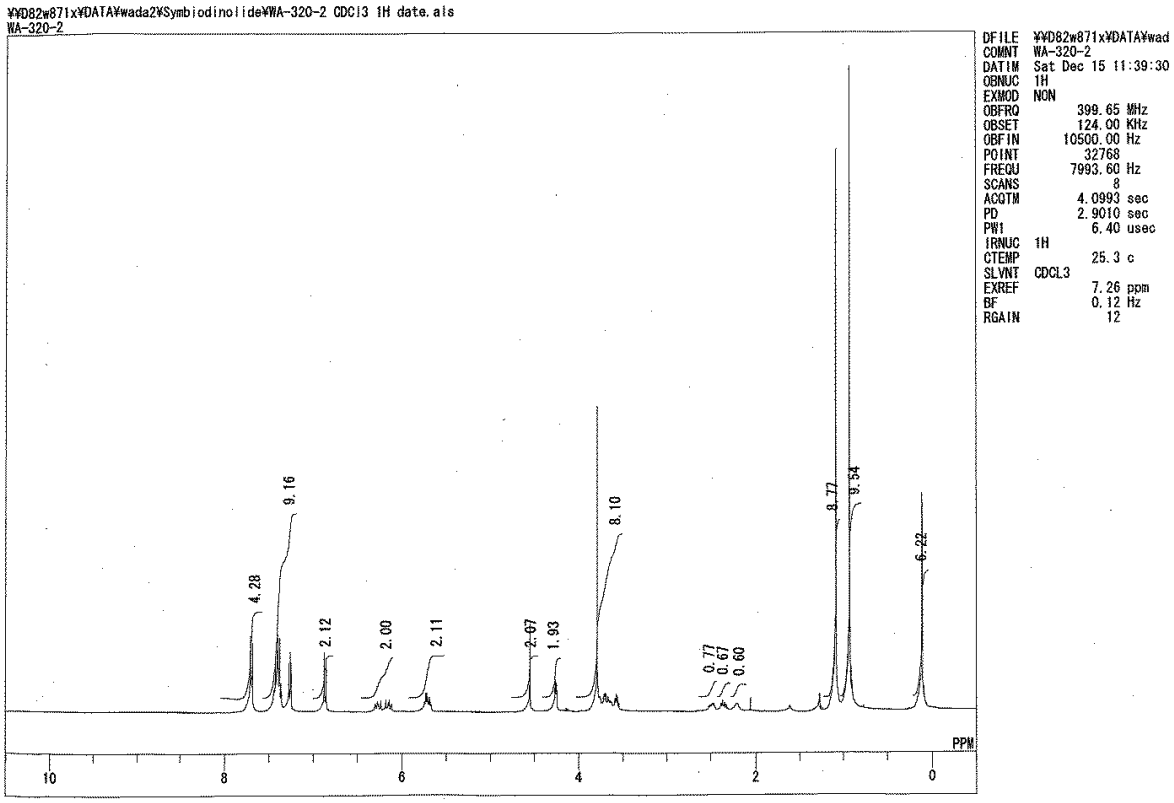
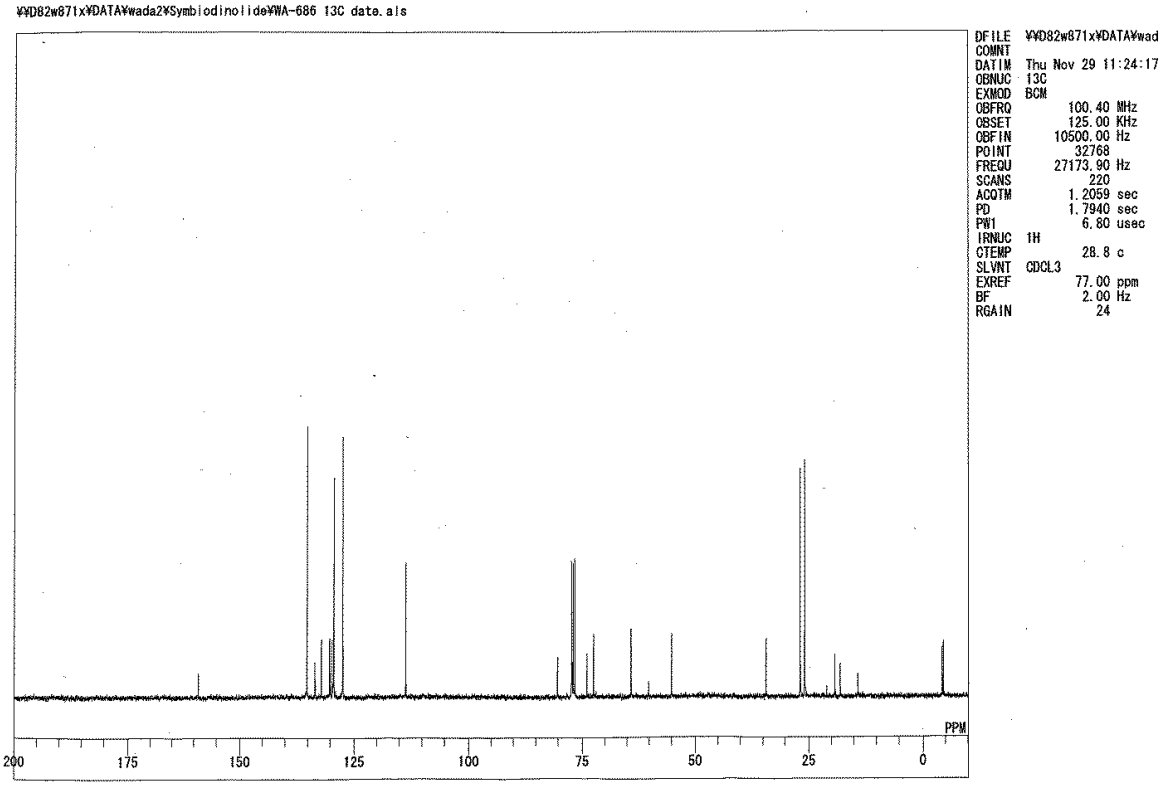


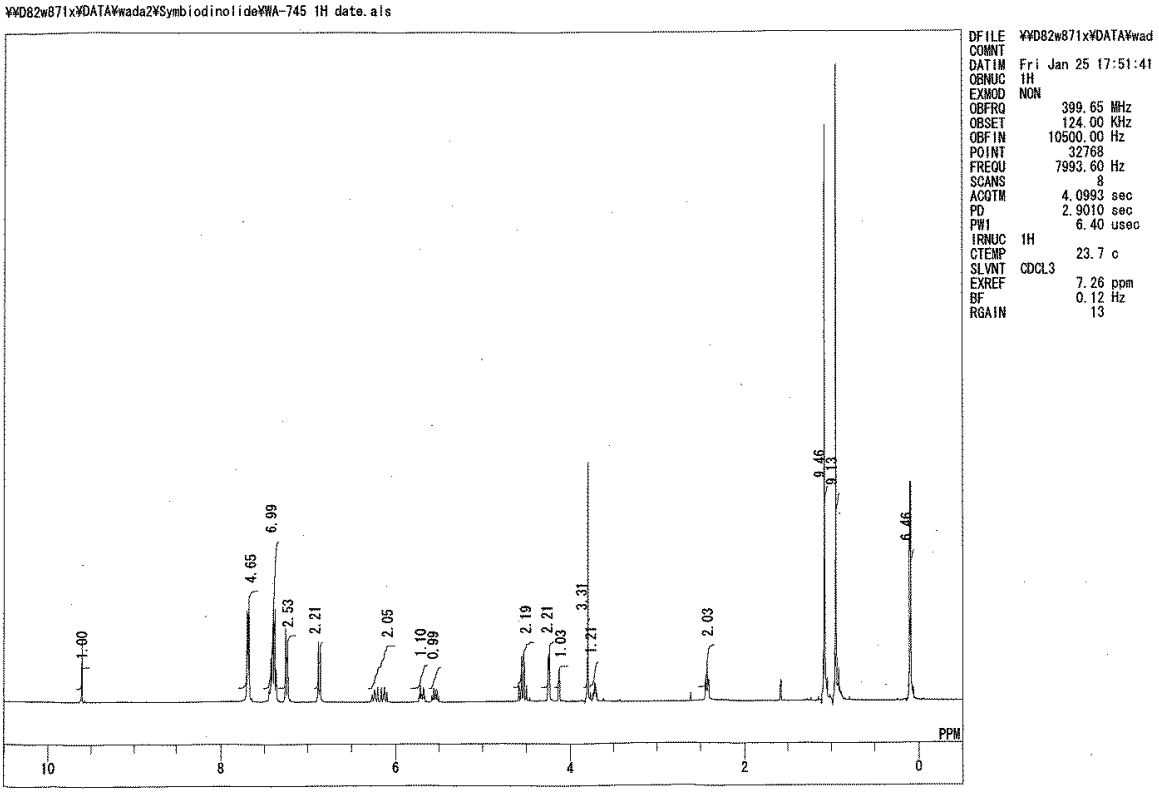
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **45**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **45**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **47**



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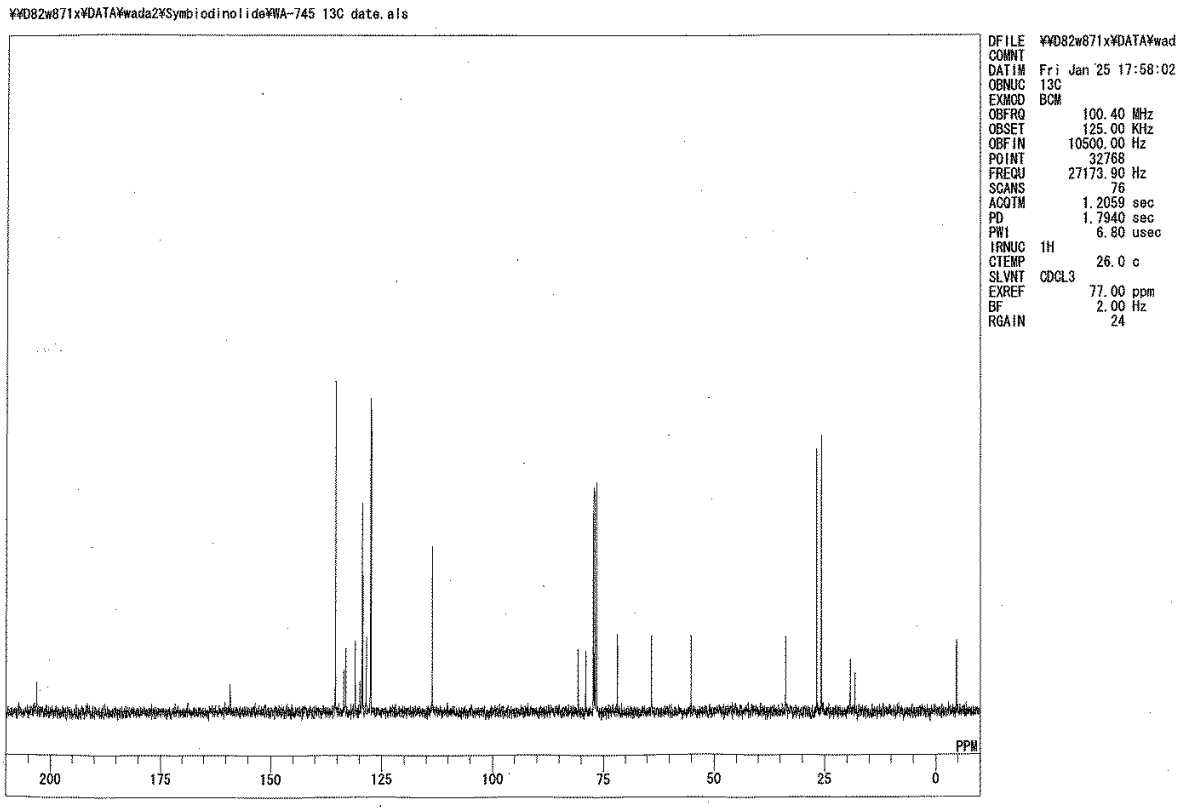
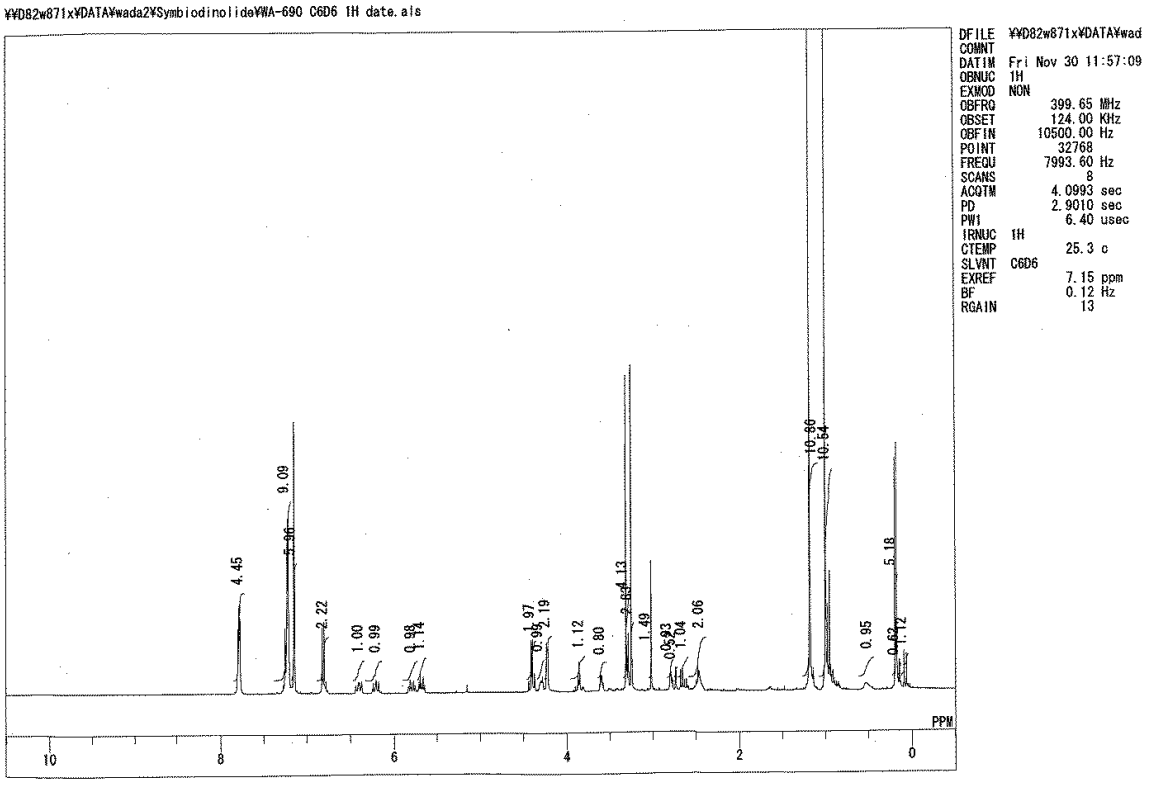
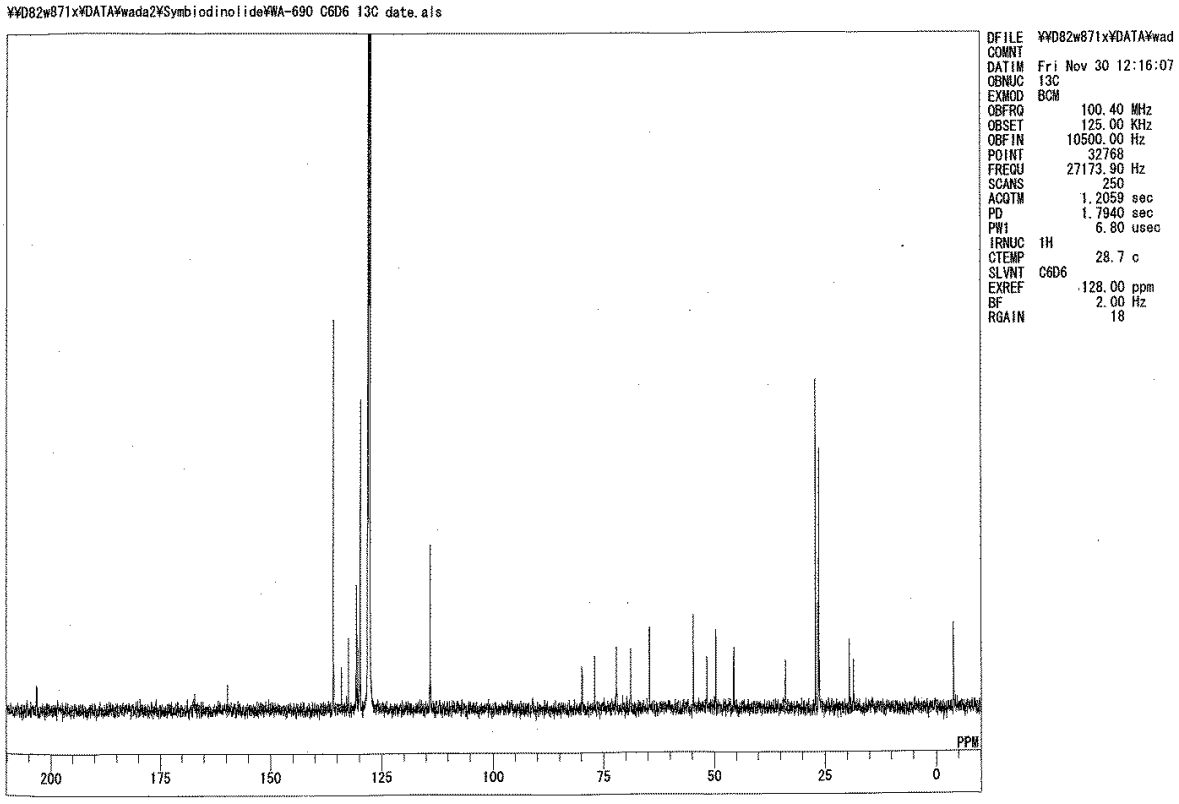


