이학석사학위논문

Programmed Serial Stereochemical Relay and Application in the Synthesis of Morphinans

Desymmetrization-Based Asymmetric Total Synthesis of Oxycodone

2018년 2월

서울대학교 대학원

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지도교수 데이비드 첸

이 논문을 이학석사학위논문으로 제출함

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박건호의 석사학위논문을 인준함

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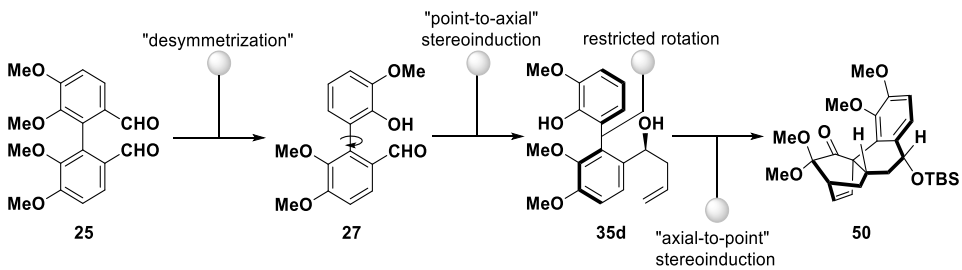
CHAPTER ONE

Molecular Desymmetrization And Rationally Designed Serial Stereochemical Induction

ABSTRACT

In this Chapter, a rationally designed synthetic strategy based on a newly proposed “serial stereochemical induction” is presented. In this proof-of-concept study, configurational stabilities of several biaryl intermediates were evaluated followed by investigation of these intermediates under unconventional stereoinduction events. As a result, highly functionalized polycyclic intermediates were prepared stereoselectively and potentially applicable in target-oriented total synthesis.



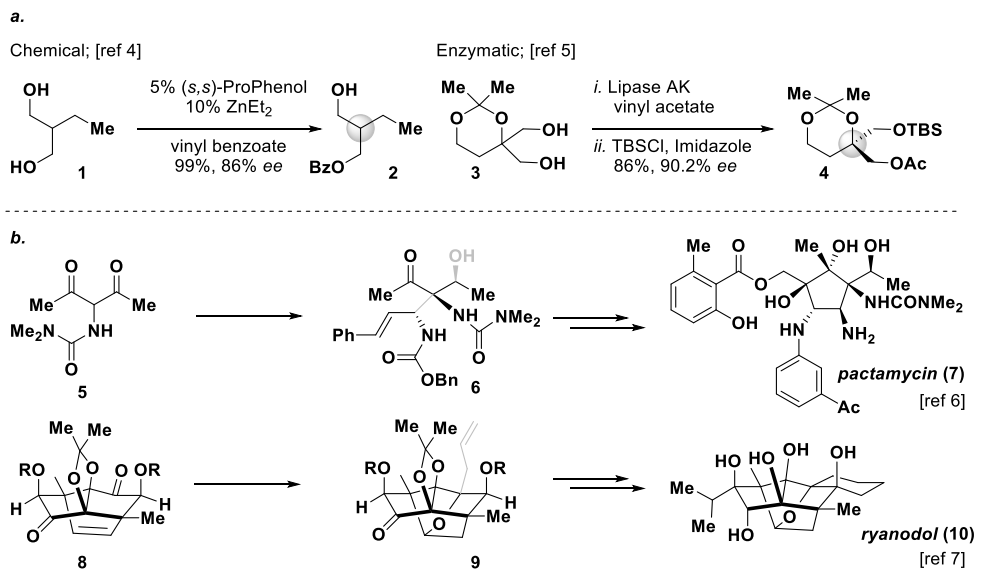
Keywords: atropisomerism, configurational stabilities, desymmetrization, intramolecular Diels-Alder, oxidative dearomatization, stereochemical induction

Student Number: 2014-22396

INTRODUCTION

Molecular desymmetrization is an operation in which one of the two identical structural domains separated by an internal plane of symmetry within the molecule of interest is selectively modified. In doing so, a new molecular entity is generated which no longer possesses an internal plane of symmetry (Figure 1). This operation has a long standing history in organic synthesis ranging from the preparation of low molecular weight building blocks to highly elaborated molecular architectures (Scheme 1).[1] Both chemical and enzymatic desymmetrizations have been demonstrated with remarkable successes,[2] and desymmetrization with concurrent generation of optical activity bestows an even greater synthetic value.[3] In the realm of target-oriented synthesis, implementation of desymmetrization-based strategy requires creative insights of the molecular framework and a rich repertoire of synthetic knowledge in order to maximize the efficiency and elegance of the overall synthetic design (Scheme 1b). Lastly but not least, although there already exists ample of desymmetrization methodologies at the disposal of synthetic chemists, the opportunities to invent and develop novel desymmetrization concepts and processes cannot be understated.

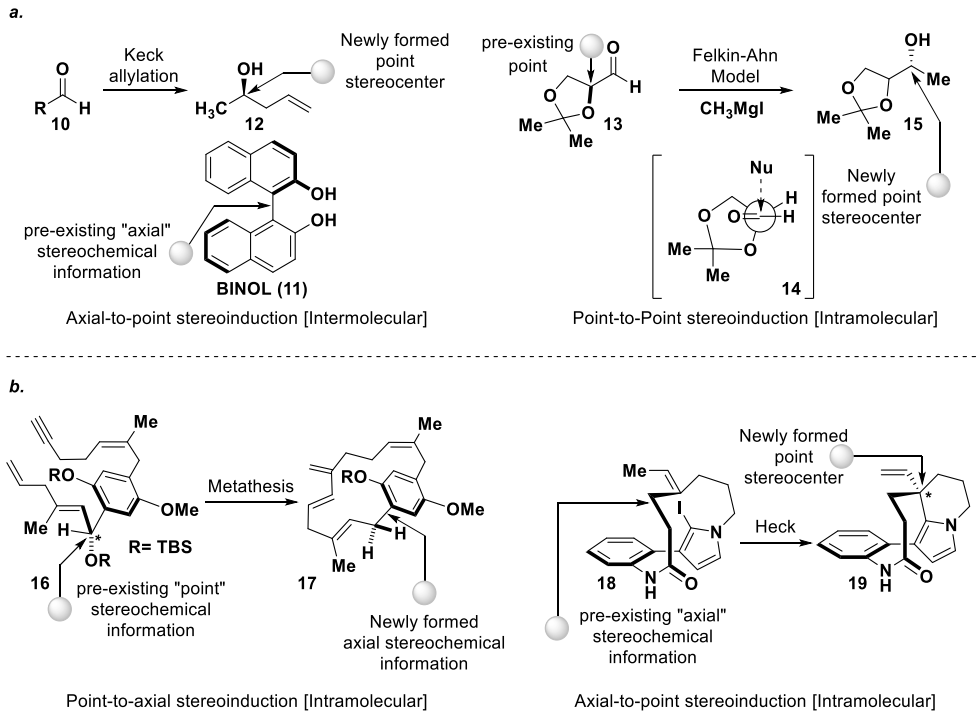
Figure 1: Graphical Illustration of Desymmetrization



Scheme 1: *a.* Desymmetrization in Preparation of Synthetic Building Blocks; *b.* Application of Desymmetrization in Complex Molecular Synthesis.

On the other hand, organic compounds are characterized by their atomic connectivities as well as the stereochemical information embedded within. Thoughtful introduction of stereochemical information in both relative and absolute sense is essential in any synthetic program, and can be broadly categorized into substrate and reagent controlled approach. In principle, these processes operate on the notion that the newly generated stereocenter is dictated by the pre-existing stereochemical information within the substrate and/or the reagent. These pre-existing stereochemical information are often found in the form of a "point" stereochemistry (for example, a tetrahedral carbon bearing four different substitutents) or an "axial" stereochemistry (for example, a biaryl system with restricted rotation), and optically active forms of these stereochemical elements can render stereoinduction in the absolute sense. While some forms stereochemical induction are routinely practiced, for example, a Felkin-Ahn model of carbonyl addition[8] (an illustration of "point-to-point" stereoinduction) or a Ti-BINOL mediated Keck allylation[9] (an illustration of "axial-to-point" stereoinduction), other forms of stereochemical induction are considerably rare. In the synthesis of longithorone[10] and rhazinilam[11] by the Shair and

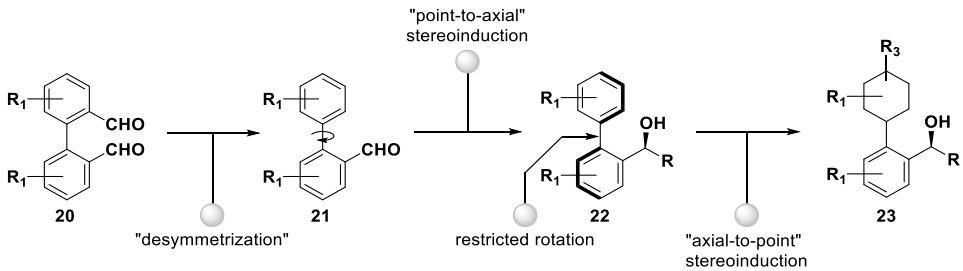
Zakarian groups, respectively, "point-to-axial" and "axial-to-point" stereochemical inductions were beautifully illustrated in the context of target-oriented total synthesis (Scheme 2). Indeed, design and implementation of these unconventional forms of stereochemical induction represents an interesting intellectual and scientific enterprise, and can provide highly effective and elegant solutions to complex synthetic problems.



Scheme 2: ***a.*** **Conventional Forms of Stereochemical Induction;** ***b.*** **Unconventional Forms of Stereochemical Induction.**

The aim this Chapter is to investigate rationally designed stereochemical inductions in organic synthesis, particularly in the context of unconventional forms of "point-to-axial" and "axial-to-point" stereoinductions. Furthermore, this study questions the possibility and effectiveness of incorporating a series of unconventional stereoinductions in a logical and predictable manner. As a test substrate for the proposed studies, biaryl system **22** with a suitably positioned substituent in proximity to its biaryl axis is expected to exhibit "axial" stereochemical property (i.e. atropisomerism). Moreover, a "point" stereochemistry resides in this substituent will enable easy detection of both the generation and erosion of the

axial stereochemical property. The newly generated “axial” stereochemical element will be further evaluated in a subsequent “axial-to-point” stereoinduction, and in doing so introduce new “point” stereochemistry on one or both of the aryl rings in **23** (Scheme 3). Last but not least, the synthesis of biaryl system **22** is expected to originate from the desymmetrization of the readily accessible synthetic precursor **20**.

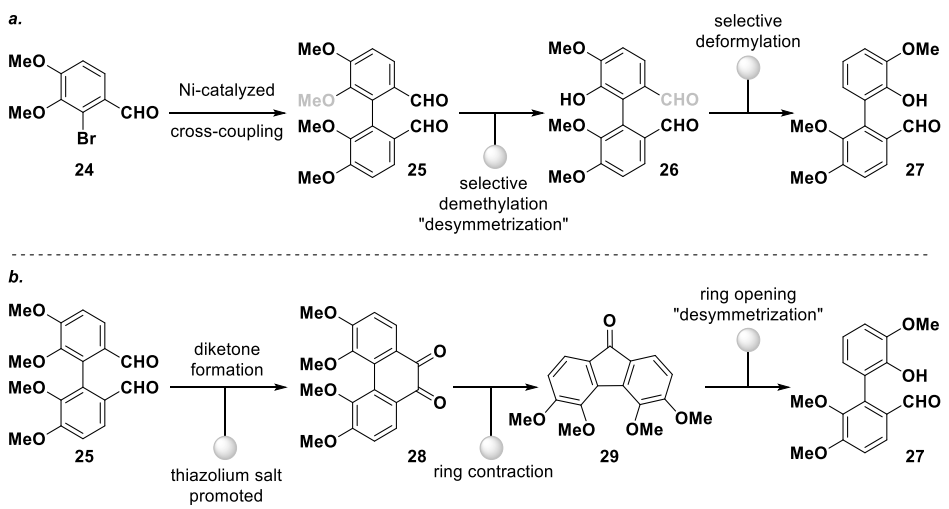


Scheme 3: Proposed Desymmetrization and Serial Stereochemical Relay.

RESULTS and DISCUSSION

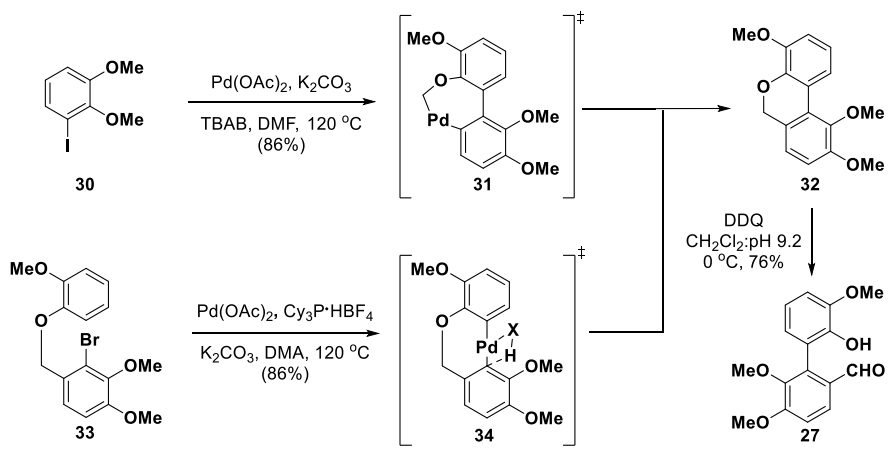
1.1 Synthetic Investigations in a Desymmetrization-Based Approach to Biaryl System 27

Investigation of the proposed “serial stereochemical induction” began with the preparation of biaryl phenolic aldehyde system **27**, as illustrated in Schemes 4 and 5. In this context, recognizing biaryl dialdehyde **25** (optically active and racemic) could be readily obtained according to literature procedures,[12] the early synthetic endeavors toward biaryl phenolic aldehyde **27** were focused on desymmetrization of dialdehyde **25** through selective demethylation and deformylation (Scheme 4a).[13],[14] Although this objective could be realized, the overall efficiency and practicality of this desymmetrization process proved inadequate to support the ensuing synthetic investigations. Undeterred by this early setback in the desymmetrization-based approach to phenolic aldehyde **27**, the attention was turned to biaryl ketone **29** which could be prepared from biaryl dialdehyde **25** through an oxidative ring contraction (Scheme 4b).[15],[16] Unfortunately, ring opening of tricyclic ketone also suffered from low yield and poor reproducibility to permit a reliable supply of biaryl phenolic aldehyde **27**.



