DISSERTATION

Total Synthesis of Psiguadial B

（サイグアジアール B の全合成）

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Contents

Introduction

Terpenes, an important class of naturally occurring hydrocarbons, are generally derived from the five-carbon isoprene units and are present in plants, fungi, bacteria, insects, and so on. Terpinoids, which are further chemically modified derivatives of terpenes, are biologically synthesized from mevalonic acid. Sesquiterpenes, a class of terpenes consisting of three isoprene units, constitute the largest group among this family, and some of them have unique features (Figure 1). For example, Caryophyllene which was isolated from an essential oil of *Humulus lupulus* possesses a unique bicyclic skeleton involving nine- and four-membered carbocycles. While most of terpenes are obtained as colorless oils or crystals, Guaiazulene is a blue-colored crystalline hydrocarbon.

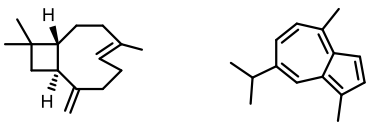


Figure 1. Some examples of sesquiterpenes

The complexity in the structure of terpenoids is remarkably increased by conjunction with phenol moieties through biosynthetic processes. This type of secondary metabolites is called meroterpenoids, and they often show intriguing biological activities. For example, Applanatumin A is reported to exhibit potent antifibrotic activity in TGF-β1-induced human renal proximal tubular cells (Figure 2).[1]

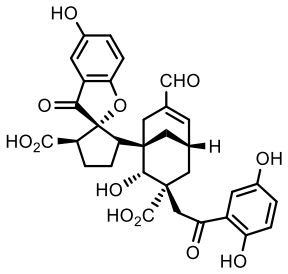


Figure 2. Structure of Applanatumin A

Psidium guajava L., whose edible fruits are commonly called "guava", is an evergreen shrub of Myrtaceae. The leaves of this plant have been used as a folk medicine in China for the treatment of diarrhea and hyperglycemia, and the medicinal ingredients have attracted much attention from chemists. To date, seventeen meroterpenoids, as typified by Psiguadials, have been isolated from the extract of the leaves by several research groups. These natural products possess characteristic hybrid structures commonly composed of a sesquiterpenoid moiety and two aromatic rings as shown in Figure 3.[2] Some of them exhibited significant biological activities including inhibitory effects on protein tyrosine phosphatase 1B (PTP1B) and the growth of human hepatoma cell (HepG2).

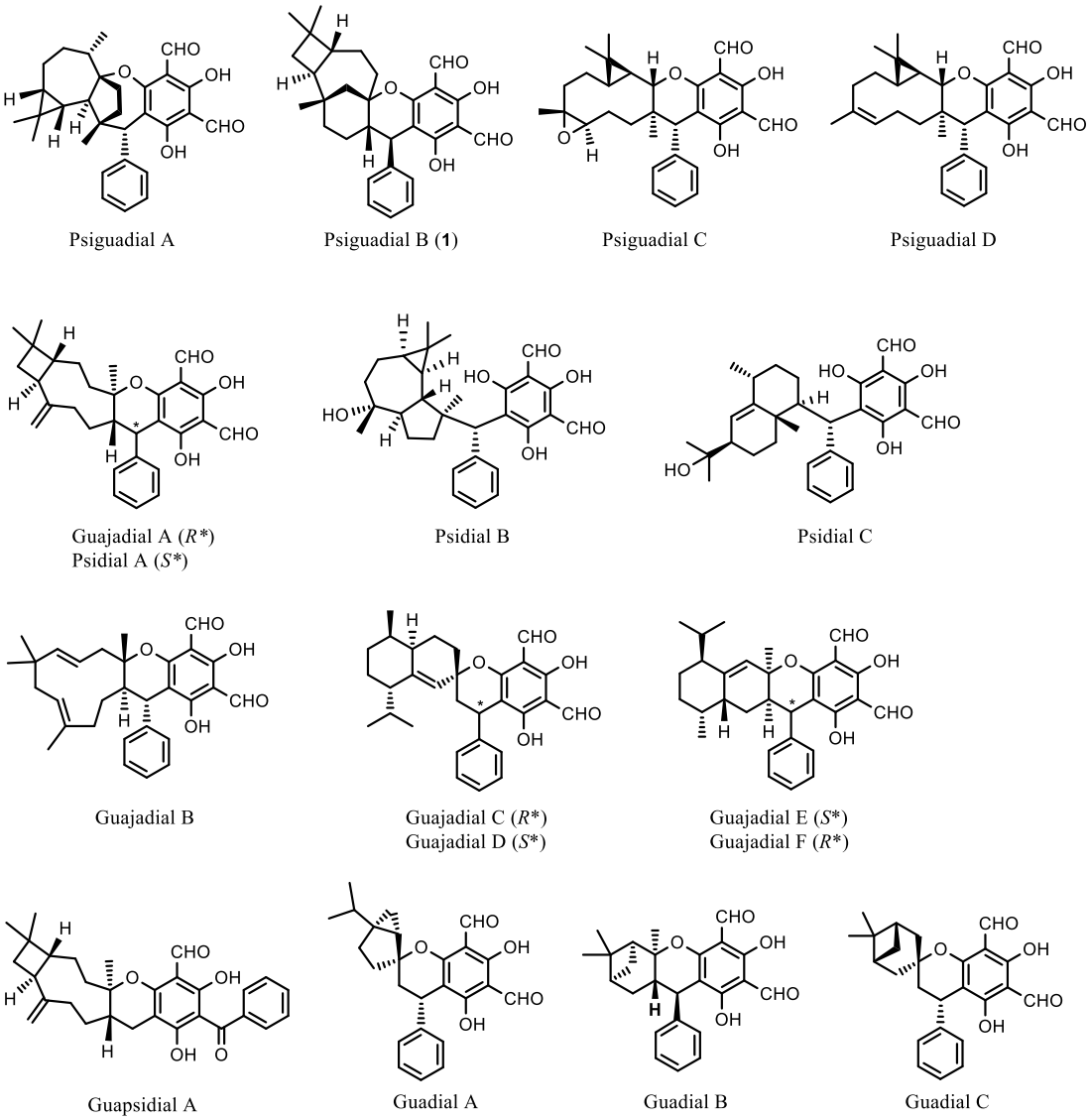
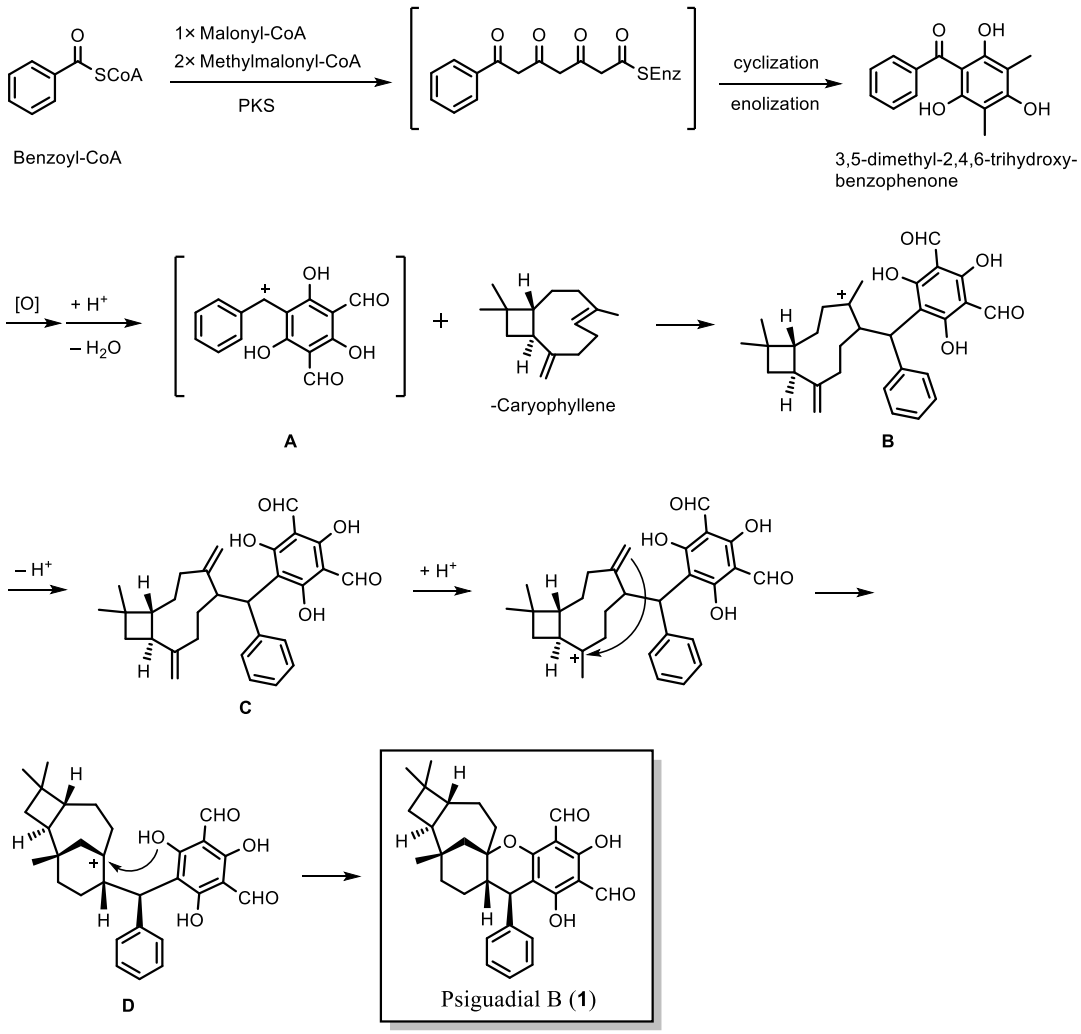


Figure 3. Natural meroterpenoides isolated from *Psidium guajava* L.

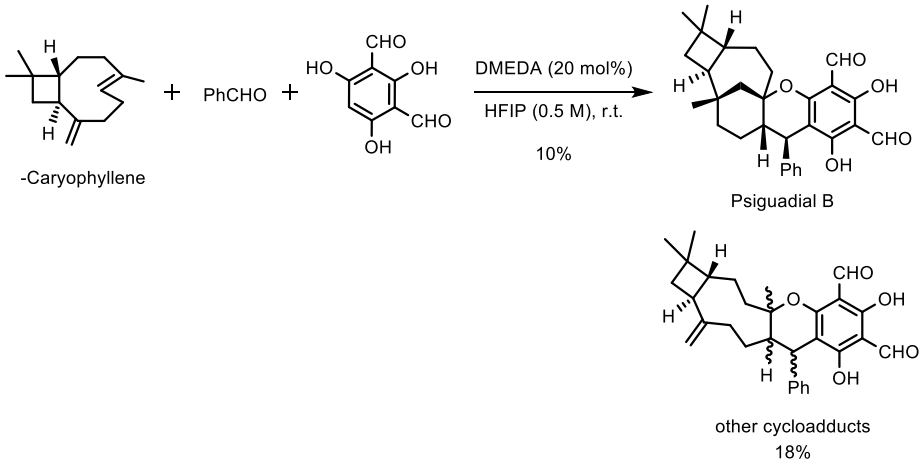
Among them, Psiguadial B (**1**), isolated by Shao and co-workers in 2010, was found to exhibit stronger antitumor activity against HepG2 cells (IC_{50} : 46 nM) than others.[2c] Furthermore, Rizzo and co-workers have recently reported that the extract abundantly containing **1** has a physiological activity similar to estradial and tamoxifen, and also *in vivo* activity against solid Ehrich murine breast adenocarcinoma.[3]

The two aromatic rings of **1** are thought to come from Benzoyl-CoA, and the biological precursor of its sesquiterpene substructure is supposed as *β*-caryophyllene (Scheme 1).



Scheme 1. Proposal of biosynthetic pathway for Psiguadial B

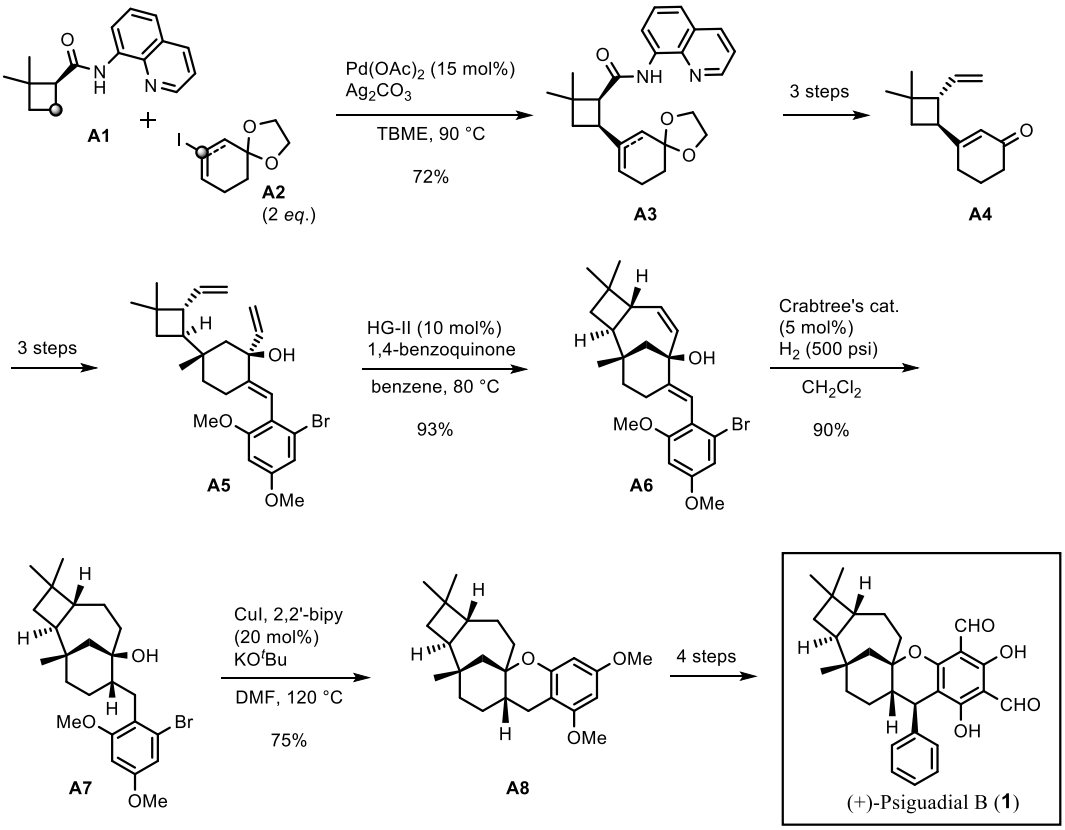
First, Benzoyl-CoA is combined to polyketide by condensation with one molecule of malonyl-CoA and two molecules of methylmalonyl-CoA. Next, cyclization and enolization of the polyketide could lead to 3,5-dimethyl-2,4,6-trihydroxybenzophenone, which had previously been isolated from the *P. guajava*.[4] It is supposed that an acid triggered oxidization and dehydration of the compound produces a carbocation **A** which is attacked by the tri-substituted alkene moiety of *β*-caryophyllene. The resulting intermediate **B** would undergo β-elimination to form diene **C**, which undergoes protonation followed by transannular cyclization to form bicycle[4.3.1]decane skeleton. Finally, the phenolic hydroxyl group of the resulting intermediate **D** would capture the bridgehead cation to afford **1**. This plausible biosynthetic route has been studied by examination of a chemical reaction by Tran and co-workers (Scheme 2).[5] Upon treatment with a catalytic amount of dimethylethylenediamine (DMEDA) at an ambient temperature, the mixture of *β*-caryophylene, phloroglucinol, and benzaldehyde produced **1** along with other cycloadducts. In this case, cation **A** would arise from the reaction of phloroglucinol with benzaldehyde. While the semi total synthesis by Tran is very simple, the products were obtained as a complex mixture of the isomeric compounds.



Scheme 2. Biomimetic synthesis of Psiguadial B by Tran

Recently, Reisman and co-workers reported the first enantioselective total synthesis of (+)-Psiguadial B by an entirely different route from the biomimetic synthesis.[6] Their synthetic strategy was to construct the seven-memberd ring of the tricyclo[6.3.1.$0^{2,5}$]dodecane skeleton after connection of the cyclobutane and cyclohexane segments (Scheme 3). First, chiral cyclobutane amide **A1** was stereoselectively linked with iodocyclohexenone derivative **A2** using Pd-catalyst and silver carbonate through C(sp^3)-H activation of the cyclobutane moiety to afford **A3**. Next, ring-closing metathesis of allylic alcohol **A5** obtained from introduction of a

vinyl group into cyclohexanone **A4** was implemented to form the seven-membered ring, followed by reduction of the two olefins of **A6** under the condition of homogeneous reaction. After copper-catalyzed etherification of **A7** progressed to form pyran **A8**, the total synthesis of (+)-**1** was completed via introductions of a phenyl group at the benzylic position and two formyl groups on the aromatic ring.



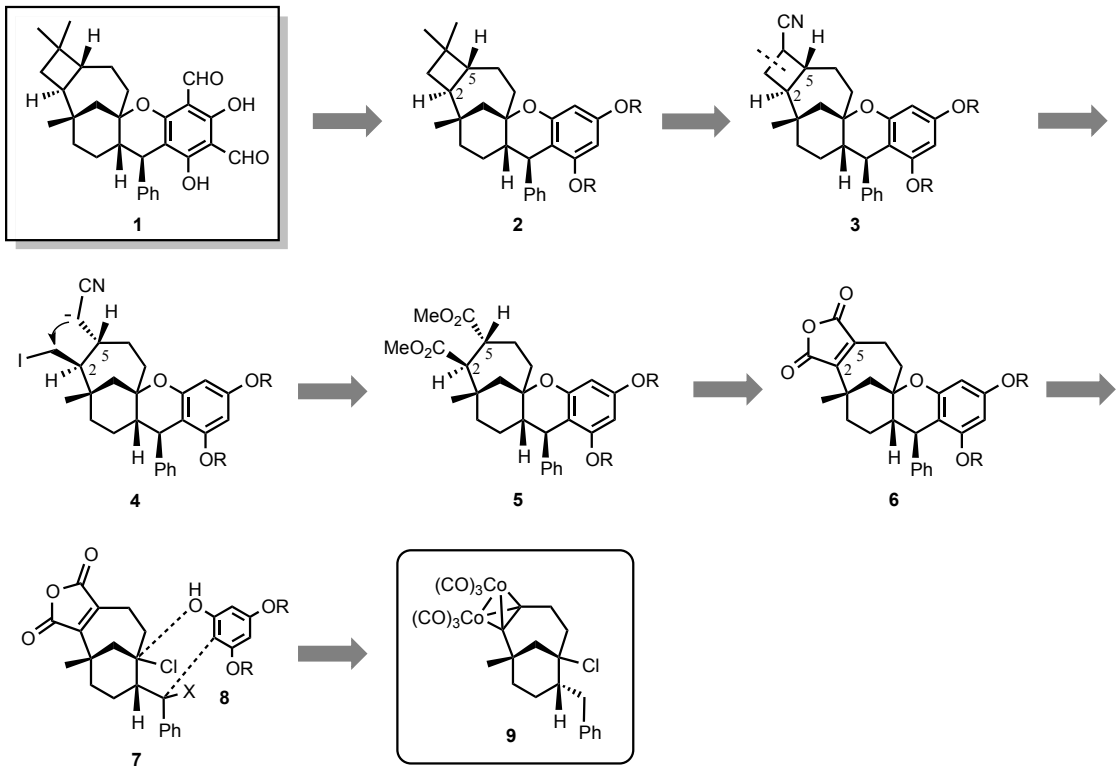
Scheme 3. Enantioselective total synthesis of (+)-Psiguadial B by Riesmen and co-workers

On the other hand, the author has developed efficient methods for the synthesis of cycloheptane derivatives by the cyclization reactions or formal cycloaddition reactions of alkyne dicobalt complexes. Herein, the author describes the achievement of the total synthesis of **1** using the novel reactions and methodologies for assembling the unique structure.

Chapter I

Construction of Bicyclo[4.3.1]decane Skeleton via Double Cyclization Reaction of Alkyne Dicobalt Complex

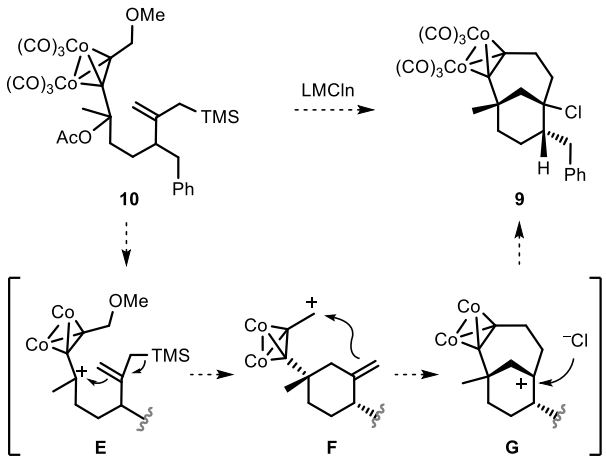
For achieving the total synthesis of **1**, it was required to develop an efficient method for the construction of the fused-tricyclic terpene skeleton as well as the stereoselective introduction of the two aromatic rings. Thus, the author carried out the retrosynthetic analysis of **1** as depicted in Scheme 4. The two formyl groups on the aromatic ring of **1**, that may be sensitive to both reduction and oxidation, are to be introduced at the later stage of the total synthesis. The dimethylcyclobutane **2** would be derived from cyclobutanecarbonitrile **3**, the four-membered ring of which would be constructed by an intramolecular cyclization reaction of iodonitrile **4** under basic conditions.



Scheme 4. Retrosynthetic analysis for Psiguadial B

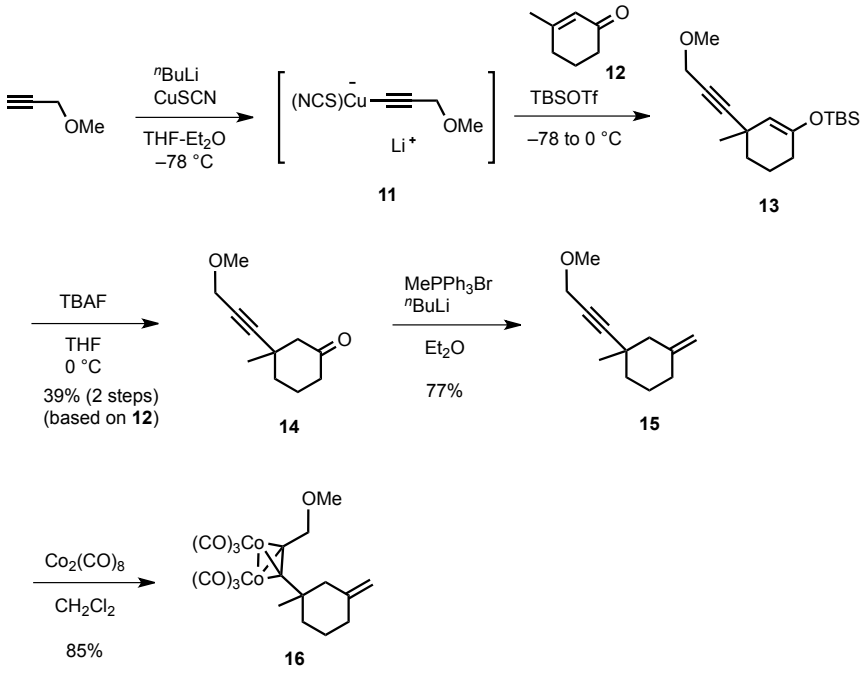
With a view to controlling the stereochemistry at the C2 and C5 positions of **4**, maleic anhydride **6** was designed as the key intermediate of the total synthesis. Thus, the corresponding maleate may undergo the stereoselective conjugate reduction, giving rise to *trans*-diester **5**. The hydrobenzopyran moiety of **6** is to be formed by a formal cycloaddition reaction of bicyclo[4.3.1]decane segment **7** with phloroglucinol derivative **8**. The author planned to utilize the novel transformation of an acetylene-dicobalt complex into a maleic anhydride mediated by ammonium cerium(IV) nitrate (CAN), which was originally reported by Tanino *et al*.[7] Therefore, cobalt complex **9** possessing a bicyclic carbon framework was set as the target molecule at this point.

For developing an efficient method for the construction of the bicyclo[4.3.1]decane skeleton of **9**, the author designed a new cascade reaction of acetylene-dicobalt complex **10** having an allylsilane moiety and two leaving groups (Scheme 5).[8] On treatment with a suitable metal chloride ($LMCl_n$) which acts as a Lewis acid, cobalt complex **10** would undergo the first cyclization reaction through cationic species **E**. This type of C-C bond formation which proceeds through a hexacarbonyl dicobalt-propargyl cation intermediate is well known as the "Nicholas reaction". Since the cyclization product possesses a methoxyl group at the propargyl position and an electron rich alkene moiety, the second cyclization reaction may occur through the cationic intermediate **F**. The resulting cationic species **G** would be captured by a chloride ion, giving rise to the desired bicyclo[4.3.1]decane derivative **9** with a chloride moiety at the bridgehead position.



Scheme 5. Design of cascade cyclization reaction for constructing the bicyclo[4.3.1]decane skeleton

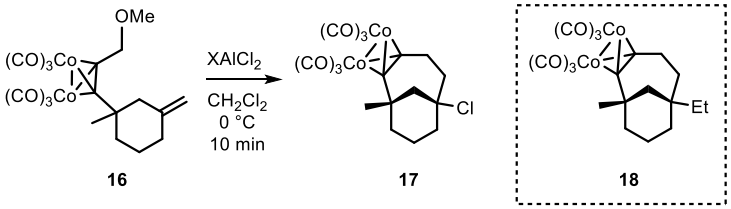
Initially, the author attempted the preliminary experiments on the second cyclization step of the cascade reaction, and model substrate **16** was synthesized in 4 steps as depicted in Scheme 6. Cuprate **11**, which was generated by the successive treatment of methyl propargyl ether with butyllithium and copper(I) thiocyanate,[9] was reacted with 3-methyl-2-cyclohexen-1-one (**12**) in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). The resulting enol silyl ether **13** was treated with tetrabutylammonium fluoride to afford ketone **14** which in turn was subjected to the Wittig reaction, giving rise to alkene **15**. The complexation of **15** with dicobalt octacarbonyl yielded the cyclization precursor **16** which was expected to undergo a cyclization reaction to form a bicyclo[4.3.1]decane skeleton.



Scheme 6. Synthesis of model substrate **16**

With the model substrate in hand, the cyclization reactions were investigated under the influence of several Lewis acids. It is known that the use of boron or aluminum reagents such as boron trifluoride etherate or ethylaluminum dichloride is suitable for the Nicholas reactions, while acetylene dicobalt complexes tend to undergo decomposition in the presence of titanium(IV) chloride. It is also noteworthy that the Lewis acidity of an aluminum reagent is readily tunable by choosing suitable substituents on the aluminum atom. The results of the cyclization reaction of **16** with aluminum reagents are shown in Table 1.[10] The initial attempt using ethylaluminum dichloride effected the desired cyclization reaction, but the product was found to be **18** possessing an ethyl group at the bridgehead position (entry 1). The result led the author to replace the ethyl group of ethylaluminum chloride by the treatment with *tert*-butyl alcohol or phenols. Indeed, the reaction with $^{t}BuOAlCl_2$ afforded the desired chloride **17**, albeit in low yield (entry 2). Aluminum phenoxides generally exhibit higher Lewis acidity than aluminum alkoxides, and the use of phenoxyaluminum dichloride led to formation of **17** in 42% yield (entry 3). After several examinations, the use of aluminum reagent derived from 2,4-dichlorophenol was found to give **17** in the highest 60% yield (entry 5), while the use of Lewis acids with higher acidity were not so effective (entries 6 and 7).