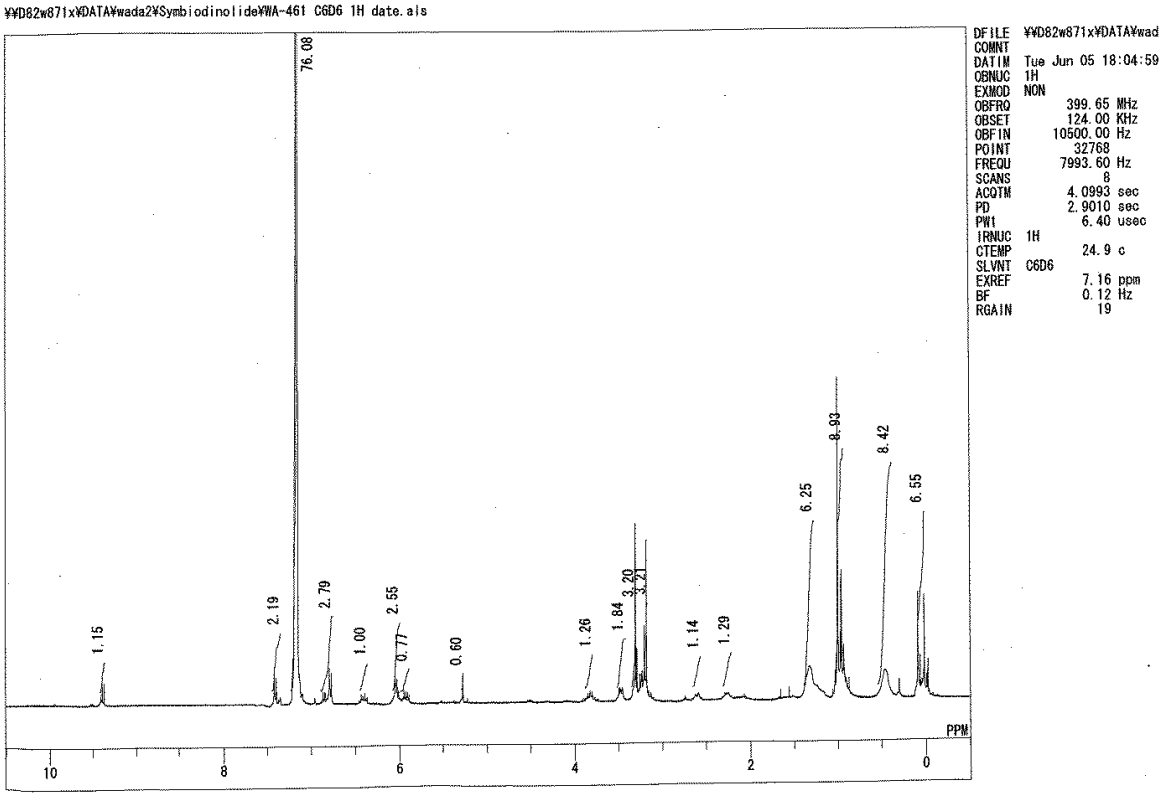
^{1}H NMR (400 MHz, C_6D_6) spectrum of **48**



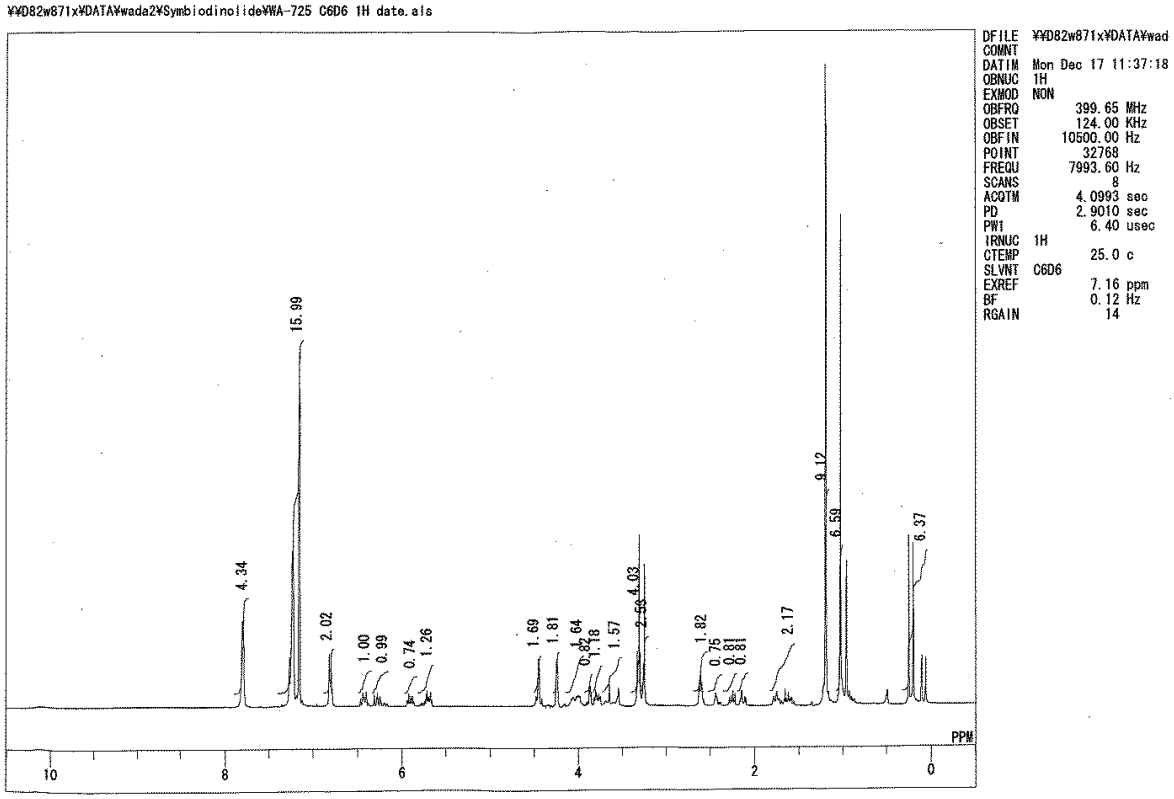
^{13}C NMR (100 MHz, C_6D_6) spectrum of **48**



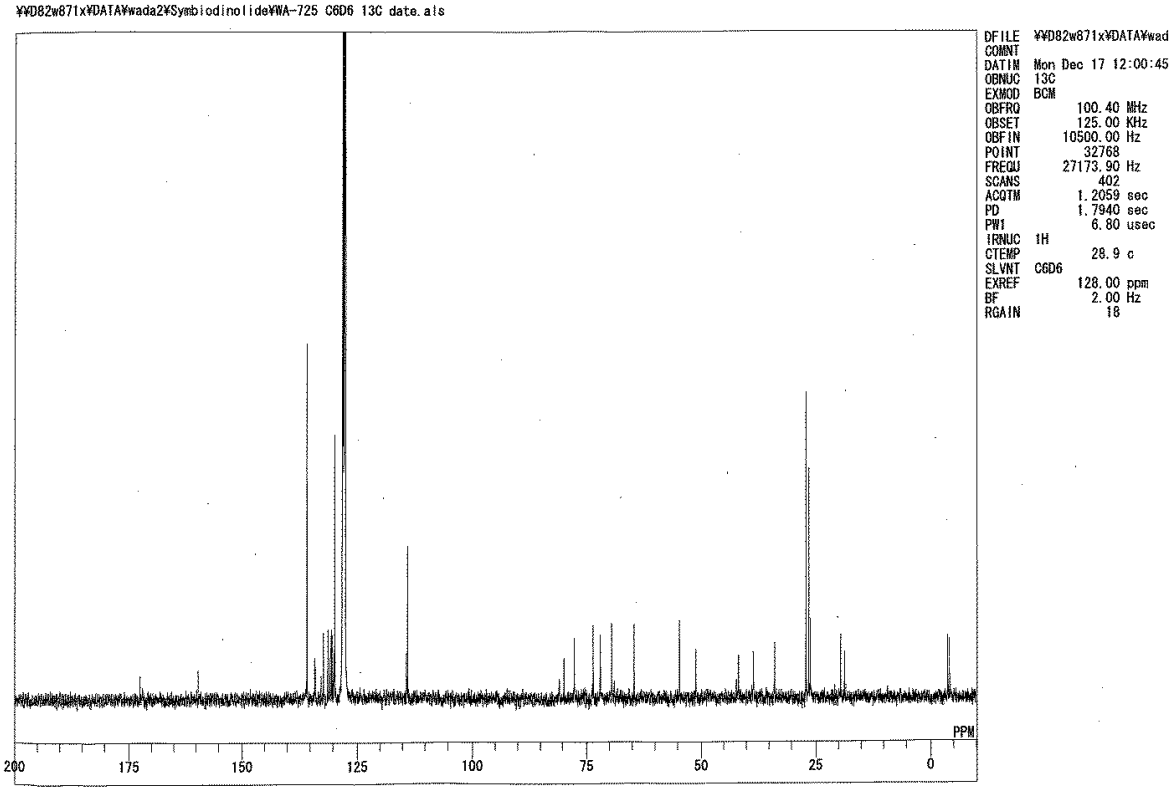
^{1}H NMR (400 MHz, C_6D_6) spectrum of **52**



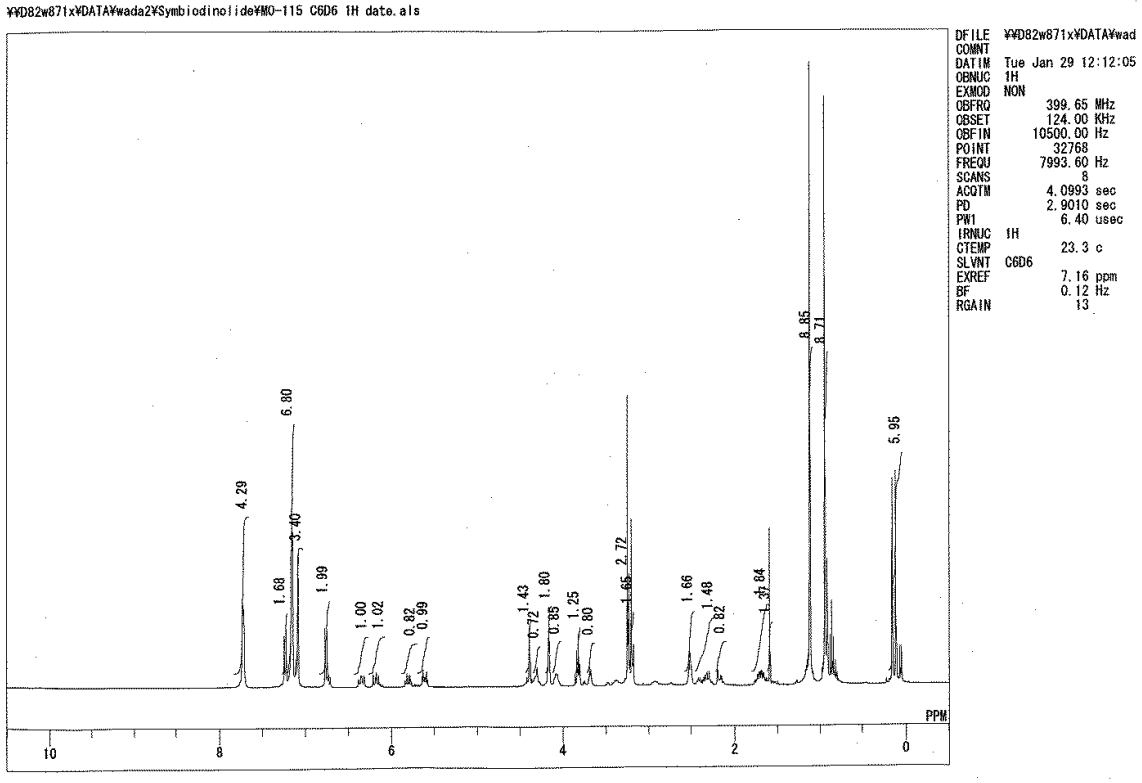
^{1}H NMR (400 MHz, C_6D_6) spectrum of **53**



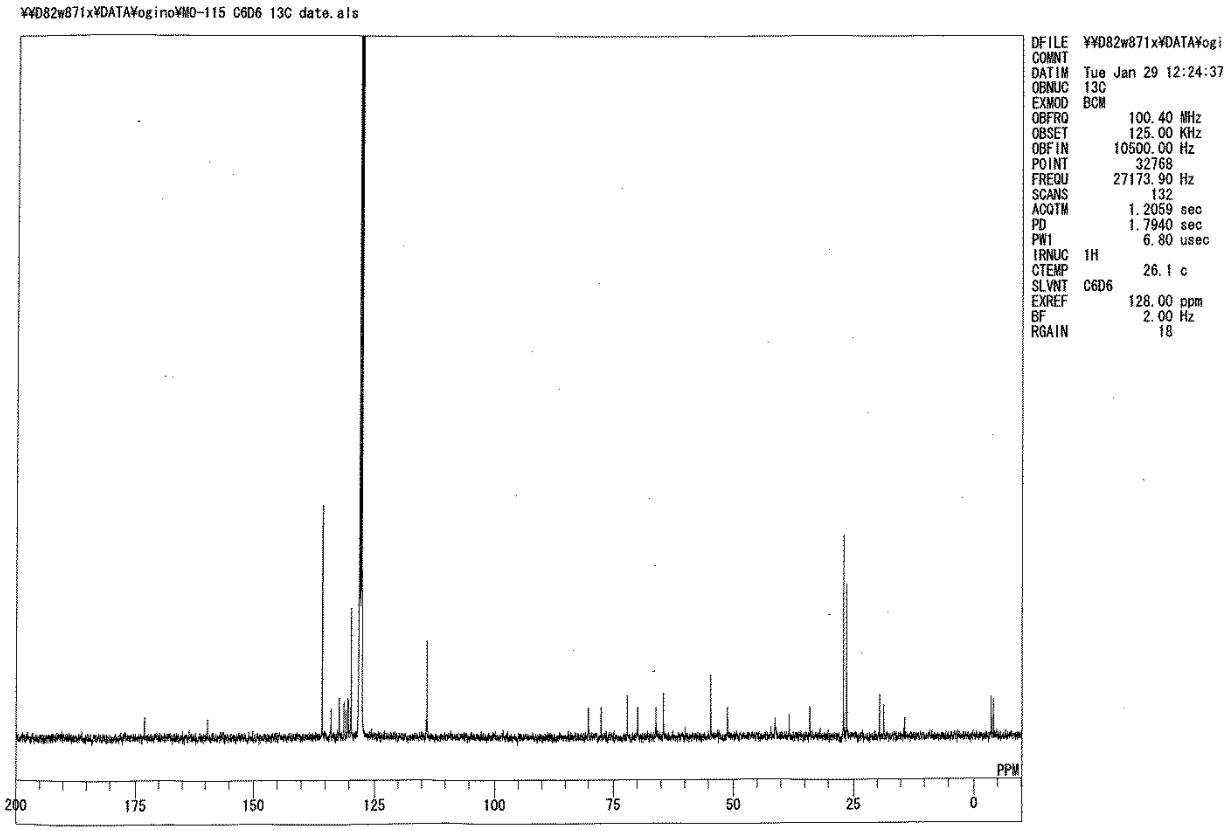
^{13}C NMR (100 MHz, C_6D_6) spectrum of **53**



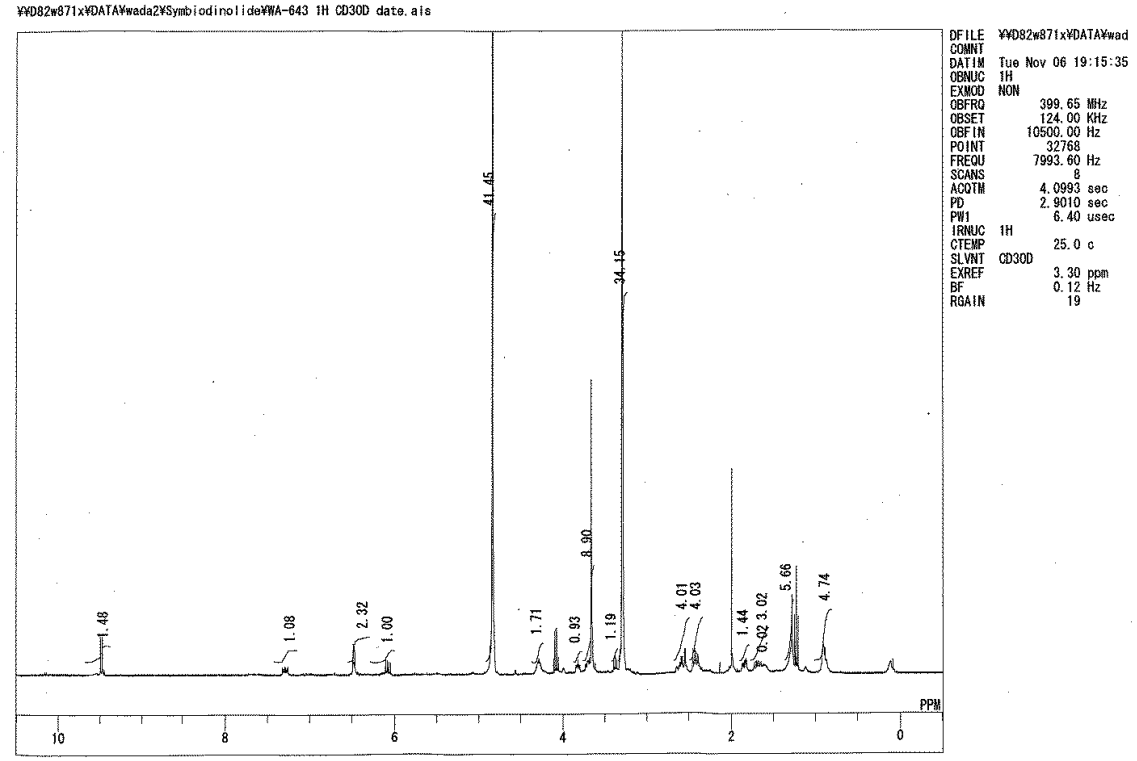
^{1}H NMR (400 MHz, C_6D_6) spectrum of **54**