Scheme 4: *a*. Synthesis of Phenolic-Aldehyde 27 *via* Desymmetrization of Biaryl 25; *b*. Synthesis of Phenolic-Aldehyde 27 *via* Desymmetrization of Tricyclic Ketone 29.

As shown in Scheme 5, a successful synthetic entry to biaryl phenolic aldehyde **27** was ultimately realized through one of the earliest demonstration of CH-activation chemistry in biaryl synthesis.[17] Inspired by the pioneering work of Dyker,[18] tricyclic biaryl ether **32** was readily prepared from iodide **30** through the intermediacy of the postulated palladacycle **31** [$Pd(OAc)_2$, K_2CO_3, TBAB, DMF, 86%]. Further oxidation of biaryl ether **32** under DDQ conditions smoothly delivered the targeted biaryl phenolic aldehyde **27** (76%) as an equilibrating mixture with its hemiacetal isomer. Although this developed sequence proved feasible on moderate scale, the handling of large quantity of pyrophoric butyllithium in the preparation of iodide **30** proved operationally less attractive. To address this shortcoming, biaryl ether **33**[19] was synthesized through an experimentally less hazardous sequence and further underwent a related CH-activation based biaryl formation to provide tricyclic ether **32**.[20] This second-generation synthesis of tricycle **32** followed by subsequent oxidation to phenolic aldehyde **27** was routinely performed on 100 mmol scale to support the later synthetic investigations.

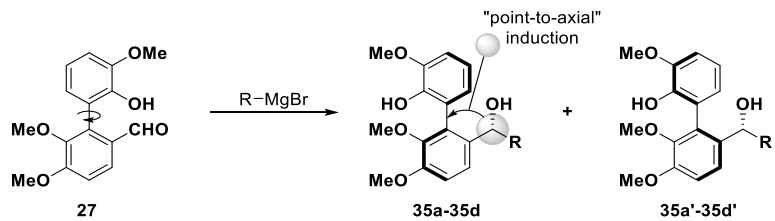


Scheme 5: Successful Preparation of Phenolic-Aldehyde 27 through Palladium Catalyzed CH-Activation Process.

1.2 Point-to-Axial Stereoinduction

With ample quantities of phenolic aldehyde **27** in hand, the stage was set to investigate the first stereoinduction event as outlined in Scheme 3, namely the "point-to-axial"

stereoinduction. In this context, it has been reported that biaryl systems closely related to phenolic aldehyde **27** are configurationally labile at ambient temperature therefore does not exhibit atropisomeric property.[21] Treatment of phenolic aldehyde **27** with organometallic reagents (refer to table 1) afforded the corresponding products in high yield, and more importantly, each of the biaryl products **35a-35d** was isolated as a chromatographically separable mixture of diastereoisomers (Table 1). This latter observation clearly suggested the newly formed biaryl systems **35a-35d** exhibited atropisomeric properties, and as a validation of the proposed "point" induced atropisomerism.



27 35a-35d 35a'-35d'

Entry	*Condition*	*Result*
1	Methylmagnesium bromide, THF, -78 °C to 23 °C	35a:35a'~1:1, 92%
2	Phenylmagnesium bromide, THF, -78 °C to 23 °C	35b:35b'~6:1, 90%
3	*t*BuLi, THF, -78 °C to 23 °C	35c:35c'~4:1, 92%
4	Allyl magnesium bromide, THF, -78 °C to 23 °C	35d:35d'~1:1, 97%

Table 1: Various Organometallic Addition to Phenolic-Aldehyde 27.

1.3 Axial-to-Point Stereoinduction

1.3.1 Temperature-Dependent Configurational Stability Study

Before pressing onto the next stereochemical induction event, namely the "axial-to-point" stereoinduction, an assessment of the configurational stability of the newly synthesized biaryl systems **35a-35d** was deemed necessary. In this study, each of the chromatographically separated and isomerically pure (by ^{1}H NMR analysis) atropisomeric pairs **35a/35a'-35d/35d'** was subjected to thermal conditions and their isomeric ratio was monitored by ^{1}H NMR analysis. As summarized in Table 2, biaryl systems **35a/35a', 35b/35b', 35d/35d'** were configurationally stable up to moderately elevated temperature (70 ℃), whereas the *t*butyl systems **35c/35c'** demonstrated extended stability up to 100 ℃.

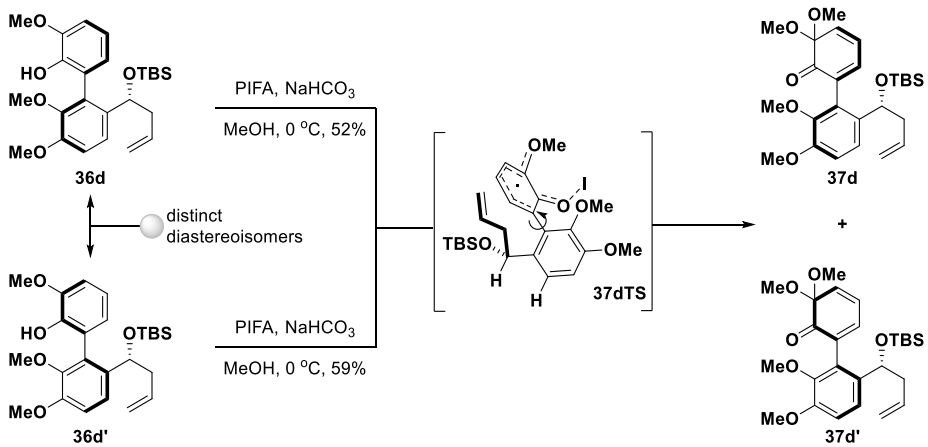
Compd. \ Temp. °C	40	70	90	100	110	120
35a	1:0	1:0.10	1:0.43	1:0.88	0.79:1	0.69:1
35a'	0:1	0.07:1	0.16:1	0.39:1	0.60:1	0.70:1
36b	1:0	1:0.13	1:0.43	1:0.98	0.68:1	0.63:1
36b'	0:1	0.06:1	0.23:1	0.44:1	0.58:1	0.65:1
37c	1:0	1:0	1:0	1:0.09	1:0.35	0.53:1
37c'	0:1	0:1	0:1	0.06:1	0.18:1	0.52:1
38d	1:0	1:0	1:0.36	0.93:1	0.71:1	0.71:1
38d'	0:1	0:1	0.53:1	0.70:1	0.70:1	0.70:1

*Note: Detailed NMR information included in the experimental section

Table 2: Temperature-Dependent Configurational Stability Study.

1.3.2 Oxidative Dearomatization of Biaryl Phenols 36a/36a', 36b/36b', 36d/36d' and 35c/35c'

Having established the configurational stability profile under thermal conditions for biaryl systems **35a**-**35d**, investigations of the proposed "axial-to-point" stereochemical induction was pursued in earnest. In accordance to the conceptual workflow outlined in the Introduction section (Scheme 3), the attention was turned to the dearomatization of biaryl systems **35a**-**35d**. A cursory survey of the well-documented dearomatization protocols revealed the hypervalent iodine[22] conditions as the synthetically most attractive option, which was applied to the silylated biaryl phenols **36a**/**36a'**, **36b**/**36b'**, **36d**/**36d'** and phenolic alcohol **35c**/**35c'**. Specifically, isomerically pure phenols **36a**/**36a'**, **36b**/**36b'**, **36d**/**36d'** and **35c**/**35c'**were treated with PIFA in the presence of methanol, and very unexpectedly all substrates afforded a near 1:1 mixture of the corresponding oxidative dearomatized products (Scheme 6) as observed by ^{1}H NMR analysis (refer to experimental section).

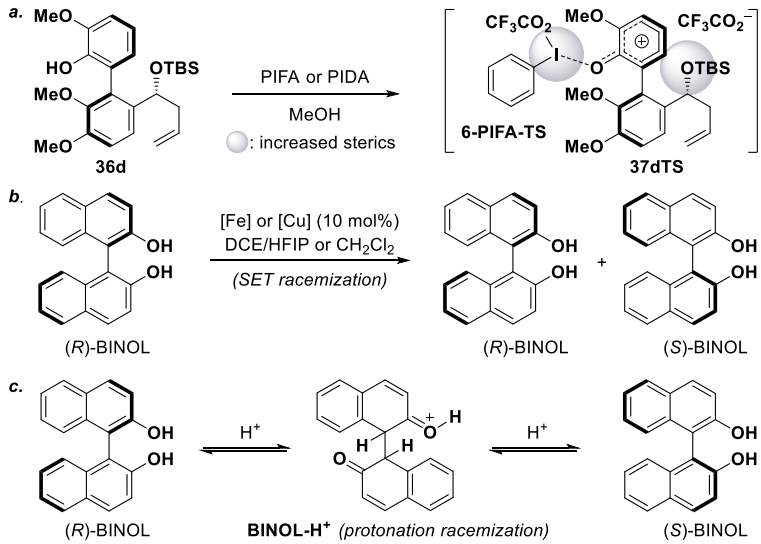


Scheme 6: Hypervalent Iodine-Mediated Oxidative Dearomatization of Atropisomerically Pure Phenols 36a/36a', 36b/36b', 36d/36d' and 35c/35c'.

It was initially speculated that the oxidative dearomatized products exhibited lowered rotational barriers about the biaryl axis, and a preliminary computational study was supportive of this hypothesis.[23] However, this scenario seemed unlikely considering the structural similarity between the oxidative dearomatization precursors and the corresponding dearomatized products.

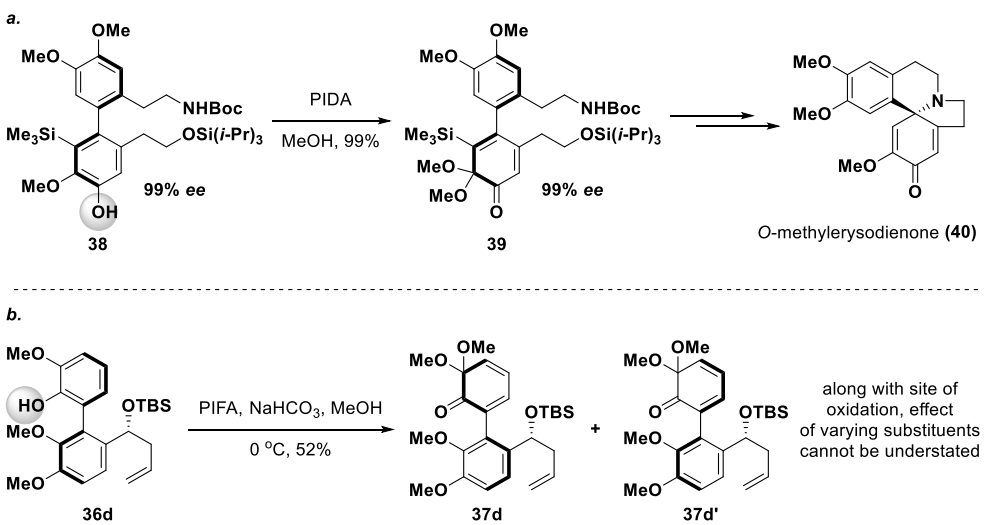
Moreover, if the oxidative dearomatized products no longer exhibit atropisomeric property, ^{1}H NMR signature of the oxidative dearomatized products would appear as a single component. This suggests the phenolic systems **36a**/**36a'**, **36b**/**36b'**, **36d**/**36d'** and **35c**/**35c'** underwent atropisomeric epimerization during the course of the reaction, and the oxidative dearomatized products still possess atropisomeric property. While seeking clues to reconcile this unexpected result, studies from the Pappo laboratory demonstrated several enantiomerically enriched BINOL systems underwent racemization under oxidative SET (single electron transfer) conditions.[24] Moreover, racemization of enantiomerically pure BINOL under acidic conditions was also recently reported and supported by computational studies.[25] Both the SET and protonation induced racemization invoked intermediates closely resemble those generated during the oxidative dearomatization of phenols **36a**/**36a'**, **36b**/**36b'**, **36d**/**36d'** and **35c**/**35c'**, suggesting the intermediacy of configurationally labile species in all

of these processes (Scheme 7).



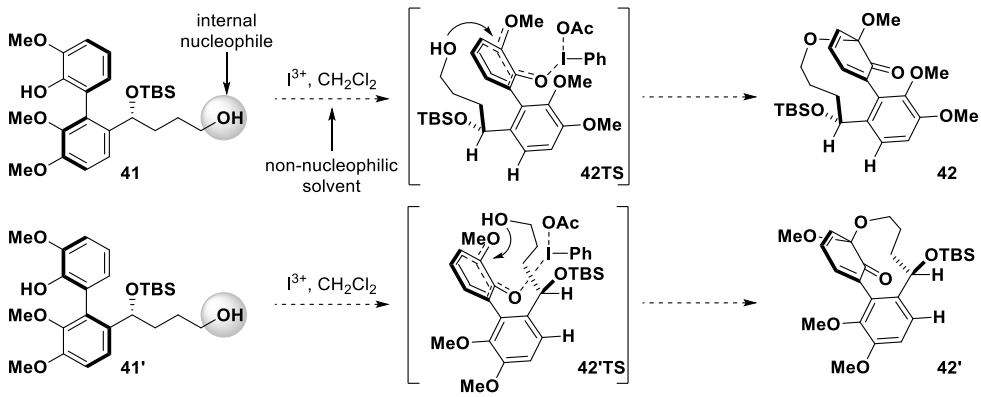
Scheme 7: *a.* Oxidative Dearomatization of 36d via Associative Mechanism; *b.* Racemization of (*R*)-BINOL under SET Conditions; *c.* Acid Promoted Racemization of (*R*)-BINOL.

Lastly, it is worth noting that Matsumoto and coworkers have demonstrated a related oxidative dearomatization of biaryl phenol **38** to afford dienone **39** with complete retention of stereochemical integrity (Scheme 8),[22] albeit the site of phenol oxidation differs from substrates **36a**/**36a'**, **36b**/**36b'**, **36d**/**36d'** and **35c**/**35c'**.