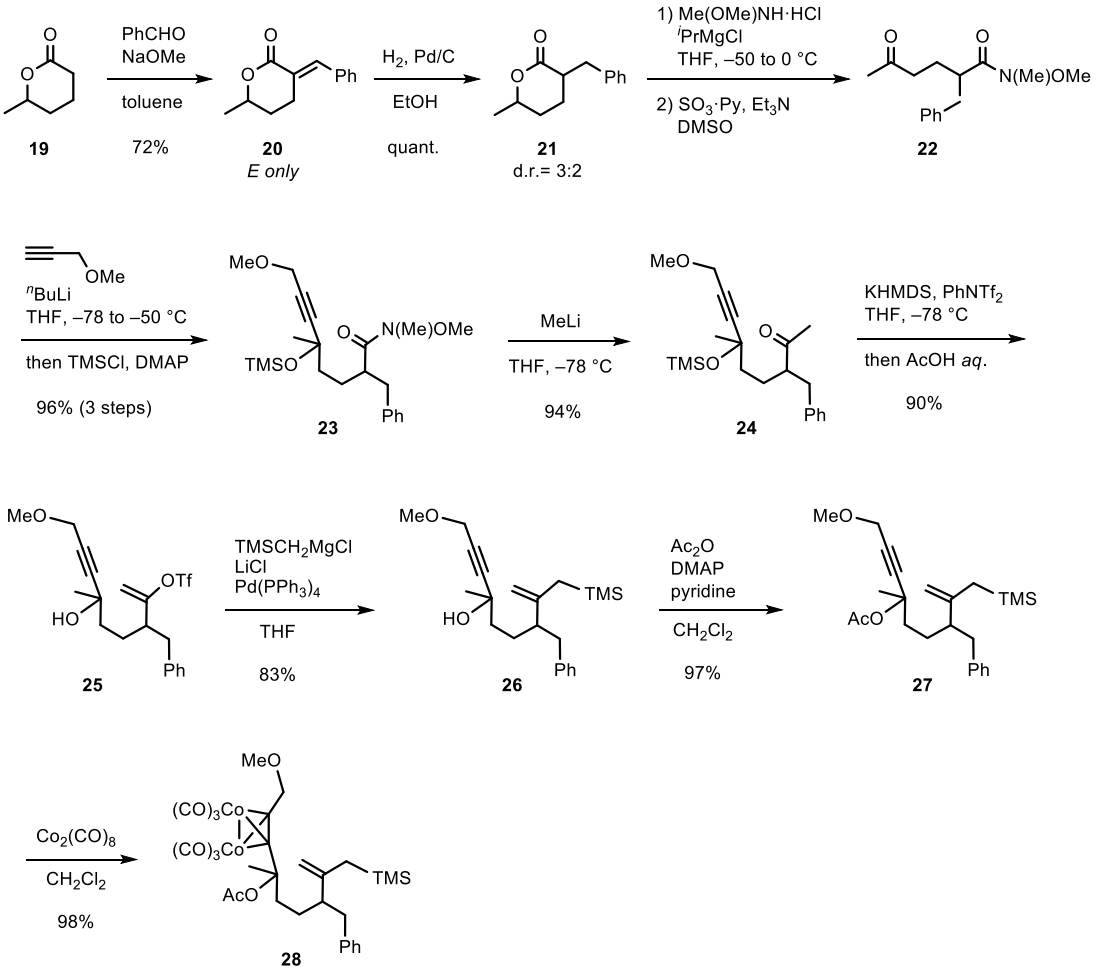
Table 1. Examination of Lewis acid for seven-membered ring formation



16 **17** **18**

entry	$XAlCl_2$	results
1	$EtAlCl_2$	**18** (40%)
2	$^{t}BuOAlCl_2$	**17** (11%)
3	$PhOAlCl_2$	**17** (42%)
4	4-Cl-$PhOAlCl_2$	**17** (39%)
5	2,4-diCl-$PhOAlCl_2$	**17** (60%)
6	2,4,6-triCl-$PhOAlCl_2$	**17** (25%)
7	$C_6F_5OAlCl_2$	**17** (47%)

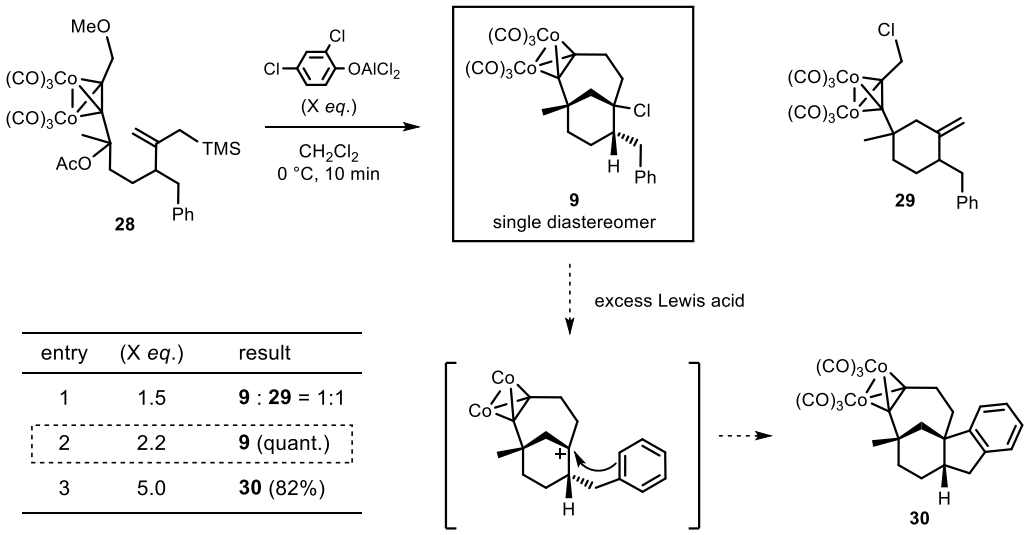
These preliminary results encouraged the author to undertake the synthesis of the substrate of the cascade double cyclization reaction (Scheme 7). Starting with commercially available lactone **19**, lactone **21** which appeared in literature[11] was synthesized through the aldol condensation with benzaldehyde and hydrogenation of the resulting α-benzylidenlactone **20**. The ring opening reaction mediated with Me(MeO)NMgCl followed by oxidation of the resulting secondary alcohol afforded ketoamide **22**. Successive treatment of **22** with lithium acetylide of methyl propargyl ether followed by TMSCl and DMAP gave amide **23** which was reacted with MeLi to yield ketone **24**. The allylsilane moiety for the intramolecular cyclization reaction was constructed by the Pd catalyzed cross-coupling reaction of enol triflate **25** with (trimethylsilyl)methylmagnesium chloride. After acetylation of the resulting alcohol **26**, the complexation with dicobalt octacarbonyl gave the cyclization precursor **28**.



Scheme 7. Synthesis of acetylene dicobalt complex **28**

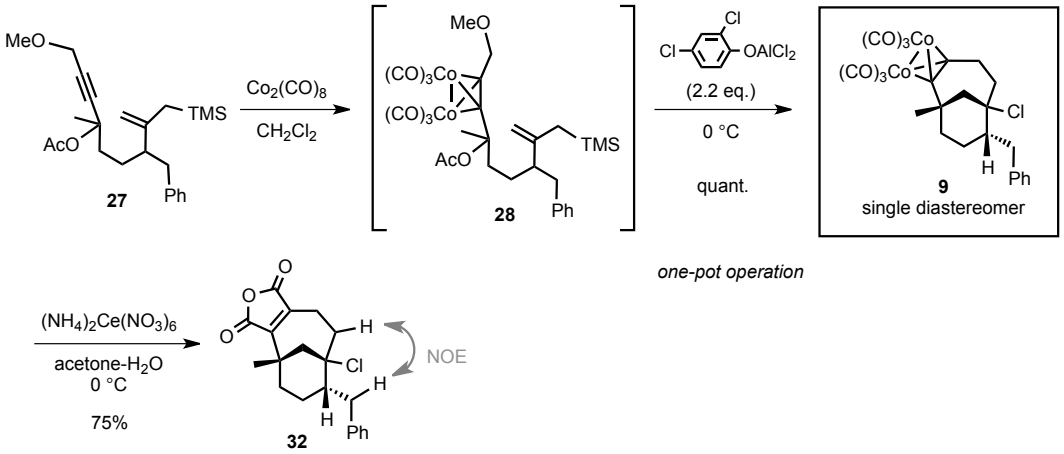
Subsequently, cobalt complex **28** was subjected to the double cyclization reaction mediated by 2,4-dichlorophenoxyaluminum dichloride which was found as the best reagent in the previous model study. As shown in Table 2, the equivalent of the aluminum reagent was found to influence the chemical yield of the desired product **9**. Thus, the use of 1.5 equiv. of the aluminum reagent led to formation of a 1:1 mixture of the bicyclic compound **9** and monocyclic compound **29** (entry 1), but the use of an increased amount (2.2 equiv.) of the aluminum reagent gave a satisfactory result (entry 2). On the other hand, the reaction promoted by an excess amount (5.0 equiv.) of the Lewis acid resulted in formation of new compound **30** instead of the desired product **9** (entry 3). The five-membered carbocycle of **30** would be formed by the intramolecular Friedel-Crafts reaction of the bridgehead cation. These results indicated that the cascade cyclization reaction of **28** proceeds through the cationic intermediates that are in equilibrium with the corresponding chlorides, and the use of an excess amount of Lewis acid facilitates the next cyclization step.

Table 2. Double cyclization reaction of **28**



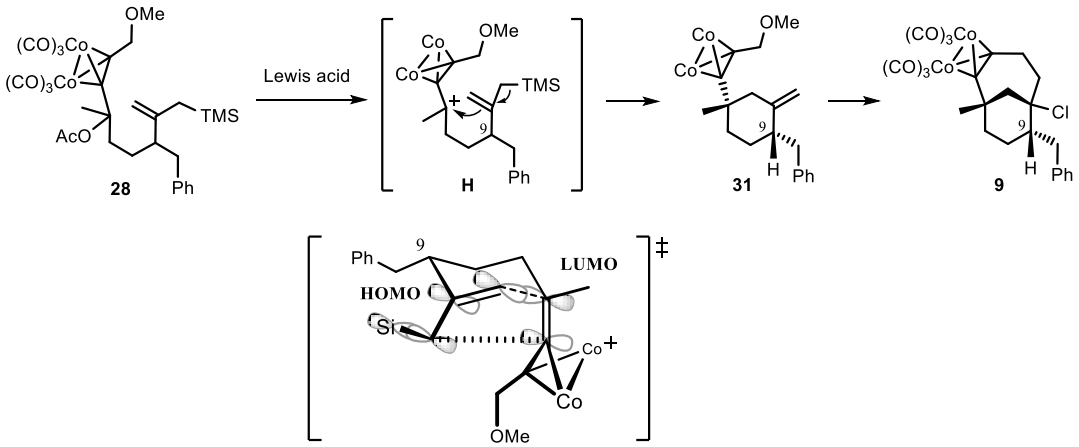
entry	(X *eq.*)	result
1	1.5	**9** : **29** = 1:1
2	2.2	**9** (quant.)
3	5.0	**30** (82%)

The double cyclization reaction proceeded in highly stereoselective manner, and the configuration of product **9** was determined after conversion to the corresponding maleic anhydride **32**. The benzyl group was found to be oriented to the concave side of the bicyclic skeleton by the NOE experiments, the relationship between the protons in which was displayed in Scheme 8.



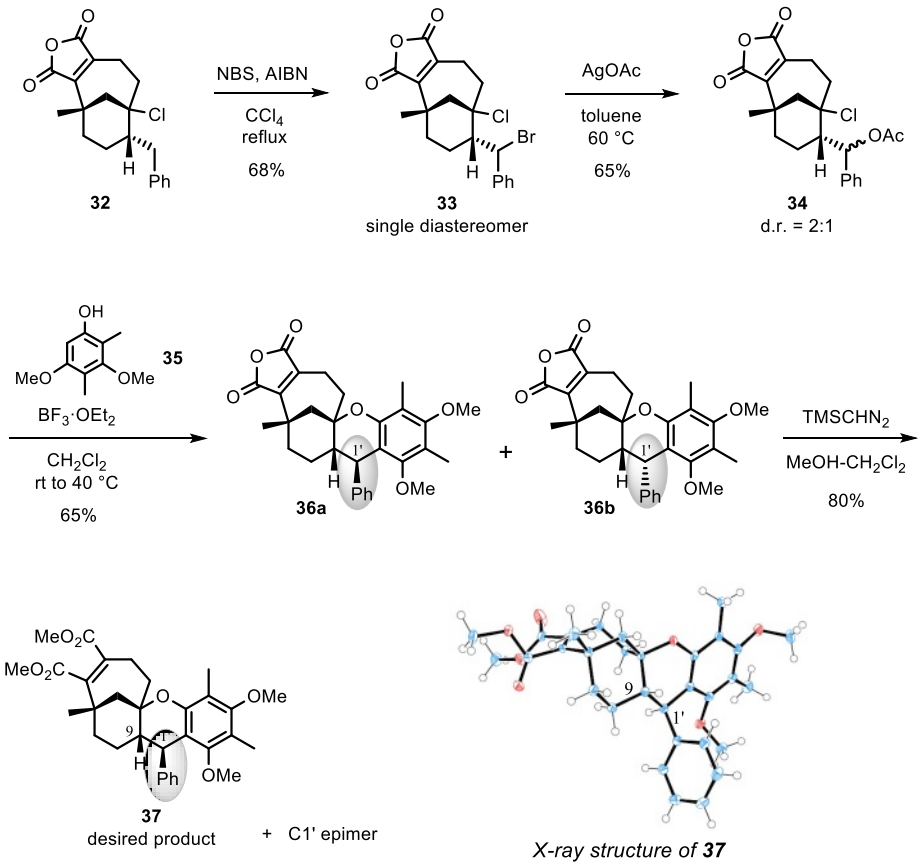
Scheme 8. Transformation into maleic anhydride **32**

Judging from the relative stereochemistry between the benzyl group and the bridgehead carbon atoms of the bicyclic skeleton, the monocyclic intermediate **31** should possess the benzyl group and the cobalt complex moiety *cis* to each other (Scheme 9). This stereochemical relationship is formed in the first cyclization step of cationic species **H**, and it should be noted that a simple chair-like transition state model in which the bulky substituents occupy the equatorial positions is not consistent with the results. Therefore, alternative chair-like transition state model, in which the cobalt complex moiety is directed to the axial position, was considered on the basis of the secondary orbital interaction (SOI). Thus, SOI between the bonding σ orbital on the C(allylic)-Si bond and the antibonding π* orbital in the LUMO side would contribute to stabilize the transition state leading to the *syn* product **31**.[12,13]



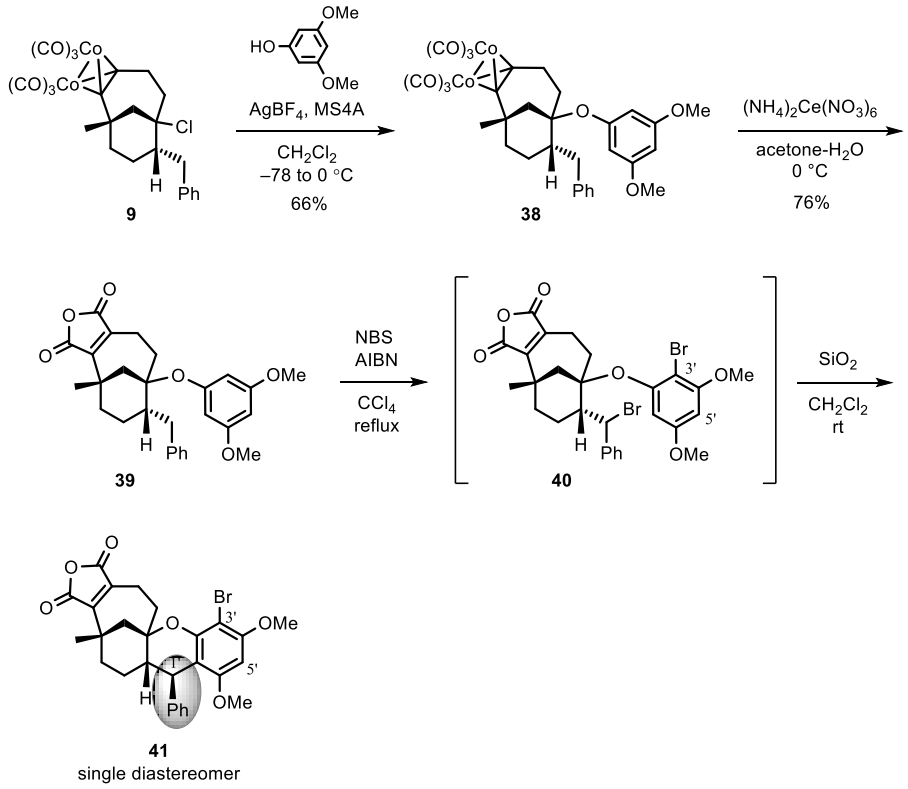
Scheme 9. Contribution of SOI (dotted line) in the transition state

With the key bicyclic compound in hand, the stage was set for the construction of the hydrobenzopyran structure via a Friedel-Crafts reaction (Scheme 10). Upon heating with AIBN and NBS, maleic anhydride **32** underwent selective bromination at the benzylic position, and the resulting bromide **33** was converted to acetate **34** by the reaction with silver acetate. The Friedel-Crafts reaction of **34** with phloroglucinol derivative **35** was attempted under the influence of boron trifluoride etherate, giving rise to hydrobenzopyran derivative **36** in 65% yield. This formal cycloaddition approach to the core skeleton of the natural product **1** seemed attractive, but the product was obtained as an inseparable 1:1 mixture of epimers at the C1' position. Treatment of the diastereomeric mixture of **36a** and **36b** with (trimethylsilyl)diazomethane in methanol afforded a separable mixture of diester **37** and its epimer, the stereochemistry of which was determined by the X-ray crystallographic analysis.



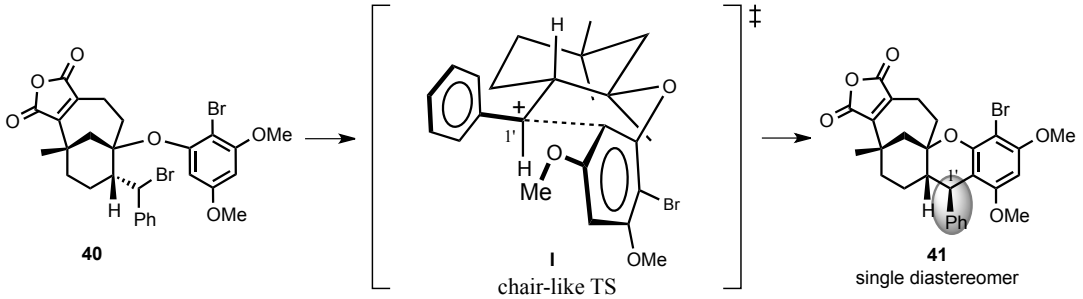
Scheme 10. Formation of benzopyron **36** by intermolecular Friedel-Crafts reaction

Next, the author focused on the stereocontrolled construction of the hydrobenzopyran ring by a stepwise strategy, that is, formation of an ether bond at the bridgehead position followed by the intramolecular Friedel-Crafts alkylation reaction (Scheme 11). Chloride **9** was reacted with 3,5-dimethoxyphenol under the influence of $AgBF_4$ to afford aromatic ether **38** the cobalt complex moiety of which was converted to maleic anhydride by the oxidation with CAN. The resulting compound **39** was subjected to benzylic bromination with NBS and AIBN, giving rise to dibromide **40**. Surprisingly, the crude dibromide **40** underwent a cyclization reaction during the silica gel chromatography to yield hydrobenzopyran derivative **41** as a single diastereomer. The stereochemistry of **41** was supposed to be consistent with that of natural compound **1**, because of the similar coupling constants between H(C1') and H(C9) in both **41** and compound **37**.



Scheme 11. Synthesis of benzopyran **41** by intramolecular Friedel-Crafts reaction

The intramolecular Friedel-Crafts reaction would proceed through a six-membered chair-like transition state **I** in Scheme 12. The steric repulsion between the phenyl group of the benzyl cation moiety and the bicyclic core skeleton would fix the conformation of the transition state, and the substituted aromatic ring attacks the cationic center to form the hydrobenzopyran ring possessing the C1' phenyl group at the equatorial position.



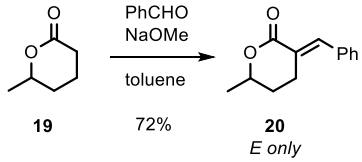
Scheme 12. Chair-like transition state (TS) of the intramolecular Friedel-Crafts reaction

In conclusion, the author succeeded in developing a new method for constructing the complex polycyclic skeleton of Psiguadial B (**1**). The terpenoid substructure of **1** was constructed on the basis of a cascade double cyclization reaction of an acetylene dicobalt complex, which afforded the bicyclo[4.3.1]decane derivative with a benzyl group with correct configuration. The substituted aromatic ring was introduced to the bridgehead position of the intermediate, and bromination under radical conditions followed by intramolecular cyclization reaction resulted in formation of the benzopyran moiety in a stereoselective manner. The remaining task, namely, the construction of the dimethylcyclobutane moiety and functionalization of the aromatic ring are described in the next chapter.

Experimental Section

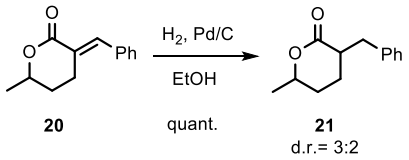
General Information

All the reactions were carried out in a round-bottomed flask with an appropriate number of necks and side arms connected to a three-way stopcock and/or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by a rotary pump and then flushed with argon prior to use. Solutions and solvents were introduced by a hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry THF was freshly prepared by distillation from benzophenone ketyl before use. Anhydrous solvents were purchased from Kanto Chemical Co. Inc. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer by attenuated total reflection (ATR). Wavelength of maximum absorbance are quoted in cm^{-1}. 1H-NMR spectra were recorded on a JEOL ECA-500 (500 MHz) in $CDCl_3$. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ^{13}C-NMR spectra were recorded on a JEOL ECA-500 (125 MHz) in $CDCl_3$. Chemical shifts are reported in part per million (ppm). High resolution mass (HRMS) spectra were recorded on a JEOL JMS AX-500, JEOL JMS-SX102A or JEOL JMS-T-100GCV at the S1GC-MS & NMR Laboratory, Graduate School of Agriculture, Hokkaido University. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.



19 72% **20** *E only*

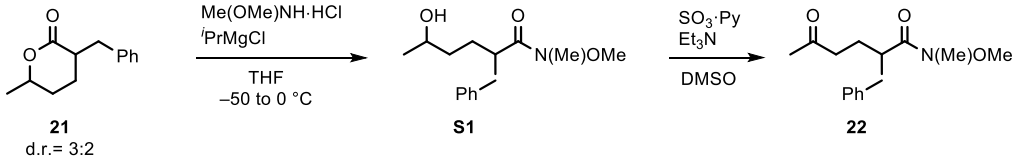
Compound 20 : To a solution of the δ-hexanolactone **19** (4.70 g, 44.3 mmol) and benzaldehyde (9.65 mL, 66.4 mmol) in toluene (90 mL) was added NaOMe (4.07 g, 75.3 mmol) in small portion at -10 °C for 1 h under argon atmosphere. Then the reaction was stirred at room temperature for 2 h, and was quenched with EtOAc (70 mL) and a 10% sulfuric acid solution (70 mL). After the mixture was neutralized with a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting solid was washed with Heaxane-$^{i}Pr_2O$ (3:1) to give 6.44 g of **20** (74%) as a white solid: IR (ATR) ν 3431, 2966, 2931, 1637, 1495, 1454, 1389, 1176, 1128, 985, 732, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.81 (s, 1H), 4.92 (t, *J* = 4.9 Hz, 1H), 3.44 (q, *J* = 5.1, 1H), 3.33 (s, 1H), 2.67 (ddd, *J* =13.7, 4.6, 1.1 Hz, 1H), 2.36 (ddd, *J* = 12.0, 6.3, 1.7 Hz, 1H), 2.34 (s, 1H), 2.31 (s, 1H), 2.26 (d, *J* = 13.7 Hz, 1H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.47 (d, *J* = 6.9 Hz, 1H), 1.43 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.69, 177.55, 168.97, 149.47, 149.35, 138.18, 126.43, 122.13, 121.36, 74.44, 58.37, 46.15, 45.49, 41.85, 40.34, 39.69, 29.65, 21.20, 21.10, 19.21, 18.50; HRMS (EI): Calcd for (M+) C21H24O5: 356.1624; found: 356.1620.



20 quant. **21** d.r.= 3:2

Compound 21 : To a solution of **20** (3.03 g, 14.5 mmol) in EtOH (50 mL) was added 10%Pd/C (150 mg, 5 wt%), then the reaction was stirred at room temperature for 2.5 h under hydrogen atmosphere. After the reaction mixture was filtrated through a pad of celite, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 3:1) to give 2.96 g of **21** (quant.) as a white solid: m.p. 68-70 ºC; IR (ATR) ν 3431, 2966, 2931, 1637, 1495, 1454, 1389, 1176, 1128, 985, 732, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m), 7.24-7.19 (3H, m), 4.46-4.42 (0.6H, m), 4.36-4.33 (0.4H, m), 3.41 (0.4H, dd, *J* = 13.7, 4.0 Hz), 3.35 (0.6H, dd, *J* = 13.7, 4.0 Hz), 2.80 (0.4H, dd, *J* = 13.7, 9.7 Hz), 2.76-2.70 (0.6H, m), 2.66-2.59 (1H, m), 1.92-1.79 (2H, m),

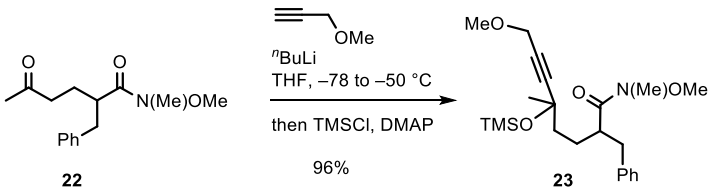
1.63-1.47 (2H, m), 1.35 (1.2H, d, J = 6.3 Hz), 1.34 (1.8H, d, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.11, 173.18, 139.06, 138.87, 129.20, 129.06, 128.46, 126.44, 126.41, 78.02, 74.40, 42.29, 39.91, 37.61, 36.81, 30.67, 28.14, 25.01, 22.58, 22.08, 21.02; HRMS (FI$^+$): Calcd for (M^+) $C_{13}H_{16}O_2$: 204.1150; found: 356.1141.



21 d.r.= 3:2 **S1** **22**

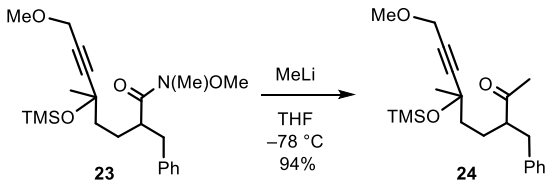
Compound 22 : To a suspension of **21** (6.00 g, 29.4 mmol) and Me(MeO)NH·HCl in THF (150 mL) was slowly added ^{i}PrMgCl (2.0 M in Et_2O, 66.0 mL, 132 mmol) at -50 ºC, then stirred at 0 ºC for 30 min under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous NH_4Cl solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude **S1** (8.19 g) was used for next step without further purification.

To a suspension of **S1** (8.75 g, 29.4 mmol) and Et_3N (21.2 mL, 147 mmol) in DMSO (60 mL) was added SO_3·Py (11.7 g, 73.5 mmol) in small portion, then stirred at room temperature for 1.5 h under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with Hexane-EtOAc (1:1). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 1:1→1:2) to give 8.19 g of **22** (quant.) as a yellow oil: IR (ATR) ν 2932, 1713, 1651, 1453, 1419, 1388, 1366, 1173, 987, 751, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (2H, m), 7.19-7.17 (3H, m), 3.30 (3H, s), 3.18-3.11 (1H, m), 3.11 (3H, s), 2.99 (1H, dd, J = 13.2, 9.2 Hz), 2.66 (1H, dd, J = 13.2, 9.2 Hz), 2.43-2.35 (2H, m), 2.09 (3H, s), 1.89-1.85 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.08, 175.69, 139.70, 139.85, 128.95, 128.22, 126.15, 61.06, 42.17, 40.74, 38.66, 31.82, 29.74, 26.16; HRMS (FI$^+$): Calcd for (M^+) $C_{15}H_{21}NO_3$: 263.1521; found: 263.1514.



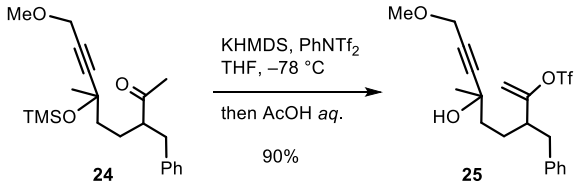
22 **23**

Compound 23 : To a solution of methyl propargyl ether (3.72 mL, 44.1 mmol) in THF (75mL) was slowly added ^{n}BuLi (2.6 M in Hexane, 14.4 mL, 38.2 mmol) at -78 °C, then stirred at room temperature for 20 min under argon atmosphere. A solution of **22** (8.18 g, 29.4 mmol) in THF (75 mL) was added dropwise to the reaction mixture at -78 °C, then stirred at -60 °C for 30 min. TMSCl (5.57 mL, 44.1 mmol) and DMAP (718 mg, 5.88 mmol) was added to the mixture at -78 °C, then stirred at room temperature for 3 h. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was through a short pad of silica gel to give 11.5 g of **23** (96%) as a pale yellow oil: IR (ATR) ν 2955, 2934, 1658, 1454, 1248, 1172, 1102, 1051, 1024, 985, 902, 753, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (2H, m), 7.19-7.15 (3H, m), 4.11 (0.8H, s), 4.10 (1.2H, s), 3.36 (1.2H, s), 3.35 (1.8 H, s), 3.32 (3H, s), 3.13-2.97 (1H, m), 3.10 (3H, s), 2.99 (1H, dd, *J* = 13.2, 9.2 Hz), 2.71-2.69 (1H, m), 1.91-1.81 (1H, m), 1.76-1.58 (3H, m), 1.44 (3H, s), 0.16 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.29, 140.26, 129.10, 128.23, 126.10, 90.49, 90.15, 80.15, 79.81, 77.26, 77.21, 77.00, 76.75, 69.29, 69.13, 61.12, 59.91, 57.50, 43.33, 42.56, 42.42, 38.84, 38.54, 31.97, 31.16, 30.93, 29.68, 27.67, 27.45, 2.06, 1.83, 1.59; HRMS (FD^{+}): Calcd for (M^{+}) $C_{22}H_{35}NO_4Si$: 405.2335; found: 405.2329.