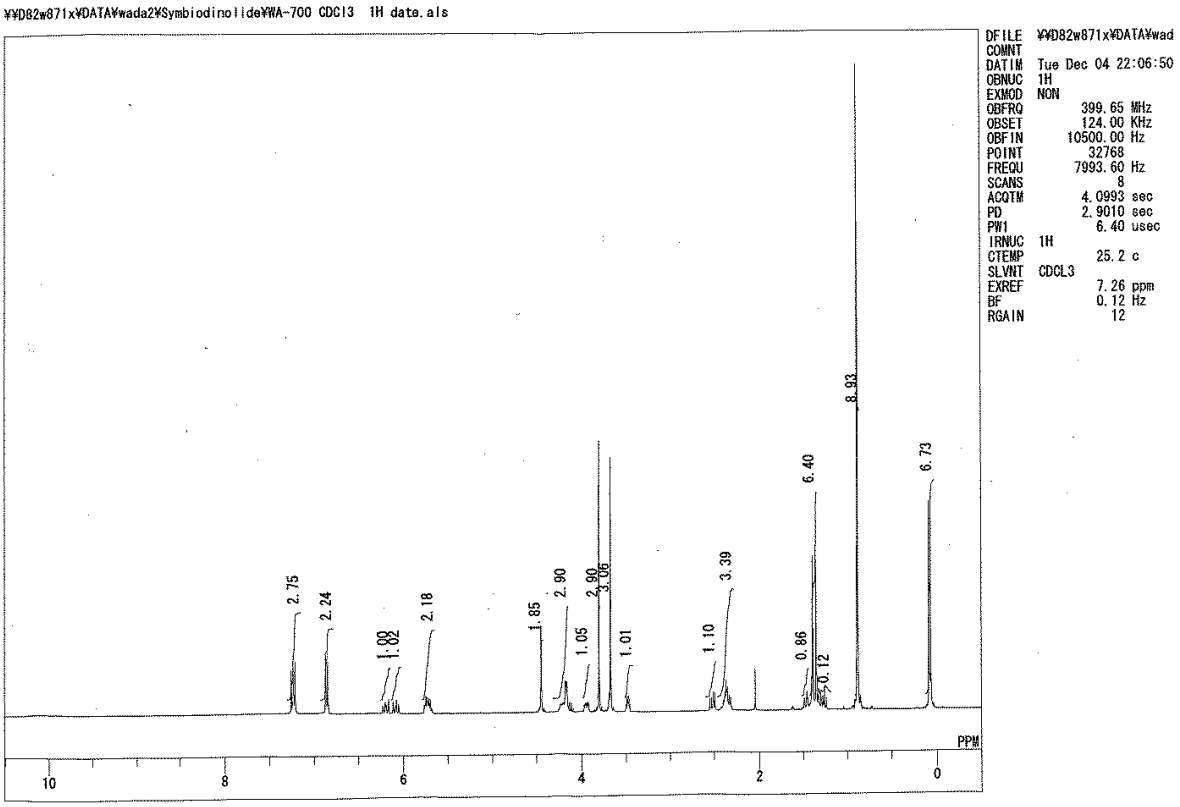
^{13}C NMR (100 MHz, C_6D_6) spectrum of **54**



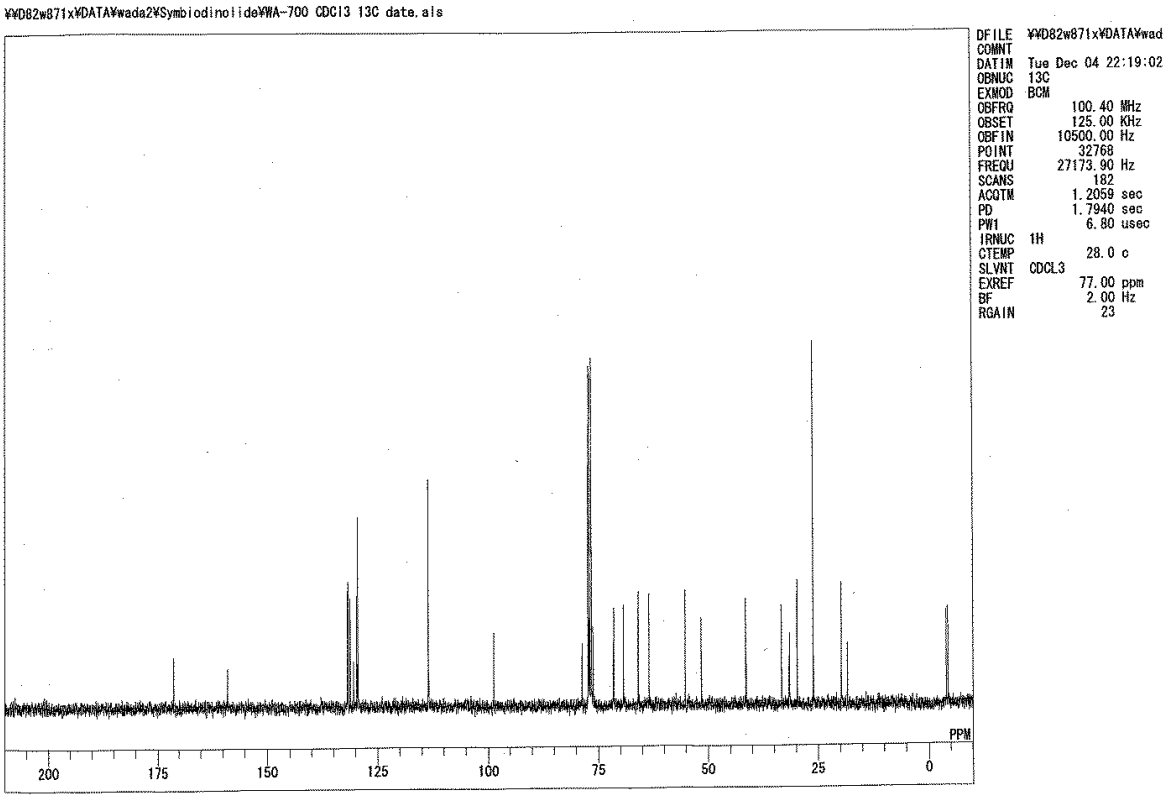
^{1}H NMR (400 MHz, C_5D_5N) spectrum of **55**



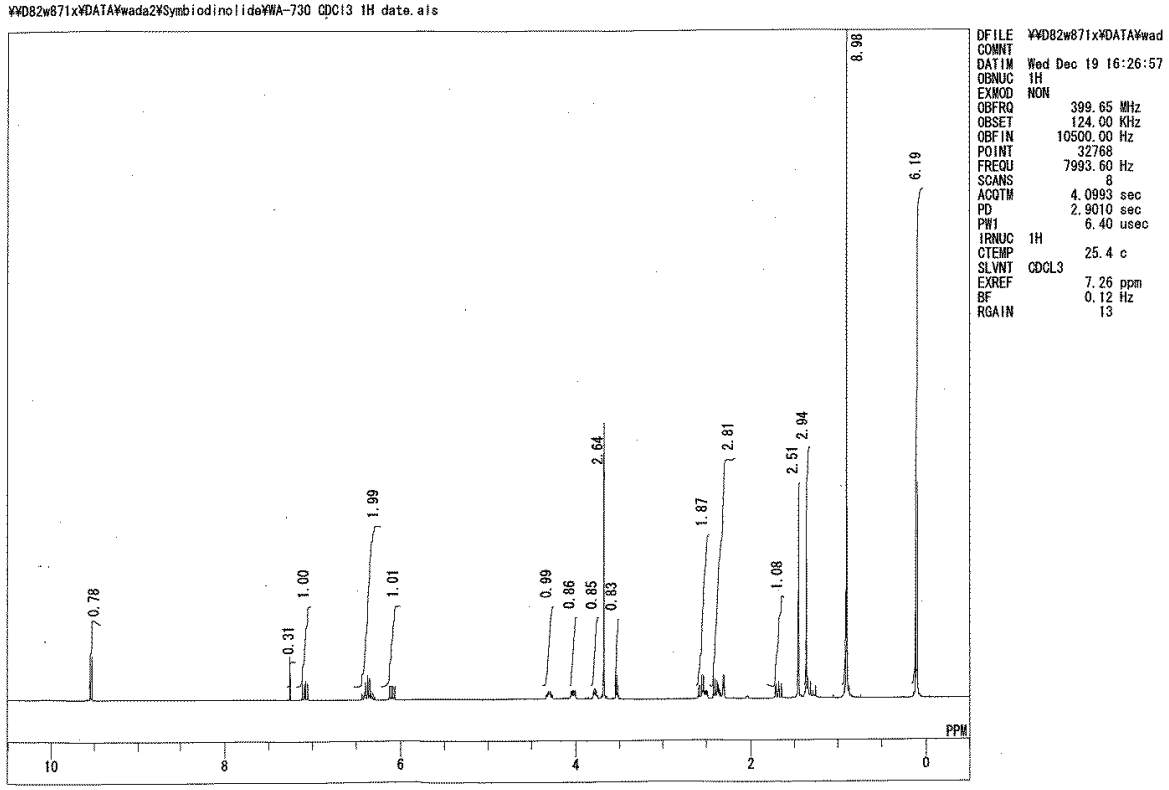
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **61**



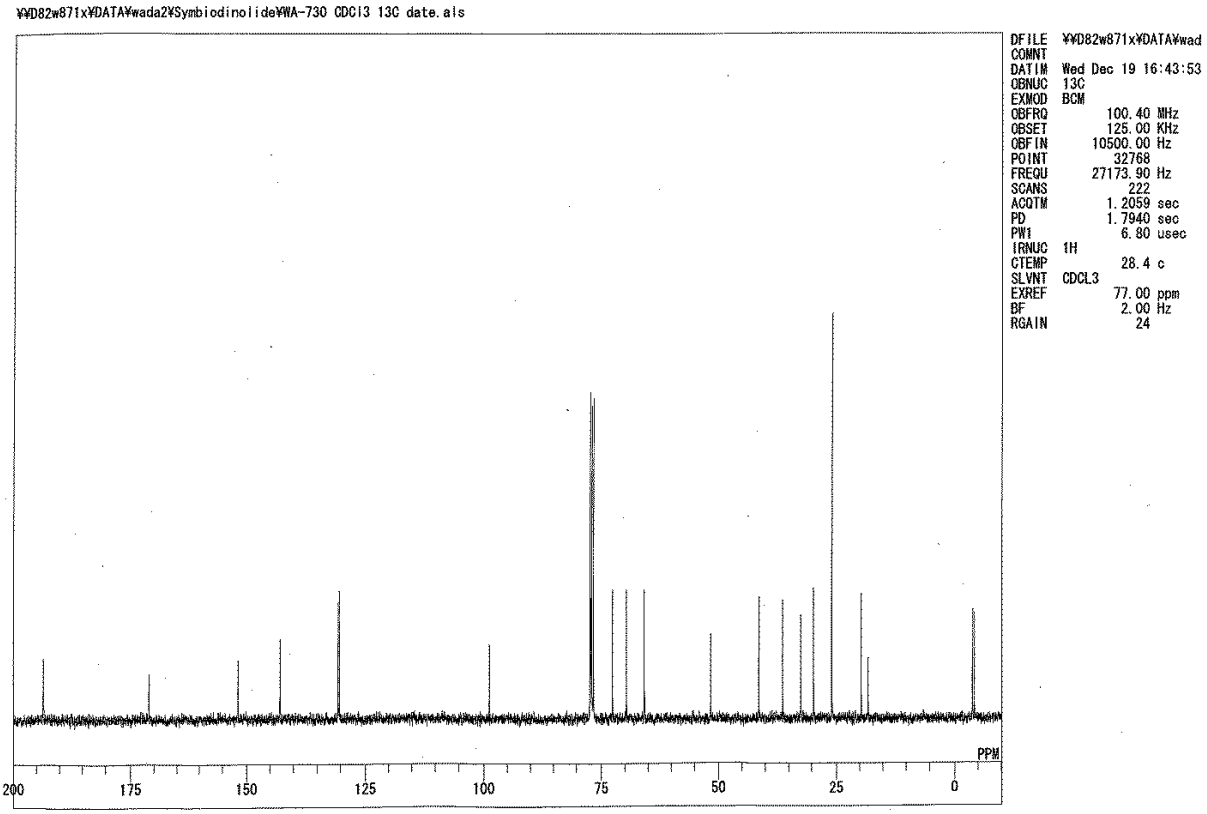
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **61**



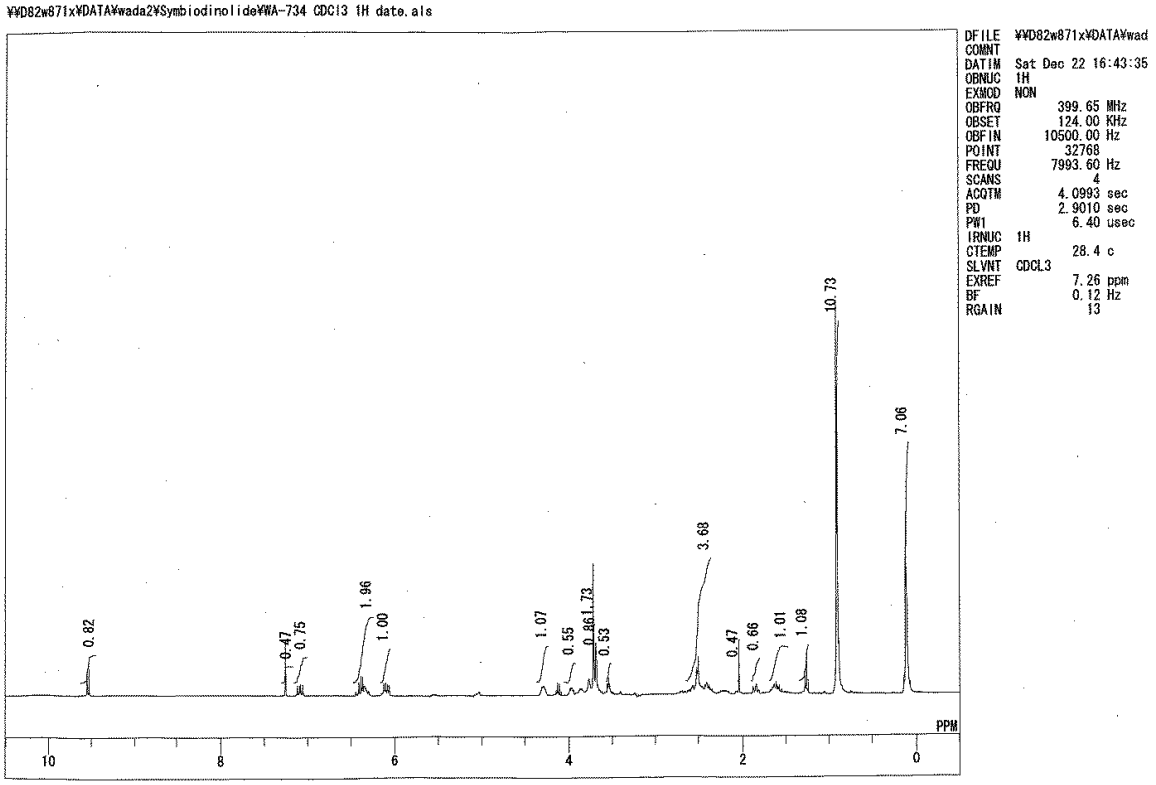
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **62**



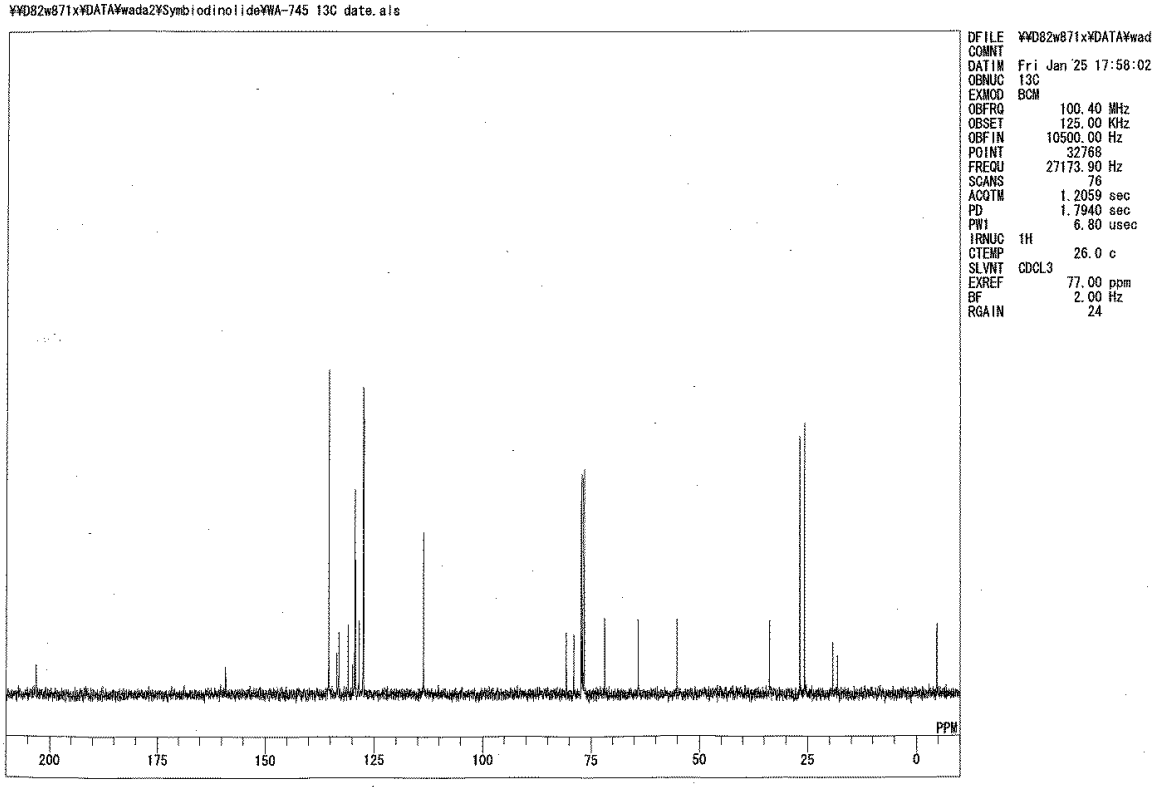
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **62**