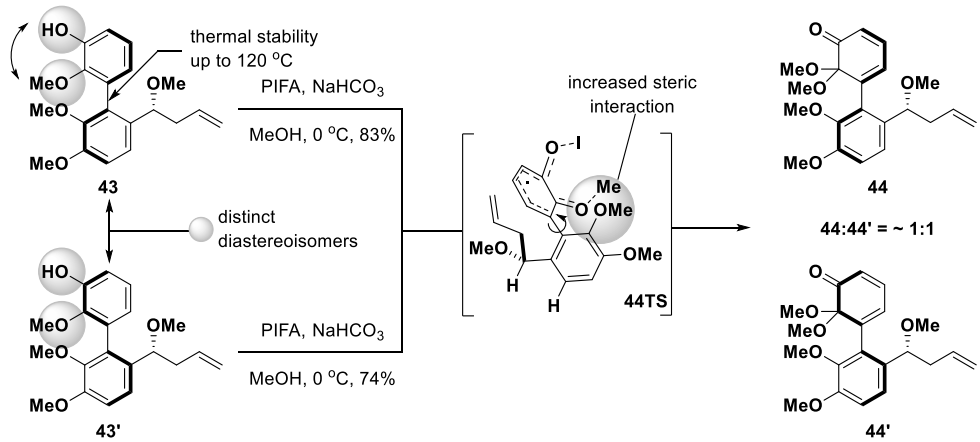
Scheme 8: *a.* Hypervalent Iodine-Mediated Oxidative Dearomatization of Biaryl Phenol 38 by Matsumoto; *b.* Hypervalent Iodine-Mediated Oxidative Dearomatization of Biaryl Phenol 36d.

Recognizing the atropisomeric epimerization may have taken place during the course of the oxidative dearomatization, a re-engineered substrate **41** was conceived to interrogate this hypothesis. As shown in Scheme 9, atropisomerically pure phenol **41** bearing a tethered primary alcohol was designed to intramolecularly capture the oxidative dearomatized intermediate thereby preserving the atropisomeric integrity. Unfortunately, the feasibility of this proposal has not been unambiguously validated.



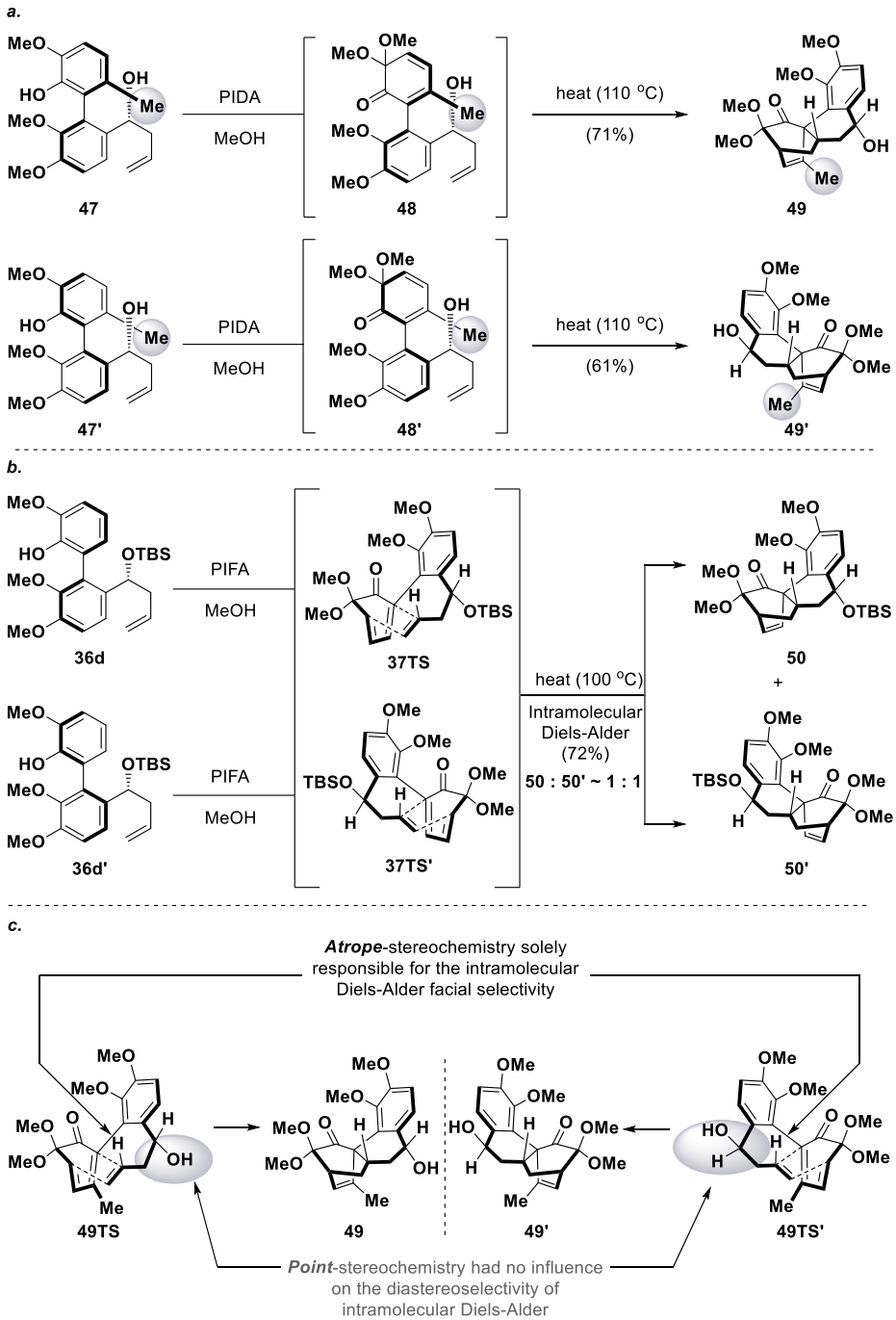
Scheme 9: Proposed Hypervalent Iodine Mediated Oxidative Dearomatization of Biaryl Phenol 41.

Continue the investigation of oxidative dearomatization through structurally related substrates, phenol systems **43**/**43'** and **47**/**47'** were synthesized and subjected to the aforementioned hypervalent iodine mediated oxidative dearomatization conditions. In this study, while isomerically pure phenols **43**/**43'** with swapped methoxy and hydroxy groups compared to **36d**/**36d'** exhibited higher configurational stability under thermal conditions, upon treatment with PIDA in the presence of methanol a near 1:1 mixture of oxidative dearomatized products was again generated (Scheme 10).



Scheme 10: Oxidative Dearomatization of Atropisomerically Pure Biaryl Phenol 43 and 43'.

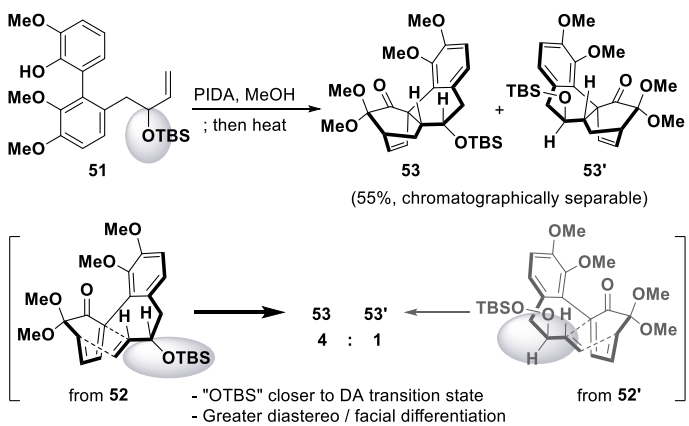
Finally, isomerically pure phenols **47**/**47′** with an additional methyl substituent not only displayed improved configurational stability under thermal conditions, but also retained their atropisomeric integrity under hypervalent iodine mediated oxidative dearomatization conditions (Scheme 11a). Isomerically pure dienones **48** and **48′** further underwent independent intramolecular Diels-Alder reactions to afford tetracyclic compounds **49** and **49′**, respectively, as a single isomer (Scheme 11a). An analogous intramolecular Diels-Alder reaction could also be realized with the mixture of dienones **37d** and **37d′** (**37d**:**37d′** ~ 1:1) to afford a mixture tetracyclic compounds **50** and **50′** (**50**:**50′** ~ 1:1), (Scheme 11b). Since dienones **37d** and **37d′** are likely to be configurationally labile under the thermal conditions employed for the intramolecular Diels-Alder reaction, these results strongly suggest the stereoselective formation of tetracycle **49**/**49′** originated solely from the "axial" stereochemistry of dienones **48**/**48′** whereas the OTBS "point" stereochemistry offered no stereoinduction (Scheme 11c).



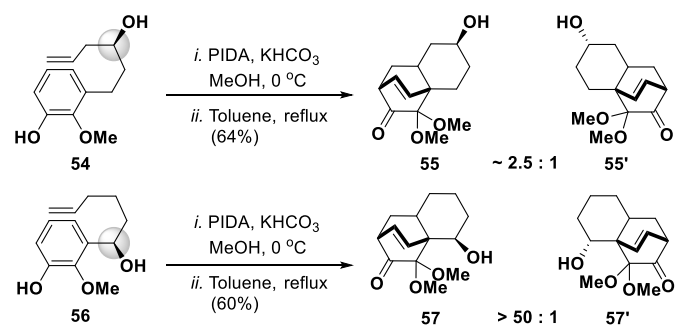
Scheme 11: *a*. Hypervalent Iodine Mediated Oxidative Dearomatization and Diels-Alder of Biaryl Phenol 47/47'; *b*. Hypervalent Iodine Mediated Oxidative Dearomatization and Diels-Alder of Biaryl Phenol 36d/36d'; *c*. Atropisomerism Dictated Stereoinduction Leading to the Stereocontrolled Formation of Diels-Alder Products 49 and 49'.

1.4 Point-to-Point Stereochemical Induction

As alluded to in the preceding section, the benzylic OTBS "point" stereochemistry in dienone **37d**/**37d'** appeared to offer no stereoinduction during the intramolecular Diels-Alder reaction leading to the formation of tetracycles **50** and **50'** (**50**:**50'** ~ 1:1). A closer examination of the plausible transition state structure **37TS** suggested this "point" stereochemical element may be too distant from the reaction center to exhibit any significant influence. To validate this hypothesis, a revised substrate **51** was synthesized and a higher level of stereoinduction was indeed observed in formation of tetracycles **53** and **53'** (**53**:**53'** ~4:1), (Scheme 12). This result was consistent with the findings from the Chen laboratory during their synthetic studies toward the total synthesis of platencin (Scheme 13).[26]



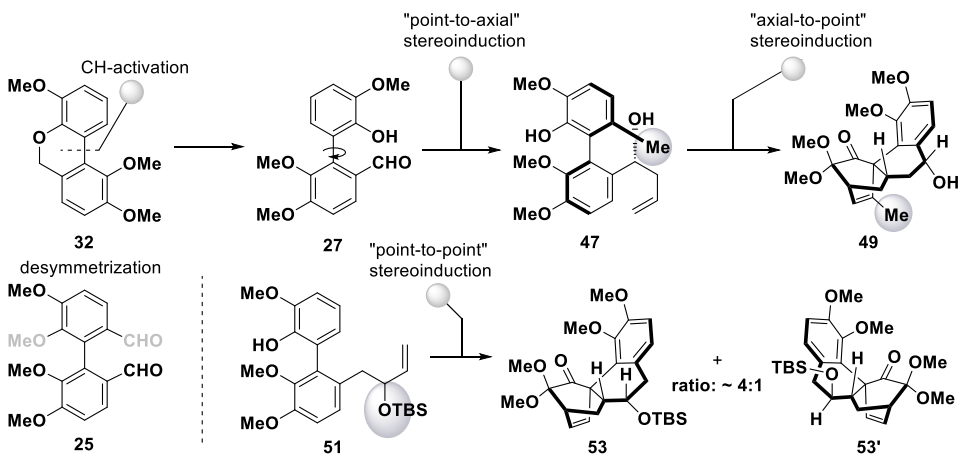
Scheme 12: Hypervalent Iodine-Mediated Dearomatization of Phenolic Biaryl 51 followed by Diastereoselective Diels-Alder Reaction.



Scheme 13: Hypervalent Iodine-Mediated Oxidative Dearomatization and Diels-Alder of Phenol 54 and 56.

Conclusion

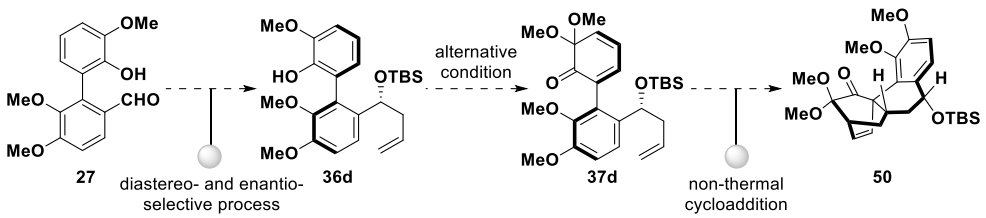
In summary, a proof-of-concept desymmetrization and serial stereochemical induction in multi-step organic synthesis has been demonstrated. The desymmetrization-based preparation of substrate **27** was feasible in the initial exploration, but later substituted with an improved and more practical solution based on two highly effective CH-activation processes. The proposed "point-to-axial" stereoinduction was achieved uneventfully, however, the subsequent "axial-to-point" stereoinduction led to the discovery of an unexpected atropisomeric epimerization which remain to be fully elucidated. A revised biaryl substrate **47**/**47'** was later found to preserve the atropisomeric property upon oxidative dearomatization, and the oxidative dearomatized intermediates further participated in a diastereoselective intramolecular Diels-Alder reaction to afford highly functionalized tetracyclic compounds. Lastly, by relocating the stereochemistry inducing element closer to the reaction center a "point-to-point" stereoinduction with greatly improved diastereoselectivity was achieved (Scheme 14).



Scheme 14: Stereoselective Synthesis of Tetracycles 49 and 53/53'.

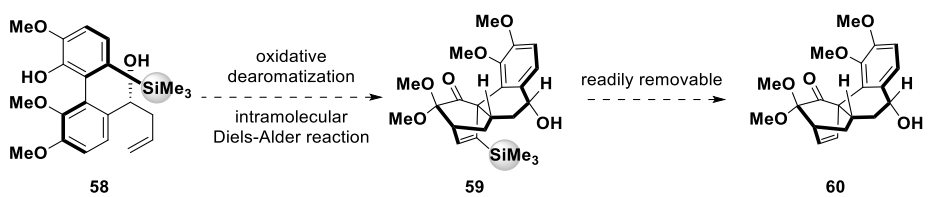
Clearly, while the revised substrate **47**/**47'** offered a viable solution to retain the atropisomeric property during the oxidative dearomatization, more in depth studies are required to fully elucidate the origin of the unexpected atropisomeric epimerization. In doing

so, “substrate-independent” solutions could be realized through alternative reagents and conditions, and possibly with implications in other related biaryl generation and functionalization processes. However, even dienone **37d**/**37d’** could be assessed in atropisomerically pure form, the subsequent transformation also need to be revisited to preserve the isomeric integrity (e.g. the intramolecular Diels-Alder reaction under thermal conditions) (Scheme 15). On the other hand, the preparation of organometallic addition products **35a**/**35a’**-**35d**/**35d’** could be revisited to render a diastereoselective and enantioselective process and kinetic resolution could be a viable option (Scheme 15).