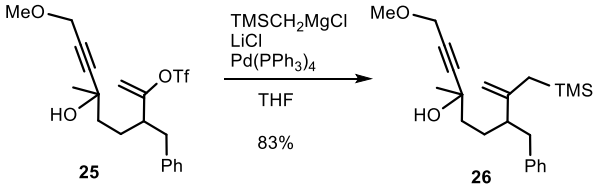


Compound 24 : To a solution of **23** (11.4 g, 28.1 mmol) in THF (140 mL) was slowly added MeLi (1.1 M in Et_2O, 37.3 mL, 42.2 mmol) at -78 °C, then stirred at -70 °C for 20 min under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous NH_4Cl solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was through a short pad of silica gel to give 9.50 g of **24** (94%) as a pale yellow oil: IR (ATR) ν 2953, 2932, 2359, 1712, 1454, 1356, 1248, 1167, 1102, 839, 753, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (2H, m), 7.19-7.14 (3H, m), 4.10 (0.8H, s), 4.09 (1.2H, s), 3.344 (1.2H, s), 3.336 (1.8H, s), 2.92-2.88 (1H, m), 2.82 (1H, sextet, *J* = 6.3 Hz), 2.71-2.66 (1H, m), 2.01 (3H, s), 1.84-1.51 (4H, m), 1.43 (3H, s), 0.16 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.01, 211.89, 139.51, 139.47, 128.79, 128.35, 126.16, 90.06, 89.88, 80.21, 80.07, 69.07, 68.96, 59.78, 57.44, 54.42, 54.35, 42.10, 42.03, 37.65, 37.39, 31.13, 30.97, 29.89, 29.65, 26.43, 26.24, 1.74; HRMS

(FI$^+$): Calcd for (M$^+$) $C_{21}H_{32}O_3Si$: 360.2121; found: 360.2107.

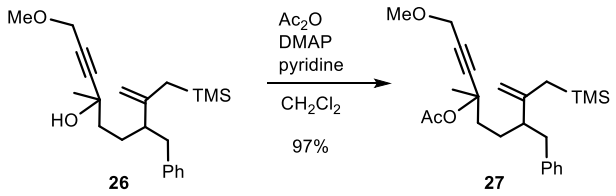


Compound 25 : To a solution of **24** (4.90 g, 13.6 mmol) in THF (45 mL) was slowly added KHMDS (0.5 M in toluene, 35.4 mL, 17.7 mmol) at -78 ºC, then stirred at -78 ºC for 30 min under argon atmosphere. A solution of $PhNTf_2$ (8.26 g, 23.1 mmol) in THF (25 mL) was slowly added to the reaction mixture, and stirred at -70 ºC for 40 min. A 70% acetic acid solution (100 mL) was added to the mixture, and stirred at room temperature for 18 h. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 3:1→2:1) to give 5.17 g of **25** as a pale yellow oil (90%): IR (ATR) ν 3414, 2932, 1663, 1413, 1207, 1140, 1100, 925, 738, 699, 607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (2H, m), 7.23-7.21 (1H, m), 7.16-7.15 (2H, m), 5.12 (0.6H, d, *J* = 4.6 Hz), 5.11 (0.4H, d, *J* = 4.0 Hz), 4.82 (0.6H, d, *J* = 4.0 Hz), 4.80 (0.4H, d, *J* = 4.0 Hz), 4.085 (0.8H, s), 4.076 (1.2H, s), 3.33 (1.2H, s), 3.32 (1.8H, s), 2.876 (0.6H, dd, *J* = 13.8, 6.9 Hz), 2.868 (0.4H, dd, *J* = 13.8, 7.5 Hz), 2.74 (0.6H, d, *J* = 7.5 Hz), 2.72 (0.4H, d, *J* = 7.5 Hz), 2.64-2.58 (1H, m), 2.06 (1H, brs), 1.82-1.59 (4H, m), 1.47 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.48, 157.32, 138.27, 129.03, 129.01, 128.39, 126.51, 104.31, 89.62, 89.50, 79.44, 79.34, 67.80, 67.65, 59.71, 57.50, 46.35, 46.21, 40.23, 40.16, 38.61, 38.50, 30.03, 29.91, 26.09, 25.88; HRMS (FD$^+$): Calcd for (M+H$^+$) $C_{19}H_{24}F_3O_5S$: 421.1297; found: 421.1280.



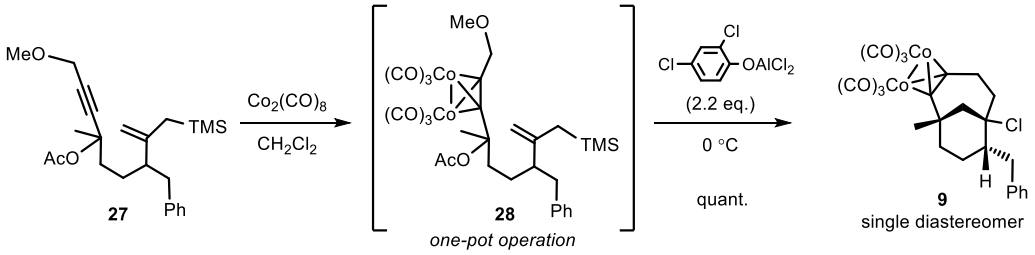
Compound 26 : To a solution of **25** (5.17 g, 12.3 mmol), LiCl (1.53 g, 36.0 mmol) and

$Pd(PPh_3)_4$ (692 mg, 0.599 mmol) in THF (60 mL) was slowly added $TMSCH_2MgCl$ (1.0 M in Et_2O, 36.0 mL, 36.0 mmol) at 0 °C, then stirred at room temperature for 30 min under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 9:1→4:1) to give 3.66 g of **26** as a pale yellow oil (83%): IR (ATR) ν 3427, 2946, 1631, 1494, 1454, 1247, 1101, 849, 734, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (2H, m), 7.27-7.25 (3H, m), 4.77-4.76 (2H, m), 4.17 (0.8H, s), 4.16 (1.2H, s), 3.41 (1.2H, s), 3.40 (1.8H, s), 2.90 (0.4H, d, *J* = 5.7 Hz), 2.88 (0.6H, d, *J* = 5.7 Hz), 2.68 (0.6H, d, *J* = 8.6 Hz), 2.66 (0.4H, d, *J* = 8.6 Hz), 2.28 (1H, quintet, *J* = 7.7 Hz), 2.18 (1H, brs), 1.83-1.60 (4H, m), 1.58 (2H, s), 1.54 (1.8H, s), 1.53 (1.2H, s), 0.12 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.30, 140.89, 140.86, 129.13, 128.03, 125.71, 107.90, 107.88, 90.23, 90.18, 78.84, 78.82, 68.10, 68.06, 59.71, 57.34, 48.23, 48.19, 40.73, 40.70, 40.43, 40.38, 29.75, 29.64, 26.95, 26.91, 25.59, -1.03; HRMS (FD^+): Calcd for (M^+) $C_{22}H_{34}O_2Si$: 358.2328; found: 358.2344.

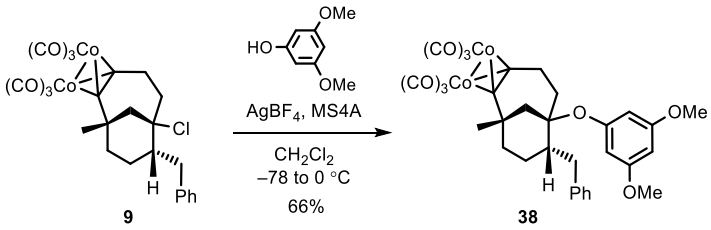


Compound 27 : To a solution of **26** (3.66 g, 10.2 mmol) in pyridine (10 mL) and CH_2Cl_2 (30 mL) were added Ac_2O (2.89 mL, 30.6 mmol) and DMAP (872 mg, 7.14 mmol), then stirred at room temperature for 7 h under argon atmosphere. After the reaction mixture was concentrated under reduced pressure, the crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 9:1→4:1) to give 3.95 g of **27** as a pale yellow oil (97%): IR (ATR) ν 2952, 2932, 1743, 1629, 1453, 1366, 1235, 1187, 1166, 1102, 1015, 943, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (2H, m), 7.18-7.14 (3H, m), 4.68-4.66 (2H, m), 4.08 (2H, s), 3.31 (1.2H, s), 3.30 (1.8H, s), 2.80 (0.4H, d, *J* = 5.8 Hz), 2.77 (0.6H, d, *J* = 5.8 Hz), 2.58 (0.6H, d, *J* = 8.6 Hz), 2.55 (0.4H, d, *J* = 8.6 Hz), 2.17 (1H, quintet, *J* = 5.7 Hz), 1.96 (1.8H, s), 1.95 (1.2H, s), 1.84-1.78 (1H, m), 1.69-1.48 (3H, m), 1.61 (3H, s), 1.47 (2H, s), 0.03 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.15, 149.21, 149.19, 140.82, 140.78, 129.12, 128.01, 125.72, 107.96, 107.94, 86.65, 86.62, 80.84, 75.03, 74.98, 59.71, 57.30, 57.28, 48.08, 40.27, 40.19, 38.68, 38.66, 26.36, 26.32, 26.23, 26.11, 25.54, 25.51, 21.81, -1.05; HRMS (FD^+): Calcd for (M^+) $C_{24}H_{36}O_3Si$:

400.2434; found: 400.2452.

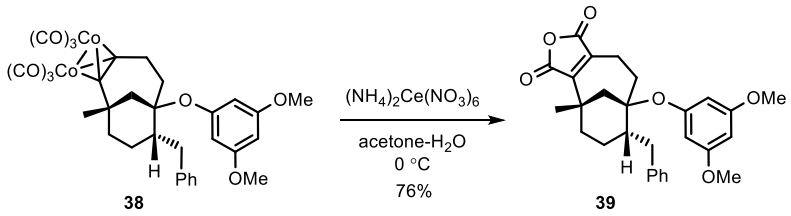


Compound 9 : To a solution of **27** (942 mg, 2.35 mmol) in CH_2Cl_2 (11 mL) was added $Co_2(CO)_8$ (965 mg, 2.82 mmol), then stirred at room temperature for 1 h under argon atmosphere. The reaction mixture was added to a solution of dichloroalminum 2,4-dichlorophenoxide [5.69 mmol, prepared from $EtAlCl_2$ (1.07 M in hexane, 5.32 mL, 5.69 mmol) and 2,4-dichlorophenol (928 mg, 5.69 mmol)] in CH_2Cl_2 (16 mL) at 0 ºC, then stirred for 5 min. After the reaction mixture was quenched with a saturated aqueous Rochell's solution, the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 40:1→20:1) to give 1.56 g of **9** as a brown oil (quant.): IR (ATR) ν 2960, 2927, 2087, 2042, 1990, 1603, 1453, 905, 734, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (2H, m), 7.23-7.20 (3H, m), 3.55 (1H, d, *J* = 12.6 Hz), 3.23-3.10 (2H, m), 2.70 (1H, d, *J* = 14.3 Hz), 2.39 (1H, t, *J* = 12.5 Hz), 2.36 (1H, d, *J* = 13.8 Hz), 2.23 (1H, dd, *J* = 13.8, 2.3 Hz), 2.19-2.10 (2H, m), 1.63 (1H, td, *J* = 13.2, 4.0 Hz), 1.57-1.52 (2H, m), 1.31 (3H, s), 1.10 (1H, qd, *J* = 13.7, 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.18 (6C), 140.50, 129.18, 128.42, 126.14, 109.58, 98.14, 79.17, 55.85, 51.62, 40.93, 40.14, 39.93, 36.54, 32.10, 31.05, 26.91; HRMS (FD^+): Calcd for (M^+) $C_{24}H_{21}ClCo_2O_6$: 557.9691; found: 557.9705.



Compound 38 : To a suspension of **9** (3.62 g, 6.48 mmol), 3,5-dimethoxyphenol (3.00 g, 19.4 mmol), and 4AMS (1.30 g) in CH_2Cl_2 (22 mL) was added $AgBF_4$ (1.51 g, 7.78 mmol) at -78 ºC

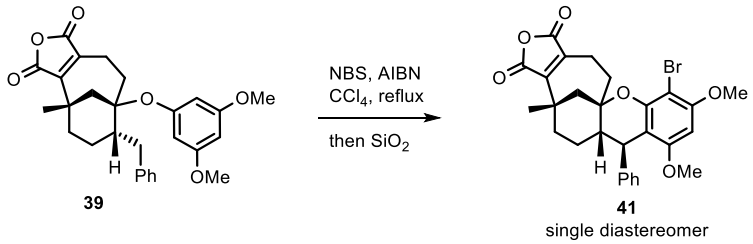
under argon atmosphere, then the reaction mixture was slowly warmed to 0 °C over 3 h and stirred at 0 °C for 6 h. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, the filtrate was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 20:1→9:1) to give 2.91 g of **38** as a brown oil (66%): IR (ATR) ν 2960, 2929, 2086, 2041, 1992, 1764, 1591, 1455, 1203, 1147, 1054, 732, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (2H, m), 7.26-7.20 (3H, m), 6.23 (1H, s), 6.20 (2H, s), 3.73 (6H, s), 3.60 (1H, d, *J* = 12.6 Hz), 3.23-3.11 (2H, m), 2.39 (1H, t, *J* = 12.0 Hz), 2.36 (1H, d, *J* = 14.3 Hz), 2.08-1.96 (2H, m), 1.99 (1H, d, *J* = 9.8 Hz), 1.80 (1H, td, *J* = 13.7, 5.2 Hz), 1.62-1.56 (1H, m), 1.58 (1H, d, *J* = 10.9 Hz), 1.51-1.48 (1H, m), 1.31 (3H, s), 1.12-1.04 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.31 (6C), 160.77, 156.28, 141.09, 129.21, 128.34, 125.91, 110.48, 103.27, 99.09, 96.09, 84.93, 55.30, 51.47, 48.03, 40.71, 39.04, 36.12, 35.67, 31.51, 30.44, 25.95; HRMS (FD^+): Calcd for (M^+) $C_{32}H_{30}Co_2O_9$: 676.0554; found: 676.0572.



38 39

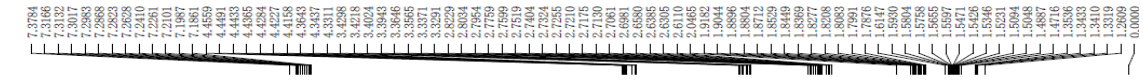
Compound 39 : To a solution of **38** (1.96 g, 2.90 mmol) in acetone (60 mL) and H_2O (3 mL) was added cerium(VI) ammonium nitrate (7.94 g, 14.5 mmol) at 0 °C, and stirred for 5 min. After the solvent was removed under reduced pressure, the residue was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 6:1→4:1) to give 1.02 g of **39** as a white solid (76%): m.p. 179-182 °C; IR (ATR) ν 2942, 1760, 1591, 1456, 1250, 1203, 1147, 1052, 915, 746, 727, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (2H, m), 7.22-7.20 (3H, m), 6.28-6.27 (1H, m), 6.25-6.24 (2H, m), 3.77 (6H, s), 3.40 (1H, d, *J* = 13.2 Hz), 2.73-2.68 (1H, m), 2.64 (1H, d, *J* = 13.8 Hz), 2.58 (1H, t, *J* = 13.8 Hz), 2.36 (1H, d, *J* = 16.1 Hz), 2.19 (1H, t, *J* = 13.2 Hz), 2.13 (1H, t, *J* = 13.2 Hz), 2.05 (1H, d, *J* = 14.9 Hz), 1.99 (1H, t, *J* = 11.5 Hz), 1.65 (1H, dd, *J* = 14.3, 2.9 Hz), 1.58 (1H, d, *J* = 13.8 Hz), 1.34 (3H, s), 1.20 (1H, td, *J* = 13.8, 4.0 Hz), 1.06-0.98 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.27, 163.81, 161.06, 156.35, 148.32, 146.12, 140.56, 129.19, 128.33, 125.96, 102.47, 95.85, 82.92, 55.34, 49.16, 45.61, 38.66, 35.64, 34.06, 32.79, 28.83, 25.54, 19.18; HRMS (FD^+): Calcd

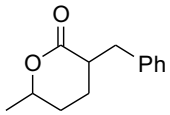
for (M^+) $C_{28}H_{30}O_6$: 462.2042; found: 462.2039.



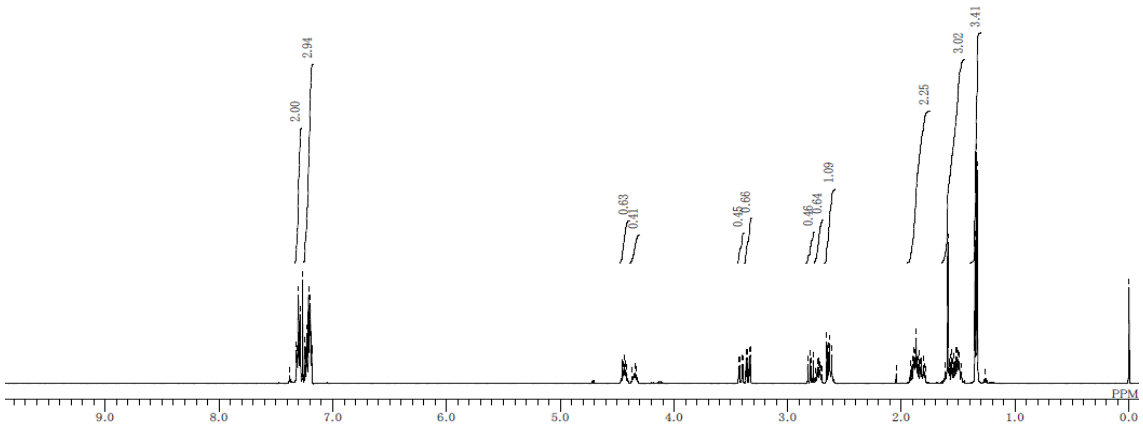
Compound 41: To a solution of **39** (866 mg, 1.88 mmol) in CCl_4 (37 mL) were added NBS (668 mg, 3.75 mmol) and AIBN (308 mg, 1.88 mmol) at room temperature, then the reaction mixture was heated instantly and refluxed for 1 h under argon atmosphere. After cooling, silica gel (ca. 2 g) and CH_2Cl_2 (20 mL) were added to the mixture at 0 °C and stirred at room temperature for 5 min. The filtrate was concentrated under reduced pressure, and the crude product was through a short pad of silica gel to give 1.50 g of **41** containing impurities.

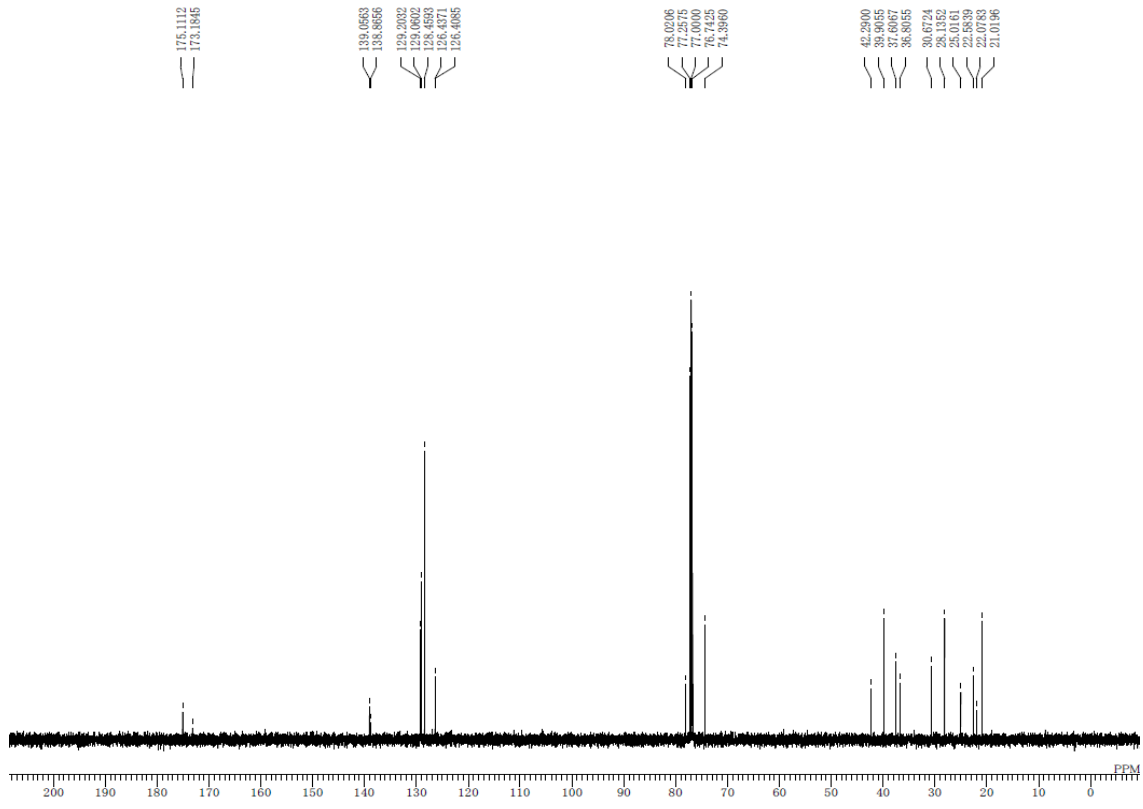
Compound 21



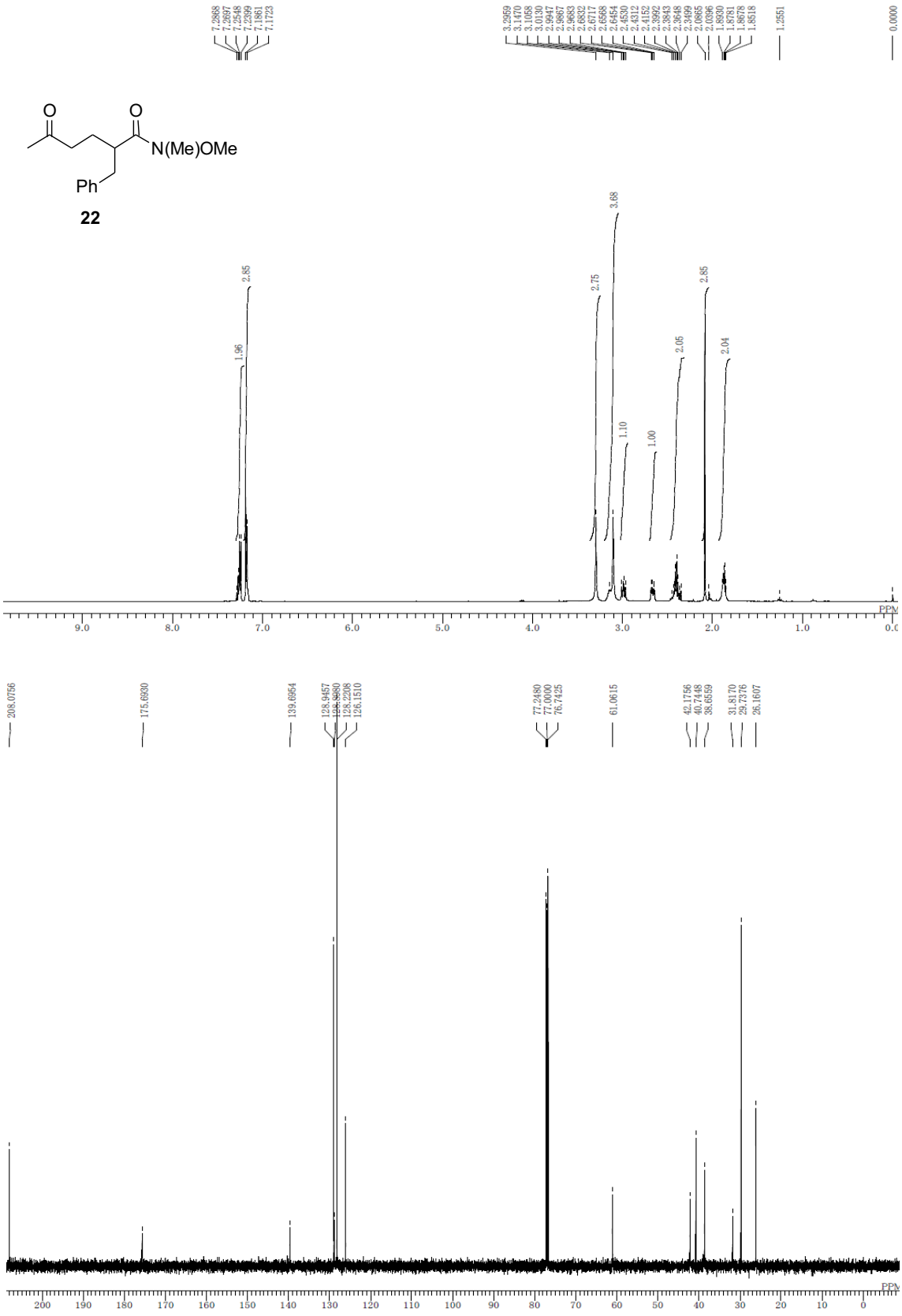


21
d.r.= 3:2





Compound 22



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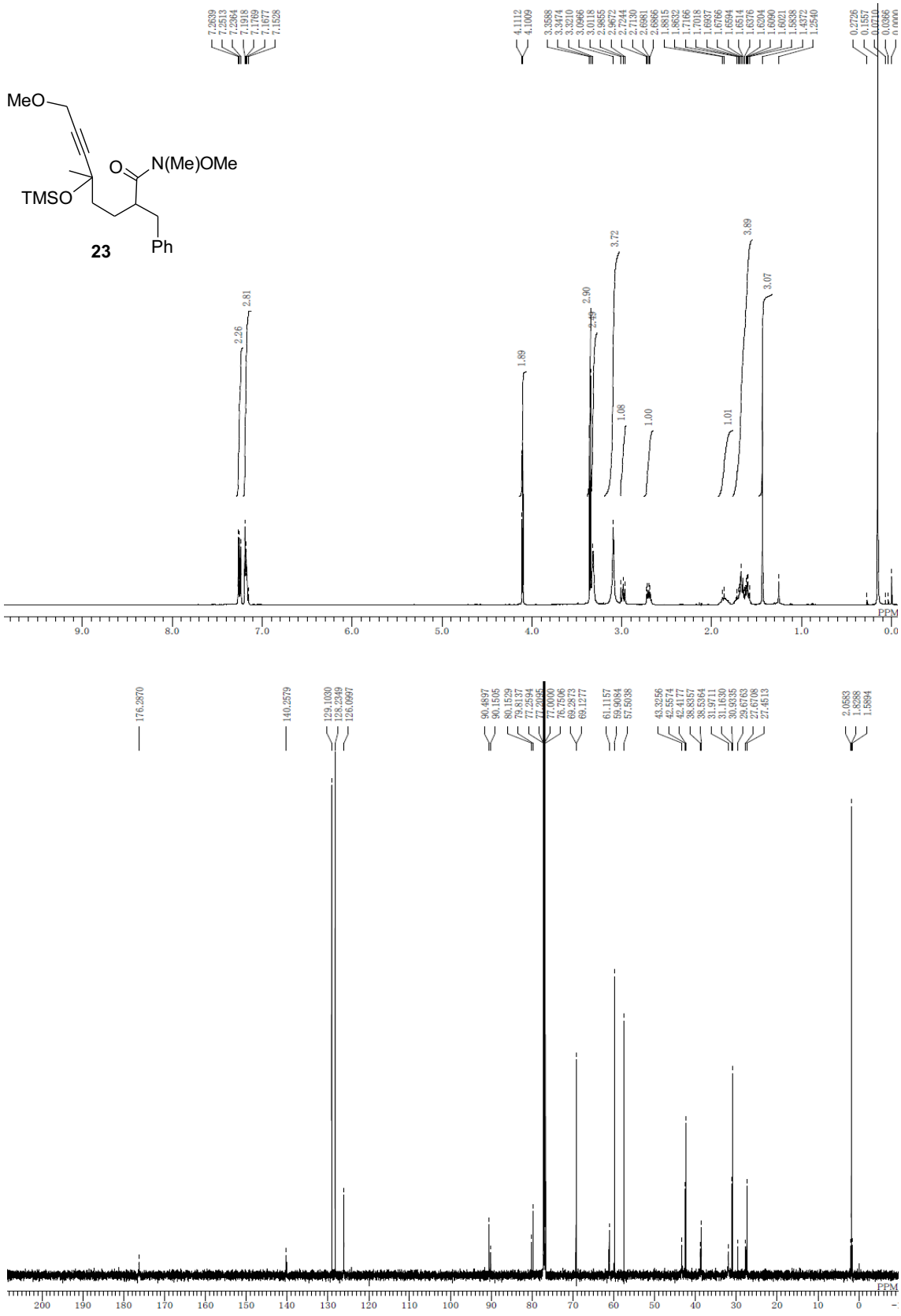