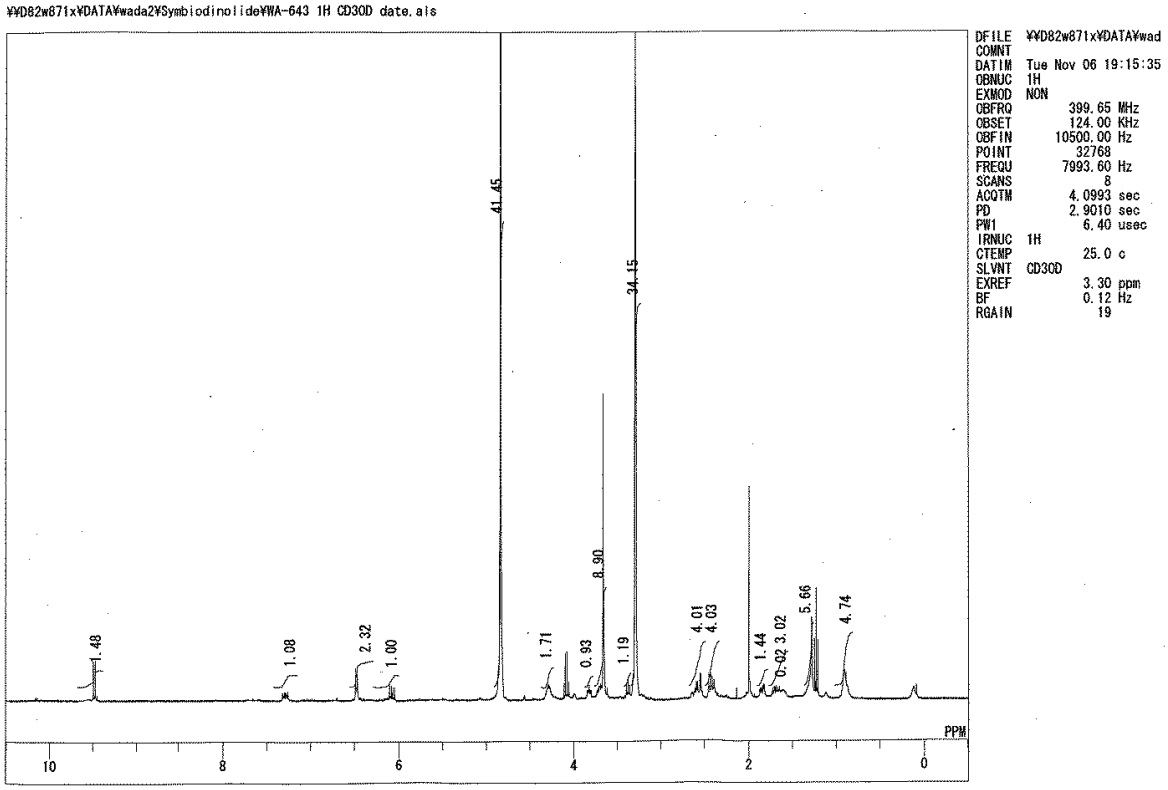
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **63**



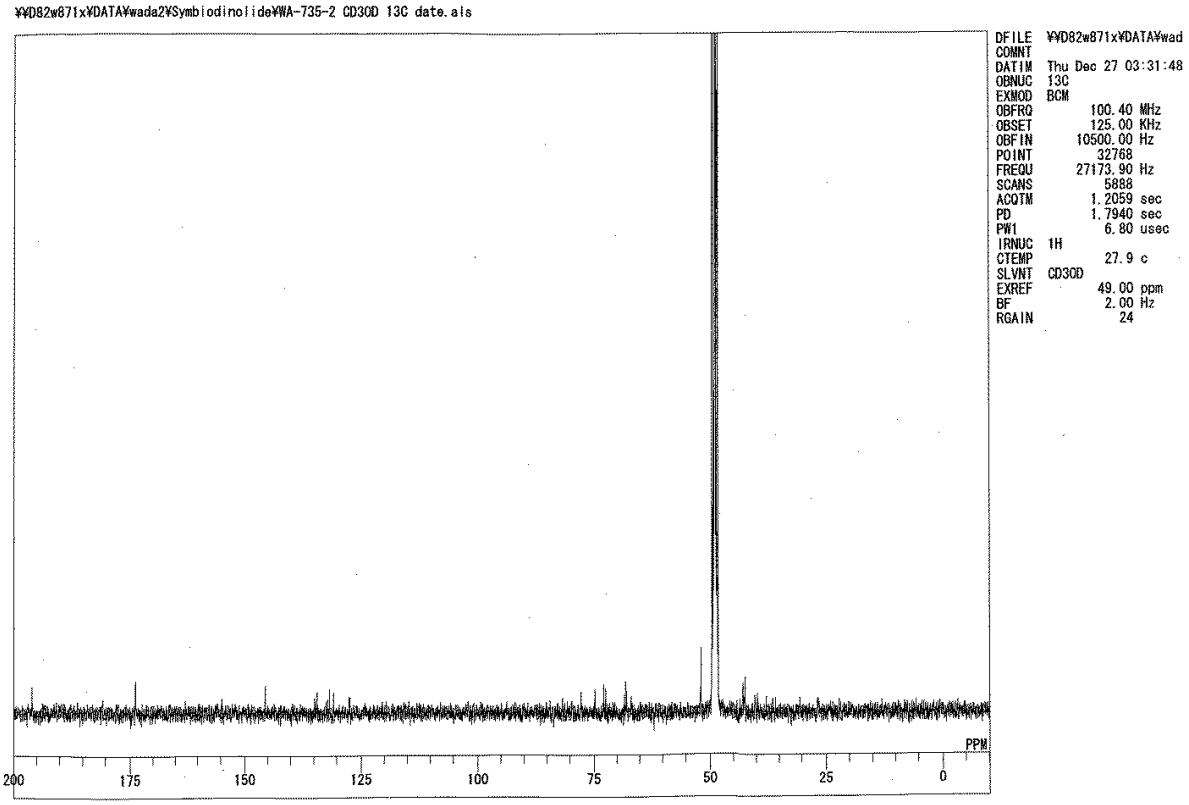
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **63**



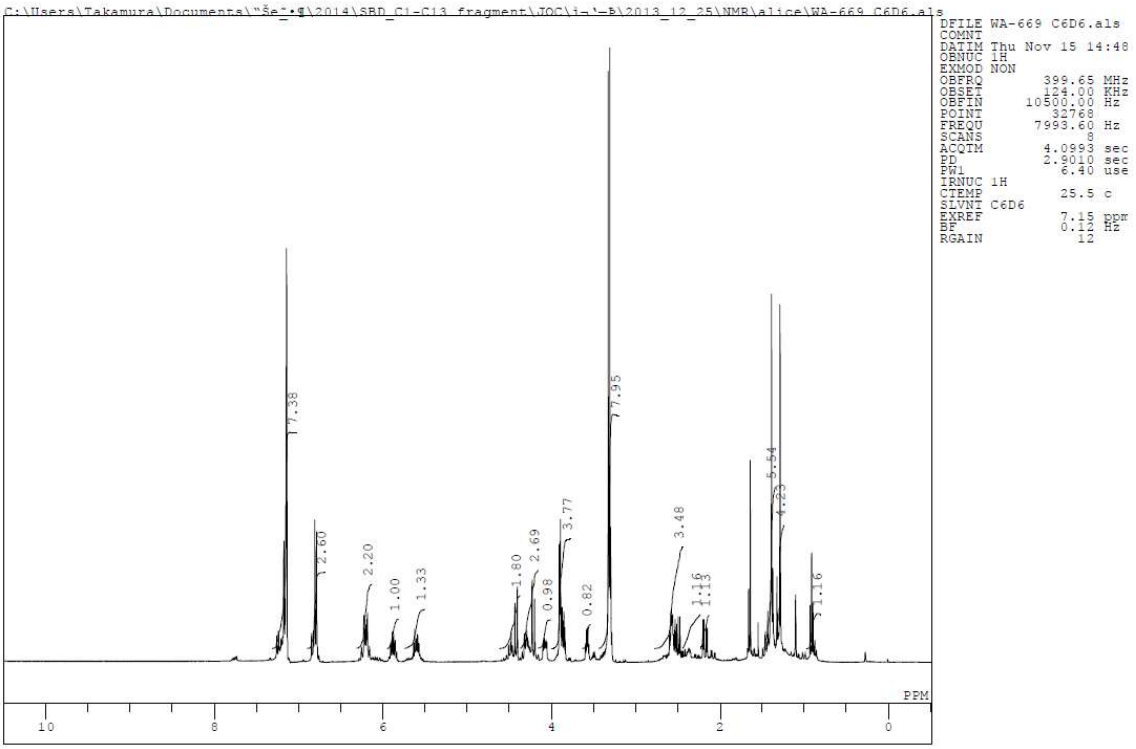
^{1}H NMR (400 MHz, CD_3OD) spectrum of **6a**



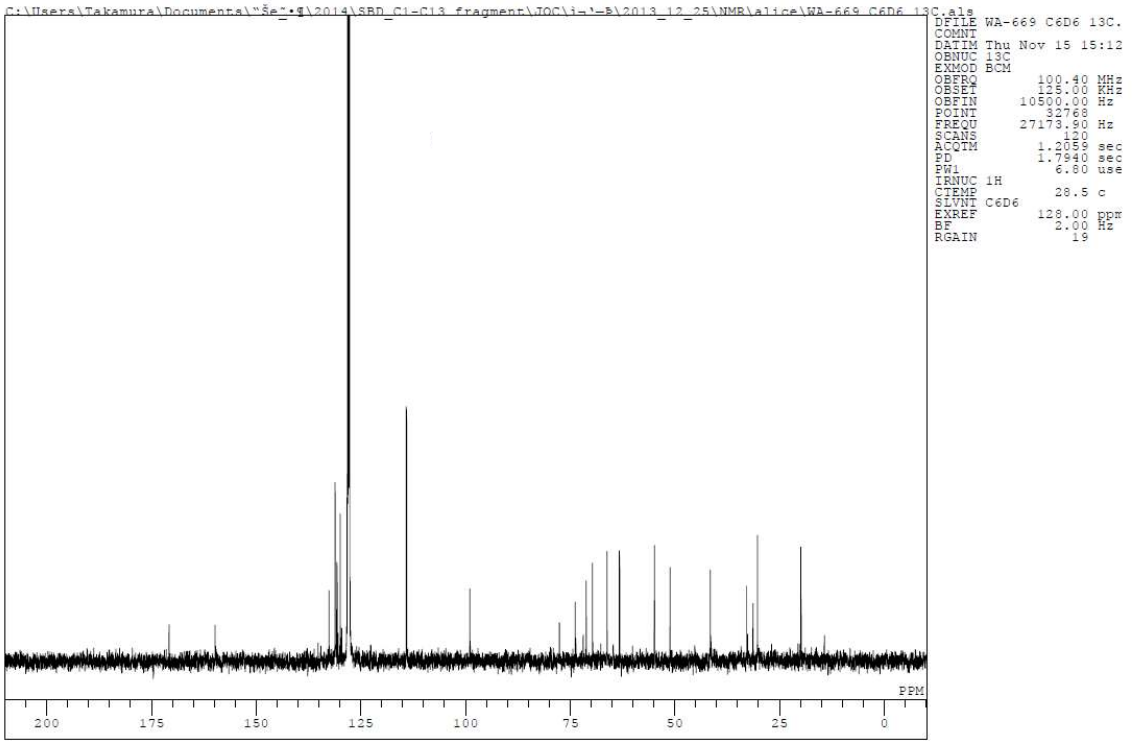
^{13}C NMR (100 MHz, CD_3OD) spectrum of **6a**



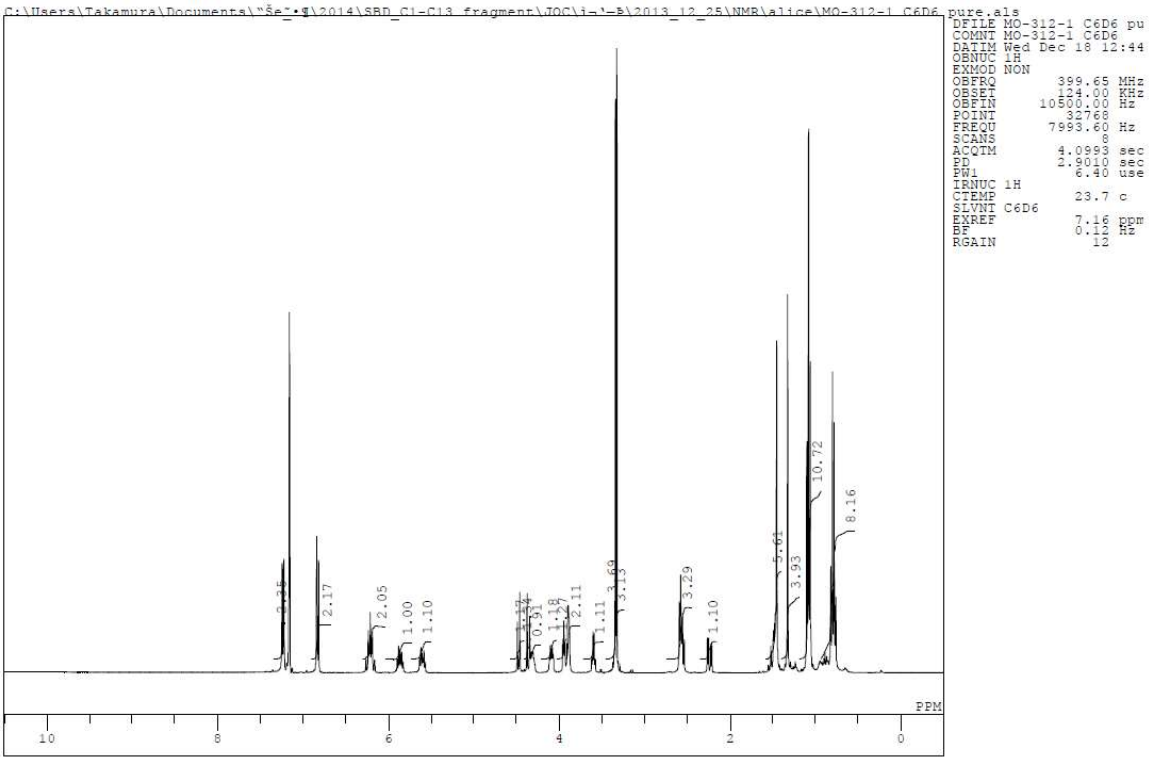
^{1}H NMR (400 MHz, C_6D_6) spectrum of **64**



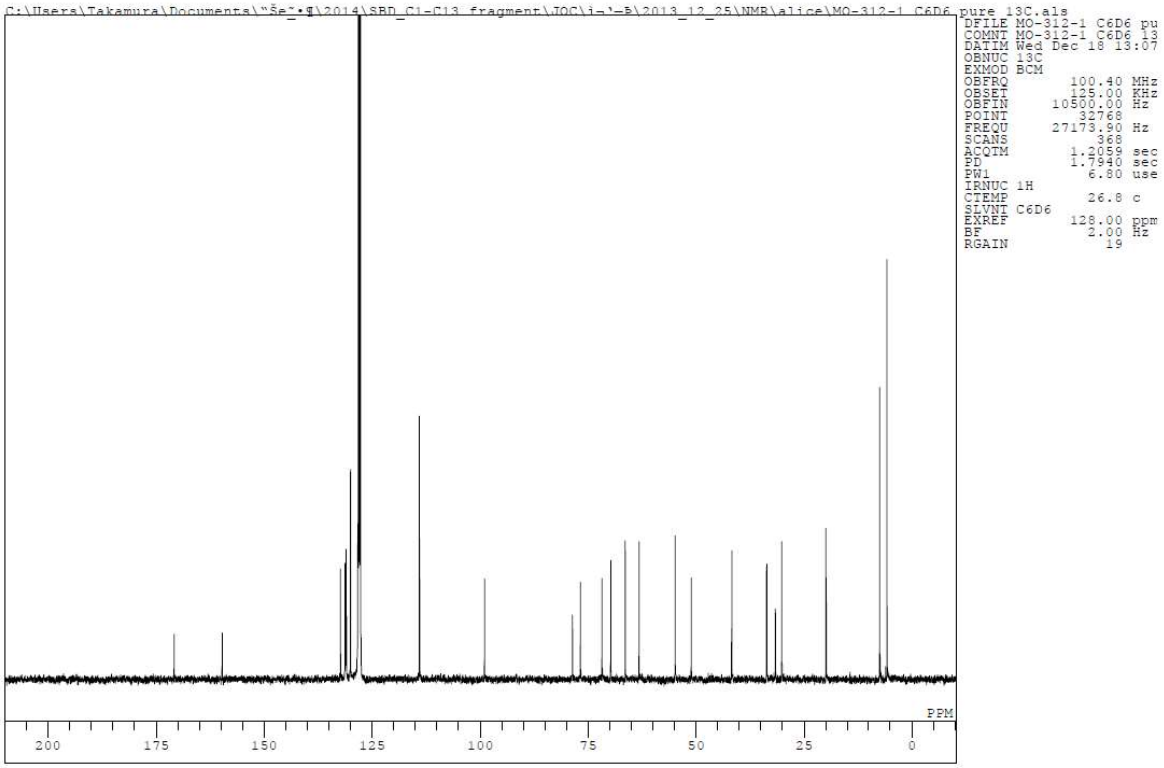
^{13}C NMR (100 MHz, C_6D_6) spectrum of **64**



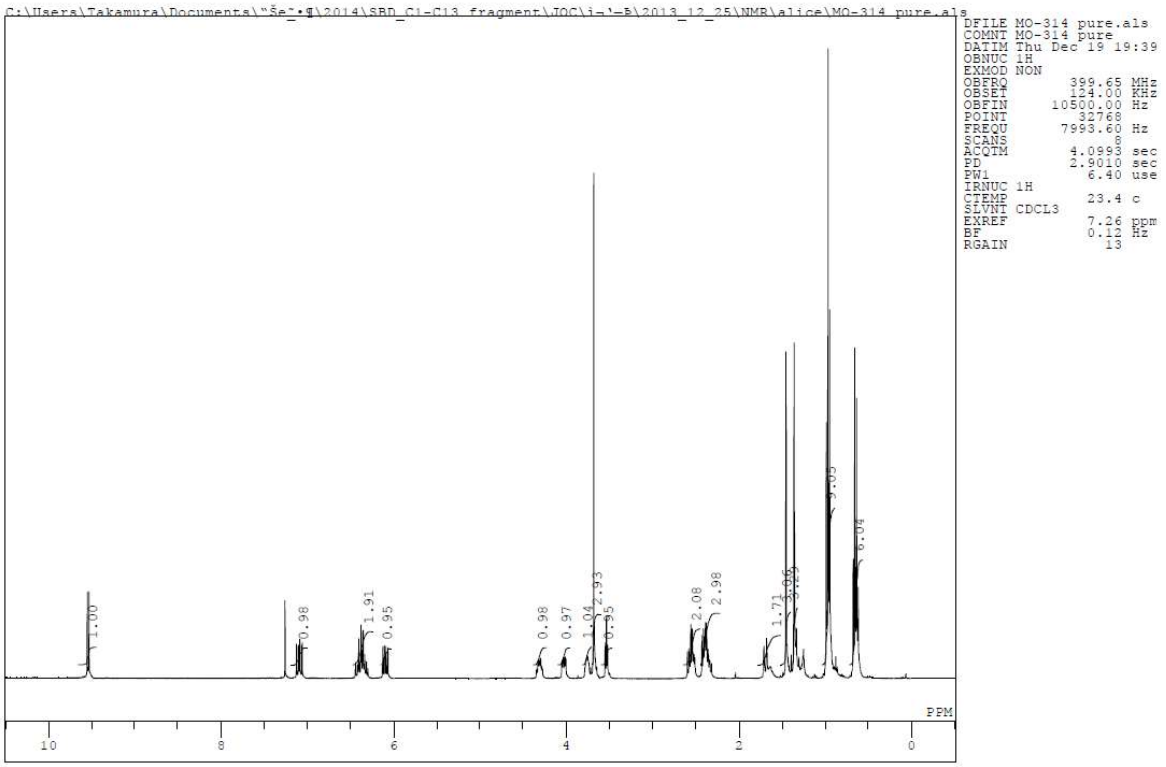
^{1}H NMR (400 MHz, C_6D_6) spectrum of **65**