Scheme 15: Proposed preparation of enantio-isomerically pure dienone 37d and non-thermal intramolecular Diels-Alder reaction

Last but not least, the methyl substituent in substrates **47**/**47’** that served to preserve the atropisomeric property could be replaced with a removable directing group (e.g. silyl) to provide more synthetic flexibility (Scheme 16).



Scheme 16: Proposed Synthesis of Tetracycle 59

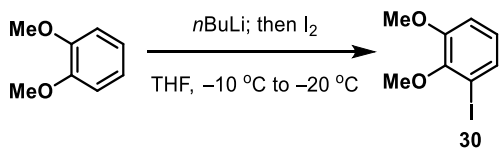
EXPERIMENTAL

General Procedures

Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2) and toluene were dried and distilled according to the standard protocols. Benzene and acetonitrile (CH_3CN) were purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc), Et_2O, CH_2Cl_2, hexanes and water were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F−254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde or potassium permanganate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer and IRTracer-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

Section 1.1

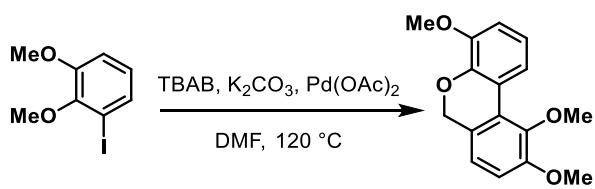
Iodide 30



30

To a stirred solution of veratrole (5.00 g, 36.2 mmol) in THF (60 mL) at –10 °C was added *n*BuLi (1.6 M in hexanes, 25.0 mL, 40.0 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h before it was cooled to –45 °C followed by the addition of a cold (–45 °C) solution of I_2 (10.1 g, 39.8 mmol) in THF (100 mL). The resulting mixture was warmed to room temperature and stirred for 2 h before it was quenched with $Na_2S_2O_3$ (100 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded iodide **30** (7.20 g, 75%) as an amorphous yellow solid. **30**: R_f = 0.75 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 3269, 2919, 2830, 1415, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.71–6.65 (m, 1H), 3.75 (s, 3H), 3.72 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.3, 148.2, 129.8, 125.5, 112.3, 92.1, 59.8, 55.4 ppm; HRMS calcd. For $C_8H_9IO_2Na^+$ $[M + Na]^+$ 286.9539, found 286.9537.

Tricycle 32

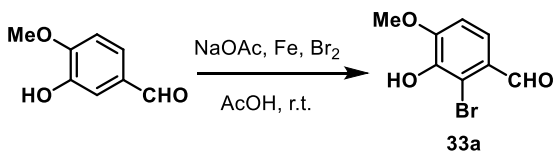


30 **32**

To a stirred solution of iodide **30** (20.6 g, 78.0 mmol) in DMF (190 mL) at room temperature was added K_2CO_3 (43.0 g, 311 mmol), $Pd(OAc)_2$ (0.72 g, 3.21 mmol) and tetra-*n*-

butylammonium bromide (25.2 g, 78.2 mmol). The resulting mixture was warmed to 120 °C and stirred for 16 h before it was cooled to room temperature and diluted with water (100 mL). The resulting mixture was extracted with Et_2O (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded tricycle **32** (9.10 g, 86%) as an amorphous white solid. **32**: R_f = 0.46 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3154, 2920, 1707, 1342, 1142, 725 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.2 Hz, 1H), 6.99 (t, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 4.98 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.71 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 148.6, 146.3, 144.5, 126.0, 123.3, 122.5, 121.3, 120.0, 120.0, 111.4, 111.1, 68.7, 59.7, 55.8, 55.8 ppm; HRMS calcd. For $C_{16}H_{16}O_4Na^+$ $[M + Na]^+$ 295.0941, found 295.0940.

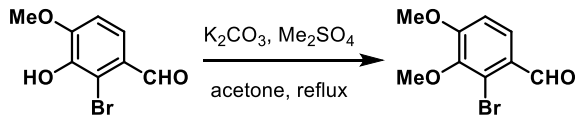
Bromide 33a



33a

To a stirred solution of isovanillin (30.0 g, 197 mmol), NaOAc (32.3 g, 394 mmol) and iron powder (0.90 g, 16.1 mmol) in AcOH (glacial, 180 mL) at room temperature was added a solution of bromine/AcOH (1:4.2, 55.4 mL, 208 mmol). The resulting mixture was stirred for 16 h before it was quenched with ice cold water (500 mL). The resulting precipitate was filtered, washed with ice cold water (4 × 70 mL) and air dried. Recrystallization of the crude material from boiling ethanol afforded bromide **33a** (34.5 g, 76%) as a gray powder. **33a**: R_f = 0.40 (silica gel, CH_2Cl_2); IR (film) ν_{max} 3667, 2985, 1738, 1265, 1057, 736 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.00 ppm (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 191.1, 153.5, 144.2, 126.8, 122.3, 113.5, 110.5, 56.6 ppm; HRMS calcd. For $C_8H_7BrO_3$ $[M]^+$ 228.9579, found 228.9467.

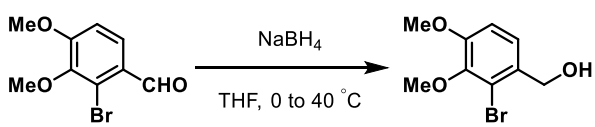
Dimethyl Ether 33b



33a 33b

To a stirred solution of phenol **33a** (81.0 g, 351 mmol) in acetone (820 mL) at room temperature was added K_2CO_3 (81.0 g, 586 mmol) and dimethylsulfate (56.0 mL, 592 mmol). The resulting mixture was warmed to reflux and stirred for 16 h before it was cooled to room temperature, and evaporated to approximately half of its original volume. The resulting mixture was diluted with water (200 mL) and extracted with Et_2O (3 × 100 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford dimethyl ether **33b** (74.7 g, 87%) as a white solid. The crude material was sufficiently pure based on thin-layer-chromatography and ^{1}H NMR analysis for the subsequent reaction. **33b**: R_f = 0.48 (silica gel, CH_2Cl_2); IR (film) ν_{max} 3674, 2985, 2901, 1679, 1280, 779 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.94 (s, 3H), 3.86 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.8, 158.6, 146.3, 127.3, 126.4, 123.0, 110.9, 60.6, 56.2 ppm; HRMS calcd. For $C_9H_9BrO_3Na^+$ $[M + Na]^+$ 266.9627, found 266.9625.

Alcohol 33c

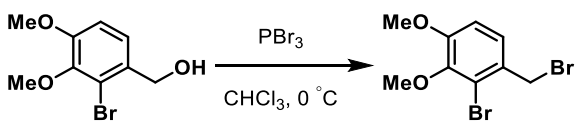


33b 33c

To a stirred solution of aldehyde **33b** (33.1 g, 135 mmol) in THF (250 mL) at 0 ℃ was added $NaBH_4$ (13.0 g, 344 mmol) in portions. The resulting mixture was warmed to 40 ℃ and stirred for 2 h before it was cooled to room temperature and quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to

afford alcohol **33c** (28.5 g, 85%) as a white solid. The crude material was sufficiently pure based on thin-layer-chromatography and ^{1}H NMR analysis for the subsequent reaction. **33c**: R_f = 0.10 (silica gel, CH_2Cl_2); IR (film) ν_{max} 3232, 1667, 1284, 1016, 818 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.66 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.34 ppm (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.9, 146.3, 132.7, 124.1, 118.3, 111.1, 64.9, 60.4, 56.0 ppm; HRMS calcd. For $C_9H_{11}BrO_3Na^+$ $[M + Na]^+$ 268.9784, found 268.9782.

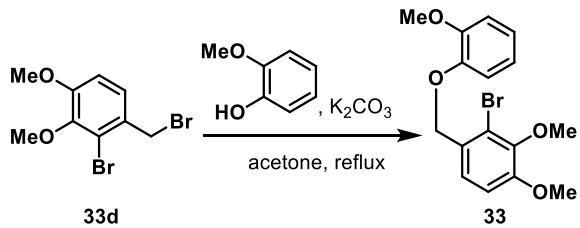
Dibromide 33d



33c **33d**

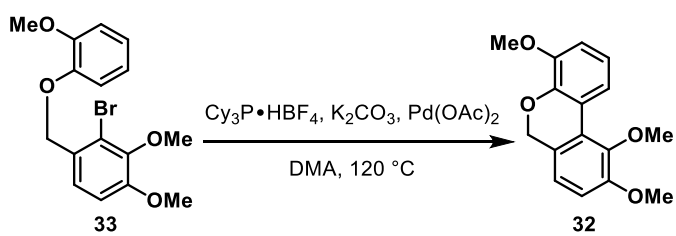
To a stirred solution of alcohol **33c** (27.7 g, 112 mmol) in $CHCl_3$ (52.2 mL) at 0 °C was added PBr_3 (8.52 mL, 89.8 mmol). The resulting mixture was stirred for 3 h before it was quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford dibromide **33d** (33.0 g, 95%) as a white solid. The crude material was sufficiently pure based on thin-layer-chromatography and ^{1}H NMR analysis for the subsequent reaction. **33d**: R_f = 0.84 (silica gel, CH_2Cl_2); IR (film) ν_{max} 2985, 2901, 1486, 1302, 810, 660 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.62 (s, 2H), 3.87 (s, 3H), 3.85 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.7, 146.9, 129.8, 126.3, 120.4, 111.2, 60.4, 56.0, 34.3 ppm; HRMS calcd. For $C_9H_{10}Br_2O_2Na^+$ $[M + Na]^+$ 330.8940, found 330.8937.

Biaryl Ether 33



To a stirred solution of dibromide **33d** (31.0 g, 100 mmol) in acetone (232 mL) at room temperature was added K_2CO_3 (27.7 g, 200 mmol) and guaiacol (9.57 mL, 86.3 mmol). The resulting mixture was warmed to reflux and stirred for 16 h before it was cooled to room temperature and diluted with water (100 mL). The resulting mixture was extracted with Et_2O (3 × 100 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:Et_2O 5:1) afforded biaryl ether 33 (30.6 g, 87%) as an amorphous white solid. **33**: R_f = 0.13 (silica gel, hexanes:Et_2O 4:1); IR (film) ν_{max} 3001, 2941, 1271, 1146, 806, 752 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.97–6.84 (m, 5H), 5.16 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.9, 149.5, 147.8, 146.2, 129.0, 123.9, 121.5, 120.7, 117.8, 114.1, 111.9, 111.1, 70.2, 60.3, 55.9, 55.8 ppm; HRMS calcd. For $C_{16}H_{17}BrO_4Na^+$ $[M + Na]^+$ 375.0202, found 375.0204.

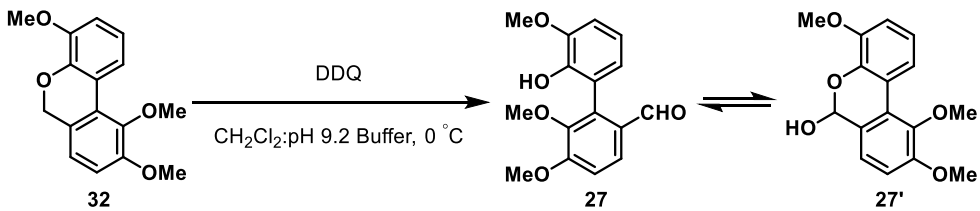
Tricycle 32



To a stirred solution of bromide **33** (18.9 g, 53.5 mmol) in DMA (freshly distilled, 190 mL) at room temperature was added K_2CO_3 (14.9 g, 108 mmol), $Pd(OAc)_2$ (0.37 g, 1.65 mmol) and Cy_3P-HBF_4 (1.18 g, 3.20 mmol). The resulting mixture was warmed to 120 °C and stirred for 16 h before it was cooled to room temperature and diluted with water (100 mL). The

resulting mixture was extracted with Et_2O (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded tricycle **32** (12.6 g, 86%) as a white solid. All physical data of tricycle **32** are identical to those obtained from the $Pd(OAc)_2$ mediated annulation of iodide **30**.

Hydroxy Aldehyde 27 and Hemiacetal 27'

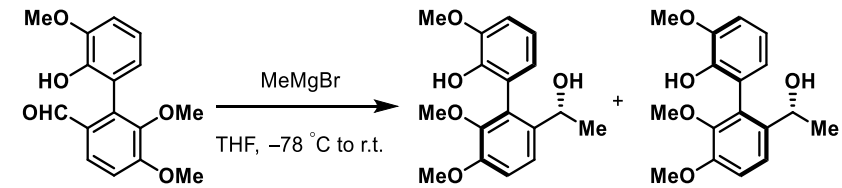


To a stirred solution of tricycle **32** (19.8 g, 72.7 mmol) in CH_2Cl_2/pH 9.2 buffer (10:1, 1.2 L) at 0 ℃ was added DDQ (16.5 g, 72.7 mmol) portionwise. The resulting mixture was stirred for 1.5 h before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was washed successively with water (until the aqueous layer became colorless), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the crude material from CH_2Cl_2/hexane afforded hydroxy aldehyde **27** and hemiacetal **27'** (15.9 g, 76%) as a pale amorphous yellow solid. ^{1}H NMR analysis indicated a mixture of hydroxy aldehyde **27** and hemiacetal **27'** (**27**:**27'**~1:3 by ^{1}H NMR analysis). **27**+**27'**: R_f = 0.33 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3408, 2987, 1739, 1651, 1266, 737 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$, **27**:**27'**~1:3): δ 9.57 (s, 0.25H), 8.21 (d, *J* = 8.2 Hz, 0.75H), 7.84 (d, *J* = 8.7 Hz, 0.25H), 7.13 (d, *J* = 8.3 Hz, 0.75H), 7.10–7.03 (m, 1.25H), 6.98–6.92 (m, 1.75H), 6.82 (dd, *J* = 5.1, 4.1 Hz, 0.25H), 6.38 (d, *J* = 6.2 Hz, 0.75H), 5.80 (s, 0.25H), 3.97 (s, 0.75H), 3.94 (s, 0.75H), 3.92 (s, 2.25H), 3.91 (s, 2.25H), 3.78 (s, 2.25H), 3.62 (s, 0.75H), 3.47 ppm (d, *J* = 6.2 Hz, 0.75H); ^{13}C NMR (101 MHz, DMSO): δ 153.4, 149.6, 145.6, 141.0, 127.1, 121.7, 121.3, 121.1, 119.2, 112.3, 112.2, 92.0,

59.6, 56.1, 56.0, 55.8 ppm; HRMS calcd. For $C_{16}H_{16}O_5Na^+$ $[M + Na]^+$ 311.0890, found 311.0889.