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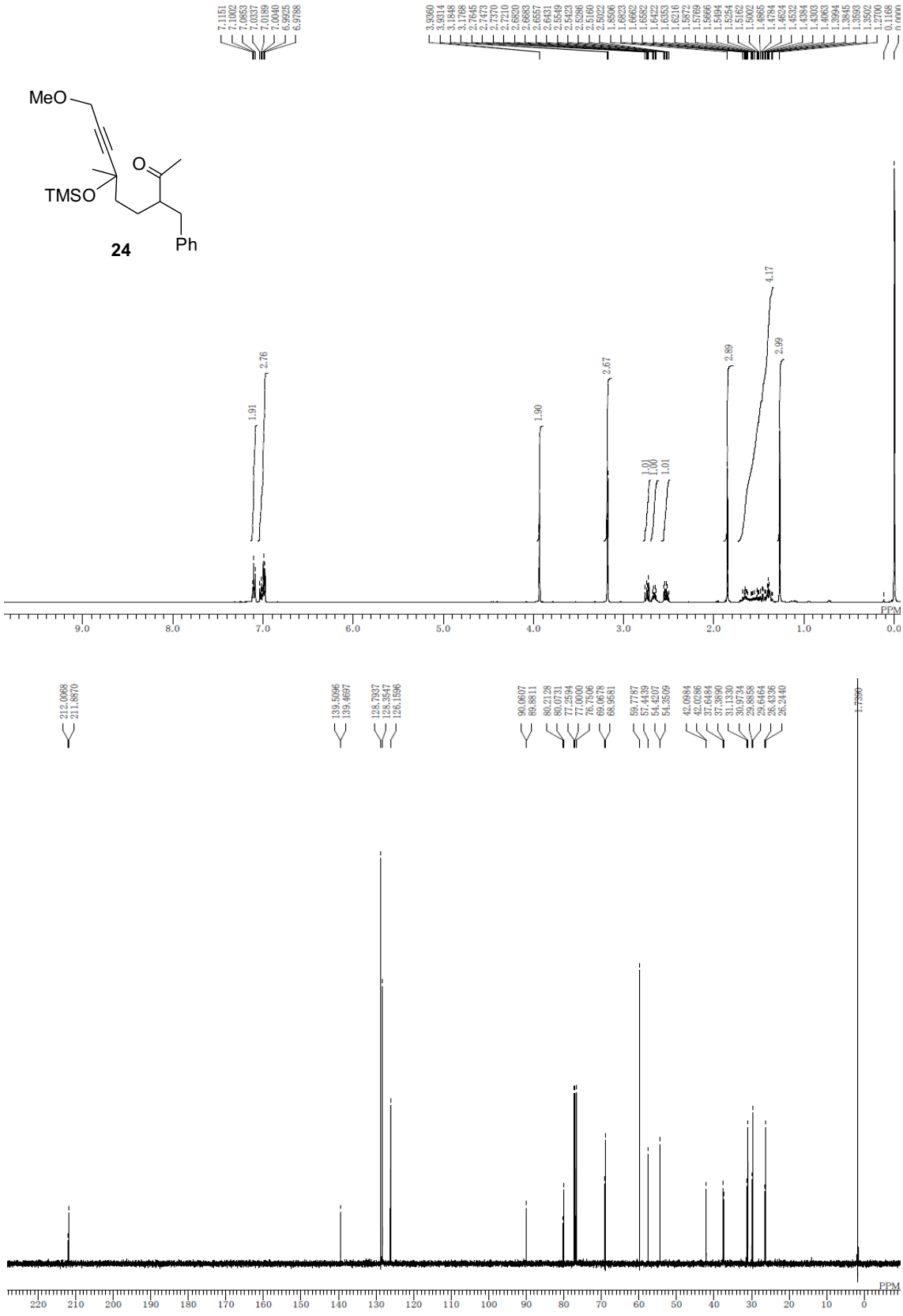

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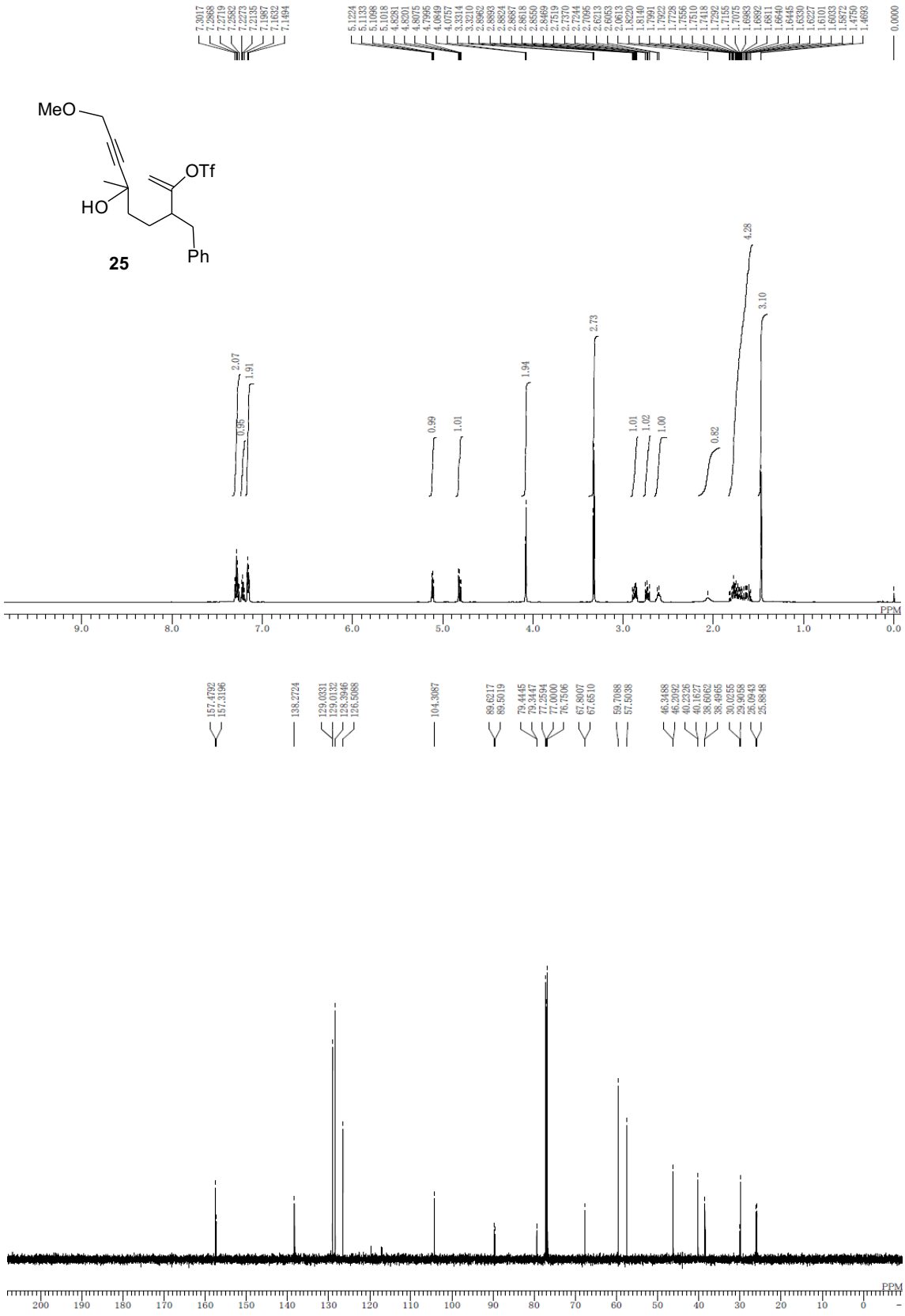
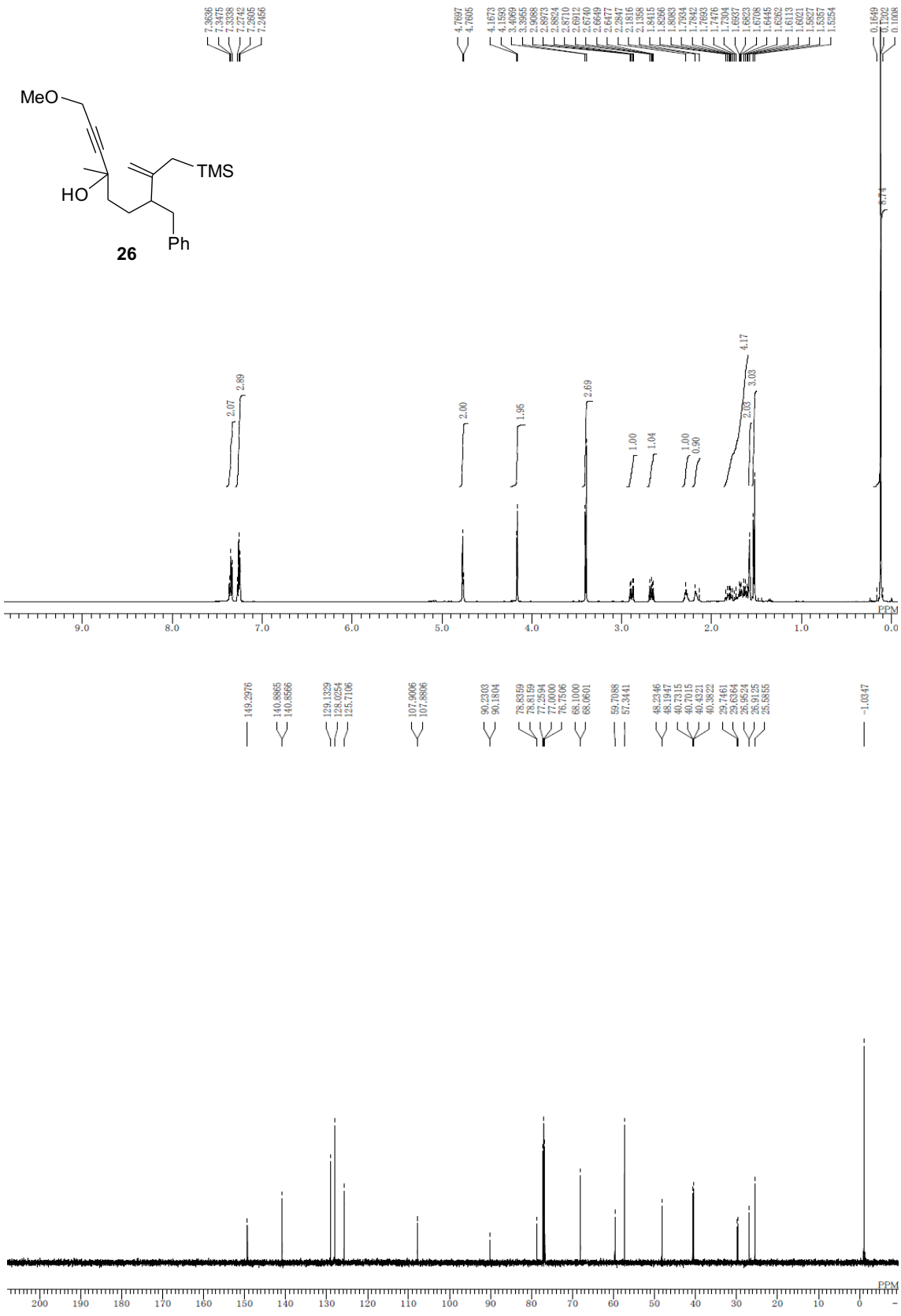
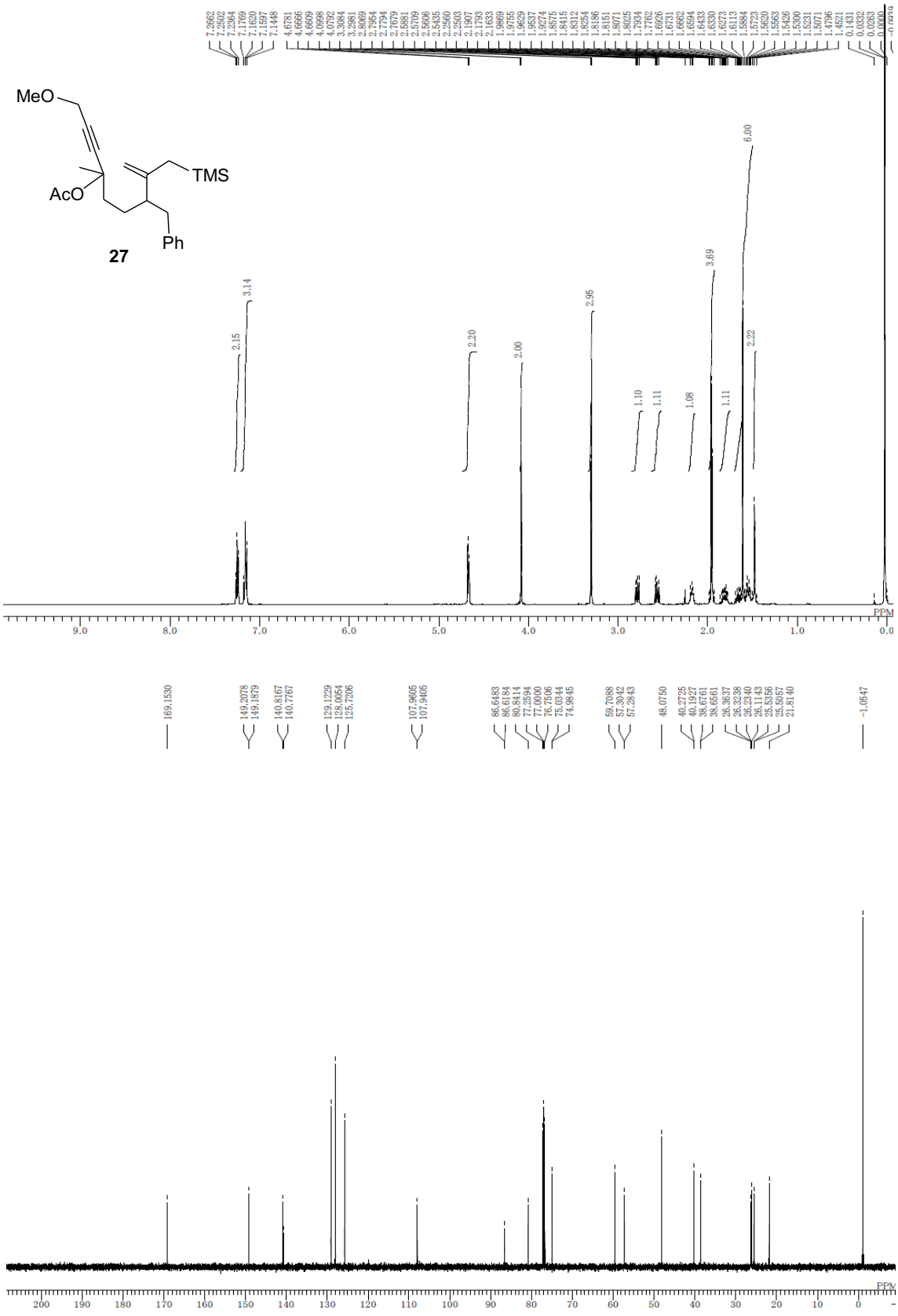


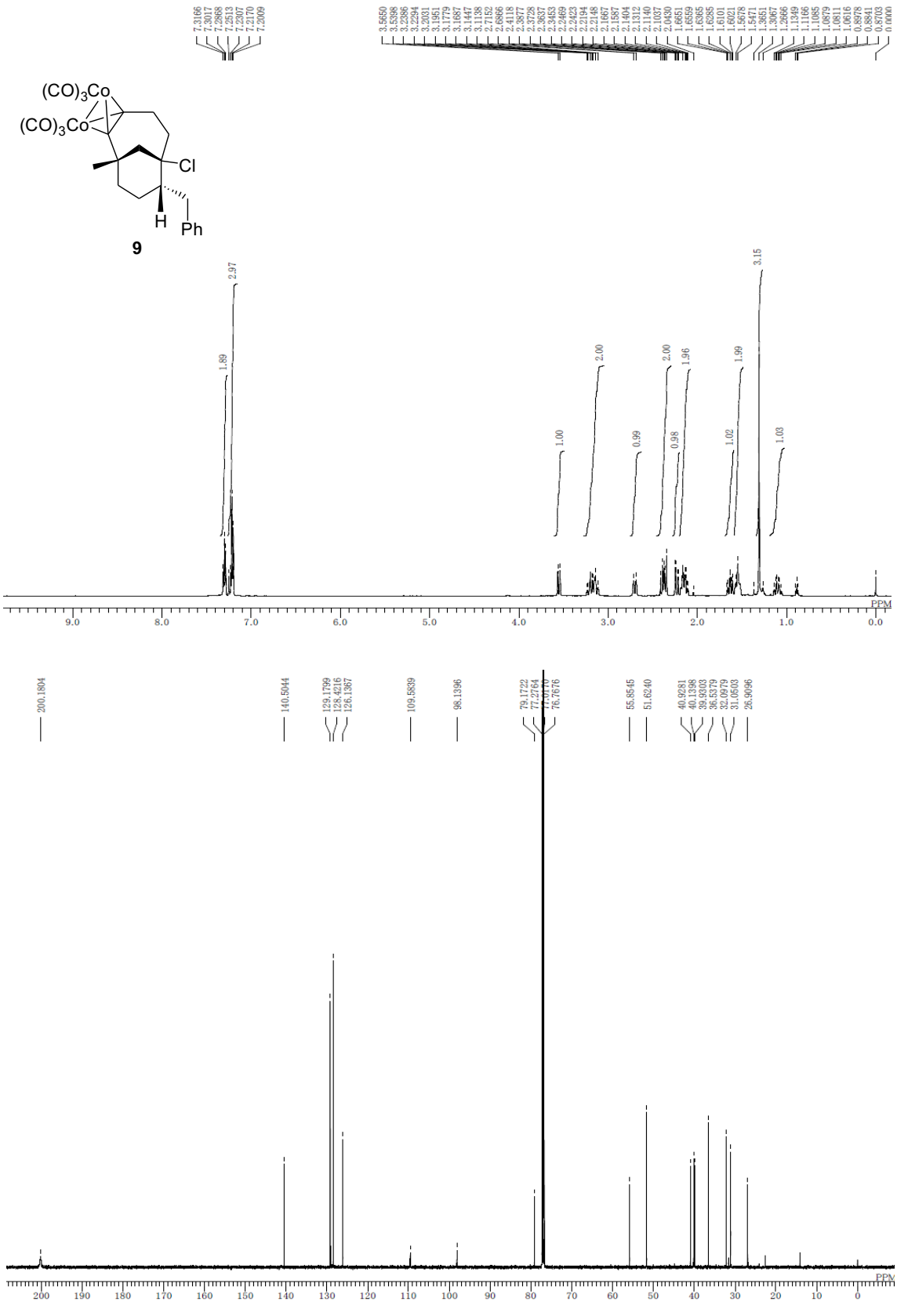
Compound 26



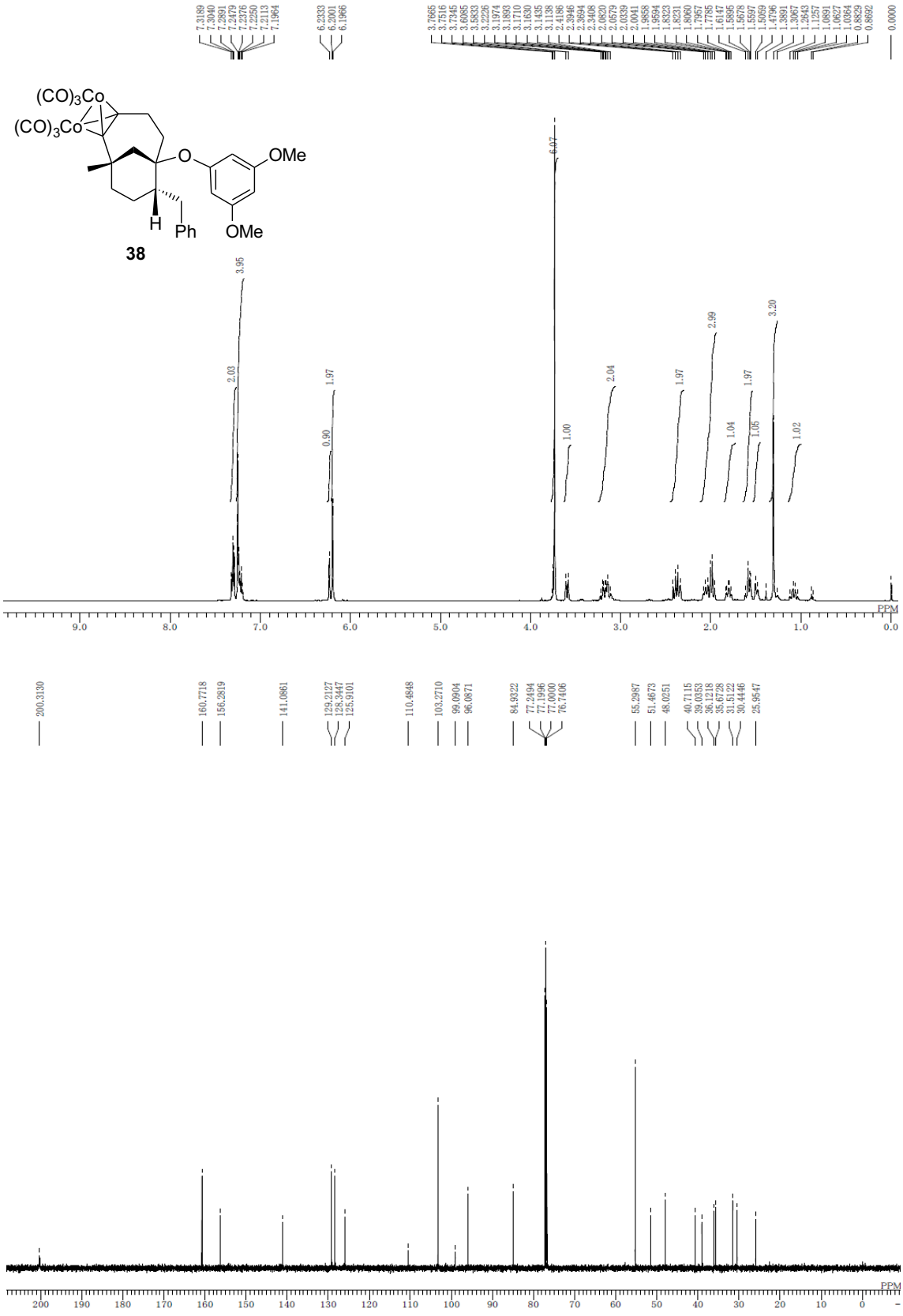
Compound 27



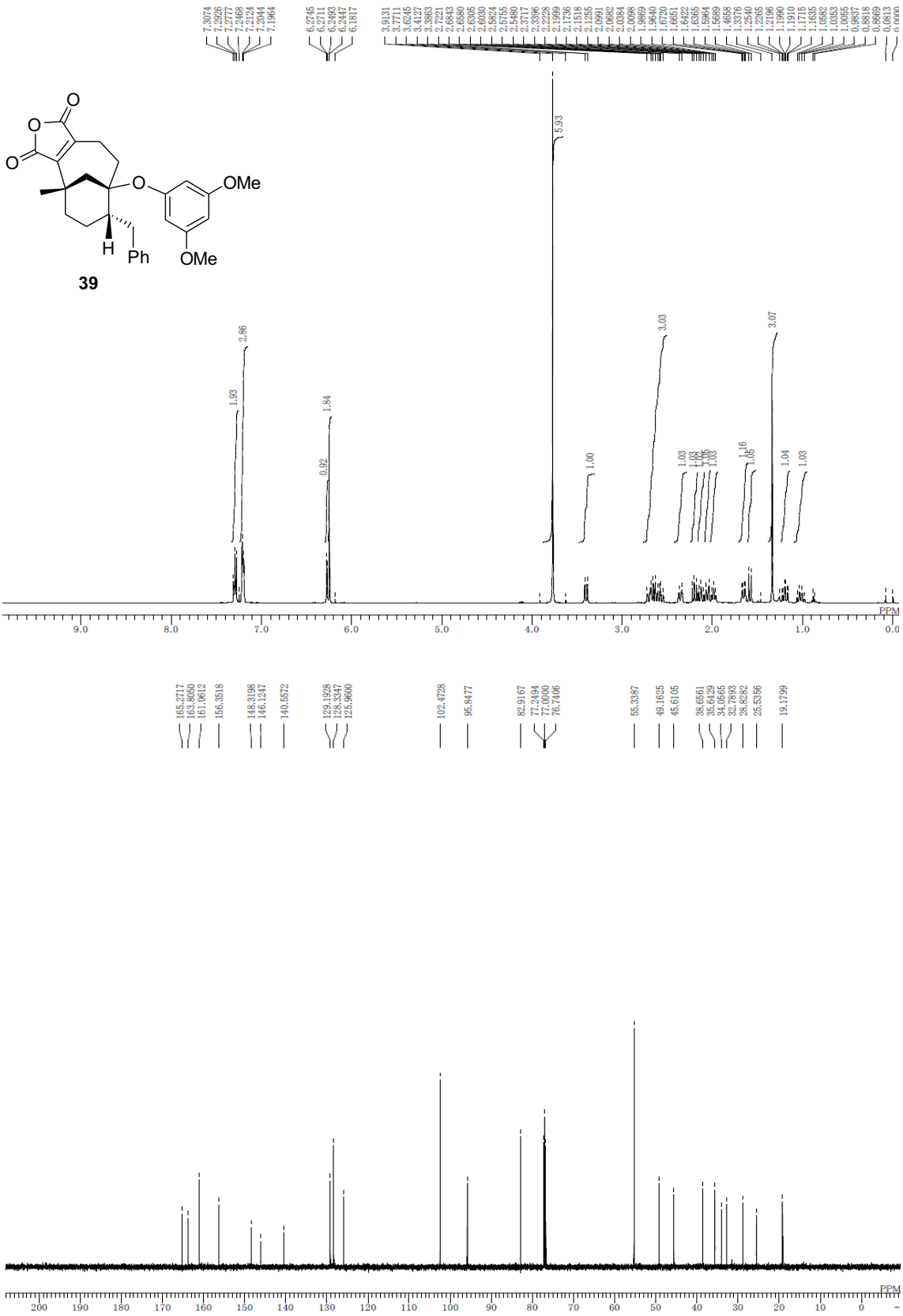
Compound 9



Compound 38



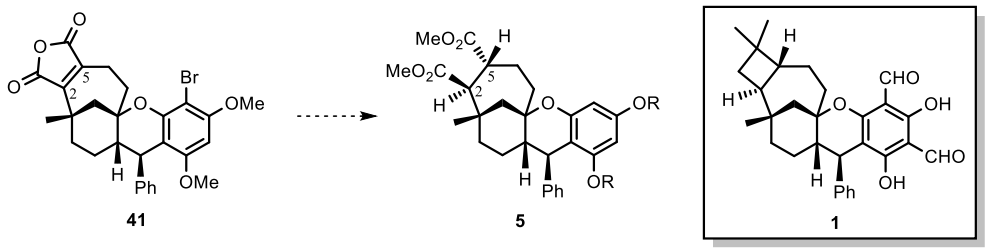
Compound 39



Chapter II

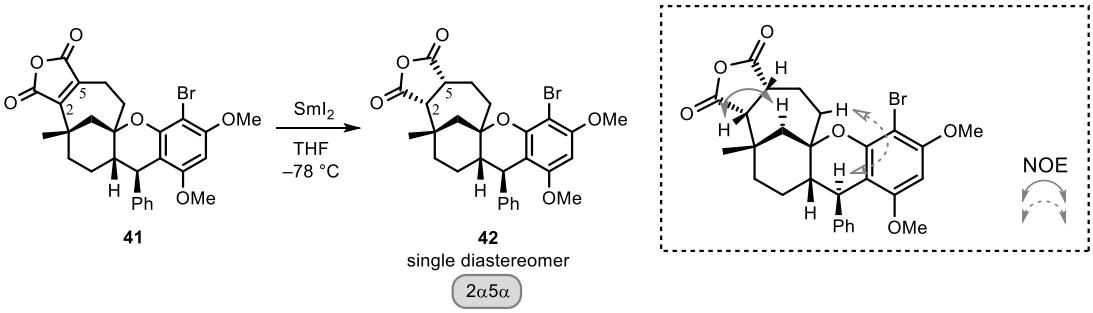
Accomplishment of Total Synthesis of Psiguadial B: Stereocontrolled Construction of the Cyclobutane Moiety

Having achieved the stereoselective synthesis of **41** as the key intermediate of Psiguadial B (**1**), the stage was set for the construction of the dimethylcyclobutane moiety. Considering the stereochemistry of the C2 and C5 positions at which the four-membered ring is fused with the bicyclo[4.3.1]decane skeleton, the author planned to transform maleic anhydride **41** into diester (2β,5α)-**5** (Scheme 13).