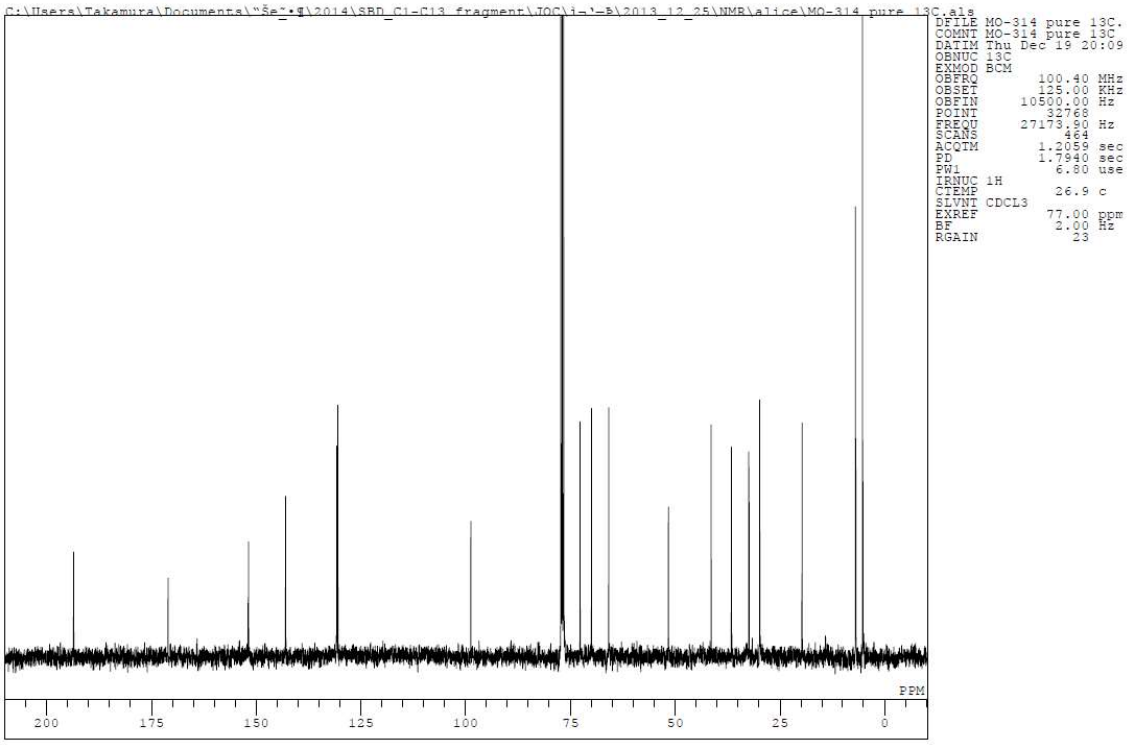
^{13}C NMR (100 MHz, C_6D_6) spectrum of **65**



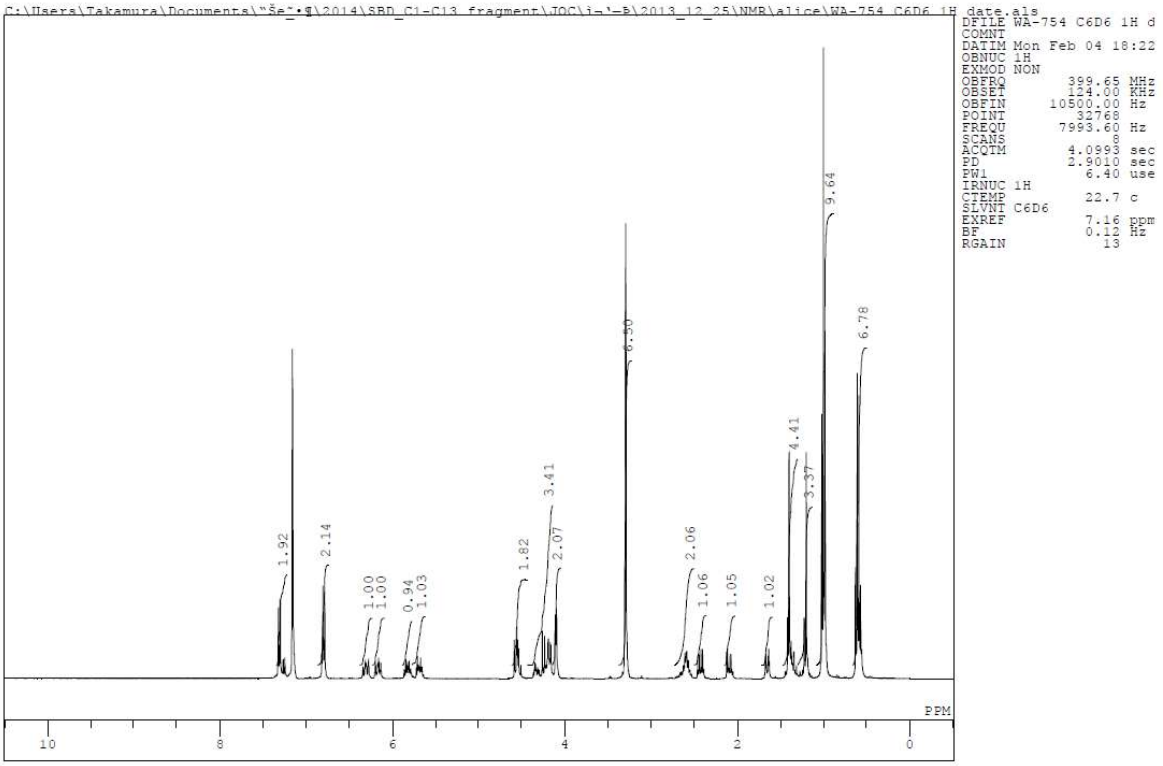
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **66**



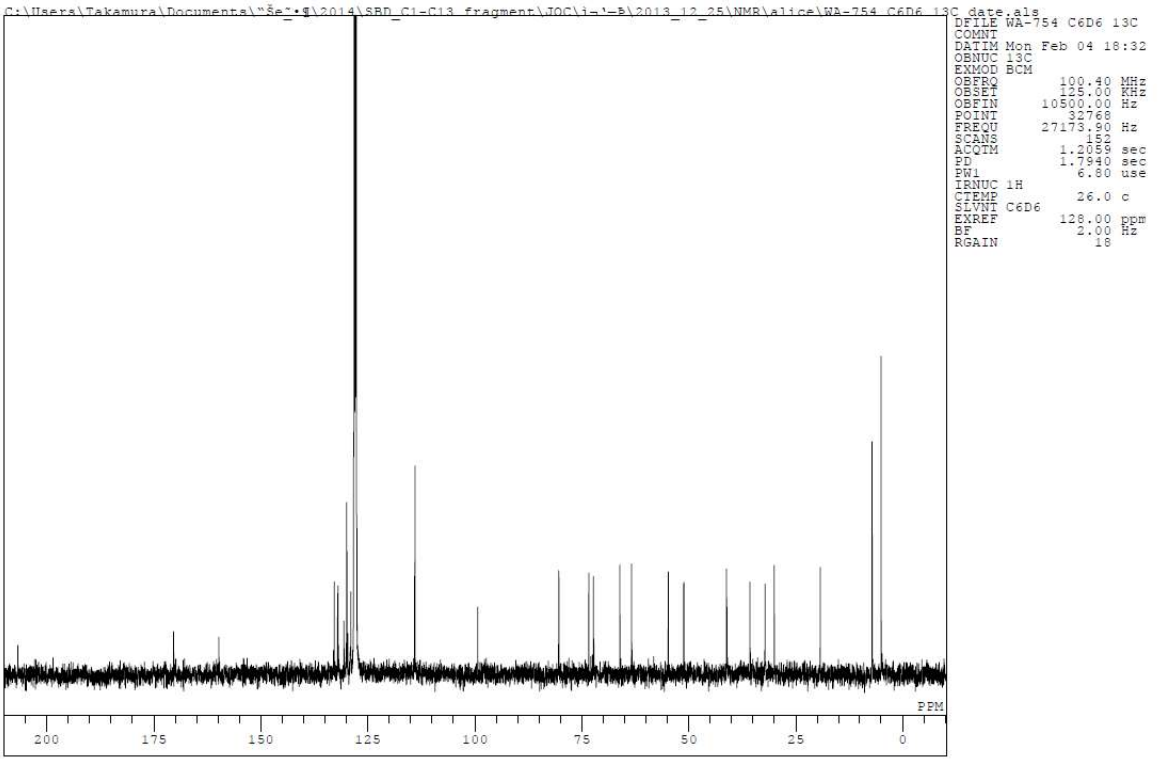
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **66**



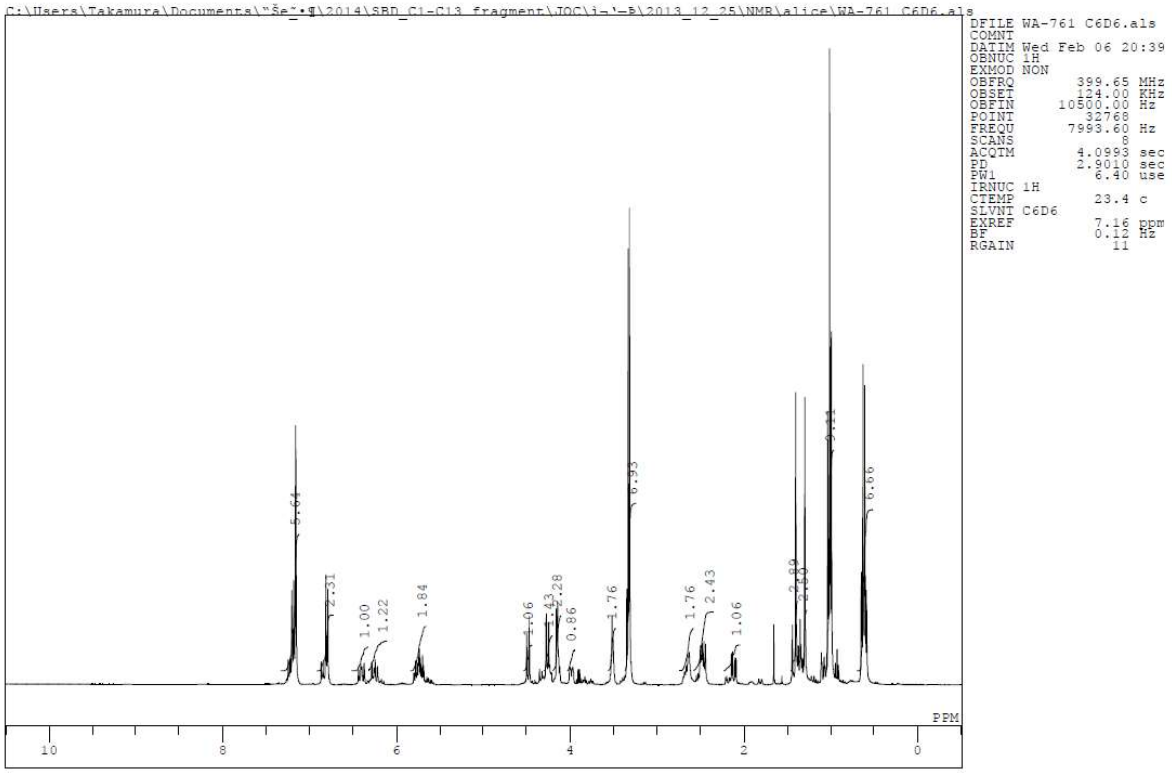
^{1}H NMR (400 MHz, C_6D_6) spectrum of **67**



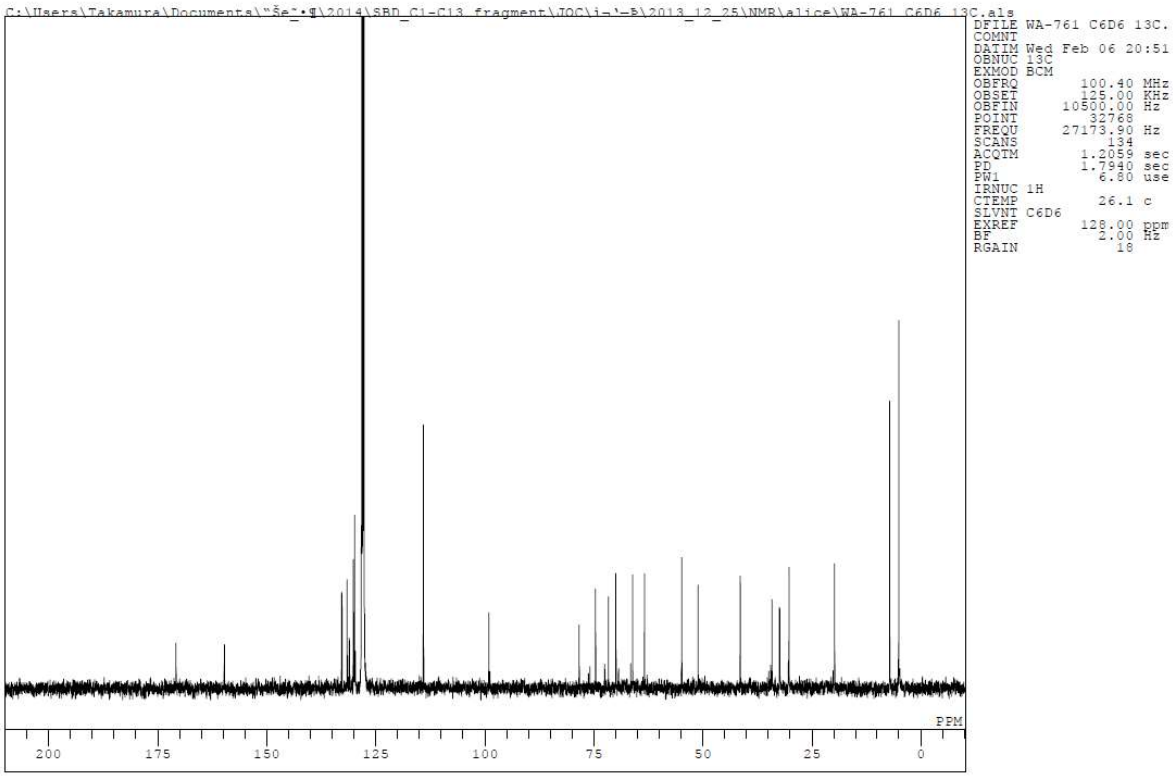
^{13}C NMR (100 MHz, C_6D_6) spectrum of **67**



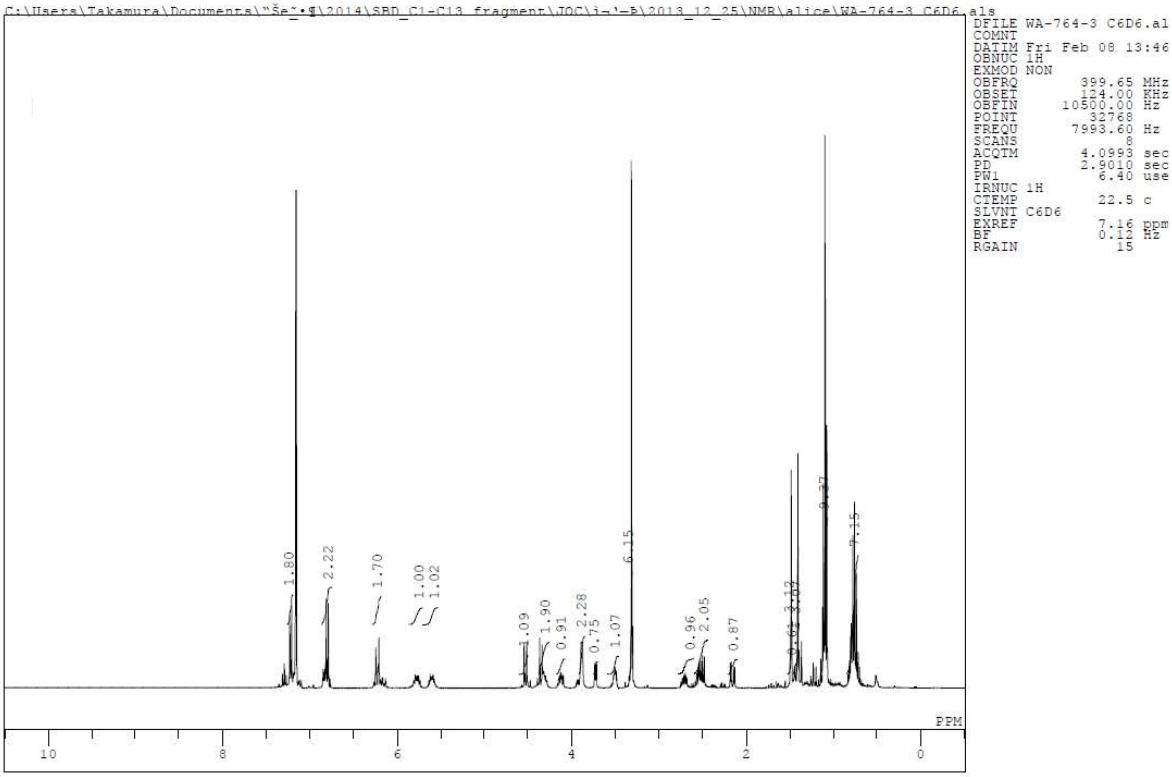
^{1}H NMR (400 MHz, C_6D_6) spectrum of **68**