Section 1.2

Alcohols 35 and 35a



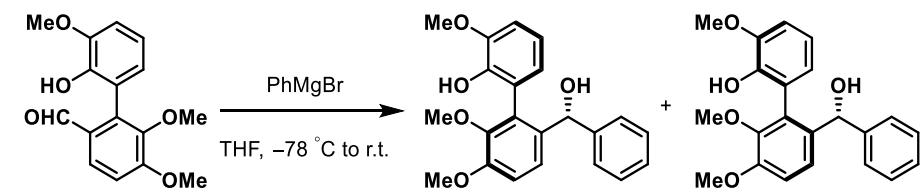
27 (mixture with hemiacetal **27'**) **35a** **35a'**

To a stirred solution of hemiacetal-hydroxy aldehyde mixture (**27+27'**, 213 mg, 0.74 mmol) in THF (15.0 mL) at –78 ℃ was added methylmagnesium bromide (3.0 M in Et_2O, 0.81 mL, 2.43 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alcohols **35a** and **35a'** (~1:1 based on ^{1}H NMR analysis, 207 mg, 92% combined yield) as an amorphous solid. Small amount of analytically pure isomers **35a** and **35a'** were obtained through column chromatography.

35a (relative stereochemistry arbitrarily assigned): R_f = 0.18 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3456, 3154, 2918, 1705, 1197, 726 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 7.48 (d, *J* = 9.3 Hz, 1H), 6.85 (d, *J* = 7.0 Hz, 1H), 6.76 (t, *J* = 9.2 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 5.63 (br, 1H), 4.87 (q, *J* = 5.8 Hz, 1H), 3.63 (s, 3H), 3.36 (s, 3H), 3.14 (s, 3H), 1.46 ppm (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1, 146.5, 146.3, 142.5, 137.2, 130.5, 123.8, 122.6, 120.8, 119.7, 112.3, 109.8, 66.5, 60.6, 55.9, 55.8, 22.9 ppm; HRMS calcd. For $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$ 327.1203, found 327.1204.

35a' (relative stereochemistry arbitrarily assigned): R_f = 0.25 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3457, 3154, 2920, 1706, 1200, 726 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.44 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.76 (t, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 5.53 (s, 1H), 4.83 (q, *J* = 6.5 Hz, 1H), 3.70 (s, 3H), 3.37 (s, 3H), 3.14 (s, 3H), 1.35 ppm (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 146.6, 146.4, 143.2, 137.4, 130.3, 123.0, 122.5, 120.8, 119.5, 112.3, 109.9, 66.8, 60.5, 55.8, 55.8, 24.0 ppm; HRMS calcd. For $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$ 327.1203, found 327.1203.

Alcohols 35b and 35b'



27 (mixture with hemiacetal **27'**) **35b** **35b'**

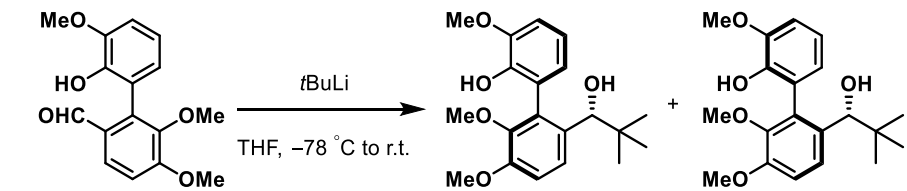
To a stirred solution of hemiacetal-hydroxy aldehyde mixture (**27+27'**, 215 mg, 0.75 mmol) in THF (15.0 mL) at –78 °C was added phenylmagnesium bromide (1.0 M in THF, 3.50 mL, 3.50 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 9:1) afforded alcohols **35** and **35'** (~6:1 based on ^1H NMR analysis, 233 mg, 85% combined yield) as an amorphous solid. Small amount of analytically pure isomers **35** and **35'** were obtained through column chromatography.

35 (relative stereochemistry arbitrarily assigned): R_f = 0.32 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3666, 3154, 2933, 1705, 1341, 1140, 727 cm^{-1}; ^1H NMR (499 MHz, C_6D_6): δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.19–7.13 (m, 3H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.74 (t, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 5.93 (s, 1H), 5.60

(s, 1H), 3.63 (s, 3H), 3.27 (s, 3H), 3.12 (s, 3H), 3.04 ppm (s, 1H); ^{13}C NMR (126 MHz, C_6D_6): δ 152.9, 147.3, 147.0, 144.7, 143.6, 137.5, 132.2, 128.2, 126.9, 126.9, 124.6, 124.2, 123.8, 120.0, 112.9, 110.1, 72.9, 60.4, 55.4, 55.3 ppm; HRMS calcd. For $C_{22}H_{22}O_5Na^+$ $[M + Na]^+$ 389.1359, found 389.1357.

35' (relative stereochemistry arbitrarily assigned): R_f = 0.45 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3622, 3234, 2857, 1680, 1391, 1162, 811 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.13–7.08 (m, 3H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 1H), 6.37 (d, *J* = 8.1 Hz, 1H), 5.76 (s, 1H), 5.40 (s, 1H), 3.62 (s, 3H), 3.23 (s, 3H), 3.07 ppm (s, 3H); ^{13}C NMR (101 MHz, C_6D_6): δ 152.7, 147.7, 147.0, 145.1, 144.2, 137.2, 132.5, 127.0, 126.8, 126.8, 124.1, 123.9, 123.8, 119.5, 112.6, 110.1, 73.0, 60.4, 55.4, 55.3 ppm; HRMS calcd. For $C_{22}H_{22}O_5Na^+$ $[M + Na]^+$ 389.1359, found 389.1359.

Alcohols 35c and 35c'



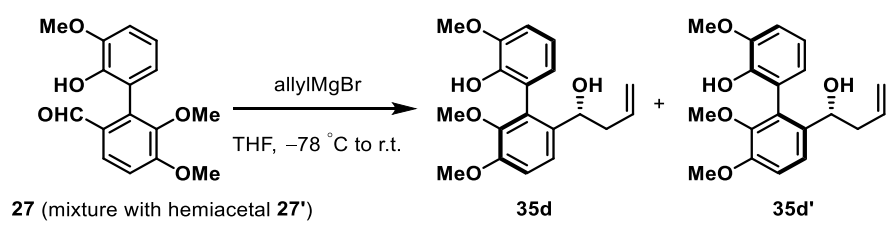
27 (mixture with hemiacetal **27'**) **35c** **35c'**

To a stirred solution of hemiacetal-hydroxy aldehyde mixture (**27+27'**, 210 mg, 0.73 mmol) in THF (15.0 mL) at –78 °C was added *tert*-butyllithium (1.7 M in pentane, 1.50 mL, 2.55 mmol). The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (hexanes:EtOAc 10:1) afforded alcohols **35c** and **35c'** (~4:1 based on ^{1}H NMR analysis, 231 mg, 92% combined yield) as an amorphous solid. Small amount of analytically pure isomers **35c** and **35c'** were obtained through column chromatography.

35c (relative stereochemistry arbitrarily assigned): R_f = 0.38 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3464, 2915, 1705, 1198, 1062, 721 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.92–6.85 (m, 2H), 6.77 (dd, *J* = 7.2, 2.0 Hz, 1H), 5.7 (br s, 1H), 4.25 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.48 (s, 3H), 0.78 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.0, 146.1, 145.9, 142.2, 134.9, 131.6, 125.3, 123.4, 122.8, 119.2, 111.5, 109.5, 77.6, 60.4, 55.9, 55.7, 36.2, 26.4 ppm; HRMS calcd. For $C_{20}H_{26}O_5Na^+$ $[M + Na]^+$ 369.1672, found 369.1671.

35c' (relative stereochemistry arbitrarily assigned): R_f = 0.55 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3456, 2920, 1704, 1204, 1050, 731 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 5.1 Hz, 2H), 6.73 (t, *J* = 4.4 Hz, 1H), 5.67 (s, 1H), 4.49 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.57 (s, 3H), 0.75 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.5, 147.3, 145.9, 143.9, 134.0, 132.2, 123.8, 123.6, 123.1, 119.3, 111.5, 110.0, 77.1, 60.6, 55.9, 55.7, 36.1, 25.9 ppm; HRMS calcd. For $C_{20}H_{26}O_5Na^+$ $[M + Na]^+$ 369.1672, found 369.1674.

Alcohols 35d and 35d'



27 (mixture with hemiacetal **27'**) **35d** **35d'**

To a stirred solution of hemiacetal-hydroxy aldehyde mixture (**27+27'**, 1.80 g, 6.24 mmol) in THF (77.0 mL) at -78 ℃ was added allylmagnesium bromide (1.0 M in THF, 16.0 mL, 16.0 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 150 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 9:1) afforded alcohols **35d** and

35d' (~3:1 based on ^{1}H NMR analysis, 2.01 g, 97% combined yield) as an amorphous solid. Small amount of analytically pure isomers **35d** and **35d'** were obtained through column chromatography.

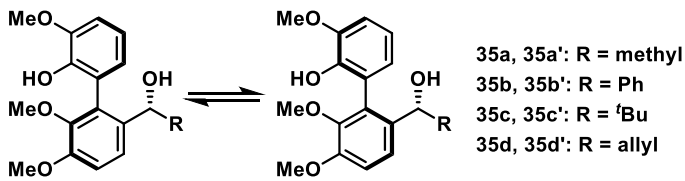
35d (relative stereochemistry arbitrarily assigned): R_f = 0.24 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3454, 3154, 2925, 1574, 1196, 722 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.33 (d, *J* = 10.0 Hz, 1H), 7.01 (d, *J* = 9.7 Hz, 1H), 6.94–6.88 (m, 2H), 6.72 (dd, *J* = 7.1, 2.1 Hz, 1H), 5.82 (s, 1H), 5.67–5.59 (m, 1H), 5.00–4.95 (m, 2H), 4.43 (t, *J* = 7.1 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.56 (s, 3H), 2.52 (s, 1H), 2.50–2.44 (m, 1H), 2.42–2.36 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 146.6, 146.3, 143.1, 135.4, 135.2, 130.4, 122.8, 122.4, 121.3, 119.3, 117.3, 111.9, 109.8, 69.8, 60.4, 55.7, 55.6, 42.4 ppm; HRMS calcd. For $C_{19}H_{22}O_5Na^+$ $[M + Na]^+$ 353.1359, found 353.1357.

35d' (relative stereochemistry arbitrarily assigned): R_f = 0.37 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3539, 3154, 2931, 1600, 1208, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.93–6.84 (m, 2H), 6.70 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.16 (s, 1H), 5.70–5.63 (m, 1H), 4.98–4.91 (m, 2H), 4.40 (t, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.55 (s, 3H), 2.97 (br s, 1H), 2.50–2.32 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 146.4, 146.1, 142.2, 135.5, 134.9, 130.7, 123.7, 122.4, 121.3, 119.5, 116.7, 112.0, 109.7, 69.8, 60.3, 55.6, 55.6, 41.5 ppm; HRMS calcd. For $C_{19}H_{22}O_5Na^+$ $[M + Na]^+$ 353.1359, found 353.1360.

Section 1.3.1

Atropisomer Thermal Stability Studies:

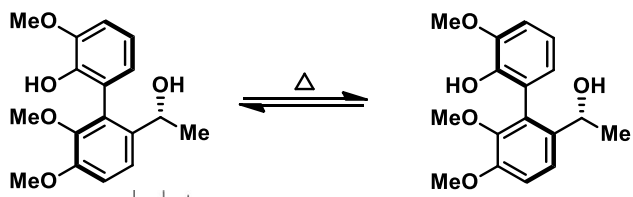
NMR samples of atropisomerically pure (obtained through silica-gel flash column chromatography and purity confirmed by ^{1}H NMR analysis) compounds **35a**, **35a'**, **35b**, **35b'**, **35c**, **35c'**, **35d** and **35d'** in C_6D_6 were subjected to heating (oil bath) and held at temperatures 40 ℃, 70 ℃, 90 ℃, 100 ℃, 110 ℃, 120 ℃ for 1 hour intervals. The samples were then cooled to room temperature after each incremental heating, and degree of atropisomerization analyzed by ^{1}H NMR analysis. Finally, all samples were further heated at 120 ℃ until atropisomeric ratio remained constant.