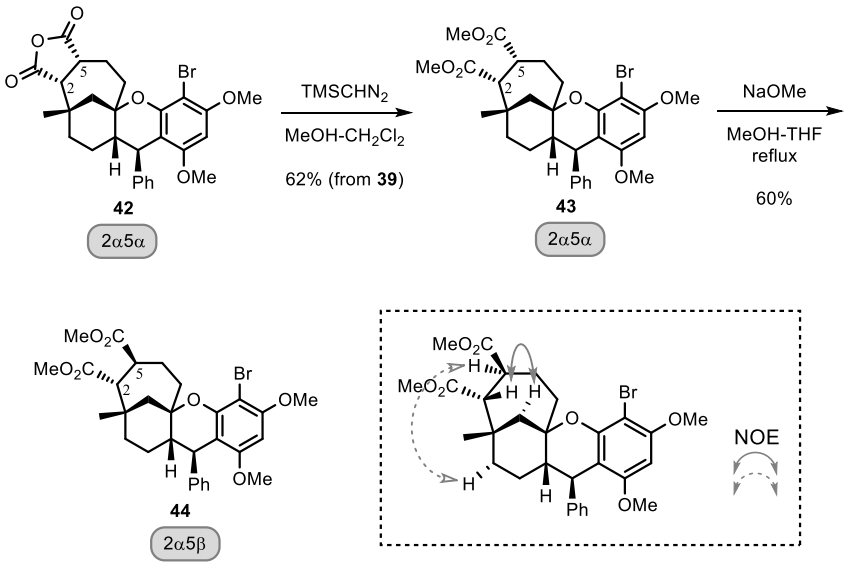
Scheme 13. Plan for transformation of **41** into **5**

Upon treatment with samarium(II) iodide in THF, maleic anhydride **41** underwent the conjugate reduction to afford *cis*-fused acid anhydride (2α,5α)-**42** as a single diastereomer (Scheme 14). The β-configuration of the two hydrogen atoms at the C2 and C5 positions was confirmed by the observation of NOEs, and the result can be explained by the stereoselective protonation of the bisenolate intermediate, which is generated through the two-electron reduction of **41**, from the convex face of the bicyclo[4.3.1]decane skeleton.



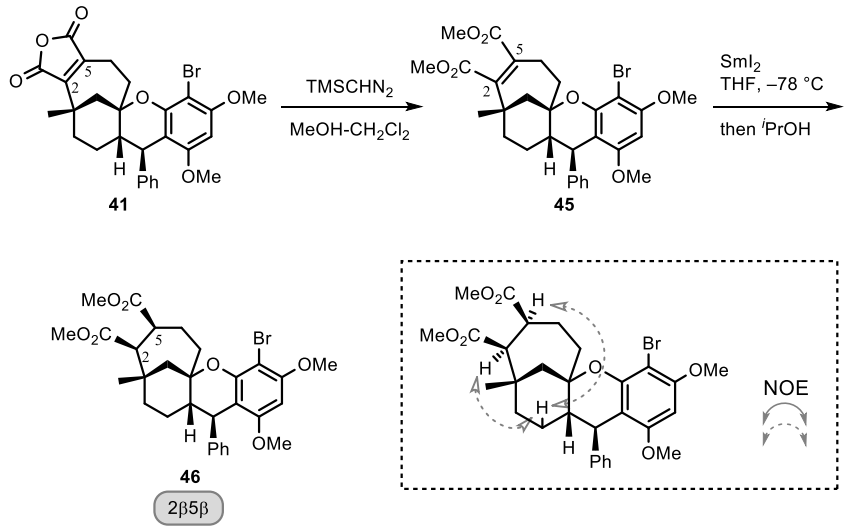
Scheme 14. Conjugate reduction of **41** with SmI_2

Acid anhydride **42** was converted to the corresponding diester (2α,5α)-**43** by the reaction with (trimethylsilyl)diazomethane in methanol, and the epimerization of the ester moiety was examined under the influence of sodium methoxide (Scheme 15). While the desired compound was (2β,5α)-**47**, the NOE experiment of the product indicated that the configuration of the C2 and C5 positions was α and β, respectively. The stereochemical outcome suggested that only the sterically less hindered C5-ester group could undergo enolization followed by protonation, giving rise to (2α,5β)-**44**.



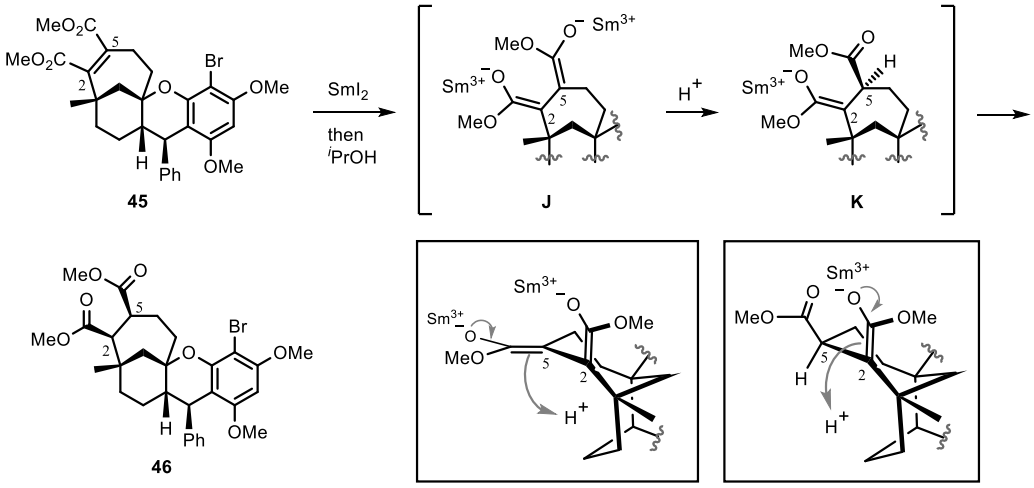
Scheme 15. Epimerization of **43** under basic conditions

On the other hand, conversion of maleic anhydride **41** to the corresponding diester **45** prior to the reduction with samarium(II) iodide led to different stereoselectivity, and diester (2β,5β)-**46** was obtained (Scheme 16). It was found that the stereoselectivity in the reduction of maleate **45** depends on the quenching method of the intermediate. Thus, the use of isopropanol followed by aqueous sodium bicarbonate solution gave the best result.



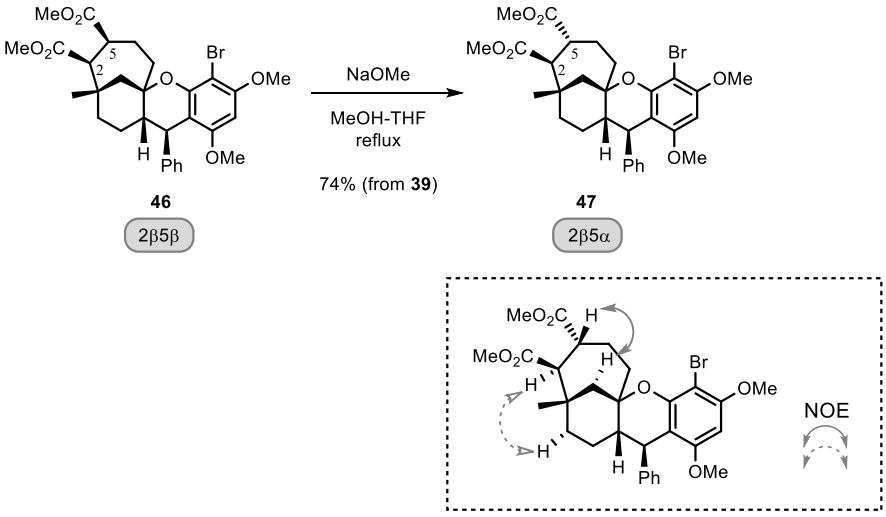
Scheme 16. Stereoselective reduction of **45** with SmI_2

The remarkable stereoselectivity in the reduction of maleate **45** can be rationalized as shown in Scheme 17. The configuration of the C2 and C5 positions are controlled at the protonation step of the bisenolate intermediate **J** which is produced through the two-electron reduction of maleate **45**. Since bisenolate **J** has the fully substituted conjugated diene structure, the two enolate moiety of the stable conformer would be in staggered relationship to each other as depicted in the figure. The first protonation of **J** would occur at the less hindered C5 enolate moiety from the α-face, because the β-face is covered with the C2 enolate moiety. The resulting C2 enolate **K** would be protonated mainly from the opposite face of the C5 ester group to afford diester (2β,5β)-**46** along with the minor epimer (2α,5β)-**44** which is generated by the protonation from the convex face of the bicyclic skeleton.



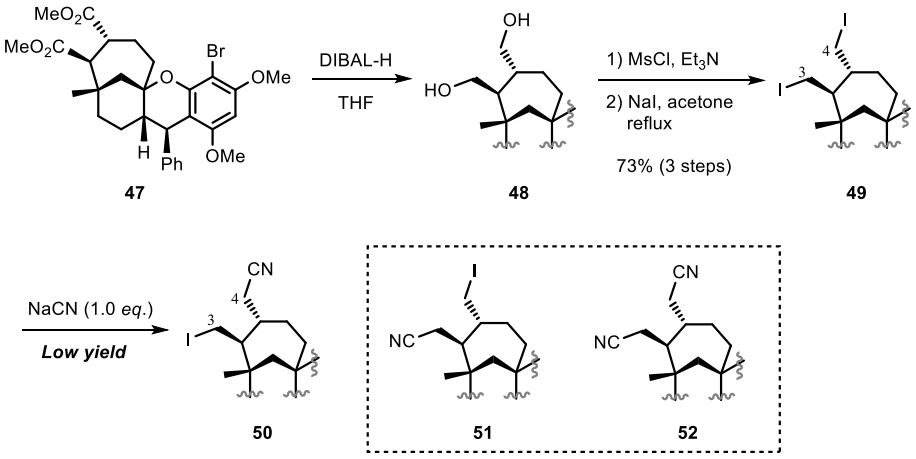
Scheme 17. Plausible mechanism on reduction of **45** using SmI_2 to provide **46**

Similarly with the case of diester (2α,5α)-**43**, diester (2β,5β)-**46** underwent epimerization mediated by sodium methoxide only at the less hindered C5 position, giving rise to the desired diester (2β,5α)-**47** (Scheme 18). Confirmation of the stereochemistry of the C2 and C5 positions was performed by the NOE experiment.



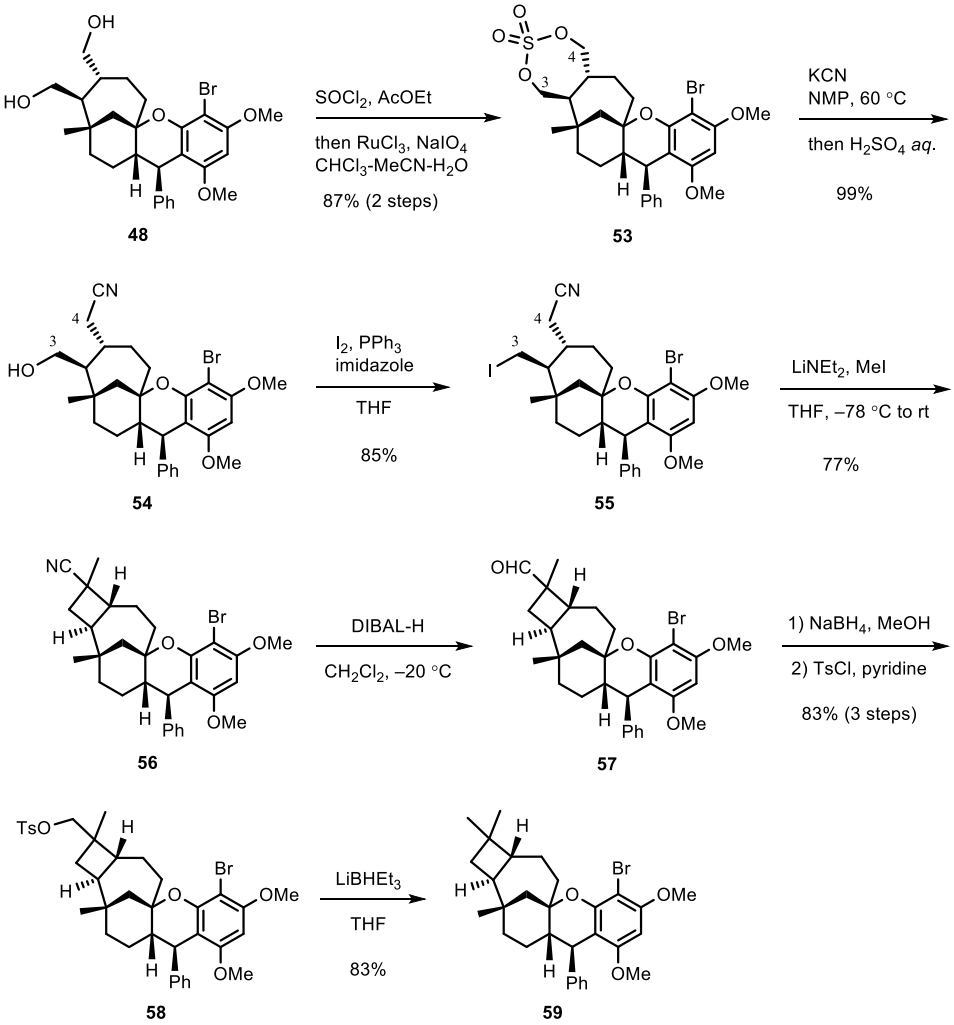
Scheme 18. Epimetization of **46**

The desired intermediate (2β,5α)-**47** in hand, the stage was set for the synthesis of δ-iodonitrile **50** as the substrate of the intramolecular S_N2 reaction for constructing the four-membered ring (Scheme 19). Reduction of (2β,5α)-**47** with DIBAL-H yielded 1,4-diol **48** which was further converted to diiodide **49** through mesylation followed by a substitution reaction with sodium iodide. The initial attempts for converting the less hindered C4 iodide moiety to the corresponding nitrile by the reaction with sodium cyanide resulted in formation of a mixture of iodonitrile **50**, its regioisomer **51**, and dinitrile **52**.



Scheme 19. Attempt on conversion from diester **47** into δ-iodonitrile **50**

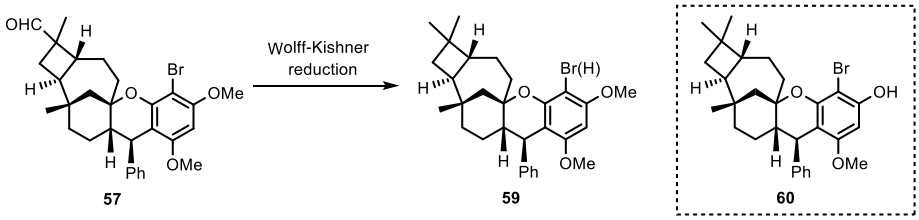
With a view to reducing the reactivity at the C3 position, the author planned to use cyclic sulfonate **53**, which was readily obtained from 1,4-diol **48** by known method,[14] instead of diiodide **49** (Scheme 20). Upon heating with potassium cyanide in NMP, **53** underwent the regioselective substitution reaction at the C4 position, and the resulting monosulfate was treated with diluted sulfonic acid to give the desired cyano alcohol **54**. After conversion to iodonitrile **55**, construction of the four-membered ring and methylation of the resulting nitrile was performed by the reaction with an excess amount of lithium diethylamide followed by methyl iodide. The one-pot procedure afforded nitrile **56** in 77% yield which was transformed into the dimethylcyclobutane derivative **59** through DIBAL-H reduction to aldehyde **57**, sodium borohydride reduction to the corresponding alcohol, tosylation of the alcohol, and reduction of tosylate **58** with lithium triethylborohydride.[15]



Scheme 20. Construction of dimethylcyclobutane **59**

The author also explored an improved transformation of the intermediate aldehyde **57** into **59** by using Wolff-Kishner reduction (Table 3). The initial attempt of heating aldehyde **57** with hydrazine hydrate and potassium hydroxide failed to give the desired product **59** in good yield (entry 1), because a fair amount of demethylated product **60** was formed under violent reaction conditions. The alternative route involving the formation and reduction of the corresponding tosylhydrazone with $NaBH_3(CN)$[16] also led to unsatisfying yield (entry 2). Finally, the Wolff-Kishner reduction mediated by potassium *tert*-butoxide in dimethyl sulfoxide[17] gave **59** along with a debrominated derivative **59'** in moderate combined yield (entry 3).

Table 3. Wolff-Kishner reduction of aldehyde **57**

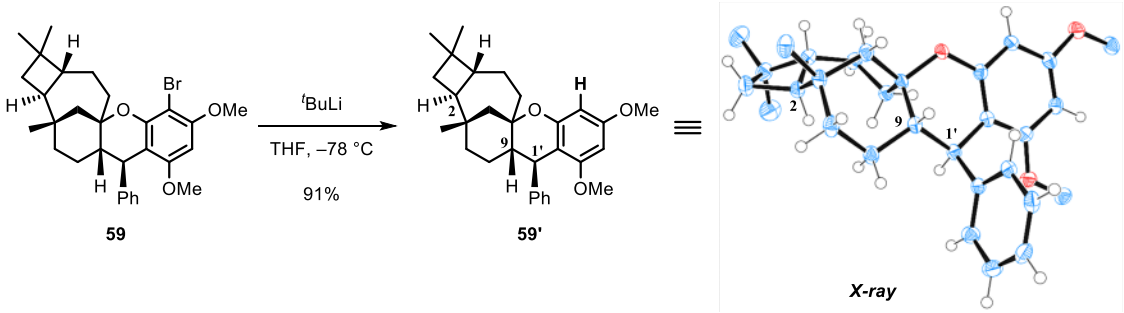


57 59 60

entry	condition	yield (2 steps)
1	$N_2H_4 \cdot H_2O$, KOH, $O(CH_2CH_2OH)_2$, 200 °C	26%[a]
2	$TsNHNH_2$, $NaBH_3(CN)$, $TsOH \cdot H_2O$ (cat.), DMF, 100 °C	25%
3	$N_2H_4 \cdot H_2O$, EtOH-THF, then ^tBuOK, DMSO, rt	54% (Br:H = 2:1)

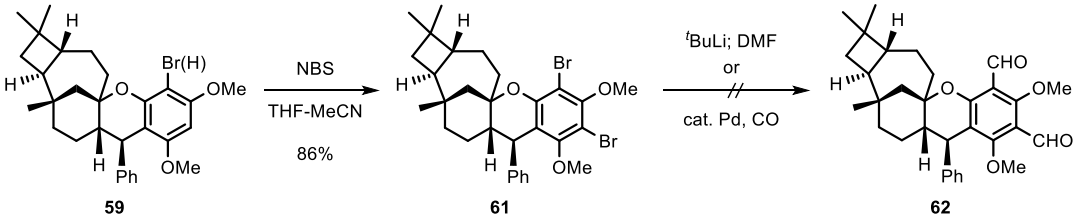
[a]17% of **60** was observed as by-product.

Debrominated compound **59'** was also obtained by the treatment of **59** with *tert*-butyllithium followed by protonation with water. Since **59'** was found to give better crystals which are suitable for the X-ray crystallographic analysis, the structure of the synthetic compound was confirmed at this point. The Ortep drawing indicated that the configuration of **59'** is consistent with that of the natural product (Scheme 21).



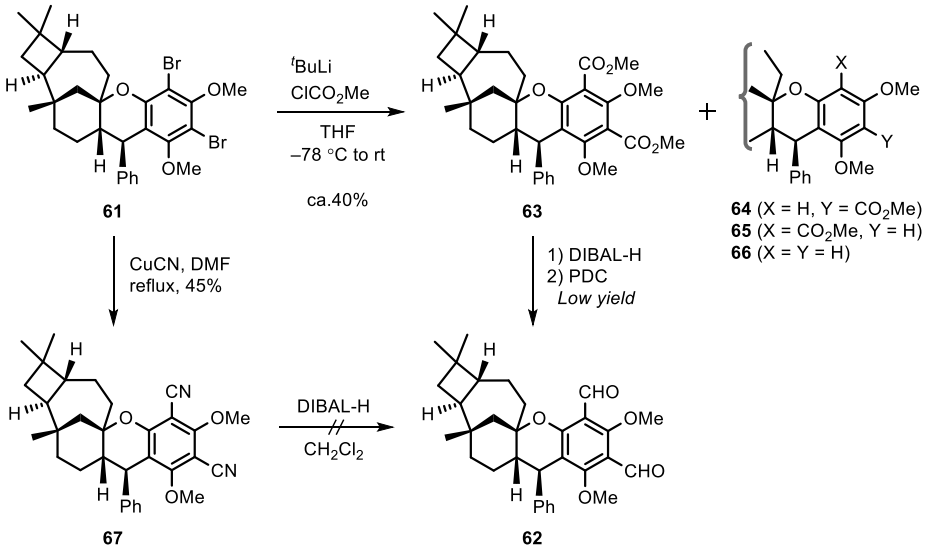
Scheme 21. Confirmation of the stereochemistries by X-ray analysis

The remaining task toward the total synthesis is the introduction of the functional groups on the substituted aromatic ring. The mixture of **59** and **59'** was converted to dibromide **61** by the treatment with NBS, and the installation of two formyl groups at once was explored (Scheme 22). However, successive treatment of aryl dibromide **61** with *tert*-butyllithium and dimethylformamide failed to give the desired dialdehyde. Another approach by a carbonylation reaction promoted by a palladium catalyst also resulted in recovery of the substrate.



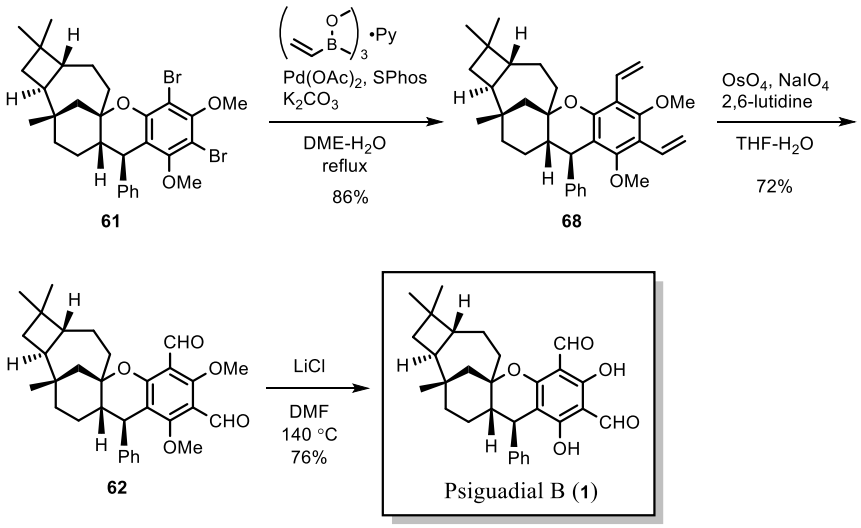
Scheme 22. Attempt on direct installation of two formyl groups to diromide **61**

On the other hand, the corresponding diester **63** was found to be obtainable, albeit in moderate yield, through the reaction of dibromide **61** with *tert*-butyllithium followed by methyl chloroformate (Scheme 23). Diester **63** could be converted to dialdehyde **62** by DIBAL-H reduction and PDC oxidation, but the low yield of these transformation was not suitable for accomplishing efficient total synthesis. The use of dinitrile **67**, which was obtained by the reaction of dibromide **61** with copper(I) cyanide, suffered from the low reactivity toward the DIBAL-H reduction.



Scheme 23. Other studies on conversion into **62**

Finally, the author succeeded in transforming dibromide **61** into the desired dialdehyde **62** as depicted in Scheme 24. Thus, dibromide **61** was subjected to the Suzuki-Miyaura coupling reaction with vinylboronic anhydride pyridine complex to give divinyl compound **68**.[18] The oxidative cleavage of the vinyl groups was accomplished by the combined use of catalytic amount of osmium(VIII) oxide and sodium periodate in the presence of 2,6-lutidine.[19] The resulting dialdehyde **62** was subjected to removal of the methyl ether groups by heating with lithium chloride,[20] giving rise to Psiguadial B in good yield.



Scheme 24. Total synthesis of Psiguadial B (**1**)

Figure 4 shows the comparison of the ^{1}H-NMR spectrum of reference data[2b] and synthetic compound **1**. It was found that the spectrum of the synthetic natural product is precisely consistent with that of the reference data.

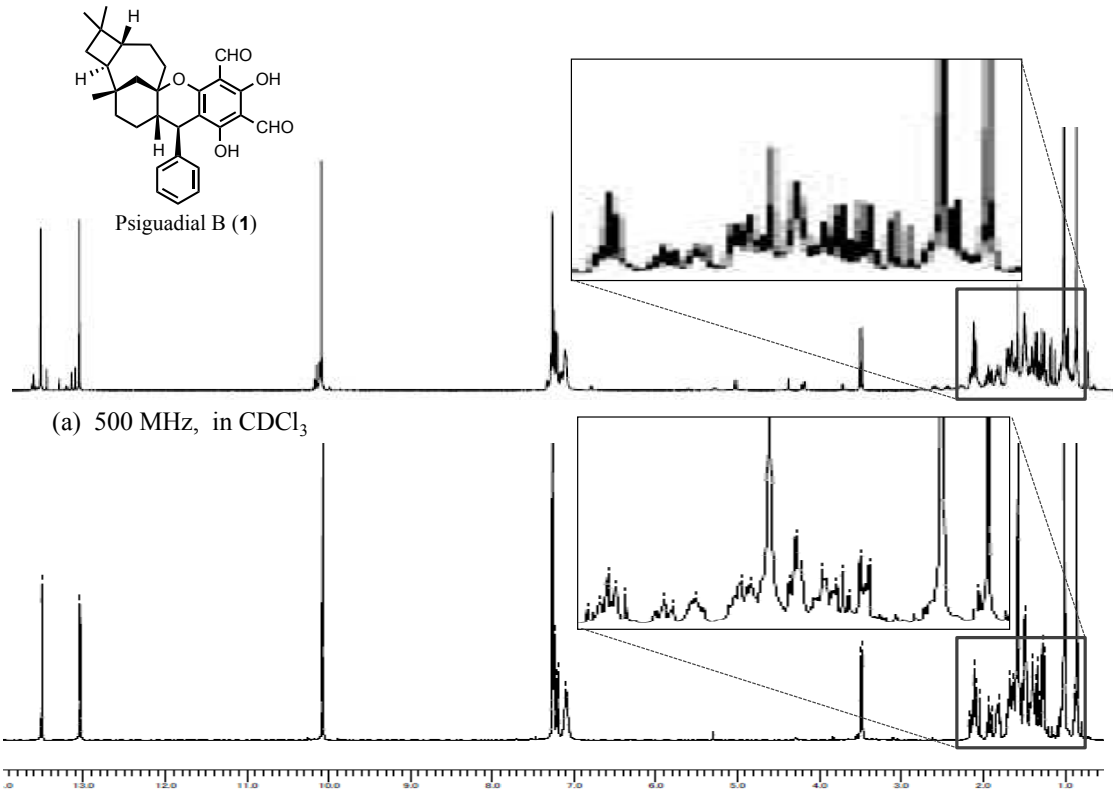


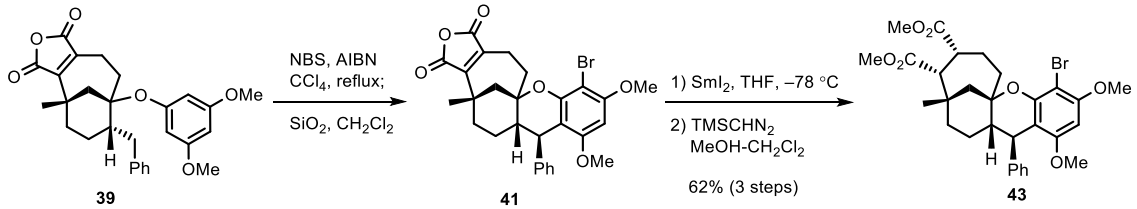
Figure 4. Comparison of 1H-NMR spectrums of **1**.