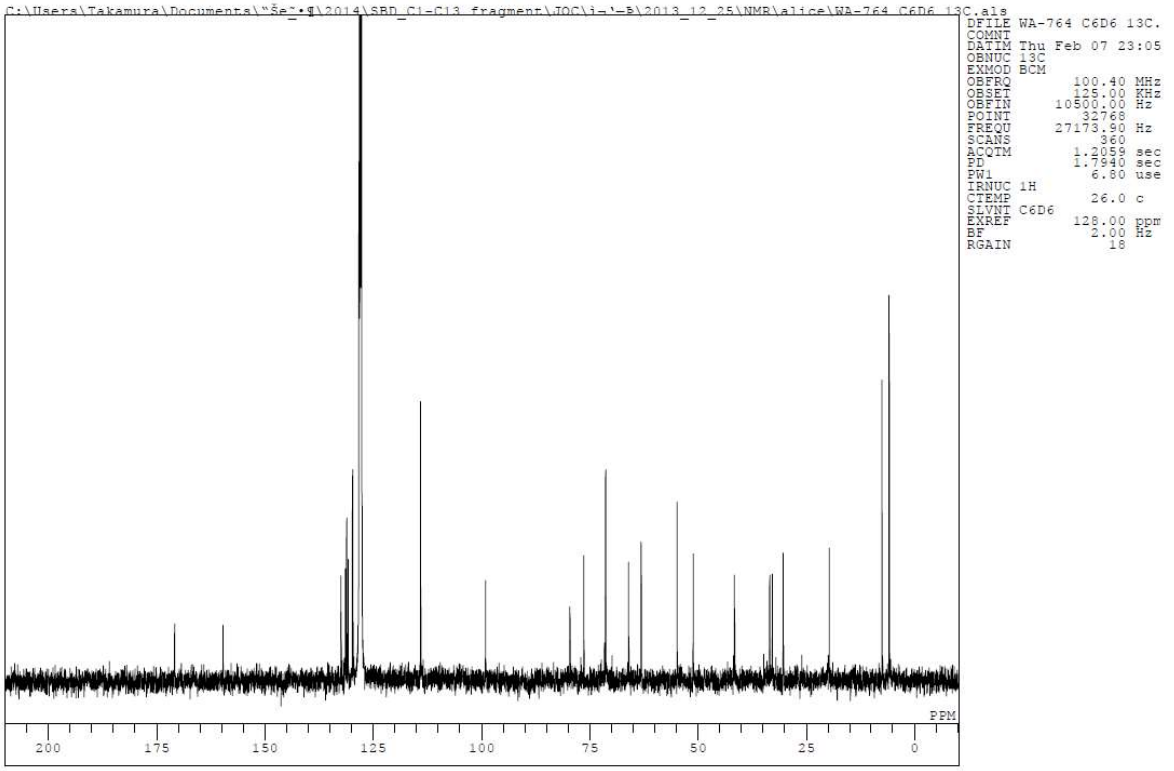
^{13}C NMR (100 MHz, C_6D_6) spectrum of **68**



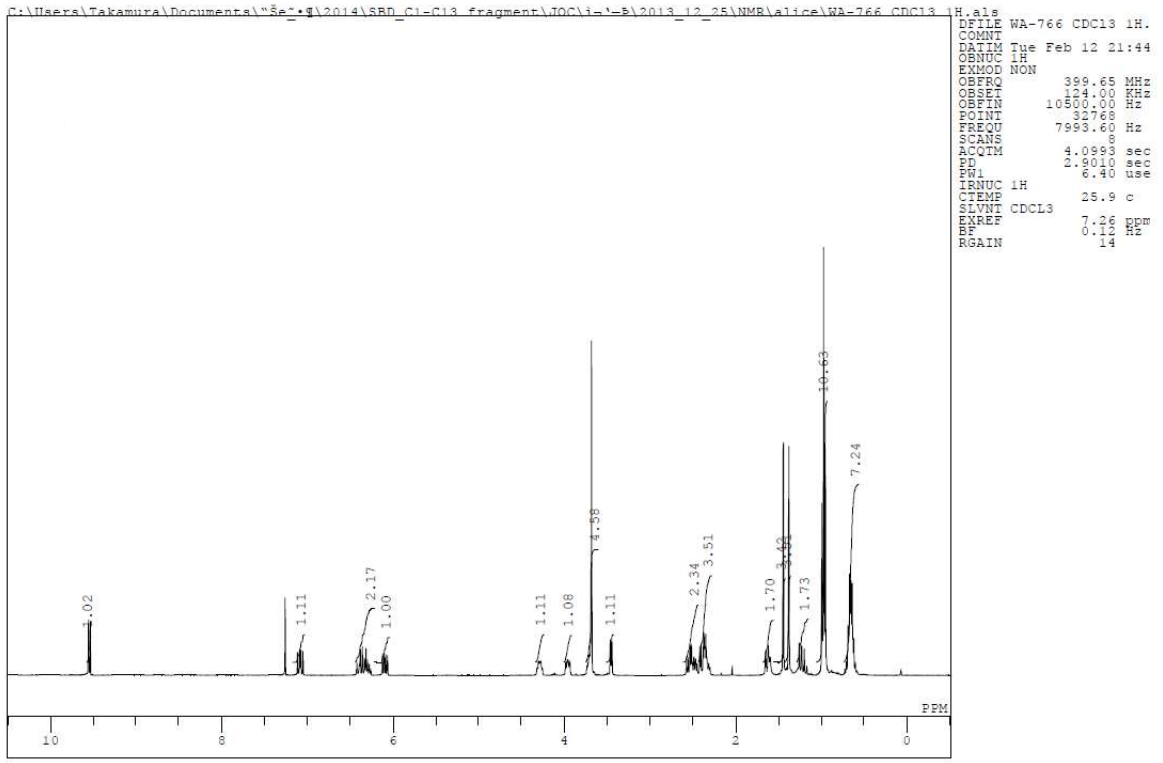
^{1}H NMR (400 MHz, C_6D_6) spectrum of **71**



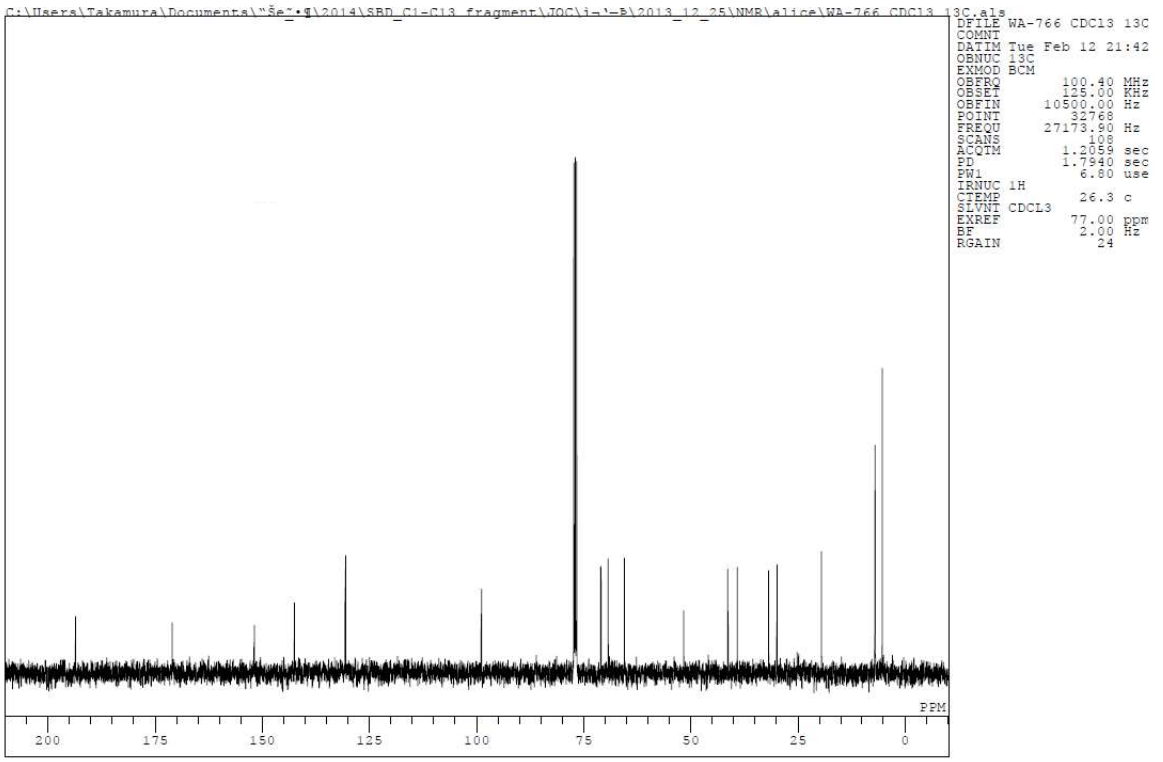
^{13}C NMR (100 MHz, C_6D_6) spectrum of **71**



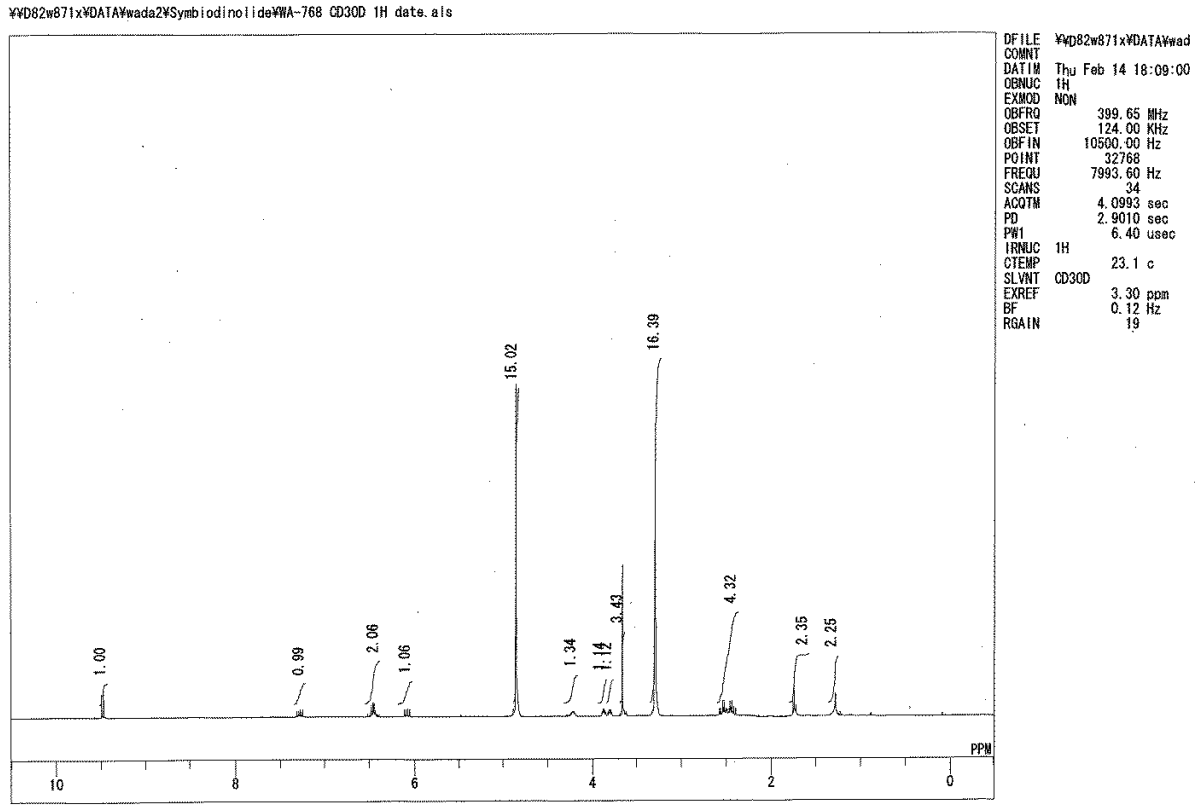
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **72**



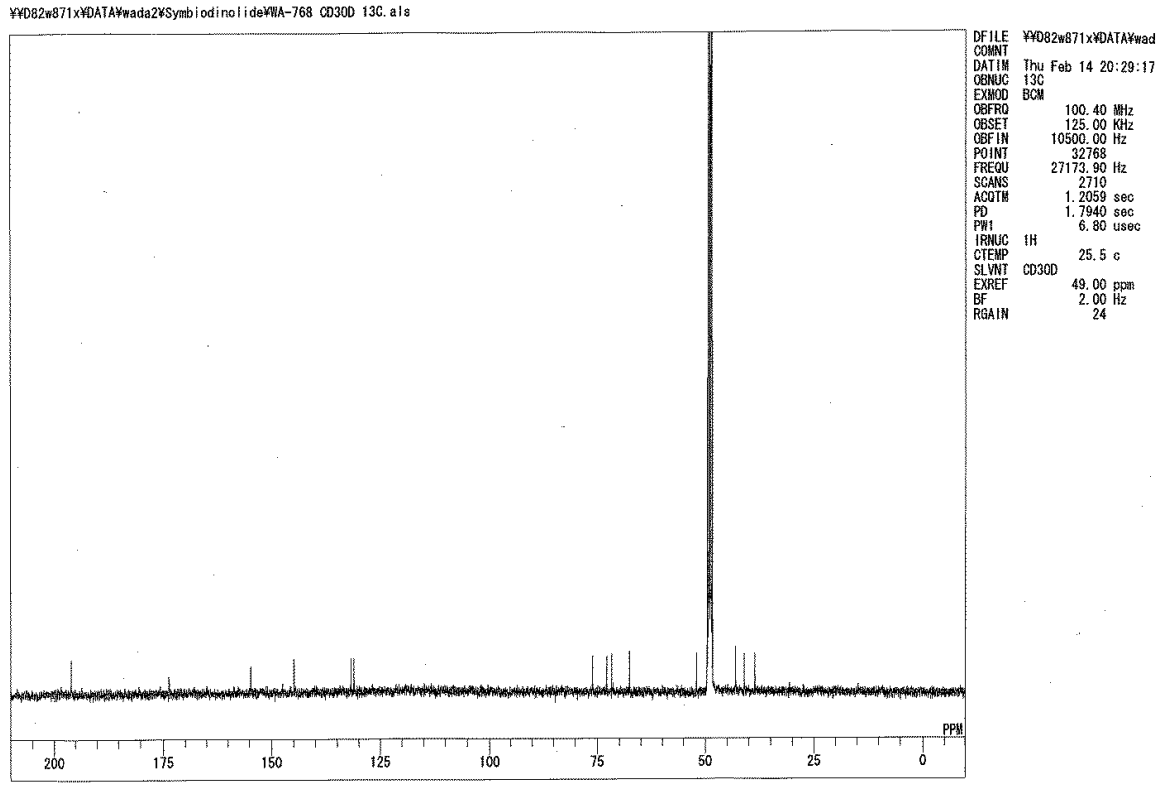
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **72**



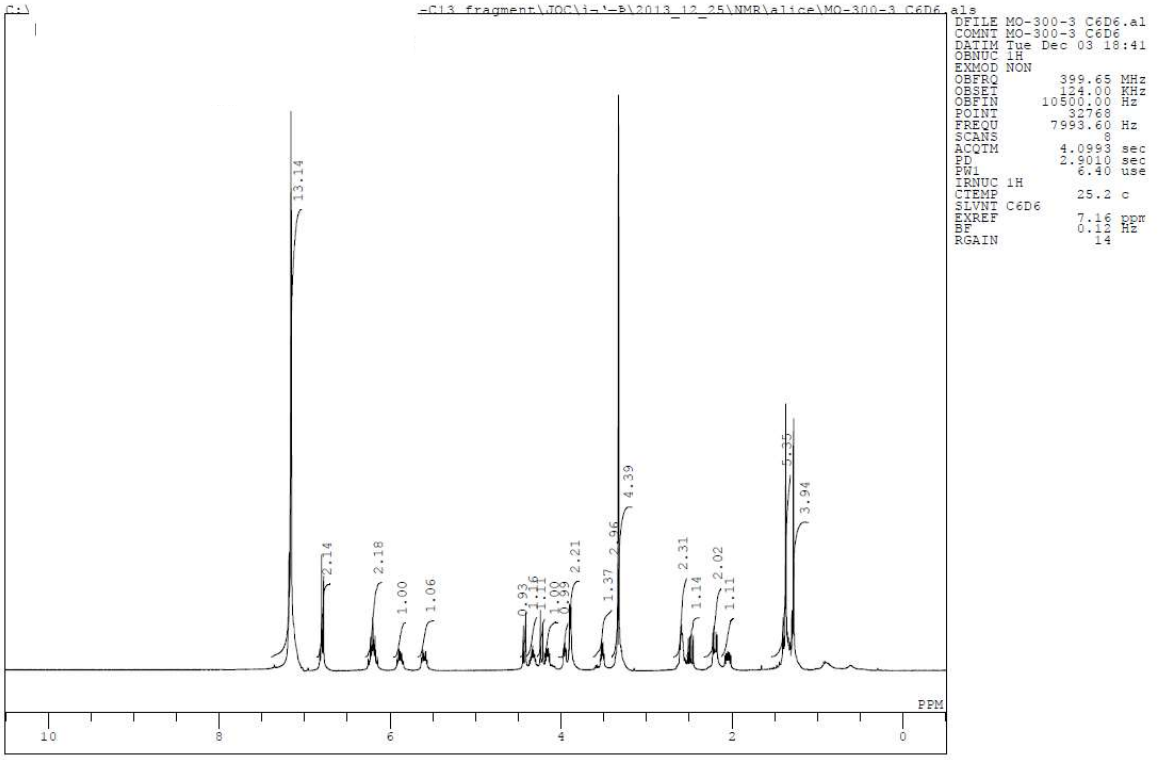
^{1}H NMR (400 MHz, CD_3OD) spectrum of **6b**