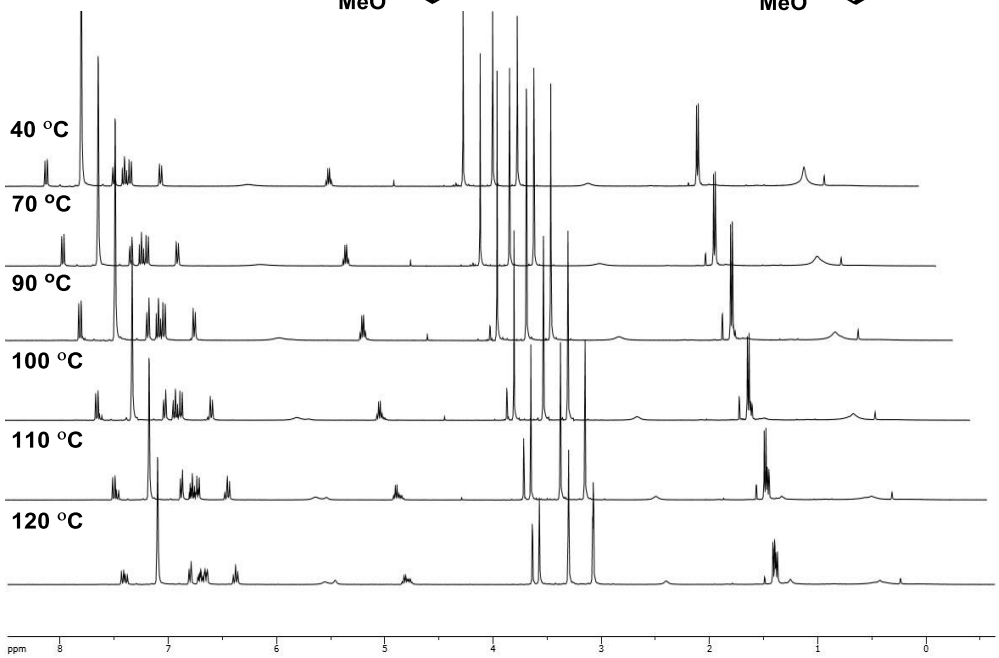


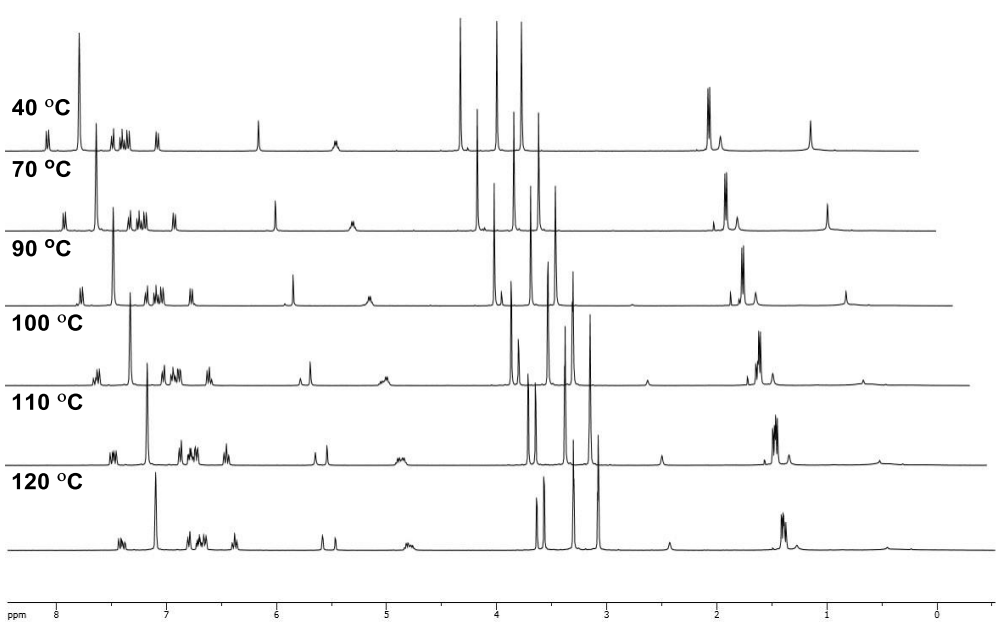
Temp. °C / Compd.	*Temperature-dependent configurational stability study*[a]					
	40	**70**	**90**	**100**	**110**	**120**
35a	1:0	1:0.10	1:0.43	1:0.88	0.79:1	0.69:1
35a'	0:1	0.07:1	0.16:1	0.39:1	0.60:1	0.70:1
35b	1:0	1:0.13	1:0.43	1:0.98	0.68:1	0.63:1
35b'	0:1	0.06:1	0.23:1	0.44:1	0.58:1	0.65:1
35c	1:0	1:0	1:0	1:0.09	1:0.35	0.53:1
35c'	0:1	0:1	0:1	0.06:1	0.18:1	0.52:1
35d	1:0	1:0	1:0.36	0.93:1	0.71:1	0.71:1
35d'	0:1	0:1	0.53:1	0.70:1	0.70:1	0.70:1

[a]*ratio of each atropisomeric pair indicated*

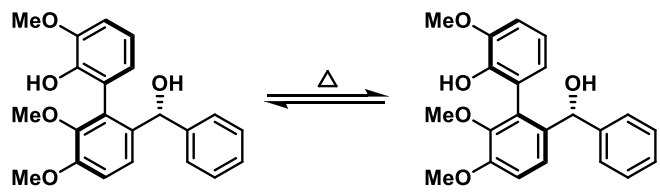
^{1}H NMR (400 MHz, C_6D_6)

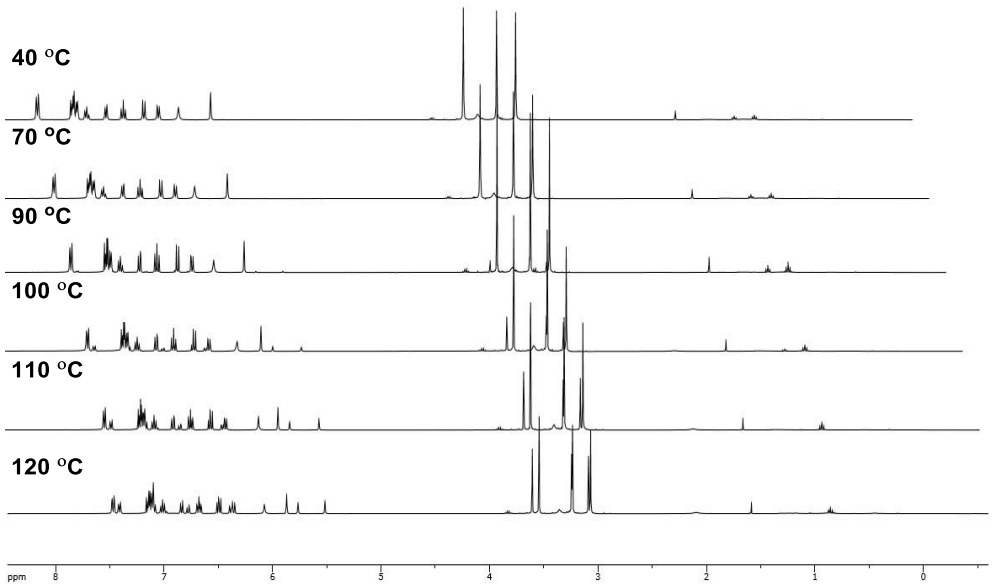


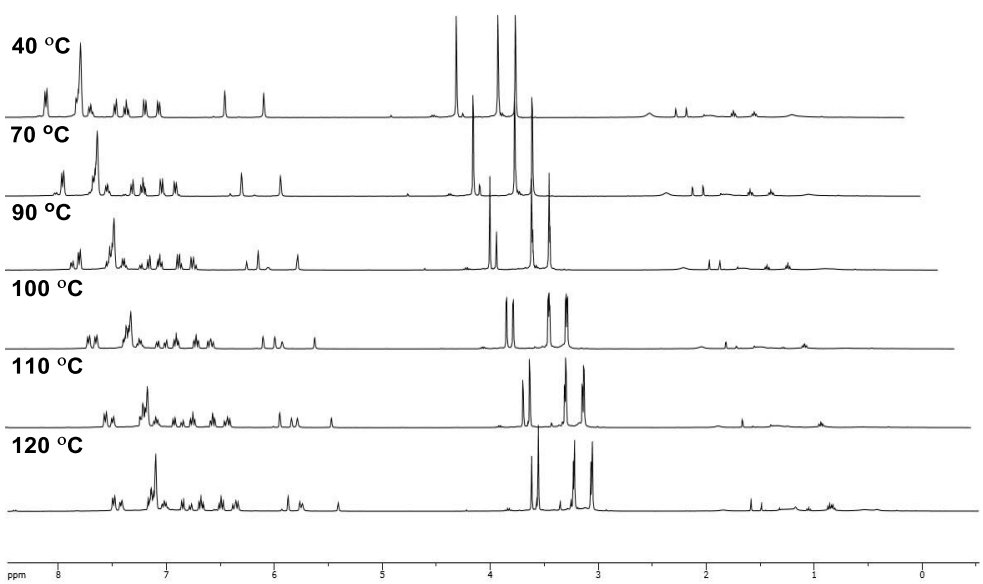




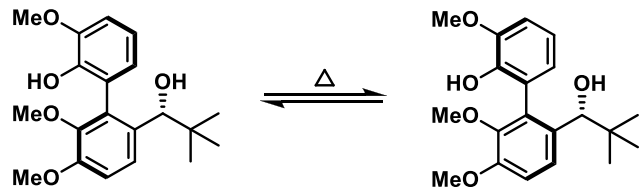
^{1}H NMR (400 MHz, C_6D_6)

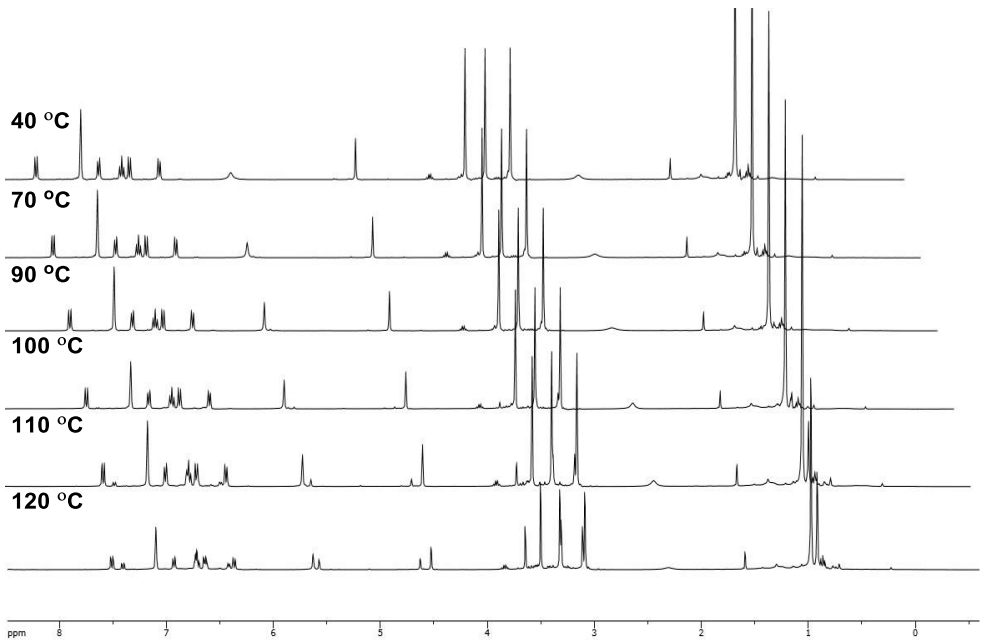


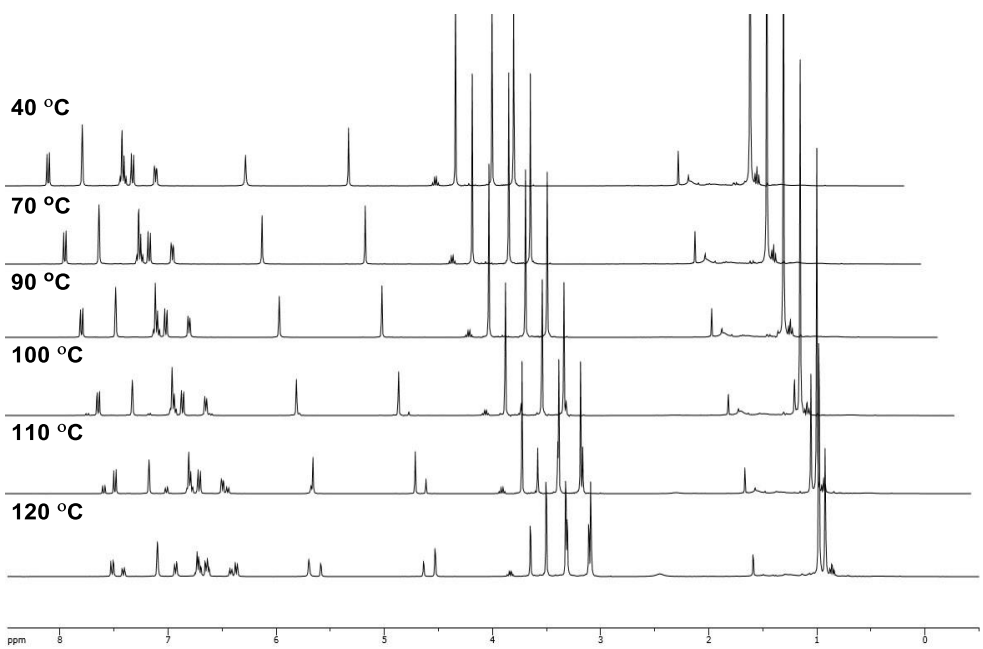




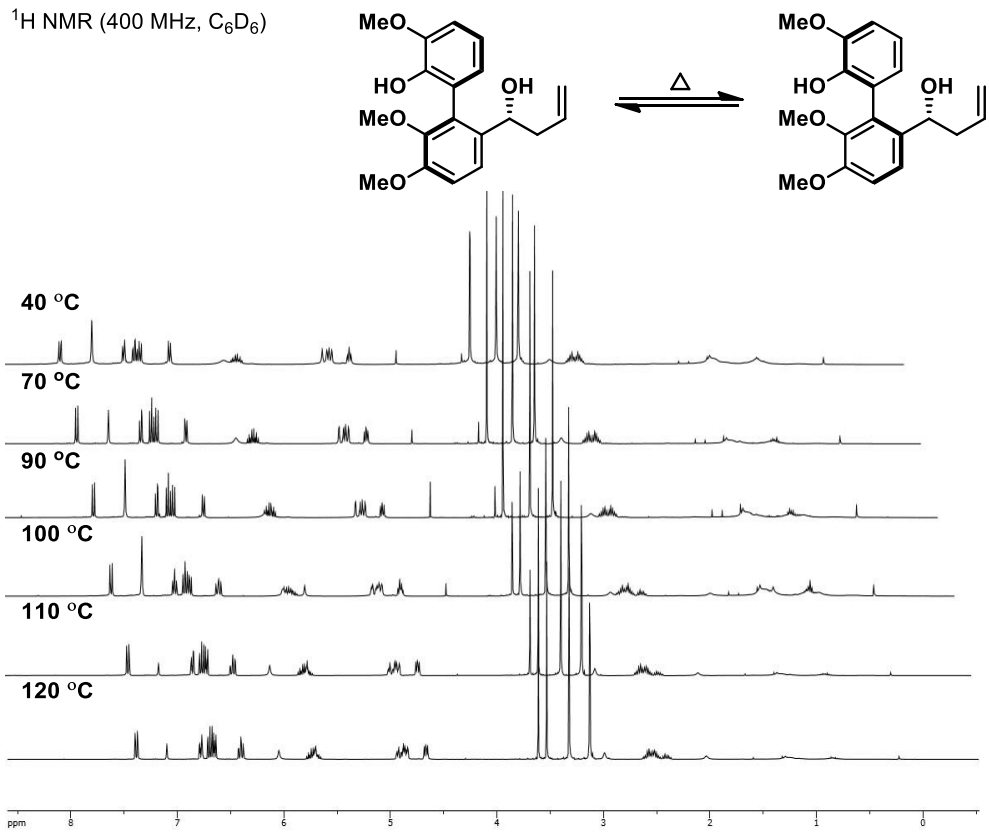
^{1}H NMR (400 MHz, C_6D_6)