(a) the natural compound reported by Ye *et al*.[2b]

(b) the final product synthesized by the author

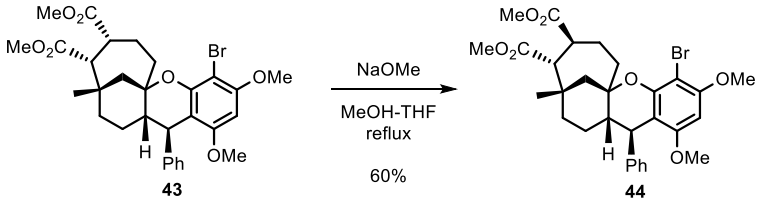
In conclusion, the author has accomplished the total synthesis of Psiguadial B starting from the key compound **41**. The stereochemistry of the C2 and C5 positions, at which the four-membered ring is fused with the bicyclo[4.3.1]decane skeleton, was controlled by the conjugate reduction of maleate **45** followed by epimerization to afford diester **47**. After constructing the four-membered ring by an intramolecular alkylation reaction of iodonitrile, the introduction of the two formyl groups via the corresponding divinyl compound afforded the natural compound **1**.

Experimental Section

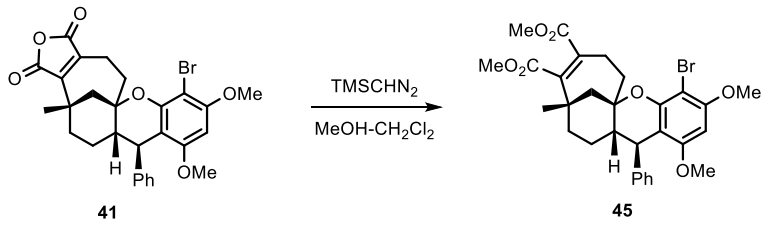


Compound 43 : To a solution of **39** (312 mg, 0.675 mmol) in CCl_4 (13 mL) were added NBS (240 mg, 1.35 mmol) and AIBN (111 mg, 0.675 mmol) at room temperature, then the reaction mixture was heated instantly and refluxed for 1 h under argon atmosphere. After cooling, silica gel (ca. 1 g) and CH_2Cl_2 (20 mL) were added to the mixture at 0 °C and stirred at room temperature for 10 min. The filtrate was concentrated under reduced pressure, and the crude product was through a short pad of silica gel to give **41** containing impurities.

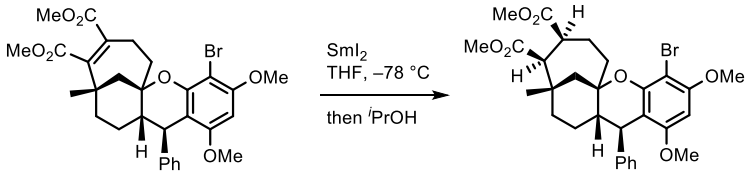
To a solution of **41** in THF (8.0 mL) was added SmI_2 (0.1 M in THF, 16.3 mL, 1.63 mmol) at -78 °C under argon atmosphere, and then the mixture was stirred for 40 min. After the reaction mixture was quenched with AcOH-THF (1:1, 1.6 mL) and warmed to room temperature, the organic layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (8 mL) and MeOH (8 mL). To the solution, $TMSCHN_2$ (2.0 M in Et_2O, 1.6 mL, 3.26 mmol) was added, and then the mixture was stirred at room temperature for 1.5 h under argon atmosphere. After the solvent was removed under reduced pressure, the residue was purified by silica gel columm chromatography (Hexane : AcOEt = 4:1→2:1) to give 246 mg of **43** as a white solid (62% from **39**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.18 (2H, m), 7.14-7.12 (1H, m), 7.07-7.03 (2H, m), 6.02 (1H, s), 3.85 (3H, s), 3.66 (3H, s), 3.65 (3H, s), 3.62 (1H, d, J = 12.0 Hz), 3.29 (1H, d, J = 5.2 Hz), 3.25 (3H, s), 2.82-2.79 (1H, m), 2.54-2.34 (4H, m), 1.84-1.78 (1H, m), 1.74-1.72 (1H, m), 1.55-1.52 (1H, m), 1.49-1.35 (3H, m), 1.32 (3H, s), 1.08 (1H, td, J = 13.9, 4.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.62, 174.31, 157.81, 155.99, 152.07, 145.76, 127.67, 125.54, 110.20, 92.36, 90.19, 79.79, 56.18, 55.43, 53.34, 52.14, 51.13, 49.88, 48.42, 45.57, 42.34, 37.02 (2C), 36.38, 34.28, 24.13, 23.19; HRMS (FD$^+$): Calcd for (M^+) $C_{30}H_{35}BrO_7$: 586.1566; found: 586.1551.



Compound 44 : To a solution of **43** (227 mg, 0.386 mmol) in THF (4 mL) and MeOH (4 mL) was added NaOMe (209 mg, 3.86 mmol) at 0 °C. The reaction mixture was refluxed for 2 h, and was quenched with a saturated aqueous NH_4Cl solution at 0 °C. After the organic layer was extracted with AcOEt, the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 4:1→3:1) to give 136 mg of **44** as a white solid (60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.19 (2H, m), 7.16-7.13 (1H, m), 7.05-7.04 (2H, m), 6.02 (1H, s), 3.85 (3H, s), 3.643 (3H, s), 3.639 (3H, s), 3.59 (1H, d, *J* = 10.9 Hz), 3.27 (3H, s), 2.98 (1H, t, *J* = 10.9 Hz), 2.69 (1H, d, *J* = 12.0 Hz), 2.53 (1H, d, *J* = 13.7 Hz), 2.07-1.78 (5H, m), 1.72-1.63 (3H, m), 1.38-1.30 (1H, m), 1.11 (3H, s), 0.97 (1H, td, *J* = 14.3, 5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.72, 174.42, 157.84, 155.96, 151.63, 145.56, 127.98, 125.63, 110.79, 93.01, 90.33, 79.76, 58.33, 56.19, 55.42, 52.01, 51.45, 50.21, 47.56, 47.40, 41.30, 36.33, 34.96, 33.70, 33.12, 27.35, 25.17; HRMS (FD$^+$): Calcd for (M^+) $C_{30}H_{35}BrO_7$: 586.1566; found: 586.1551.

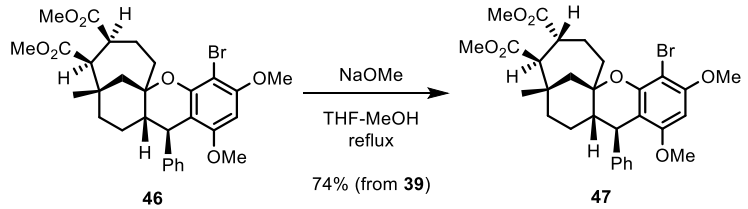


Compound 45 : To a solution of **41** (1.40 g, 1.88 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) was added $TMSCHN_2$ (2.0 M in Et_2O, 4.70 mL, 9.40 mmol) and stirred at room temperature for 4 h under argon atmosphere. After the solvent was removed under reduced pressure, the residue was through a short pad of silica gel to give 1.38 g of **45** containing impurities.



45 46

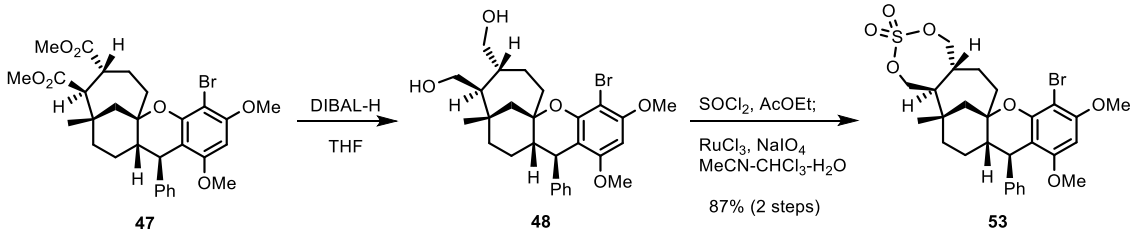
Compound 46 : To a solution of **41** (1.38 g, 1.88 mmol) in THF (19 mL) was added SmI_2 (0.1 M in THF, 47 mL, 4.70 mmol) at -78 ºC under argon atmosphere, and stirred for 1 h. After the reaction mixture was quenched with isopropanol followed by a saturated aqueous $NaHCO_3$ solution, the organic layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 20:1→9:1) to give 1.11 g of **46** as a white solid: m.p. 237-239 ºC; IR (ATR) ν 2944, 1732, 1598, 1568, 1454, 1434, 1407, 1344, 1206, 1162, 1117, 1096, 754, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.19 (2H, m), 7.16-7.13 (1H, m), 7.06-7.01 (2H, m), 6.01 (1H, s), 3.85 (3H, s), 3.69 (3H, s), 3.65 (3H, s), 3.53 (1H, d, *J* = 10.9 Hz), 3.25 (3H, s), 3.17 (1H, d, *J* = 13.2 Hz), 2.94 (1H, br), 2.81 (1H, d, *J* = 4.0 Hz), 2.55 (1H, br), 1.84-1.67 (6H, m), 1.45 (1H, d, *J* = 14.3 Hz), 1.37 (1H, q, *J* = 13.7 Hz), 1.27-1.20 (1H, m), 1.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.19, 173.45, 157.76, 156.06, 151.67, 145.71, 127.77, 125.63, 110.68, 93.26, 90.35, 80.03, 56.21, 55.45, 51.91, 51.32, 49.96, 45.34, 45.05, 43.23, 41.68, 39.70, 36.53, 31.03, 25.69, 25.64, 22.27; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{35}BrO_7$: 586.1566; found: 586.1592.



46 47

Compound 47 : To a suspension of **46** (1.11 g, 1.88 mmol) and 3AMS (ca. 400 mg) in THF (9 mL) and MeOH (9 mL) was added NaOMe (609 mg, 11.3 mmol) at 0 ºC, and stirred at room temperature for 30 min under argon atmosphere. The reaction mixture was refluxed for 6 h, and was quenched with a saturated aqueous NH_4Cl solution at 0 ºC. After the organic layer was extracted with AcOEt, the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 5:1→3:1) to give 819 mg of **47** as a white solid (74% from **39**): m.p. 271 ºC

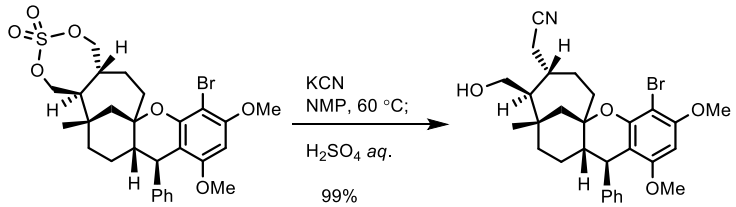
(dec.); IR (ATR) ν 2951, 1732, 1599, 1568, 1454, 1434, 1406, 1346, 1249, 1214, 1162, 1142, 1112, 1099, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (2H, m), 7.16-7.13 (1H, m), 7.06-7.01 (2H, m), 6.02 (1H, s), 3.85 (3H, s), 3.65 (3H, s), 3.62 (3H, s), 3.49 (1H, d, *J* = 11.5 Hz), 3.24 (3H, s), 3.10-3.07 (1H, m), 3.01 (1H, td, *J* = 12.0, 3.5 Hz), 2.30 (1H, q, *J* = 14.3 Hz), 2.18 (1H, d, *J* = 13.2 Hz), 2.05 (1H, d, *J* = 14.3 Hz), 1.84 (1H, t, *J* = 13.8 Hz), 1.76 (1H, td, *J* = 12.1, 4.0 Hz), 1.65-1.59 (2H, m), 1.56-1.48 (2H, m), 1.45 (1H, d, *J* = 13.7 Hz), 1.01 (1H, td, *J* = 13.8, 4.6 Hz), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.09, 174.11, 157.84, 156.07, 151.06, 145.57, 127.75, 125.57, 110.45, 92.93, 90.40, 79.03, 56.16, 55.39, 51.88, 51.34, 49.48, 46.80, 46.31, 41.79, 39.22, 36.54, 35.50, 26.84, 25.10, 23.94, 23.47; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{35}BrO_7$: 586.1566; found: 586.1551.



Compound 53 : To a solution of **47** (667 mg, 1.14 mmol) in THF (11 mL) was added DIBAL-H (1.02 M in Hexane, 5.57 mL, 5.68 mmol) at 0 ºC under argon atmosphere, and stirred at room temperature for 30 min. After the reaction mixture was quenched with ice (ca. 2 cc) at 0 ºC, and stirred vigorously over 30 min until the mixture became a colloid solution. Na_2SO_4 and AcOEt were then added to the solution, and stirred vigorously at room temperature for 30 min. After the resulting suspension was filtrated, the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **48** (685 mg) was used for next step without further purification.

To a solution of **48** (685 mg, 1.14 mmol) in AcOEt (60 mL) was slowly added $SOCl_2$ (124 μL, 1.71 mmol) at room temperature under argon atmosphere, and stirred for 20 min. After azeotropic removal of the solvent with toluene, $CHCl_3$ (11 mL), H_2O (11 mL) and MeCN (5.5 mL) were added to the crude product. $NaIO_4$ (473 mg, 2.28 mmol) and $RuCl_3 \cdot nH_2O$ (12.2 mg, ca. 0.0570 mmol) were added to the solution at 0 ºC, and stirred vigorously for 30 min. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $Na_2S_2O_3$ solution, the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 6:1→4:1) to give 589 mg of

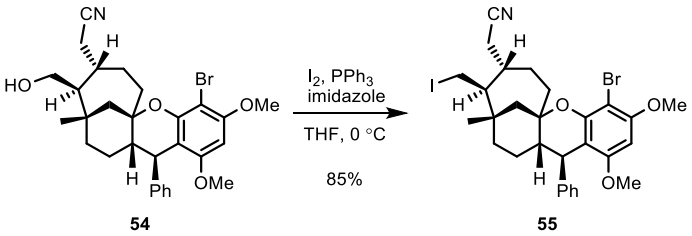
53 as a white solid (87% from **47**): m.p. 256 °C (dec.); IR (ATR) ν 2932, 2876, 2862, 1597, 1567, 1457, 1397, 1371, 1206, 1142, 1117, 1094, 975, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.21 (2H, m), 7.17-7.14 (1H, m), 7.06-7.01 (2H, m), 6.03 (1H, s), 4.42 (1H, t, *J* = 11.5 Hz), 4.24 (2H, t, *J* = 11.5 Hz), 4.11 (1H, dd, *J* = 12.6, 4.6 Hz), 3.85 (3H, s), 3.49 (1H, d, *J* = 10.9 Hz), 3.24 (3H, s), 2.38-2.31 (1H, m), 2.28 (1H, d, *J* = 13.8 Hz), 2.22-2.13 (2H, m), 1.81-1.57 (5H, m), 1.44-1.35 (1H, m), 1.40 (1H, d, *J* = 13.8 Hz), 1.05 (1H, td, *J* = 13.8, 4.6 Hz), 0.93 (1H, d, *J* = 12.6 Hz), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.90, 156.19, 150.99, 145.40, 127.87, 125.74, 110.30, 92.97, 90.50, 78.71, 73.48, 71.94, 56.23, 55.45, 49.56, 46.98, 41.79, 40.51, 35.69, 35.59, 33.16, 24.83, 24.54, 24.29, 21.75; HRMS (FD^+): Calcd for (M^+) $C_{28}H_{33}BrO_7S$: 592.1130; found: 592.1147.



53 **54**

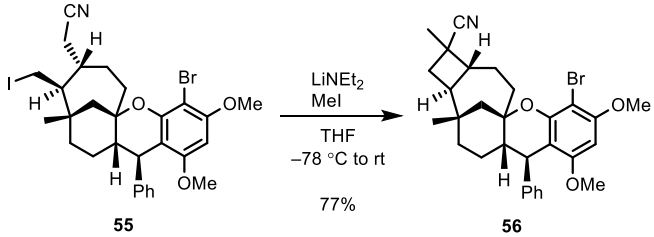
Compound 54 : To a suspension of **53** (100 mg, 0.168 mmol) and 4AMS (ca. 30 mg) in NMP (0.34 mL) was added KCN (110 mg, 1.68 mmol), and stirred at 60 °C for 18 h under argon atmosphere. After THF (5 mL) was added, the resulting suspension was filtrated through a pad of celite and washed with THF (15 mL). A 60% aqueous sulfuric acid (0.1 mL) was added to the filtrate at 0 °C, and stirred at room temperature for 2 h. After the reaction mixture was quenched with $NaHCO_3$ solid and dried over $MgSO_4$, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 3:2→2:1) to give 90.2 mg of **54** as a white solid (99%): m.p. 288-293 °C; IR (ATR) ν 3587, 2957, 2929, 2881, 2842, 1598, 1567, 1462, 1406, 1342, 1205, 1143, 1115, 1093, 751, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (2H, m), 7.16-7.13 (1H, m), 7.06-7.01 (2H, m), 6.02 (1H, s), 3.85 (3H, s), 3.80-3.77 (1H, m), 3.67-3.62 (1H, m), 3.50 (1H, d, *J* = 11.5 Hz), 3.24 (3H, s), 2.68 (1H, dd, *J* = 16.7, 6.3 Hz), 2.51 (1H, dd, *J* = 16.6, 4.6 Hz), 2.43-2.30 (1H, m), 2.22 (1H, d, *J* = 15.5 Hz), 2.20-2.16 (1H, m), 1.90-1.85 (2H, m), 1.76 (1H, td, *J* = 11.5, 4.0 Hz), 1.70-1.55 (3H, m), 1.43-1.39 (2H, m), 1.35 (1H, d, *J* = 13.8 Hz), 1.31 (1H, brs), 1.00 (1H, td, *J* = 13.8, 4.6 Hz), 0.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.87, 156.05, 151.25, 145.75, 127.75, 125.53, 120.02, 110.58, 93.00, 90.35, 79.28, 61.90, 56.20, 55.40, 49.73, 46.99, 41.87, 41.42, 36.48, 36.41, 30.08, 27.67, 25.54, 25.35, 25.00, 24.23; HRMS (FD^+): Calcd for (M^+)

$C_{29}H_{34}BrNO_4$: 539.1671; found: 539.1689.



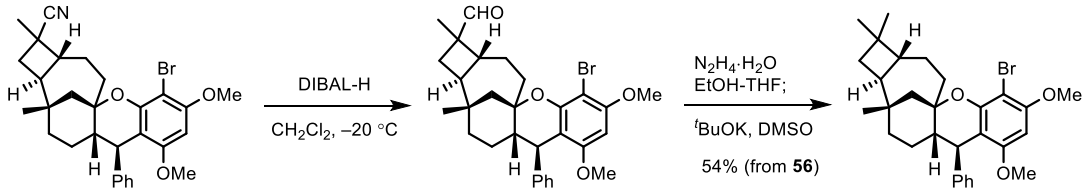
54 55

Compound 55 : To a solution of **54** (90.2 mg, 0.167 mmol), imidazole (34.1 mg, 0.501 mmol), and PPh_3 (63.8 mg, 0.251 mmol) in THF (3.3 mL) was added I_2 (65.7 mg, 0.251 mmol) at 0 ºC, and stirred at room temperature for 30 min under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $Na_2S_2O_3$ solution, the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 5:1→4:1) to give 92.3 mg of **55** as a white solid (85%): m.p. 227-230 ºC; IR (ATR) ν 3018, 2934, 2878, 2844, 1599, 1567, 1453, 1434, 1406, 1345, 1207, 1142, 1117, 1097, 752, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (2H, m), 7.16-7.13 (1H, m), 7.06-7.01 (2H, m), 6.02 (1H, s), 3.85 (3H, s), 3.52 (1H, d, *J* = 11.5 Hz), 3.35 (1H, d, *J* = 10.9 Hz), 3.24 (3H, s), 3.08 (1H, d, *J* = 12.0 Hz), 2.78 (1H, d, *J* = 16.6 Hz), 2.56 (1H, d, *J* = 16.6 Hz), 2.43-2.36 (1H, m), 2.24 (1H, d, *J* = 13.7 Hz), 2.10 (2H, br), 1.84 (1H, t, *J* = 13.8 Hz), 1.79-1.66 (3H, m), 1.58 (1H, d, *J* = 14.9 Hz), 1.45 (1H, d, *J* = 17.2 Hz), 1.39 (1H, d, *J* = 13.8 Hz), 1.02 (1H, td, *J* = 13.8, 4.6 Hz), 1.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.81, 156.04, 151.05, 145.53, 127.73, 125.55, 119.06, 110.41, 92.93, 90.37, 78.81, 56.16, 55.36, 49.64, 46.88, 41.68, 38.79, 36.81, 36.56, 32.64, 27.76, 25.61, 25.50, 25.42, 23.94, 6.34; HRMS (FD^+): Calcd for (M^+) $C_{29}H_{33}BrINO_3$: 649.0689; found: 649.0709.



55 56

Compound 56 : To a solution of **55** (190 mg, 0.292 mmol) in THF (13 mL) was slowly added $LiNEt_2$ (0.5 M in THF, 1.3 mL, 0.653 mmol) at -78 °C under argon atmosphere, and stirred for 3 min. After MeI (162 μL, 2.61 mmol) was added at the same temperature, the reaction mixture was warmed to 0 °C. The mixture was quenched with a saturated aqueous NH_4Cl solution, and the organic layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 6:1→4:1) to give 121 mg of **56** as a white solid (77%): m.p. 258 °C (dec.); IR (ATR) ν 3021, 2932, 2871, 1724, 1598, 1567, 1454, 1435, 1405, 1347, 1211, 1144, 1114, 1095, 752, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (2H, m), 7.15-7.13 (1H, m), 7.06-7.01 (2H, m), 6.01 (1H, s), 3.85 (3H, s), 3.48 (1H, d, *J* = 11.5 Hz), 3.22 (3H, s), 2.67-2.62 (1H, m), 2.38 (1H, q, *J* = 8.6 Hz), 2.15 (1H, t, *J* = 10.3 Hz), 2.06 (1H, d, *J* = 13.2 Hz), 1.91-1.82 (2H, m), 1.72 (2H, qd, *J* = 13.2, 3.5 Hz), 1.65-1.62 (1H, m), 1.57-1.52 (2H, m), 1.48-1.35 (3H, m), 1.40 (3H, s), 1.08 (1H, td, *J* = 13.2, 4.6 Hz), 0.90 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.80, 156.10, 151.36, 145.73, 127.75, 125.57, 124.83, 110.53, 93.02, 90.29, 80.52, 56.18, 55.42, 50.19, 47.21, 42.60, 41.96, 38.17, 37.34, 34.32, 33.30, 29.46, 27.96, 25.72, 23.93, 19.83, 16.65; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{34}BrNO_3$: 535.1722; found: 535.1739.

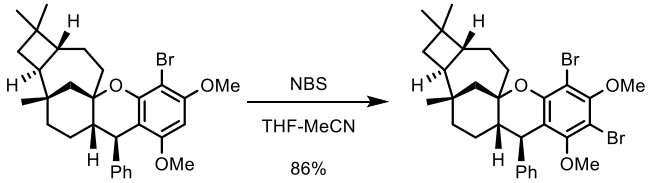


56 **57** **59**

Compound 59 : To a solution of **56** (51.2 mg, 0.0954 mmol) in CH_2Cl_2 (1 mL) was slowly added DIBAL-H (1.02 M in Hexane, 93.6 μL, 0.0954 mmol) at -50 °C under argon atmosphere, and stirred at -20 °C for 20 min. After being quenched with a saturated aqueous NH_4Cl solution, the mixture was stirred vigorously at room temperature for 30 min. A saturated aqueous Rochell's solution was then added, and the mixture was stirred vigorously at room temperature for 30 min. The organic layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. After the solution was concentrated under reduced pressure, the crude product **57** (50.5 mg) was used for next step without further purification.

To a solution of **57** (50.5 mg, 0.0954 mmol) in EtOH (1.5 mL) and THF (1.5 mL) was added $H_2NNH_2{\cdot}H_2O$ (93 μL, 1.91 mmol) in one shot at 0 °C, and stirred at room temperature for 1 h under argon atmosphere. After azeotropic removal of the solvent with toluene, the resulting crude hydrazone was dissolved in DMSO (1 mL) and added to a solution of KO^{t}Bu (161 mg,

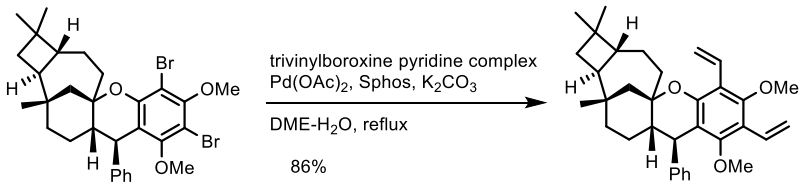
1.43 mmol) in DMSO (1 mL) dropwise over 1.5 h at room temperature under argon atmosphere. The reaction mixture was then stirred for several hours until generation of nitrogen disappeared, and quenched with a saturated aqueous NH_4Cl solution. The organic layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. After concentrated under reduced pressure, the crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 9:1) to give 27.2 mg of **59** with a small amount of the debrominated product as a white solid (54% from **56**): m.p. 230 ºC (dec.); IR (ATR) ν 2955, 2921, 2865, 1727, 1595, 1565, 1456, 1406, 1349, 1274, 1208, 1144, 1114, 1096, 929, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.19 (2H, m), 7.14-7.12 (1H, m), 7.06-7.01 (2H, m), 6.00 (1H, s), 3.84 (3H, s), 3.50 (1H, d, *J* = 11.5 Hz), 3.22 (3H, s), 2.17-2.10 (2H, m), 1.86-1.75 (2H, m), 1.72-1.68 (2H, m), 1.54-1.45 (4H, m), 1.36-1.24 (4H, m), 1.06-1.01 (1H, m), 0.99 (3H, s), 0.98 (3H, s), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.81, 155.94, 151.79, 146.15, 127.66, 125.40, 110.95, 93.04, 90.09, 81.53, 56.16, 55.41, 50.43, 47.69, 44.16, 42.10, 37.78, 36.99, 35.47, 34.96, 33.28, 30.61, 28.26, 26.13, 24.09, 20.74, 20.06; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{37}BrO_3$: 524.1926; found: 524.1938.



59 61

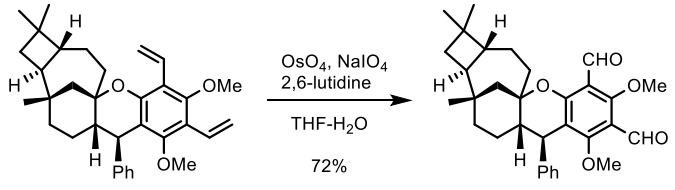
Compound 61 : To a solution of **59** (23.1 mg, 0.0488 mmol) in THF (1.0 mL) and MeCN (0.25 mL) was added NBS (17.4 mg, 0.0976 mmol) at 0 ºC, and stirred at room temperature for 1 h under argon atmosphere. After the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $Na_2S_2O_3$ solution, the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 20:1) to give 25.4 mg of **61** as a white solid (86%): m.p. 102-108 ºC; IR (ATR) ν 2935, 2865, 1568, 1541, 1453, 1393, 1342, 1198, 1143, 1087, 988, 973, 941, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (2H, m), 7.20-7.17 (1H, m), 7.13-7.04 (2H, m), 3.87 (3H, s), 3.57 (1H, d, *J* = 11.5 Hz), 3.08 (3H, s), 2.14-2.09 (2H, m), 1.88-1.81 (1H, m), 1.75-1.64 (3H, m), 1.49-1.42 (4H, m), 1.38-1.28 (4H, m), 1.05-1.01 (1H, m), 0.994 (3H, s), 0.988 (3H, s), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.01, 154.28, 151.35, 144.98, 128.23 (2C), 126.26, 119.92, 103.97, 103.77, 81.89, 60.52, 59.59, 50.48, 47.56, 44.08, 42.85, 37.68, 36.94,

35.43, 34.98, 33.28, 30.60, 28.31, 26.10, 24.00, 20.76, 20.02; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{36}Br_2O_3$: 602.1031; found: 602.1046.