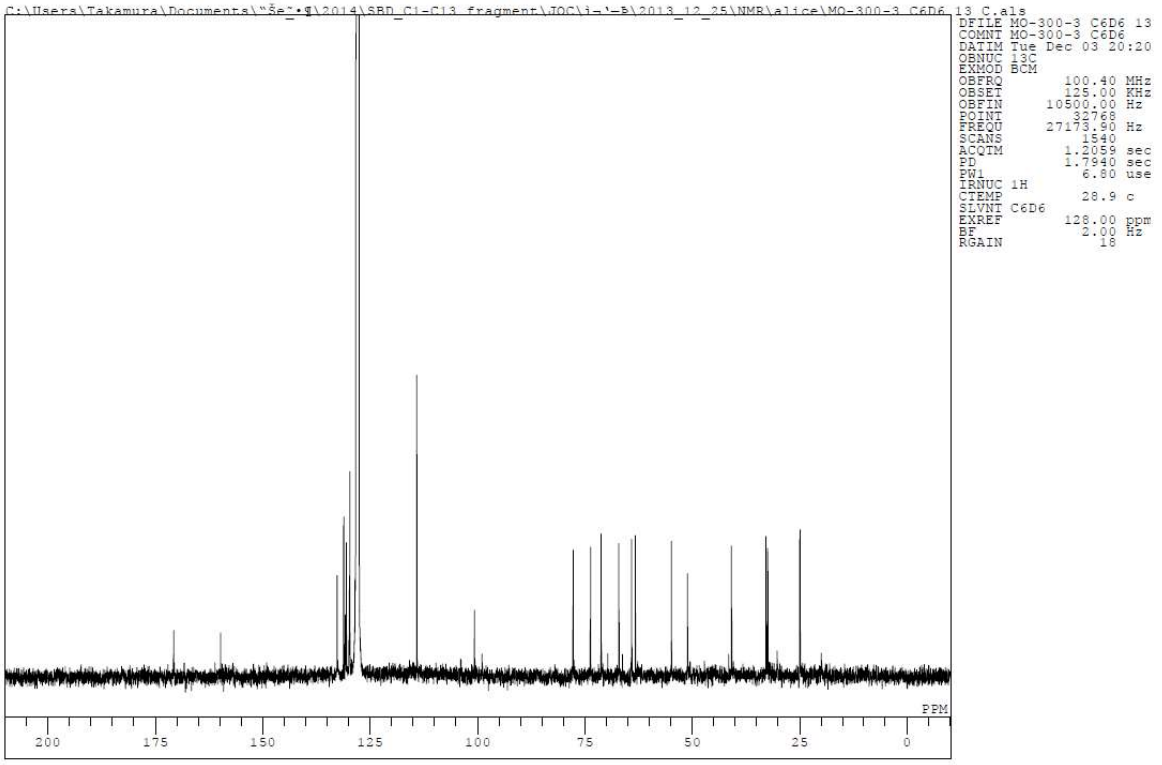
^{13}C NMR (100 MHz, CD_3OD) spectrum of **6b**



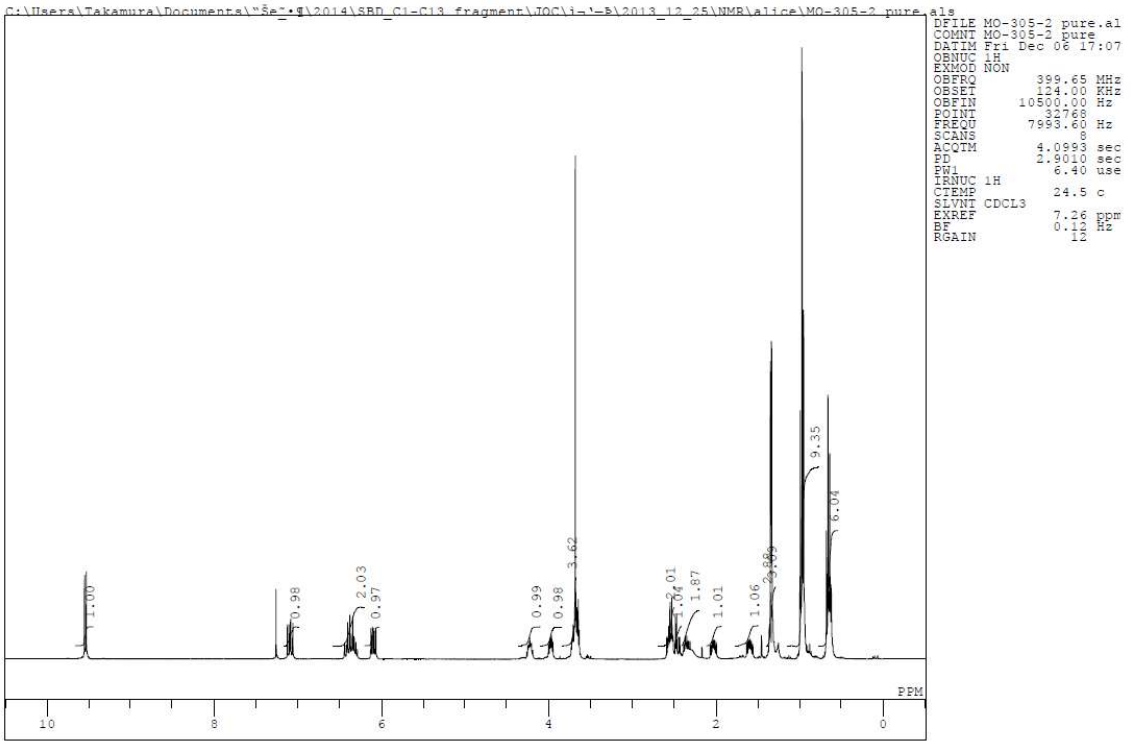
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **73**



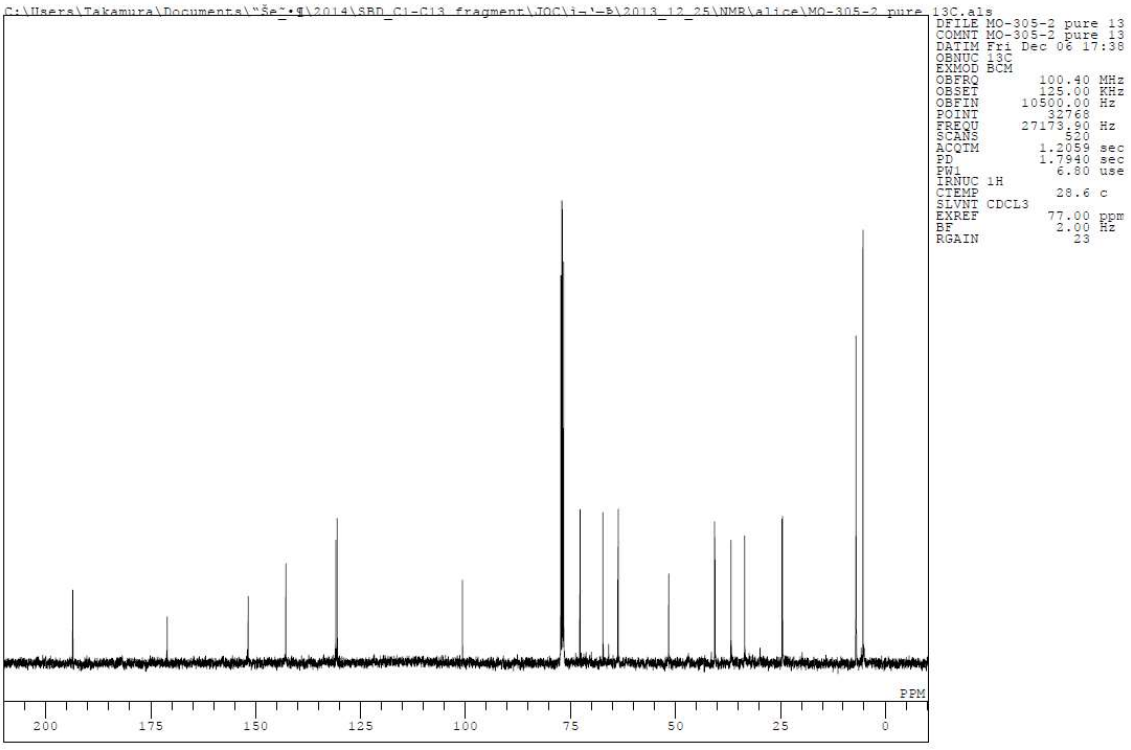
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **73**



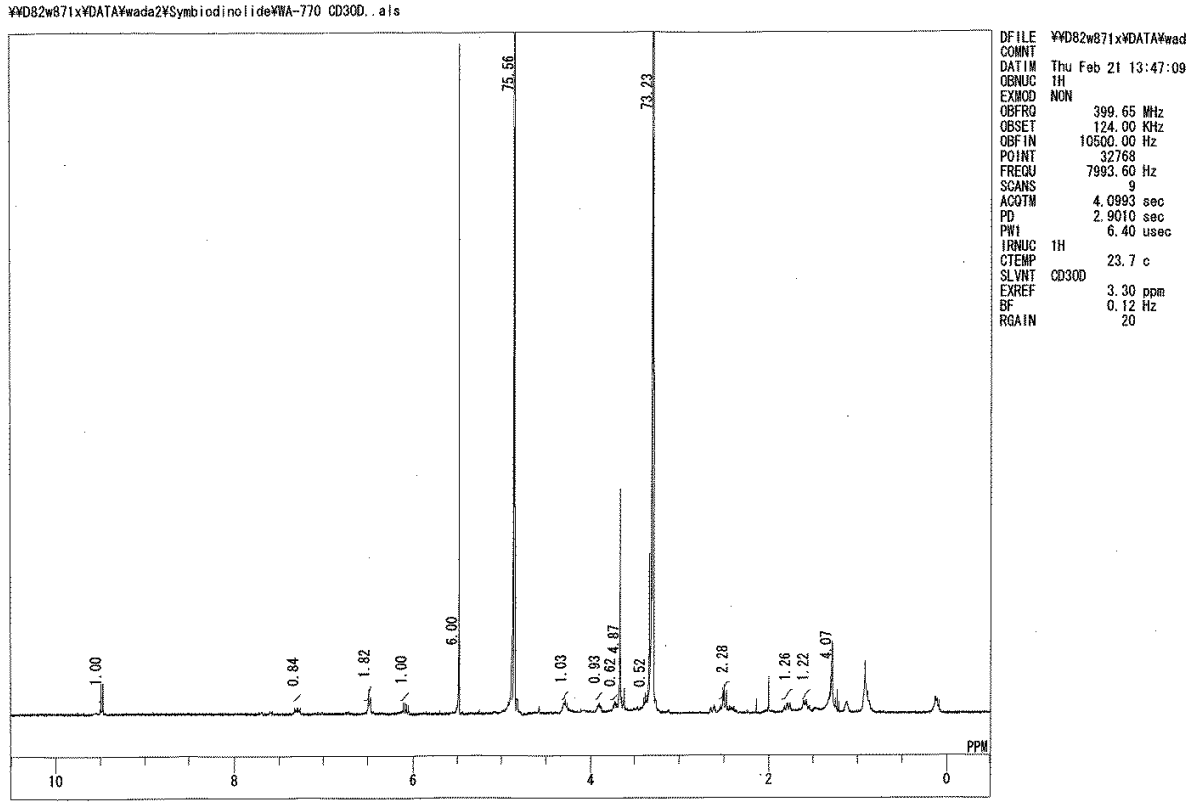
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **74**



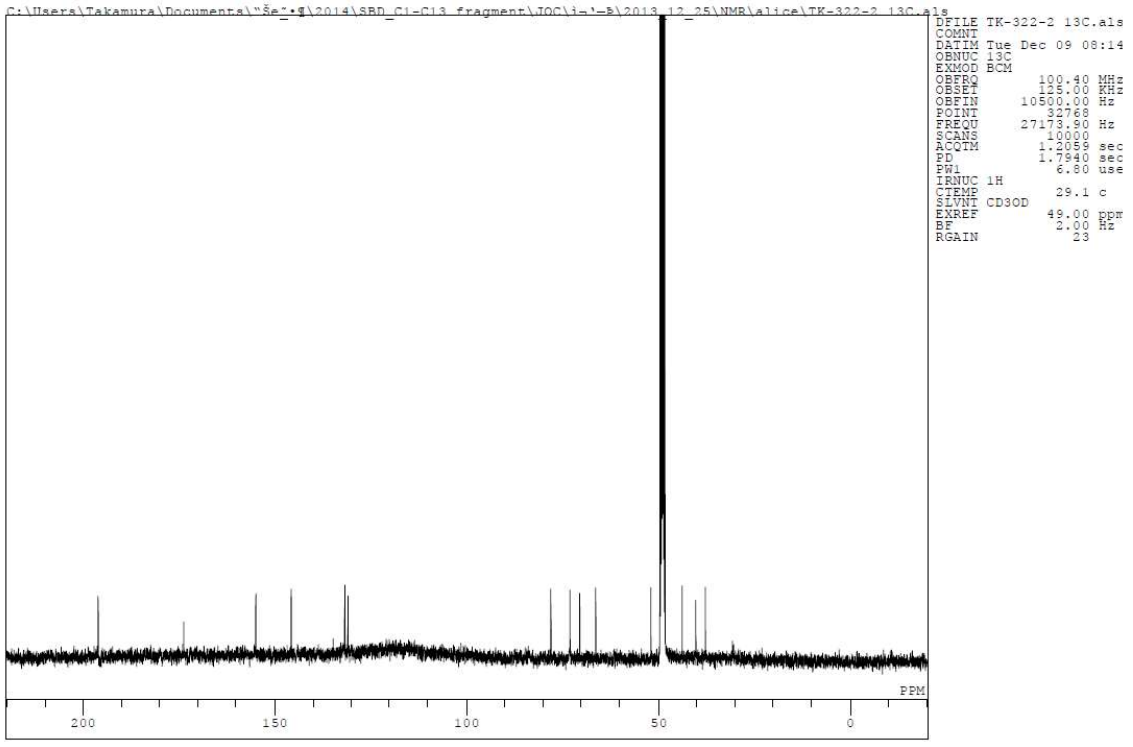
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **74**



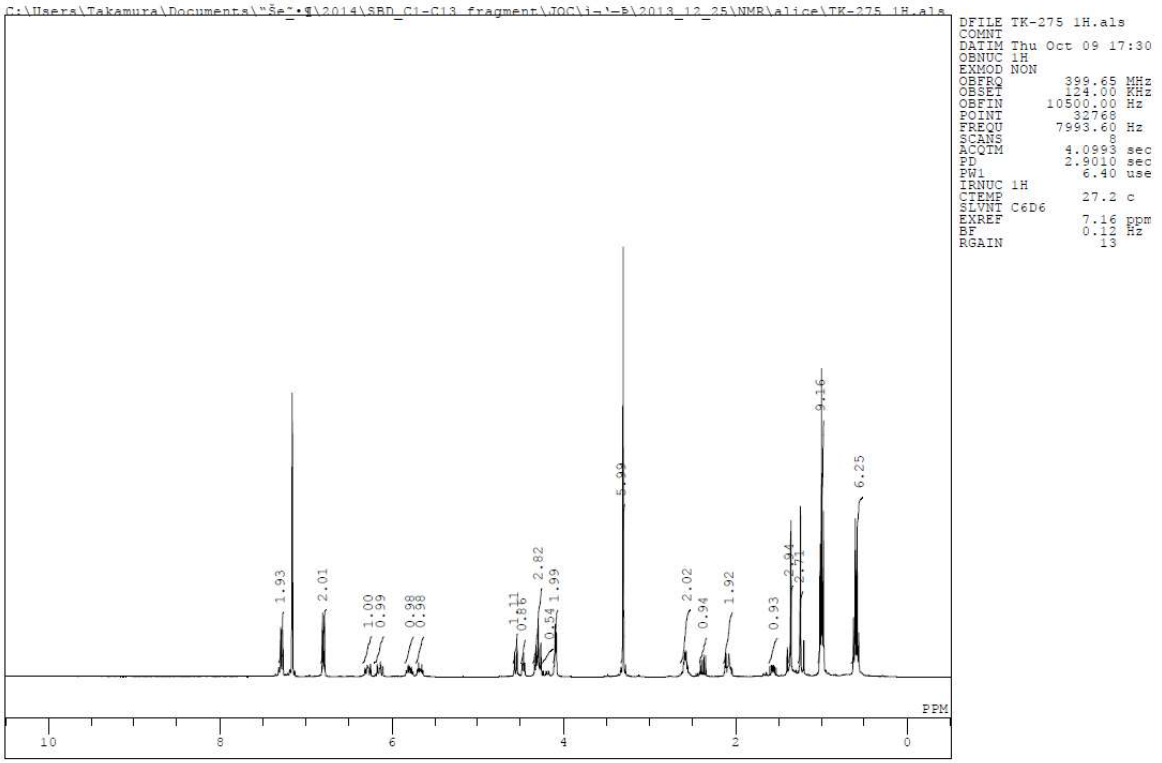
^{1}H NMR (400 MHz, CD_3OD) spectrum of **6c**



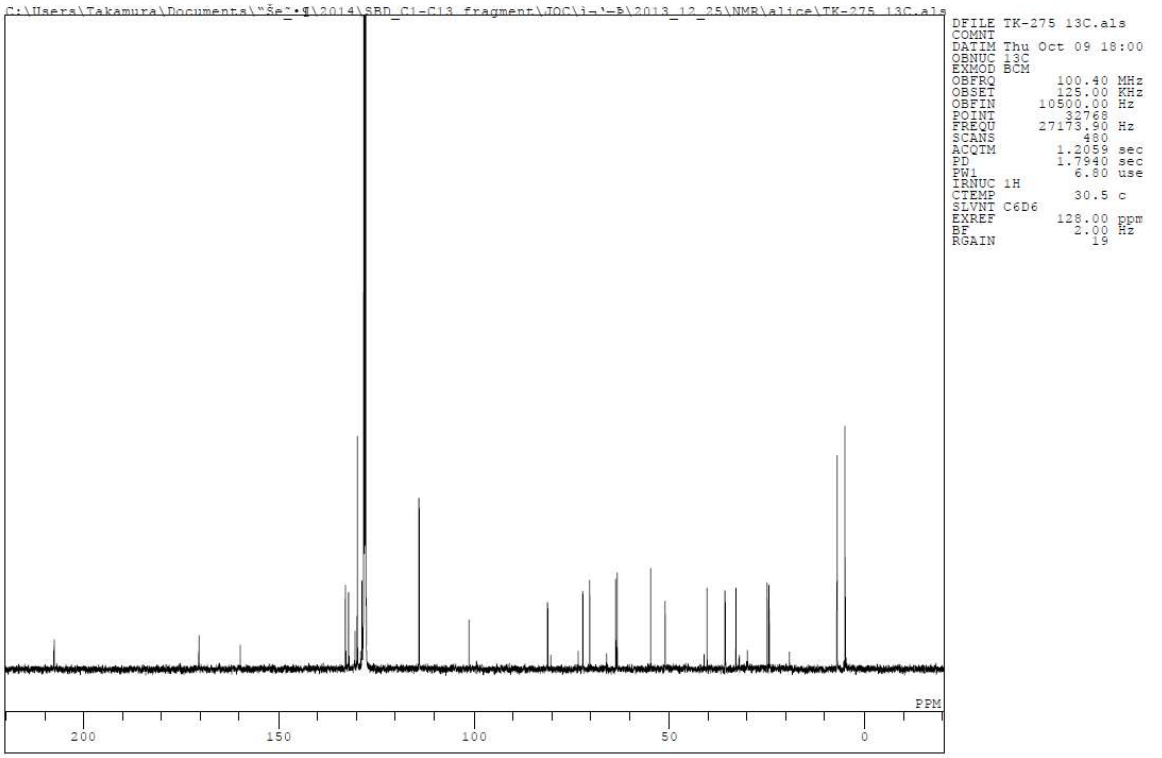
^{13}C NMR (100 MHz, CD_3OD) spectrum of **6c**