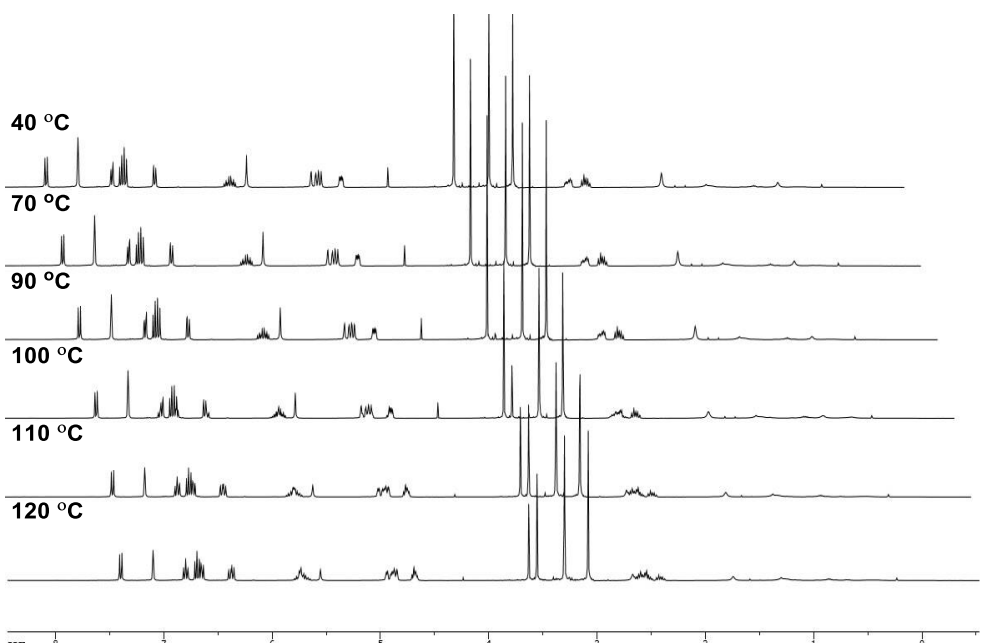






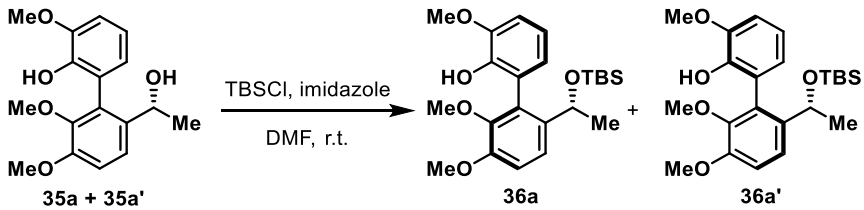
^{1}H NMR (400 MHz, C_6D_6)





Section 1.3.2

TBS Ethers 36a and 36a'



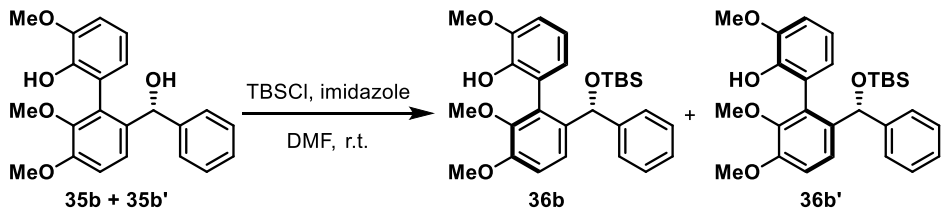
To a stirred solution of alcohol **35a** and **35a'** (335 mg, 1.10 mmol) in DMF (1.50 mL) at room temperature was added TBSCl (664 mg, 4.41 mmol) and imidazole (300 mg, 4.41 mmol). The resulting mixture was stirred for 24 h before it was quenched with NH_4Cl (40 mL, sat. aq.) and water (40 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 12:1) afforded TBS ethers **36a** and **36a'** (382 mg, 83% combined yield) as an amorphous solid. Small amount of analytically pure isomers **36a** and **36a'** were obtained through column chromatography.

36a (relative stereochemistry arbitrarily assigned): R_f = 0.46 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3530, 3054, 2856, 1600, 1551, 733 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.90–6.82 (m, 2H), 6.72–6.69 (m, 1H), 5.59 (s, 1H), 4.59 (q, *J* = 6.2 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.61 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.85 (s, 9H), –0.09 (s, 3H), –0.12 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 146.7, 145.9, 143.4, 138.9, 128.9, 122.9, 122.8, 121.2, 119.3, 112.2, 109.8, 67.5, 60.5, 55.8, 55.7, 26.6, 25.8, 18.1, –4.7, –4.9 ppm; HRMS calcd. For $C_{23}H_{34}O_5SiNa^+$ $[M + Na]^+$ 441.2068, found 441.2069.

36a' (relative stereochemistry arbitrarily assigned): R_f = 0.48 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3541, 3154, 2856, 1642, 1560, 742 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.89–6.79 (m, 2H), 6.73–6.69 (m, 1H), 5.57 (s, 1H), 4.55 (q, *J* = 6.2 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.58 (s, 3H), 1.15 (d, *J* = 6.2 Hz,

3H), 0.86 (s, 9H), –0.08 (s, 3H), –0.12 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 146.7, 145.9, 142.6, 139.2, 128.8, 124.2, 122.6, 120.9, 119.1, 111.9, 109.9, 67.4, 60.6, 56.0, 55.7, 27.2, 25.9, 25.6, 18.0, –3.6, –4.9, –5.2 ppm; HRMS calcd. For $C_{23}H_{34}O_5SiNa^+$ [M + Na]$^+$ 441.2068, found 441.2067.

TBS Ethers 36b and 36b'

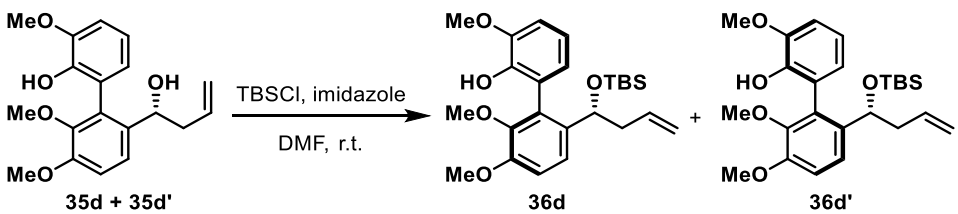


To a stirred solution of alcohols **35b** and **35b'** (160 mg, 0.44 mmol) in DMF (4.00 mL) at room temperature was added TBSCl (263 mg, 1.74 mmol) and imidazole (119 mg, 1.75 mmol). The resulting mixture was stirred for 24 h before it was quenched with NH_4Cl (40 mL, sat. aq.) and water (40 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 12:1) afforded TBS ethers **36b** and **36b'** (168 mg, 80% combined yield) as an amorphous solid. Small amount of analytically pure isomers **36b** and **36b'** were obtained through column chromatography.

36b (relative stereochemistry arbitrarily assigned): R_f = 0.20 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3533, 3038, 2857, 1572, 1458, 725 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 7.72 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 2H), 7.02 (t, *J* = 6.7 Hz, 2H), 6.83 (t, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.96 (s, 1H), 5.14 (s, 1H), 3.70 (s, 3H), 3.31 (s, 3H), 3.14 (s, 3H), 1.03 (s, 9H), 0.07 (s, 3H), –0.03 ppm (s, 3H); ^{13}C NMR (101 MHz, C_6D_6): δ 152.3, 147.5, 147.3, 145.6, 144.9, 137.3, 131.1, 127.9, 127.5, 126.9, 123.9, 123.8, 122.6, 119.4, 112.7, 110.3, 74.2, 60.3, 55.4, 55.3, 26.2, 18.6, –4.4, –4.5 ppm; HRMS calcd. For $C_{28}H_{36}O_5SiNa^+$ [M + Na]$^+$ 503.2224, found 503.2226.

36b' (relative stereochemistry arbitrarily assigned): R_f = 0.22 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3533, 3055, 2956, 1597, 1470, 742 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.59 (t, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 5.91 (s, 1H), 5.66 (s, 1H), 3.62 (s, 3H), 3.35 (s, 3H), 3.19 (s, 3H), 1.04 (s, 9H), 0.16 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (101 MHz, C_6D_6): δ 152.4, 147.5, 146.9, 145.9, 143.5, 137.3, 130.8, 127.7, 127.0, 125.6, 123.4, 121.9, 119.2, 112.5, 110.0, 74.5, 60.4, 55.5, 55.4, 26.3, 18.6, –4.4, –4.7 ppm; HRMS calcd. For $C_{28}H_{36}O_5SiNa^+$ $[M + Na]^+$ 503.2224, found 503.2223.

TBS Ethers 36d and 36d'



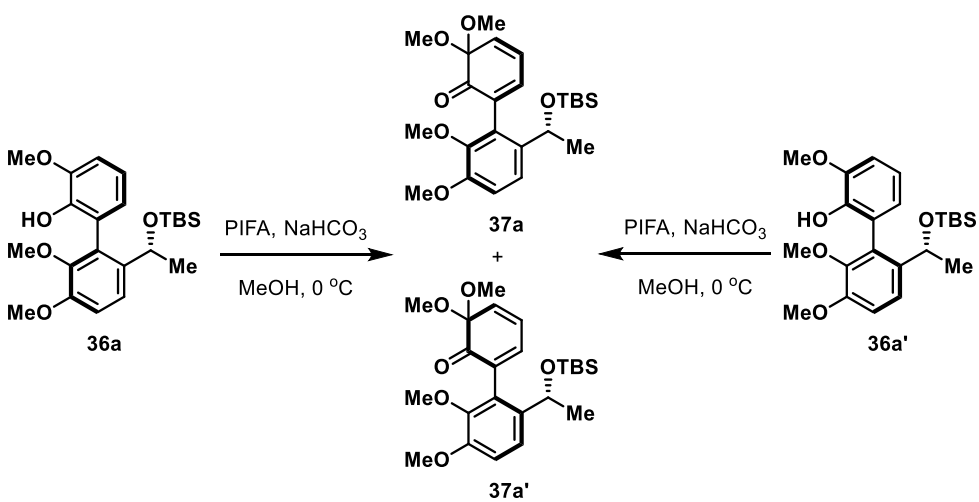
To a stirred solution of alcohols **35d** and **35d'** (170 mg, 0.51 mmol) in DMF (9.00 mL) at room temperature was added TBSCl (310 mg, 2.06 mmol) and imidazole (138 mg, 2.03 mmol). The resulting mixture was stirred for 24 h before it was quenched with NH_4Cl (20 mL, sat. aq.) and water (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 13:1) afforded TBS ethers **36d** and **36d'** (175 mg, 76% combined yield) as an amorphous solid. Small amount of analytically pure isomers **36d** and **36d'** were obtained through column chromatography.

36d (relative stereochemistry arbitrarily assigned): R_f = 0.40 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3455, 2965, 2865, 1703, 1338, 1194, 742 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.94–6.88 (m, 2H), 6.73–6.71 (m, 1H),

5.75–5.68 (m, 1H), 5.61 (br s, 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.80 (d, J = 16.2 Hz, 1H), 4.49–4.44 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.62 (s, 3H), 2.32–2.26 (m, 1H), 2.19–2.10 (m, 1H), 0.85 (s, 9H), –0.11 (s, 3H), –0.18 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 146.7, 146.0, 142.6, 137.2, 136.0, 129.1, 124.2, 122.4, 121.6, 119.1, 116.1, 111.5, 110.0, 71.3, 60.6, 56.0, 55.7, 44.9, 25.9, 18.1, –4.8, –5.2 ppm; HRMS calcd. For $C_{25}H_{36}O_5SiNa^+$ $[M + Na]^+$ 467.2224, found 467.2226.

36d' (relative stereochemistry arbitrarily assigned): R_f = 0.42 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3458, 2918, 2860, 1706, 1344, 1137 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.34 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 6.92–6.89 (m, 2H), 6.73–6.68 (m, 1H), 5.80–5.68 (m, 1H), 5.62 (s, 1H), 4.89 (d, J = 15.2 Hz, 1H), 4.82 (d, J = 15.4 Hz, 1H), 4.48–4.42 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.59 (s, 3H), 2.25–2.09 (m, 2H), 0.87 (s, 9H), –0.10 (s, 3H), –0.17 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 146.7, 146.0, 142.5, 137.2, 136.0, 129.1, 124.2, 122.4, 121.6, 119.1, 116.1, 111.5, 110.0, 71.3, 60.6, 56.0, 55.6, 44.9, 25.9, 18.1, –4.8, –5.2 ppm; HRMS calcd. For $C_{25}H_{36}O_5SiNa^+$ $[M + Na]^+$ 467.2224, found 467.2225.