61 68

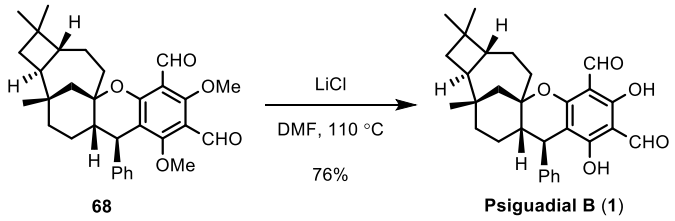
Compound 68 : To a solution of **61** (25.4 mg, 0.0420 mmol) in DME (0.3 mL) and H_2O (0.1 mL) were added trivinylboroxine pyridine complex (30.3 mg, 0.126 mmol), $Pd(OAc)_2$ (0.94 mg, 0.00420 mmol), SPhos (3.4 mg, 0.00840 mmol), and K_2CO_3 (17.4 mg, 0.126 mmol). The mixture was sonicated under argon atmosphere, and refluxed for 3 h. After cooling, the organic layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 20:1) to give 18.2 mg of **68** as a colorless oil (86%): IR (ATR) ν 3026, 2946, 2863, 1620, 1568, 1452, 1408, 1381, 1192, 1128, 1099, 1055, 1033, 1005, 978, 913, 755, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.23 (2H, m), 7.17-7.14 (1H, m), 7.13-7.07 (2H, m), 6.87 (1H, dd, *J* = 18.0, 12.3 Hz), 6.60 (1H, dd, *J* = 18.0, 11.7 Hz), 6.15 (1H, dd, *J* = 18.0, 2.6 Hz), 5.79 (1H, dd, *J* = 18.3, 2.3 Hz), 5.41 (1H, dd, *J* = 12.3, 2.6 Hz), 5.29 (1H, dd, *J* = 12.0, 2.3 Hz), 3.65 (3H, s), 3.55 (1H, d, *J* = 11.5 Hz), 2.98 (3H, s), 2.18-2.10 (1H, m), 2.05 (1H, d, *J* = 12.6 Hz), 1.85-1.75 (2H, m), 1.71-1.43 (6H, m), 1.37-1.25 (4H, m), 1.05-1.01 (1H, m), 0.99 (6H, s), 0.83 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.29, 157.11, 153.06, 146.20, 128.34, 127.96, 127.77, 125.76, 117.86, 117.55, 117.27, 117.02, 116.05, 80.36, 60.02, 59.14, 50.48, 47.76, 44.12, 42.44, 37.75, 36.86, 35.43, 35.00, 33.18, 30.62, 28.21, 26.16, 24.08, 20.76, 20.17; HRMS (FD^+): Calcd for (M^+) $C_{34}H_{42}O_3$: 498.3134; found: 498.3115.



68 62

Compound 62 : To a solution of **68** (18.2 mg, 0.0365 mmol), 2,6-lutidine (130 μL, 0.146 mmol),

$NaIO_4$ (62.5 mg, 0.292 mmol) in THF (0.45 mL) and H_2O (0.15 mL) was added OsO_4 (0.157 M in ^{t}BuOH, 23.2 μL, 0.00365 mmol) at 0 °C, and stirred at room temperature for 3 h. After the reaction was complete, the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel columm chromatography (Hexane : AcOEt = 6:1) to give 13.3 mg of **62** as a colorless oil (72%): IR (ATR) ν 2946, 2866, 1683, 1556, 1454, 1383, 1298, 1250, 1231, 1197, 1121, 1075, 1032, 1011, 993, 752, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (1H, s), 10.16 (1H, s), 7.30-7.26 (2H, m), 7.21-7.18 (1H, m), 7.13-7.04 (2H, m), 3.97 (3H, s), 3.59 (1H, d, *J* = 11.5 Hz), 2.97 (3H, s), 2.14-2.07 (2H, m), 1.90-1.79 (2H, m), 1.75-1.46 (6H, m), 1.38-1.26 (4H, m), 1.05-1.01 (1H, m), 1.000 (3H, s), 0.996 (3H, s), 0.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.82, 187.64, 166.18, 165.78, 163.10, 144.87, 128.37, 126.35, 117.98, 115.82, 115.20, 83.26, 65.05, 61.97, 49.74, 47.39, 44.08, 41.73, 37.64, 37.07, 35.44, 35.01, 33.39, 30.57, 29.09, 26.09, 23.97, 20.73, 20.19; HRMS (FD^+): Calcd for (M^+) $C_{32}H_{38}O_5$: 502.2719; found: 502.2724.



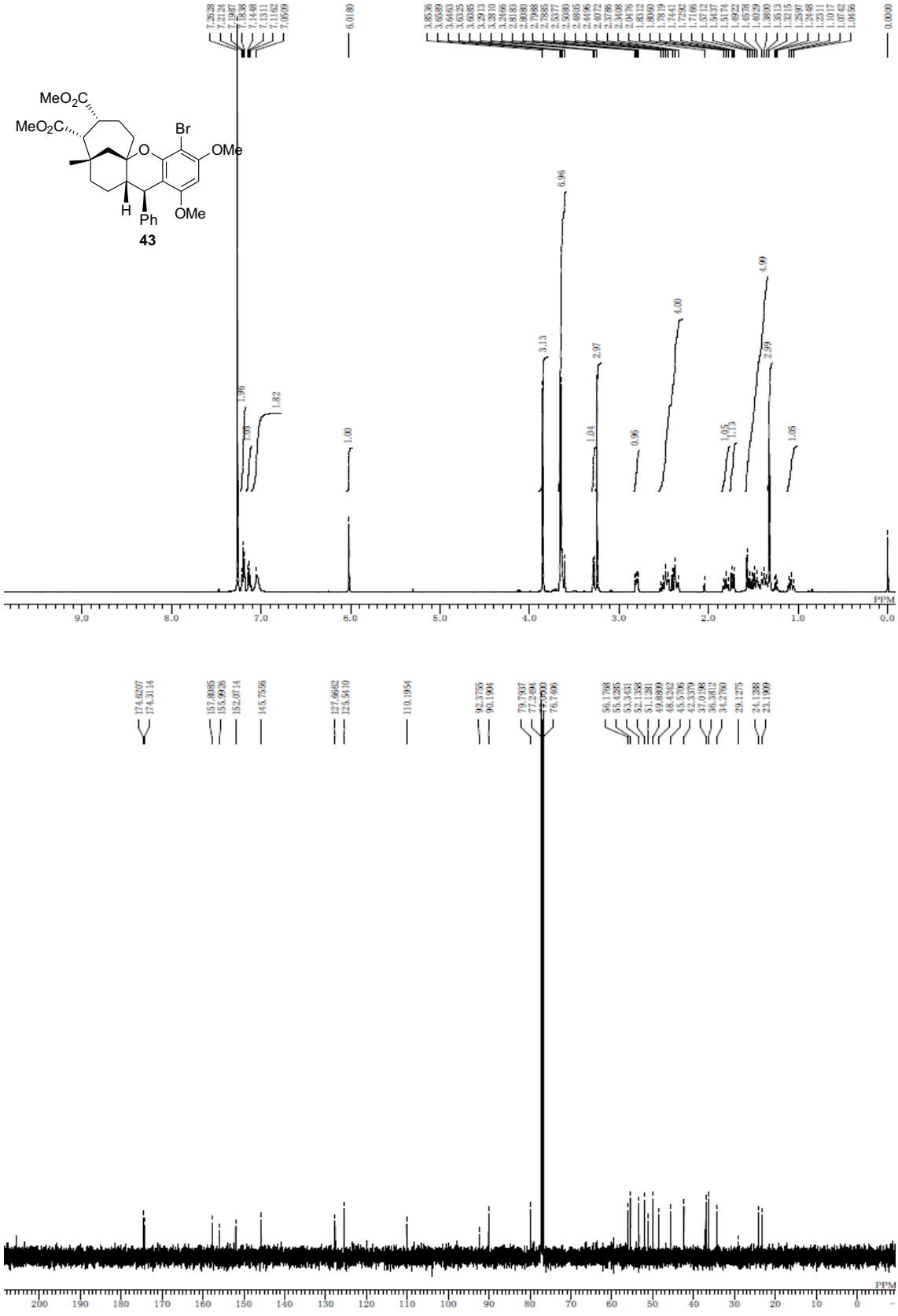
68 **Psiguadial B (1)**

Compound 1: To a solution of **68** (24.7 mg, 0.0491 mmol) in DMF (0.5 mL) was added LiCl (41.7 mg, 0.983 mmol), and stirred at 110 °C for 3 h. After cooling, the reaction mixture was quenched with a 0.1% aqueous HCl solution. The organic layer was extracted with $CHCl_3$, and the combined organic layers were dried over $MgSO_4$. After concentrated under reduced pressure, the crude product was purified by preparative thin layer chromatography (Hexane : CH_2Cl_2 = 1:1) to give 17.6 mg of **1** as a white solid (76%): m.p. 251-253 °C; IR (ATR) ν 2948, 2865, 1627, 1436, 1383, 1299, 1270, 1231, 1183, 1154, 849, 755, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.51 (1H, s), 13.04 (1H, s), 10.07 (2H, s), 7.27-7.24 (2H, m), 7.22-7.19 (1H, m), 7.14-7.07 (2H, m), 3.49 (1H, d, *J* = 11.7 Hz), 2.17-2.08 (2H, m), 1.92 (1H, t, *J* = 15.1 Hz), 1.84-1.79 (1H, m), 1.70-1.63 (3H, m), 1.51-1.47 (3H, m), 1.43-1.31 (3H, m), 1.26 (1H, d, *J* = 13.1 Hz), 1.05-1.01 (1H, m), 1.010 (3H, s), 1.006 (3H, s), 0.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.36, 191.53, 169.66, 168.53, 163.51, 143.41, 128.18, 126.23, 105.72, 104.65, 104.15, 84.14 50.02, 47.45, 44.05, 40.39, 37.61, 36.93, 35.43, 35.09, 33.46, 30.62, 29.37, 26.09, 23.90, 20.75, 20.12; HRMS (FD^+): Calcd for (M^+) $C_{30}H_{34}O_5$: 474.2406; found: 474.2421.

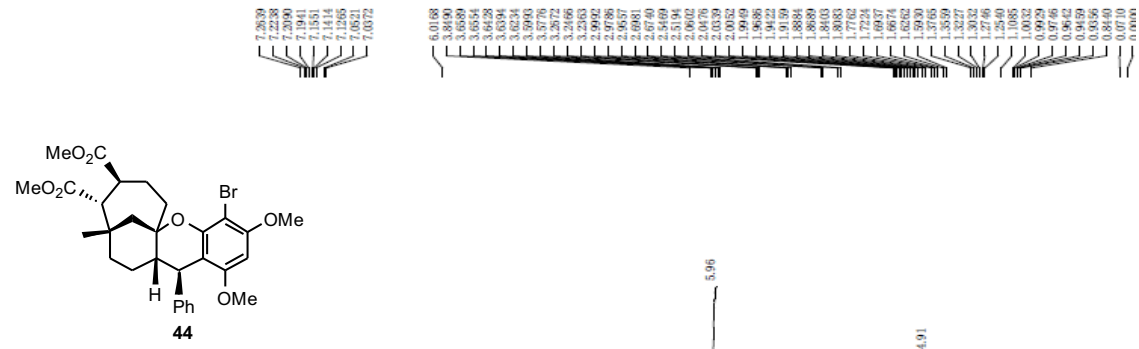
Comparison of our data for Psiguadial B with literature

1H-NMR		13C-NMR	
Ye's group[2b]	Our group	Ye's group[2b]	Our group
0.86 (3H, s)	0.86 (3H, s)	20.1	20.12
1.01 (3H, s)	1.006 (3H, s)	20.7	20.75
1.02 (3H, s)	1.010 (3H, s)	23.9	23.90
1.10 (1H)	1.05-1.01 (1H, m)	26.1	26.09
1.29 (1H)	1.26 (1H, d, *J* = 13.1 Hz)	29.4	29.37
1.37 (1H), 1.41 (1H, m), 1.41 (1H)	1.43-1.31 (3H, m)	30.6	30.62
	1.51-1.47 (3H, m)	33.4	33.46
1.49 (2H, m), 1.52 (1H)	1.70-1.63 (3H, m)	35.1	35.09
1.58 (1H), 1.65 (1H, m), 1.68 (1H)	1.84-1.79 (1H, m)	35.5	35.43
	1.92 (1H, t, *J* = 15.1 Hz)	37.0	36.93
1.82 (1H, m)	2.17-2.08 (2H, m)	37.6	37.61
1.93 (1H)	3.49 (1H, d, *J* = 11.7 Hz)	40.4	40.39
2.08 (1H), 2.16 (1H)	7.14-7.07 (2H, m)	44.1	44.05
3.49 (1H, d, *J* = 11.5 Hz)	7.22-7.19 (1H, m)	47.5	47.45
7.18 (2H)	7.27-7.24 (2H, m)	50.0	50.02
7.18 (1H)	10.07 (2H, s)	84.1	84.14
7.23 (2H, m)	13.04 (1H, s)	104.2	104.15
10.08 (2H, s)	13.51 (1H, s)	104.6	104.65
13.04 (1H, s)		105.7	105.72
13.51 (1H, s)		126.2	126.23
		128.2	128.18
		143.4	143.41
		163.5	163.51
		168.5	168.53
		169.6	169.66
		191.4	191.53
		192.3	192.36

Compound 43



Compound 44



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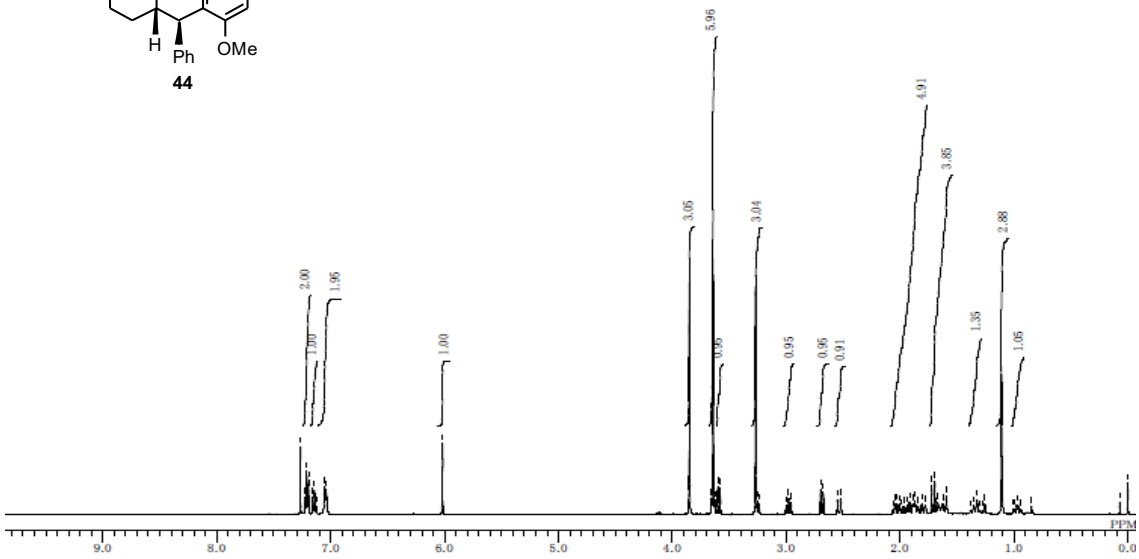
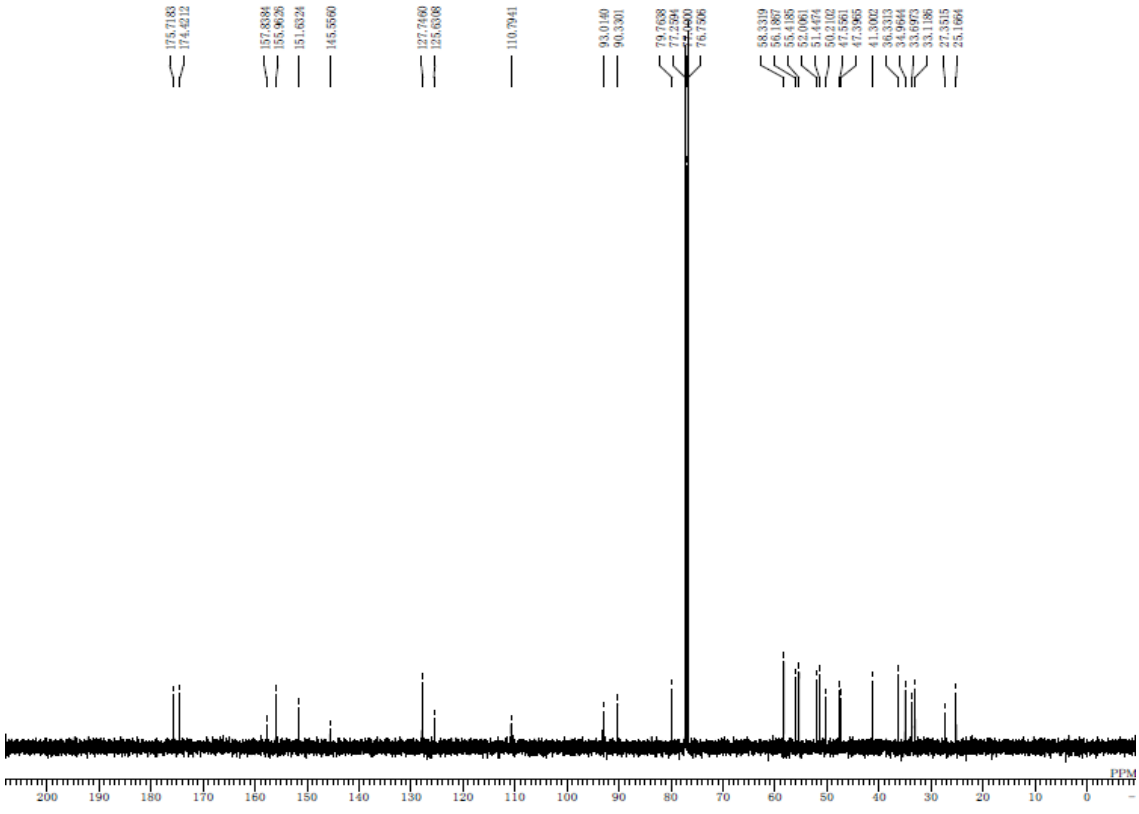
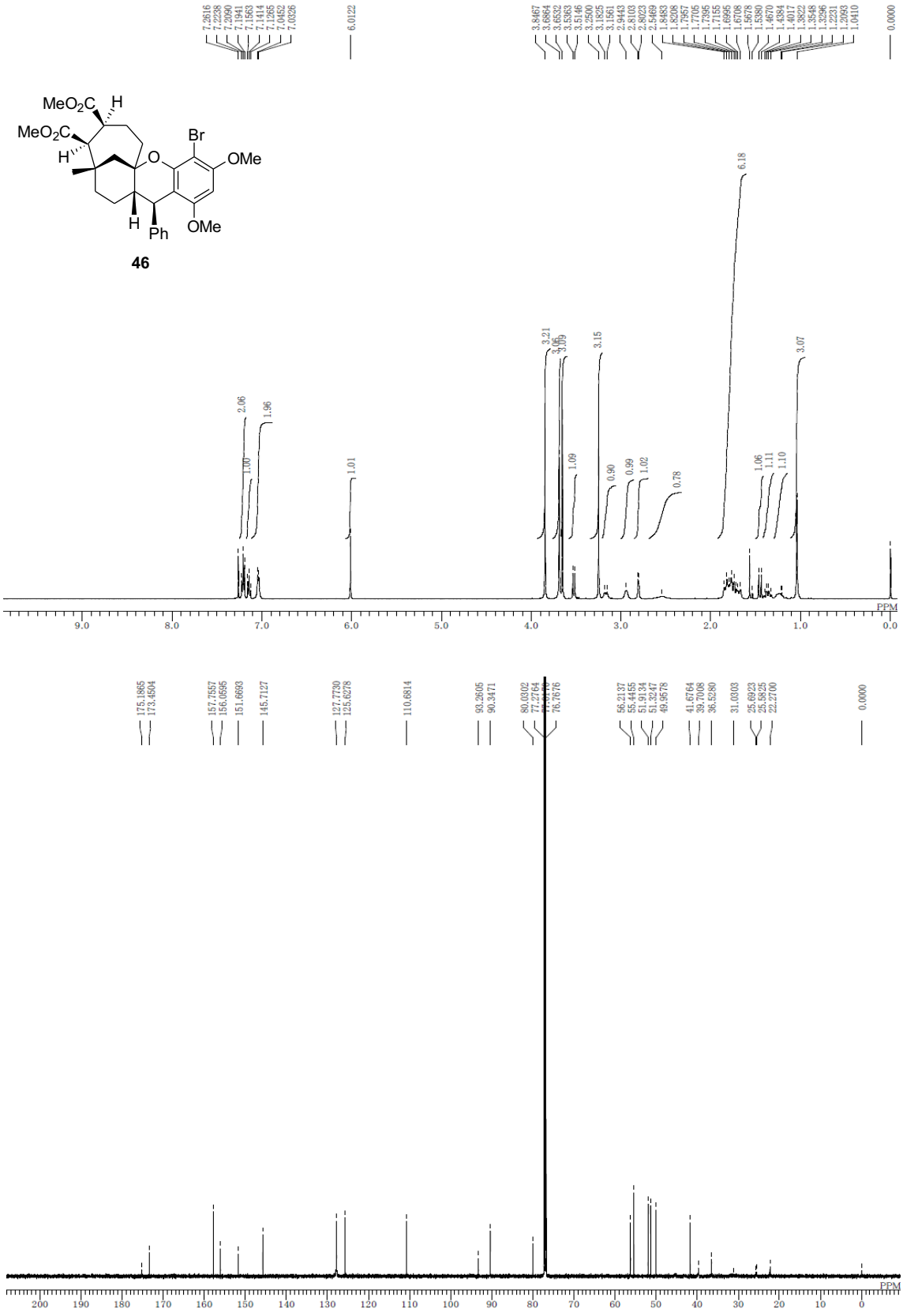
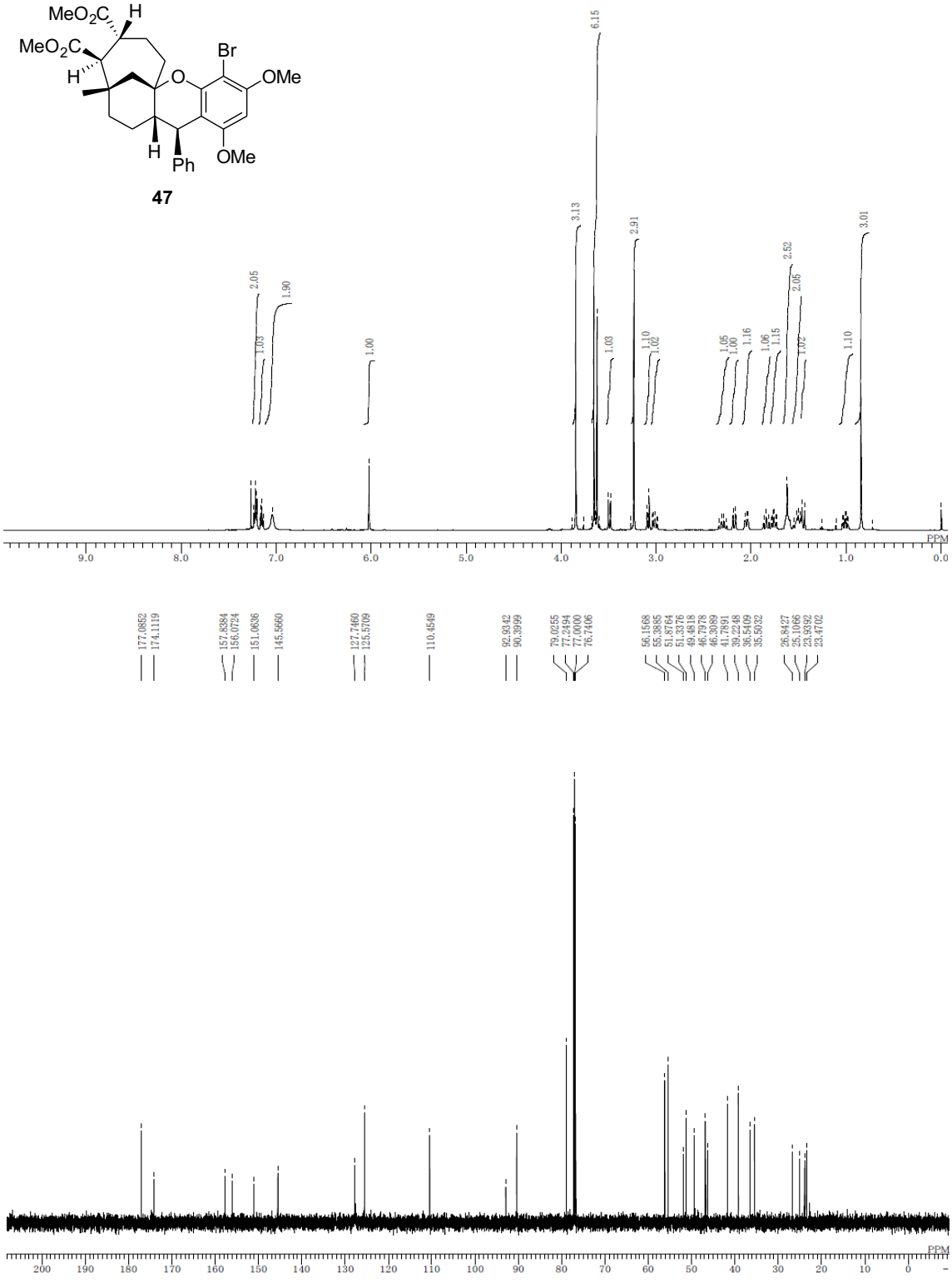