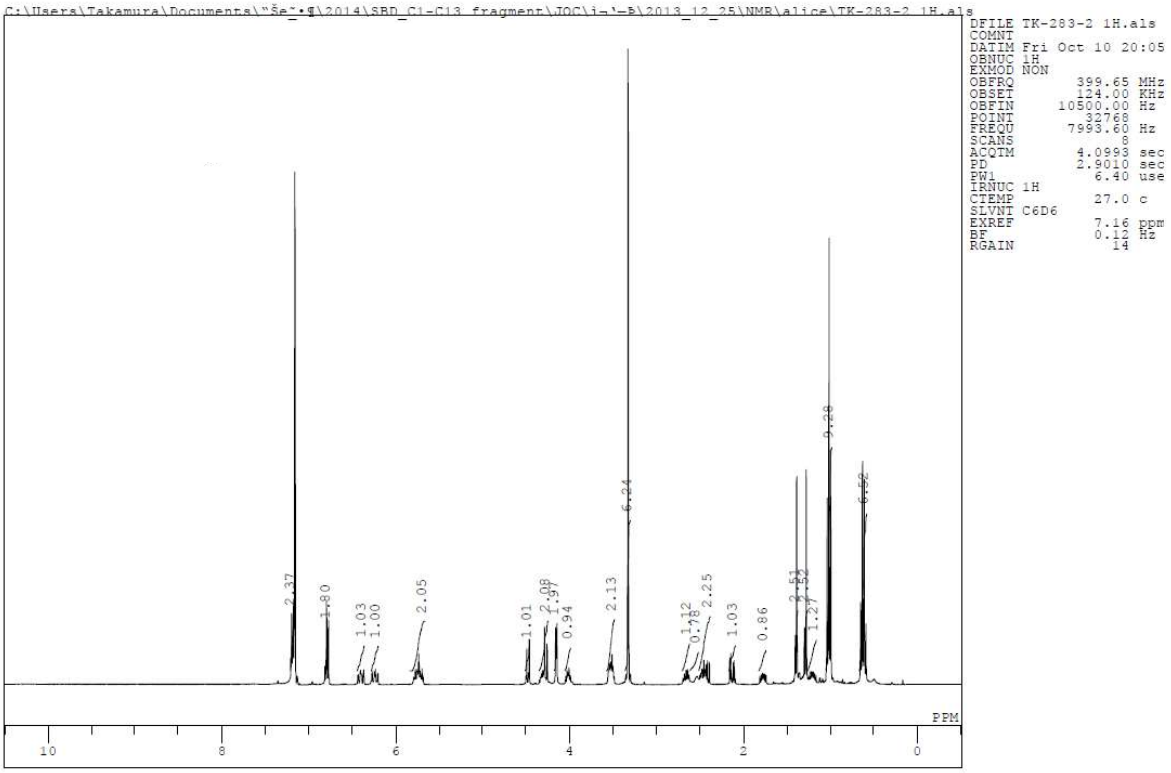
^{1}H NMR (400 MHz, C_6D_6) spectrum of **75**



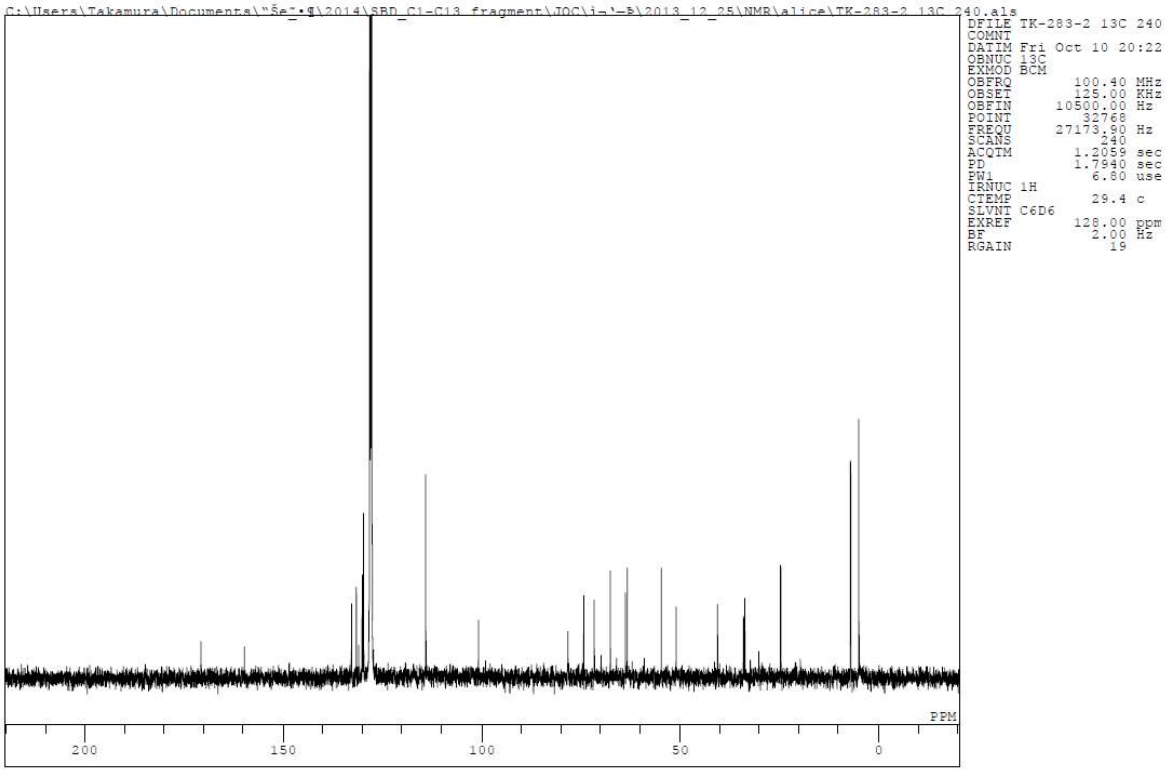
^{13}C NMR (100 MHz, C_6D_6) spectrum of **75**



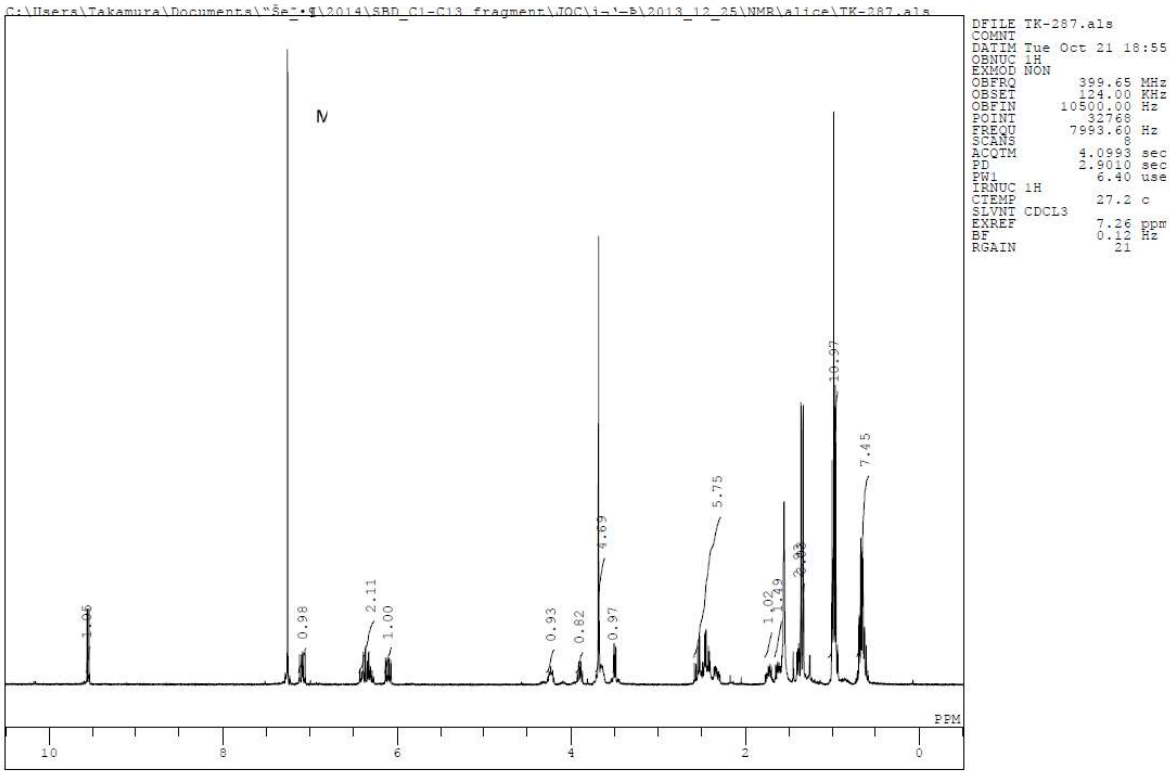
^{1}H NMR (400 MHz, C_6D_6) spectrum of **76**



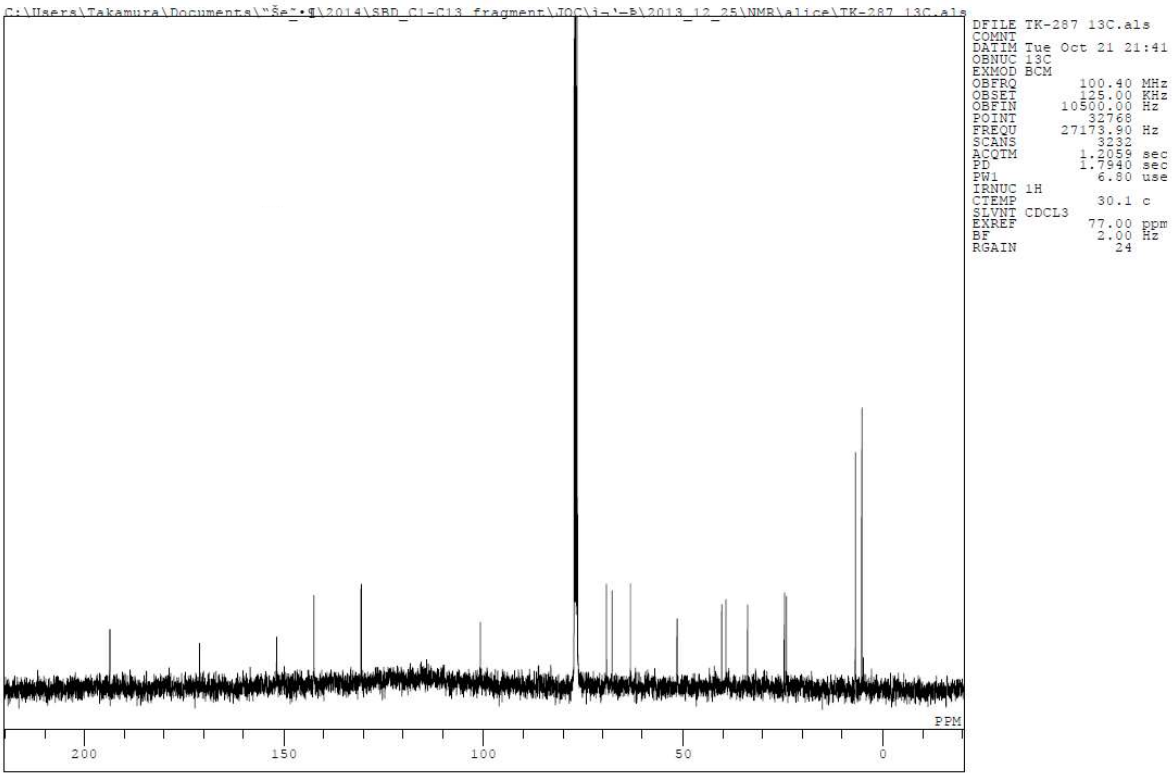
^{13}C NMR (100 MHz, C_6D_6) spectrum of **76**



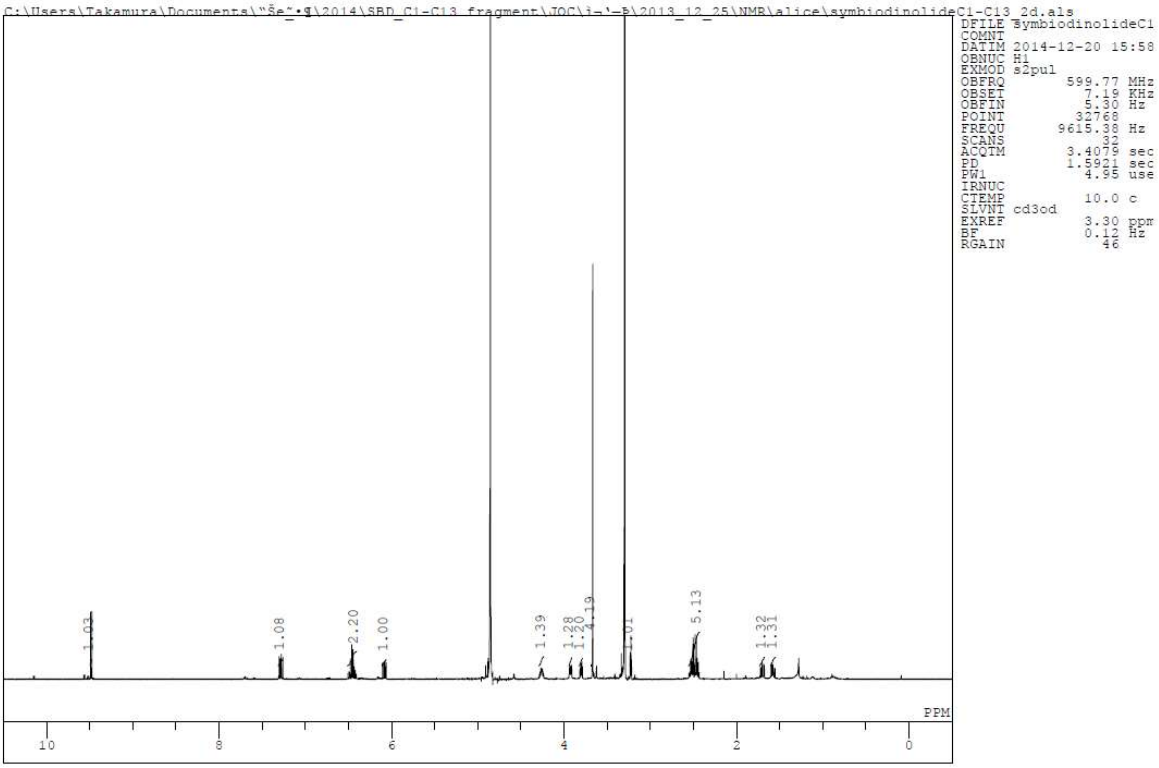
^{1}H NMR (400 MHz, C_6D_6) spectrum of **77**



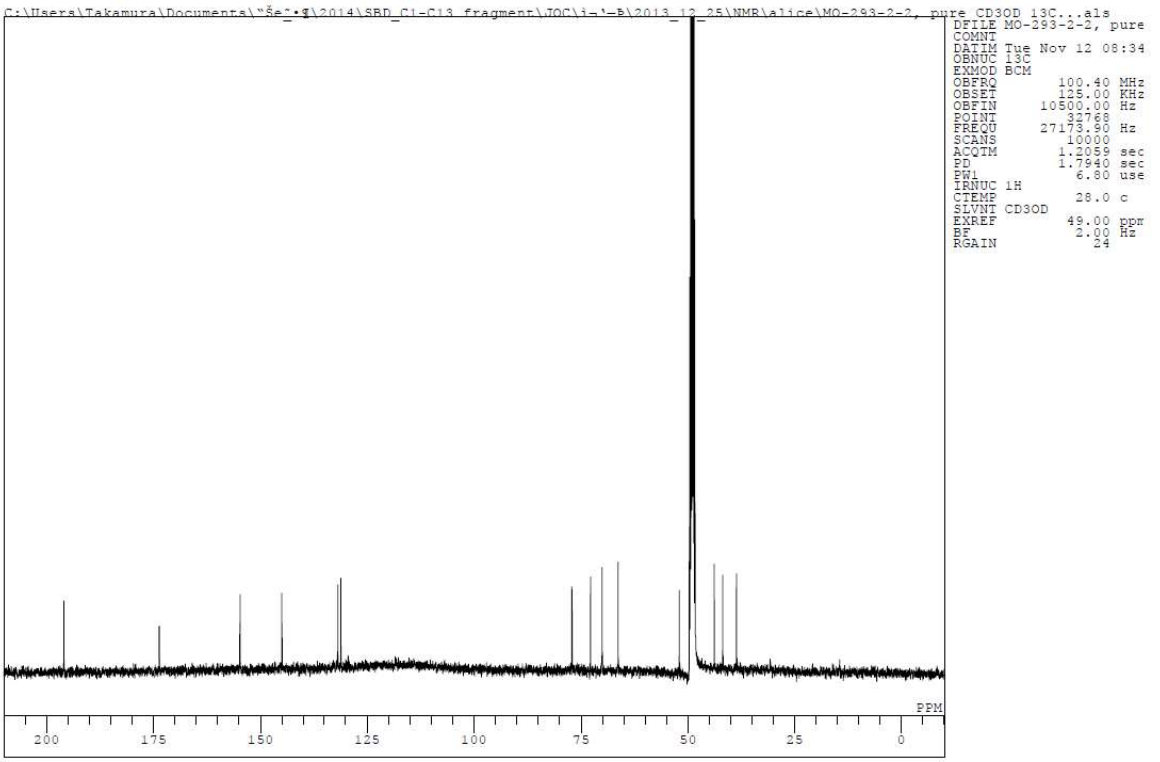
^{13}C NMR (100 MHz, C_6D_6) spectrum of **77**



^{1}H NMR (400 MHz, C_6D_6) spectrum of **6d**



^{13}C NMR (100 MHz, C_6D_6) spectrum of **6d**



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令和 2 年 9 月

和田 寛子