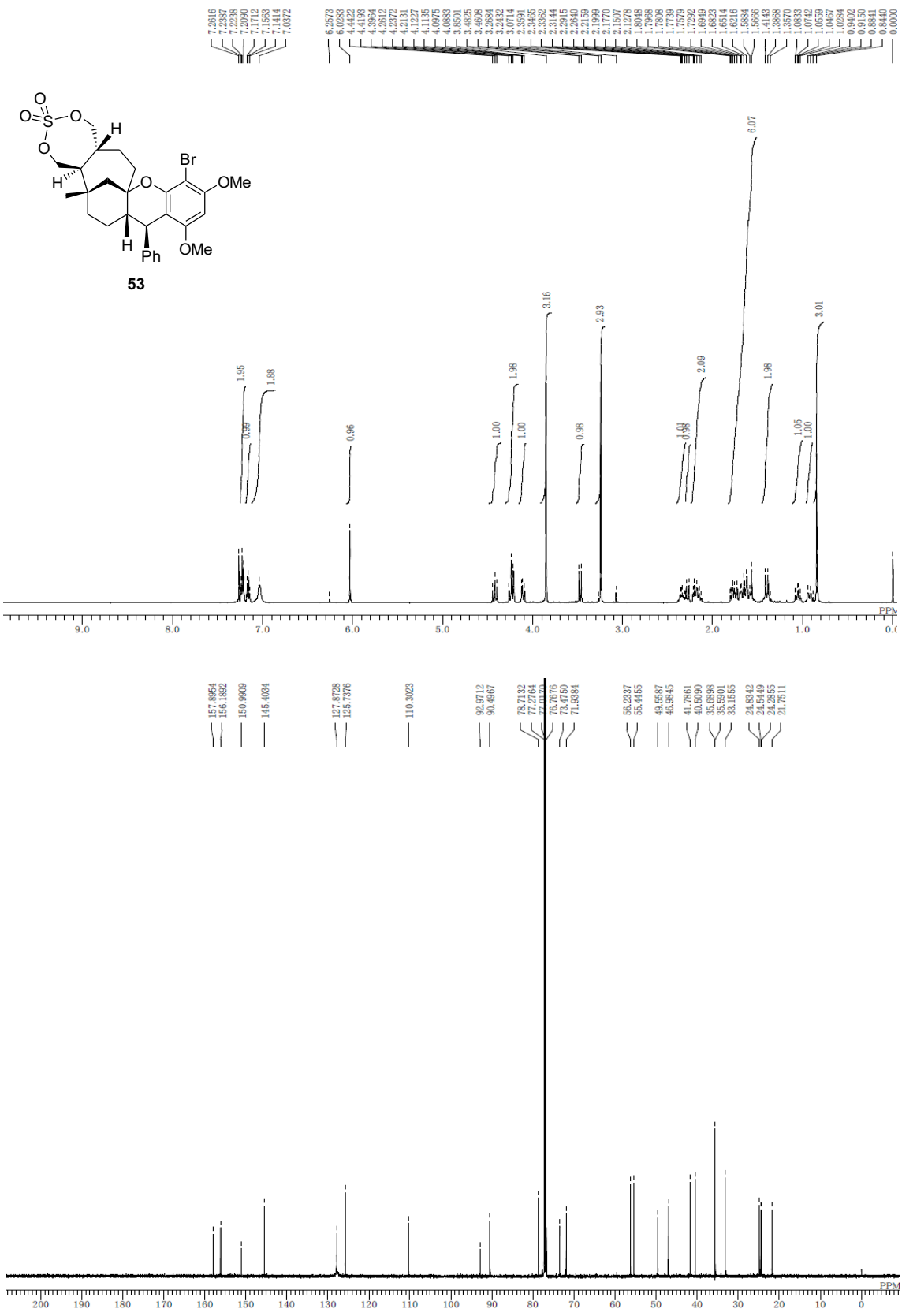
Compound 46



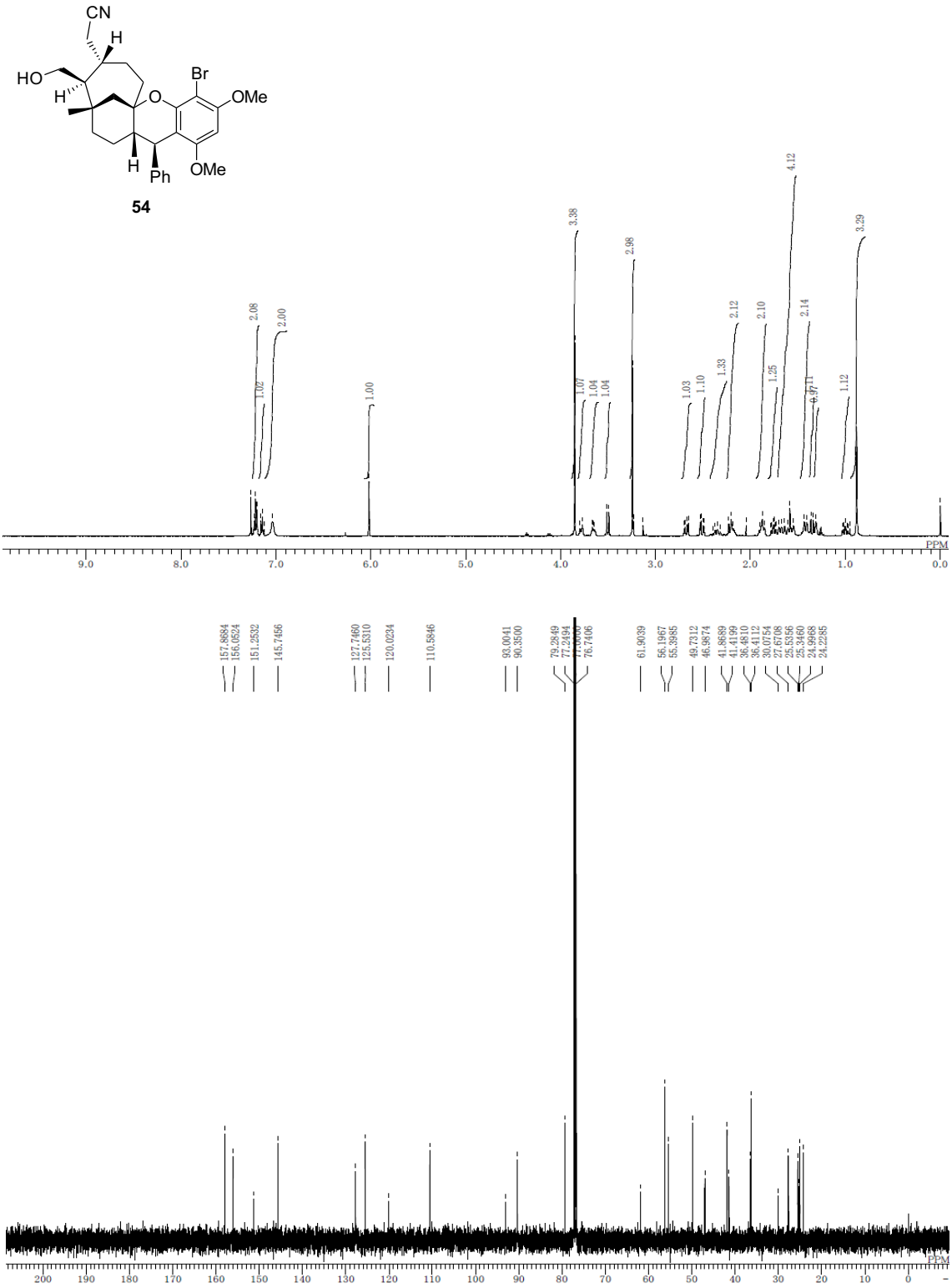
Compound 47



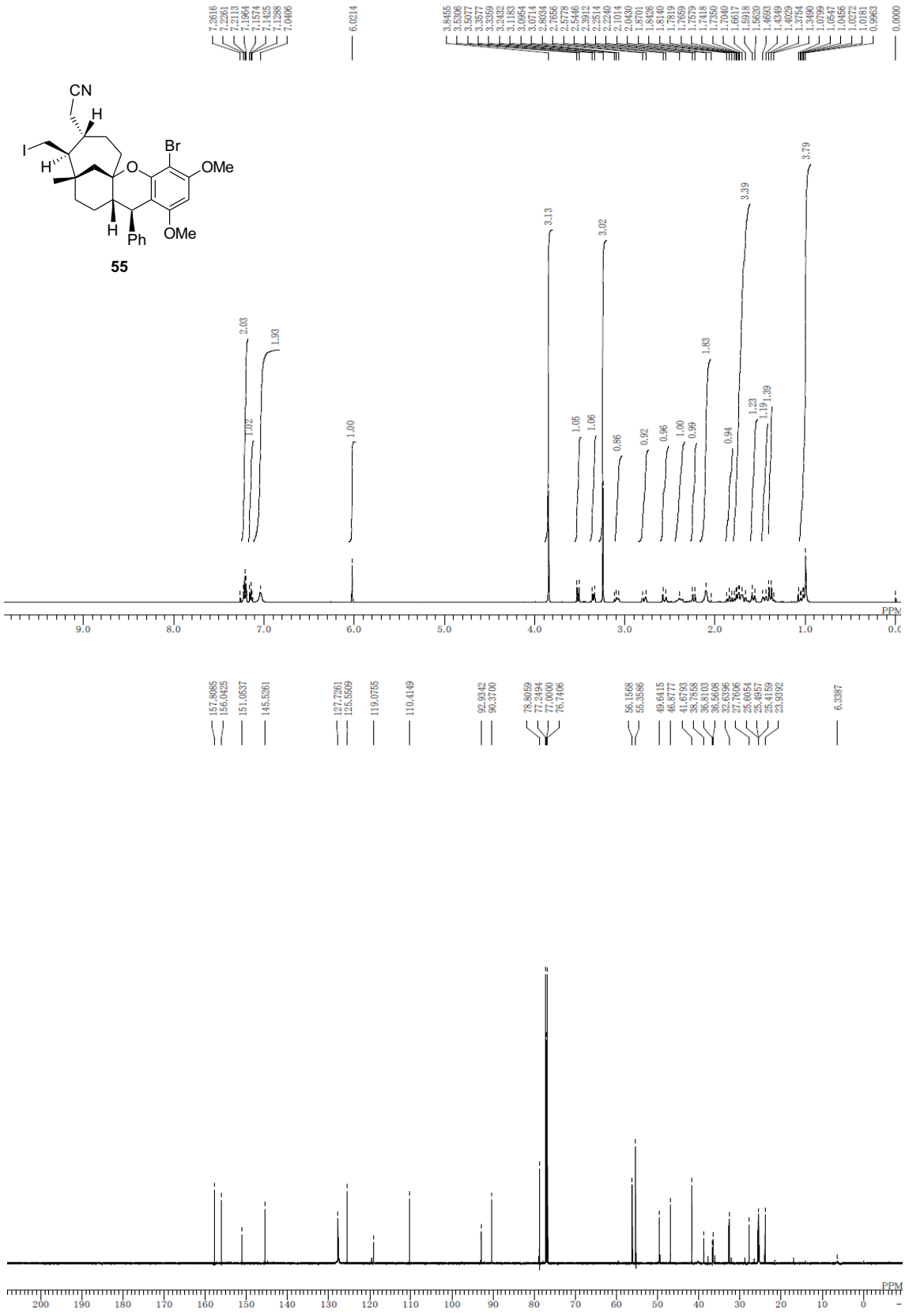
Compound 53



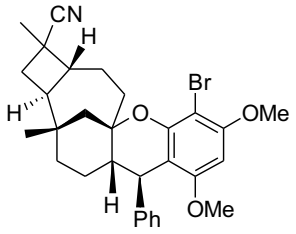
Compound 54



Compound 55

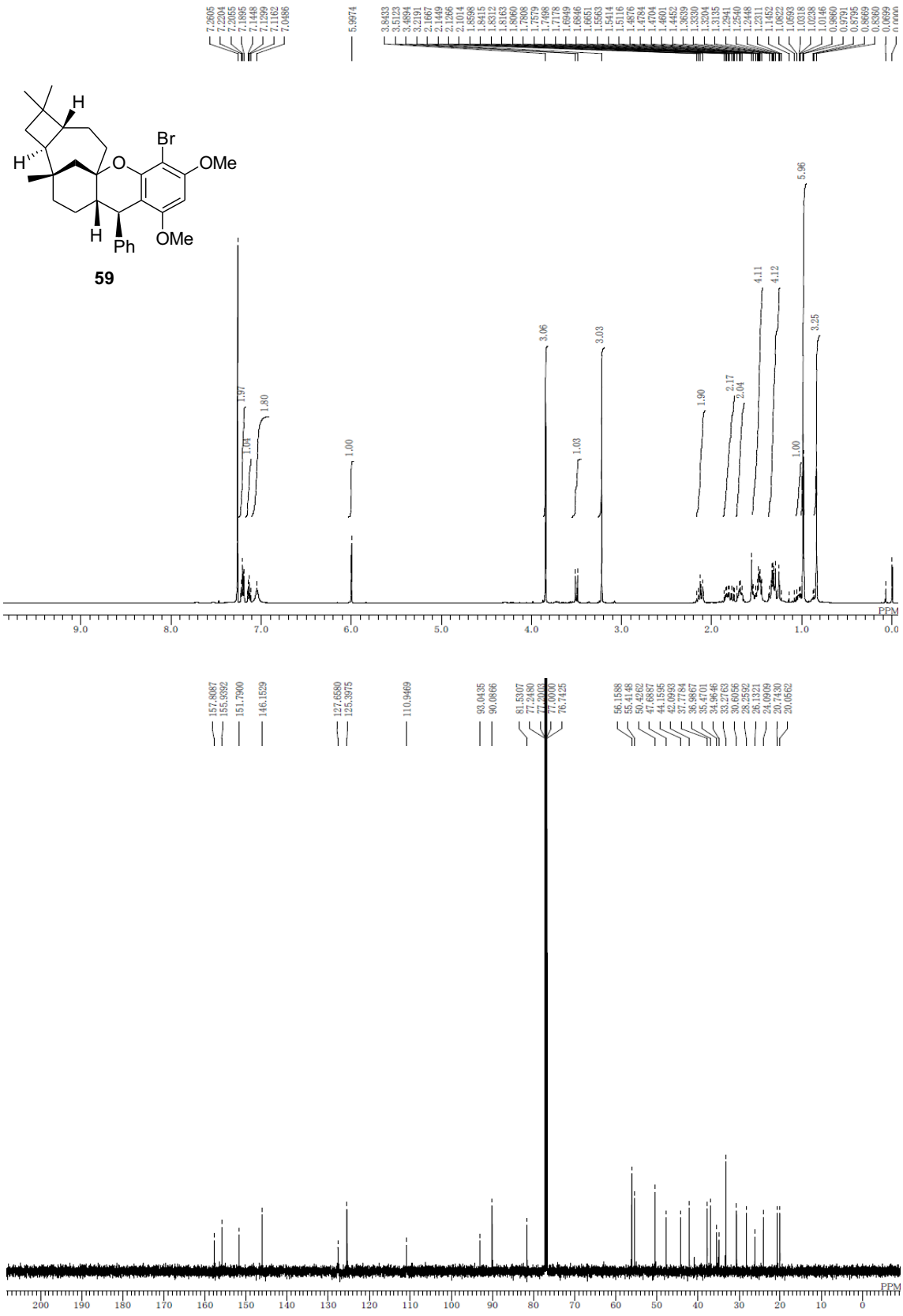


Compound 56

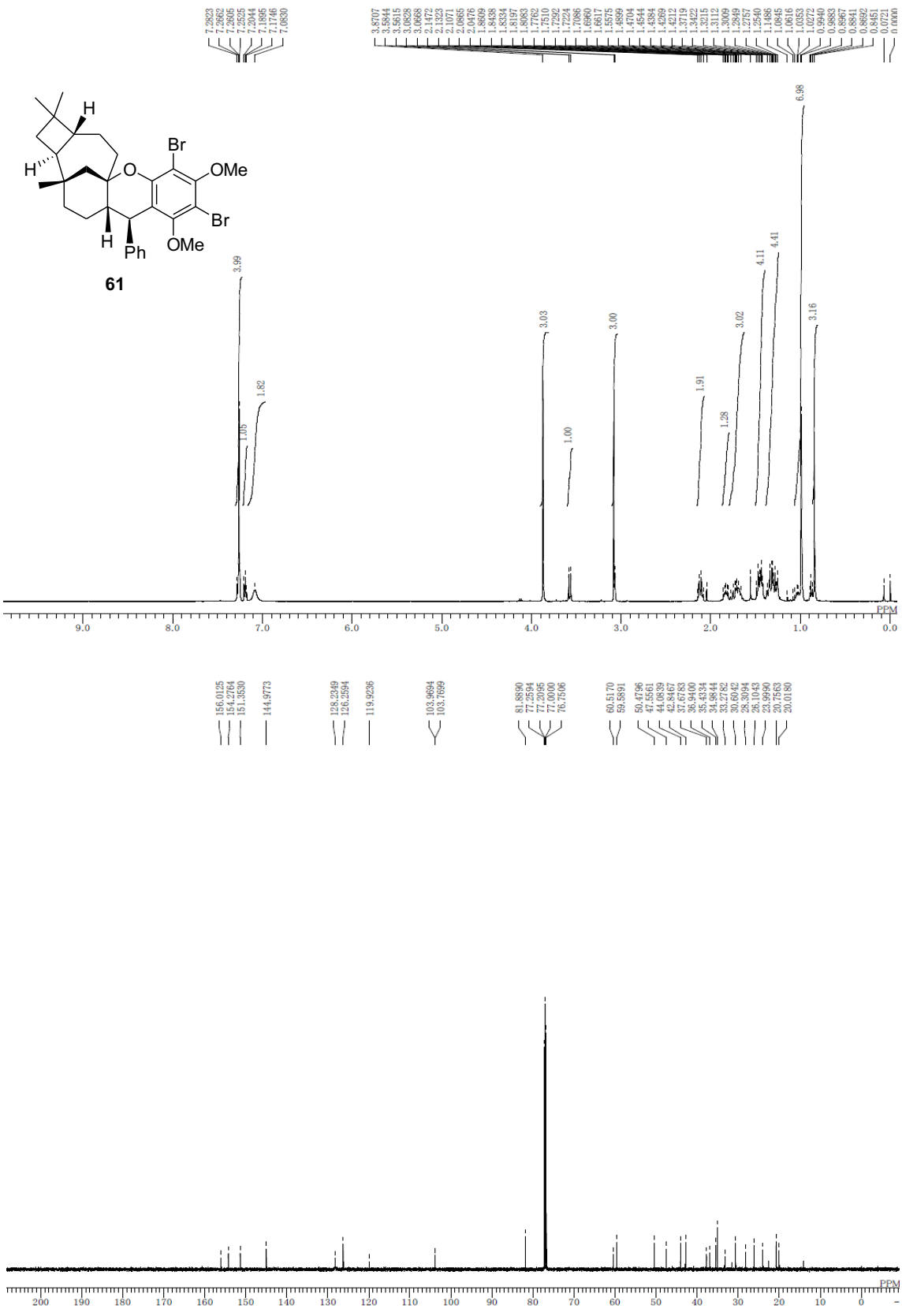


56

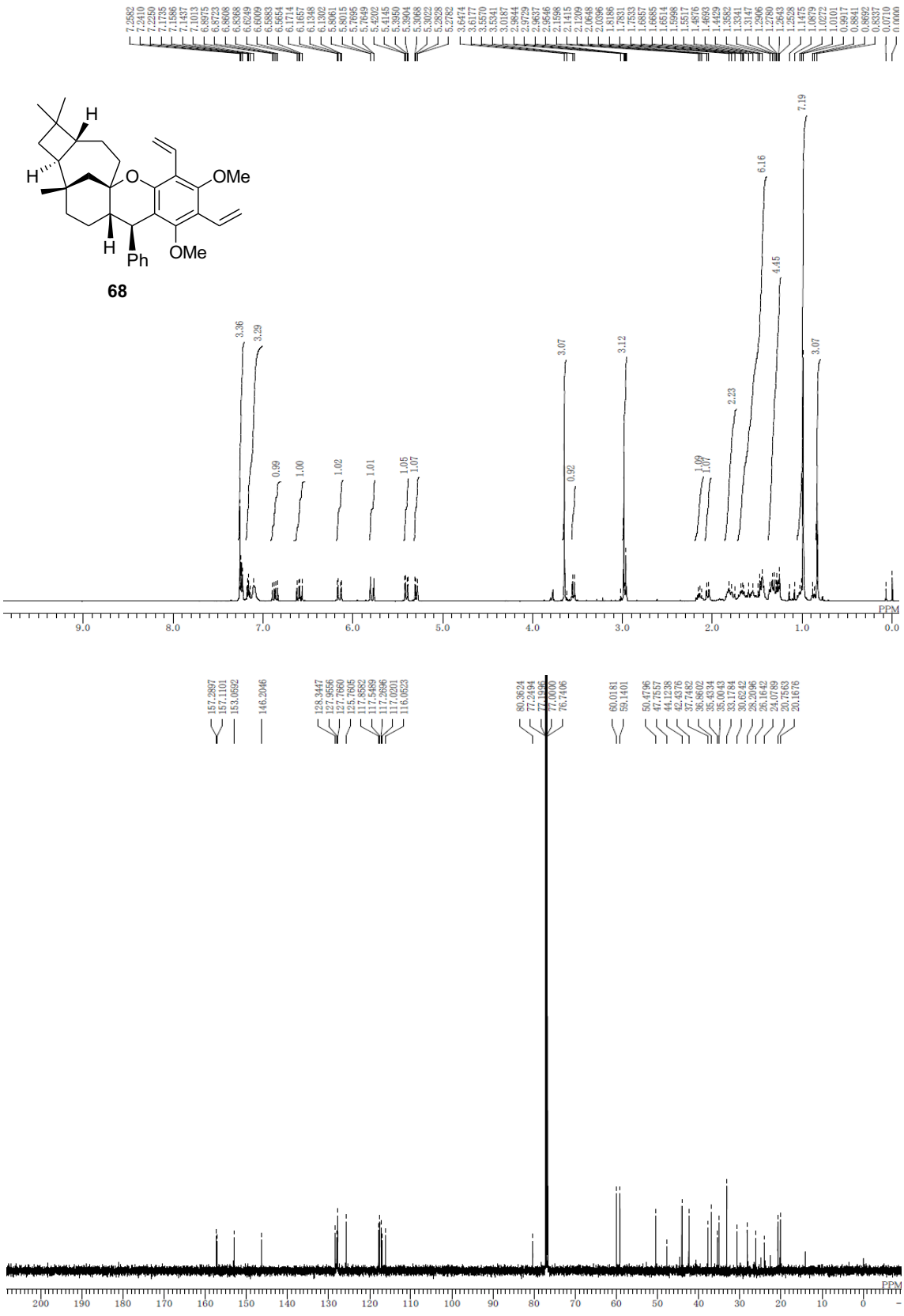
Compound 59



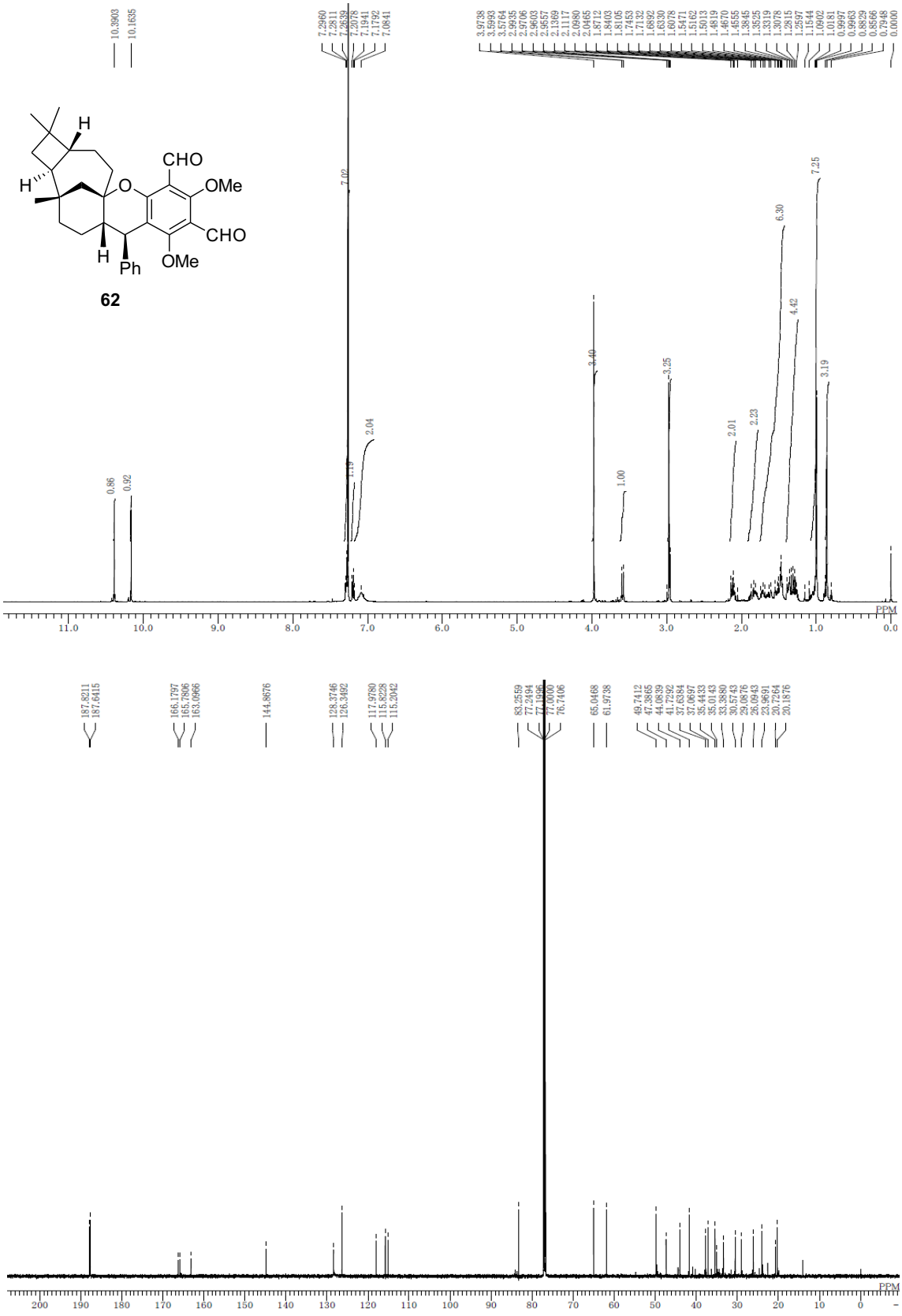
Compound 61



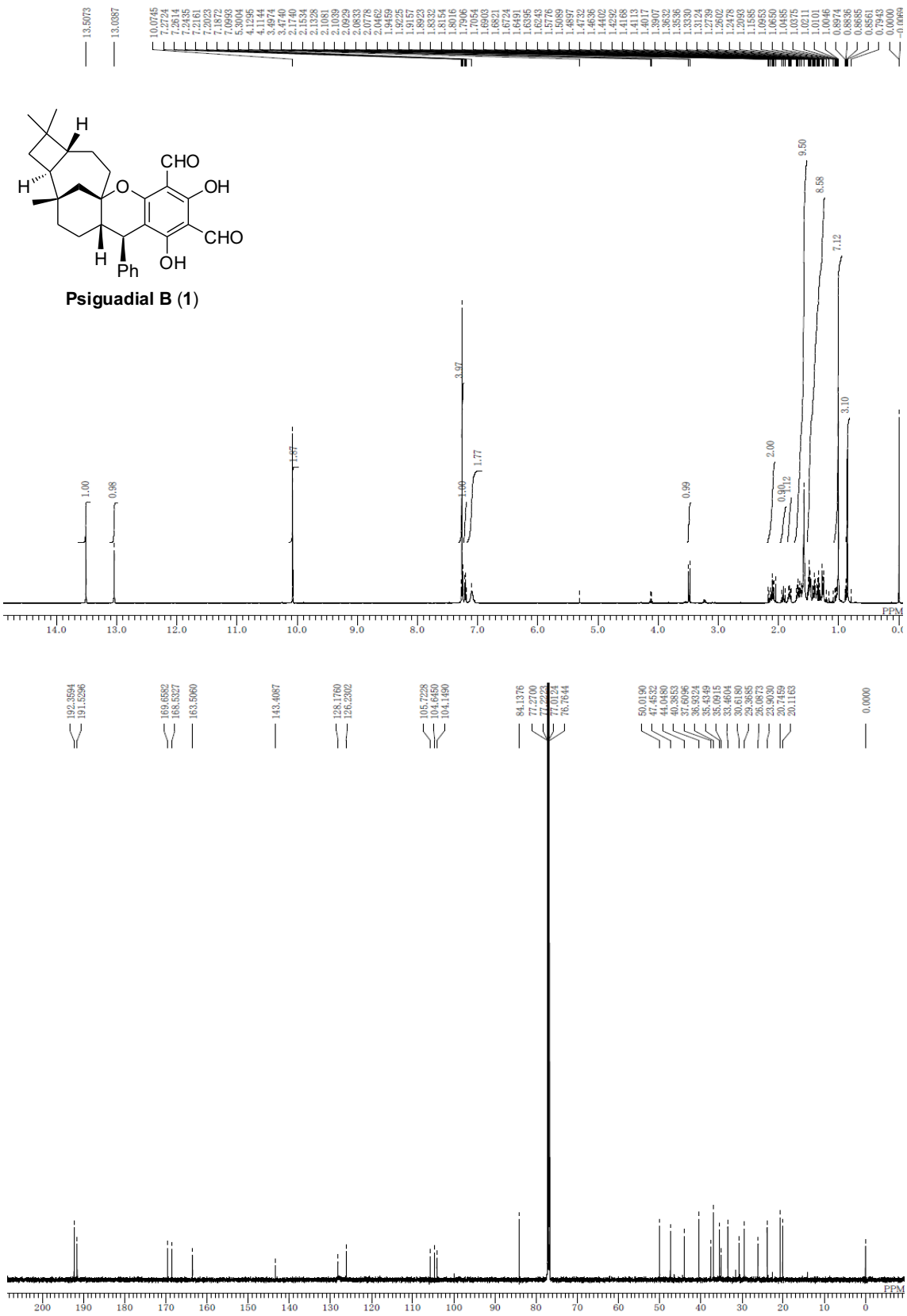
Compound 68



Compound 62



Compound 1



Conclusion

The author has accomplished the total synthesis of Psiguadial B (**1**), a meroterpenoid isolated from *Psidium guajava* L. While the bioactivities of **1** including an antitumor activity and a physiological activity have attracted much attention from organic chemists, its complex polycyclic structure required the use of new synthetic methods for achieving the total synthesis.

In chapter I, the author has developed a cascade double cyclization reaction of an acetylenedicobalt complex, which afforded the bicyclo[4.3.1]decane derivative with a benzyl group with correct configuration. The substituted aromatic ring was introduced to the bridgehead position of the intermediate, and bromination under radical conditions followed by intramolecular cyclization reaction resulted in formation of the benzopyran moiety in a stereoselective manner. The resulting compound possesses the polycyclic core skeleton of **1**.

In chapter II, a practical method for constructing the dimethylcyclobutane moiety was developed through conjugate reduction of a maleate ester. The configuration of C2 and C5 positions, at which the four-membered ring is fused with the bicyclo[4.3.1]decane skeleton, was controlled by stereoselective reduction with samarium(II) iodide followed by epimerization. Dimethylcyclobutane moiety of **1** was constructed via intramolecular cyclization reaction of δ-iodonitrile. After functionalization of the aromatic ring, the total synthesis of **1** was accomplished in 27-step-transformation from δ-hexanolactone in 2.2% overall yield.

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