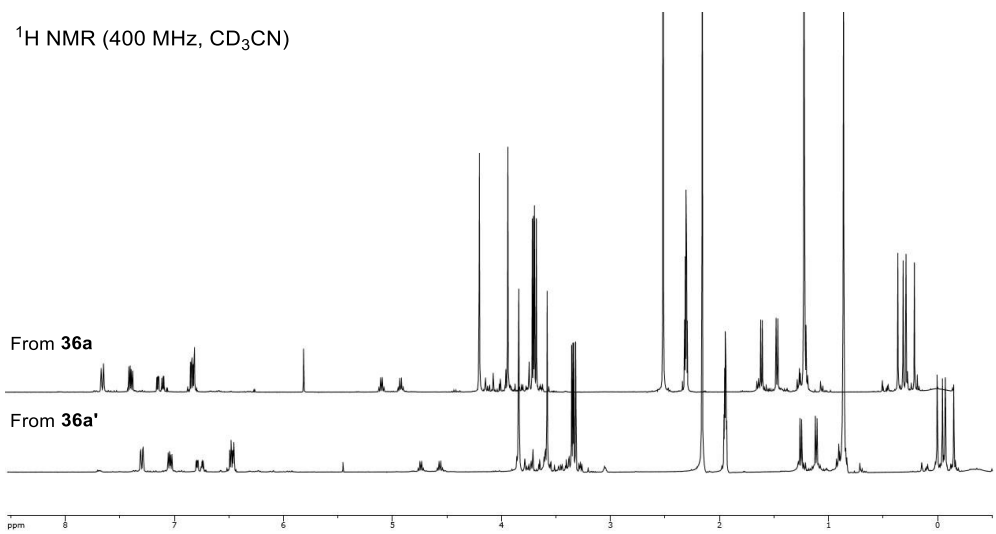
Dienones 37a and 37a'



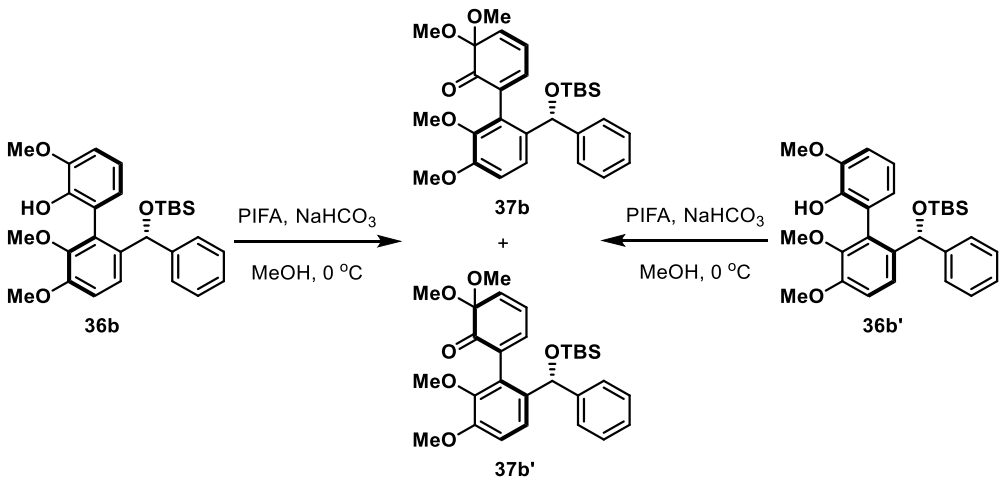
From 36a: To a stirred solution of phenol **36a** (20.0 mg, 48 μmol) in MeOH (3.0 mL) at 0 °C

was added PIFA (20.6 mg, 48 μmol) and $NaHCO_3$ (40.0 mg, 0.48 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (8 mL, sat. aq.), brine (8 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37a** and **37a'** (16.2 mg, 76%) as an orange amorphous solid.

From 36a': To a stirred solution of phenol **36a'** (14.2 mg, 34 μmol) in MeOH (2.1 mL) at 0 ℃ was added PIFA (14.4 mg, 33 μmol) and $NaHCO_3$ (30.0 mg, 0.36 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37a** and **37a'** (9.1 mg, 60%) as an orange amorphous solid.



Dienones 37b and 37b'

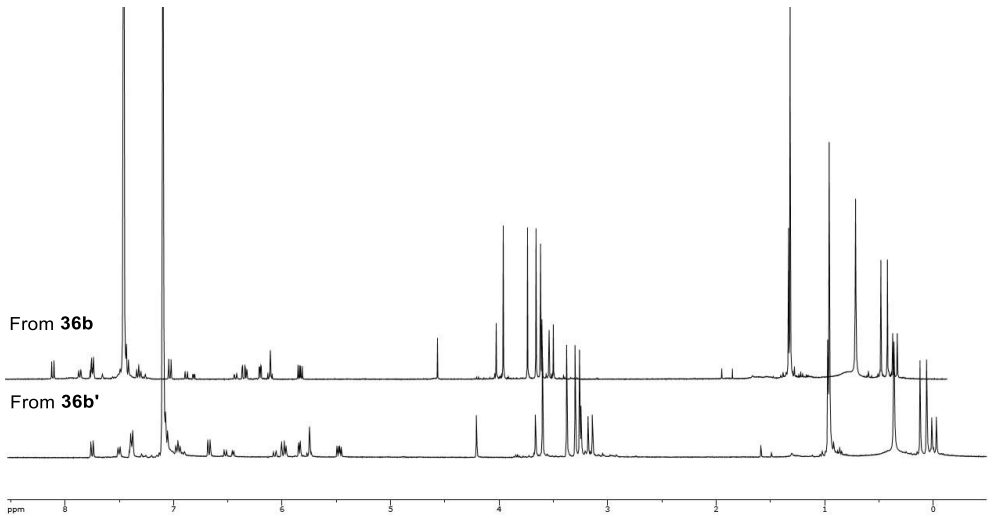


From 36b: To a stirred solution of phenol **36b** (19.0 mg, 40 μmol) in MeOH (3.2 mL) at 0 °C was added PIFA (20.5 mg, 48 μmol) and $NaHCO_3$ (33.2 mg, 0.40 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (4 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (8 mL, sat. aq.), brine (8 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37b** and **37b'** (11.8 mg, 58%) as an orange amorphous solid

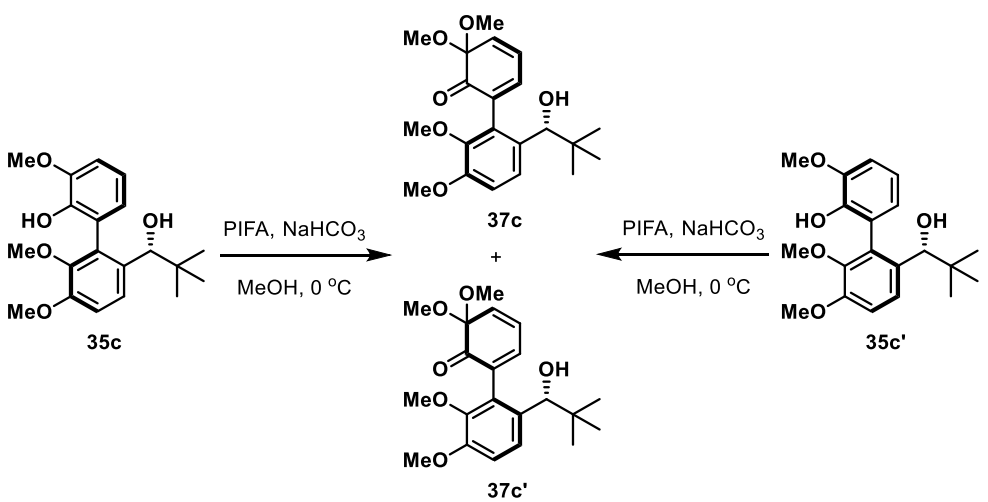
From 36b': To a stirred solution of phenol **36b'** (12.1 mg, 25 μmol) in MeOH (2.0 mL) at 0 °C was added PIFA (13.2 mg, 31 μmol) and $NaHCO_3$ (21.1 mg, 0.25 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column

chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37b** and **37b'** (7.2 mg, 56%) as an orange amorphous solid.

^{1}H NMR (400 MHz, C_6D_6)



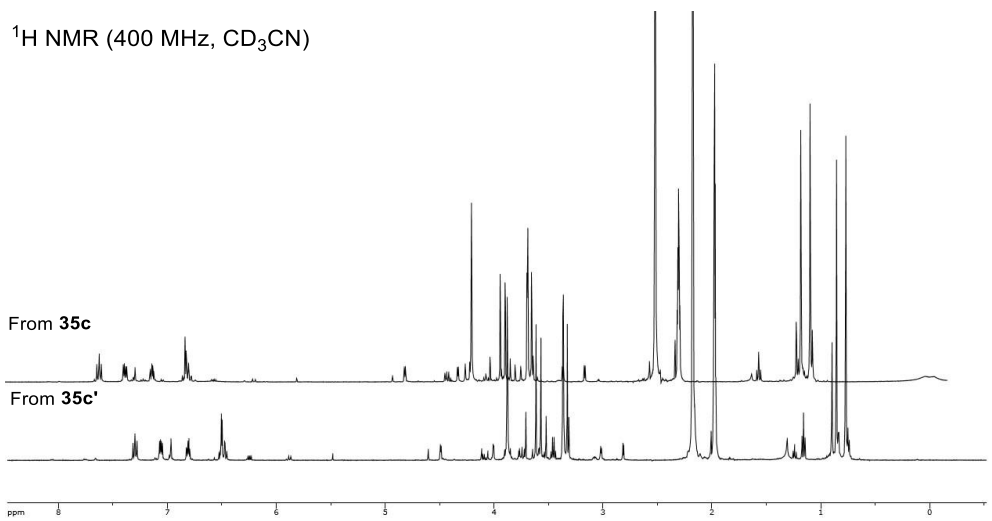
Dienones 37c and 37c'



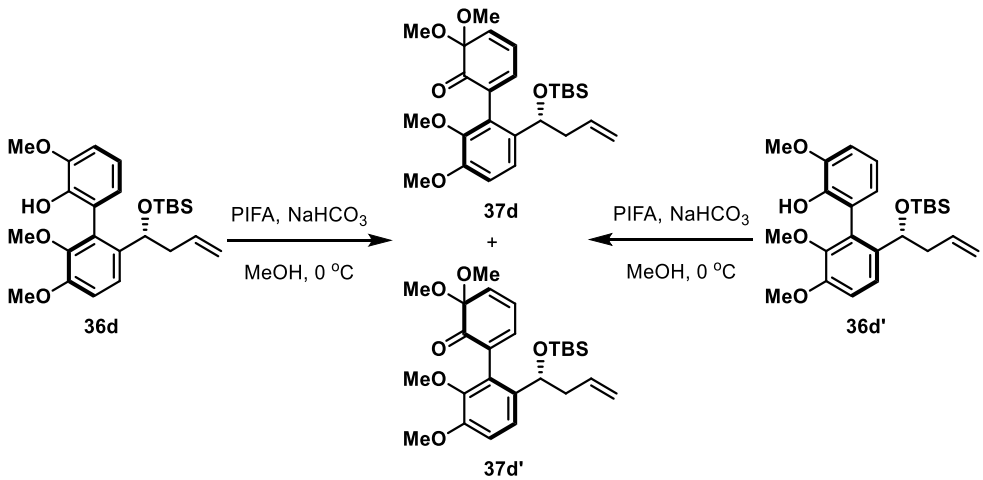
From 35c: To a stirred solution of phenol **35c** (12.8 mg, 37 μmol) in MeOH (2.0 mL) at 0 °C was added PIFA (16.7 mg, 39 μmol) and $NaHCO_3$ (31.1 mg, 0.37 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3

× 5 mL), the combined organic layer was washed with $NaHCO_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37c** and **37c'** (8.5 mg, 61%) as an orange amorphous solid.

From 35c': To a stirred solution of phenol **35c'** (12.0 mg, 35 μmol) in MeOH (2.0 mL) at 0 °C was added PIFA (13.0 mg, 30 μmol) and $NaHCO_3$ (29.1 mg, 0.35 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37c** and **37c'** (6.5 mg, 50%) as an orange amorphous solid.

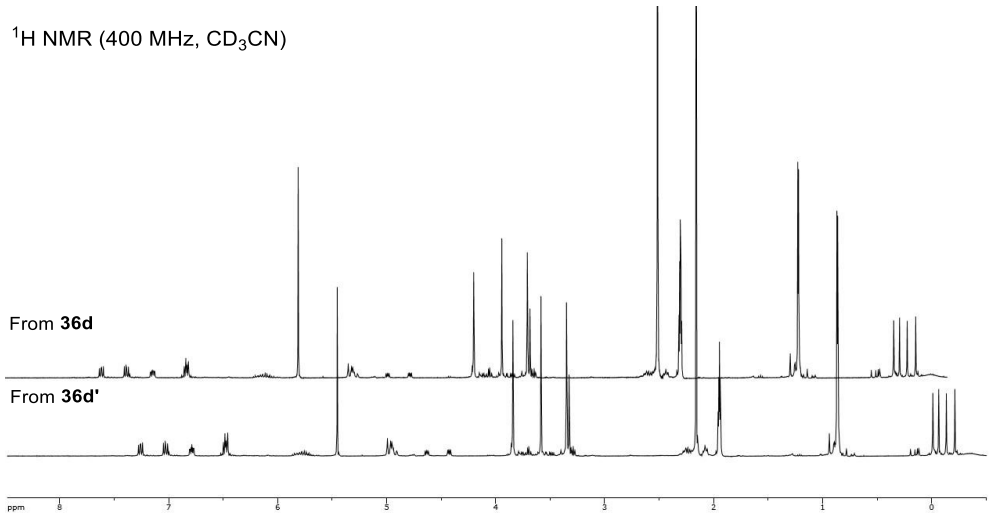


Dienones 37d and 37d'



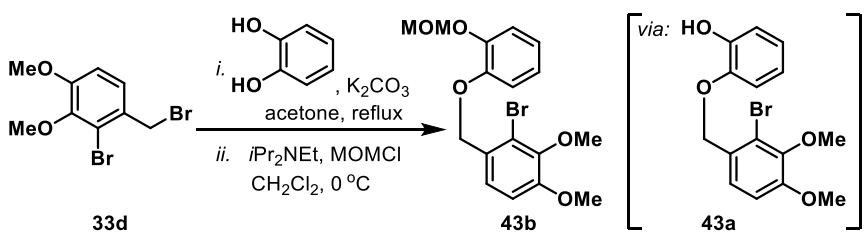
From 36d: To a stirred solution of phenol **36d** (19.1 mg, 43 μmol) in MeOH (3.0 mL) at 0 ℃ was added PIFA (19.4 mg, 45 μmol) and $NaHCO_3$ (34.2 mg, 0.41 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (8 mL, sat. aq.), brine (8 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37d** and **37d'** (10.7 mg, 52%) as an orange amorphous solid

From 36d': To a stirred solution of phenol **36d'** (11.5 mg, 26 μmol) in MeOH (1.8 mL) at 0 ℃ was added PIFA (13.2 mg, 31 μmol) and $NaHCO_3$ (21.0 mg, 0.25 mmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (2 mL). The resulting mixture was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with $NaHCO_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37d** and **37d'** (7.3 mg, 59%) as an orange amorphous solid.



Preparation of biaryl phenol 43 and 43'

Biaryl Ether 43b

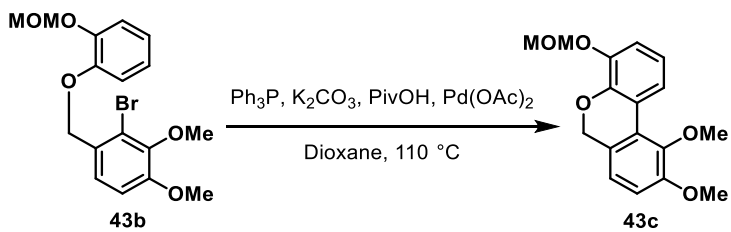


(i) To a stirred solution of dibromide **33d** (450 mg, 1.45 mmol) in acetone (150 mL) at room temperature was added K_2CO_3 (602 mg, 4.36 mmol) followed by catechol (192 mg, 1.74 mmol). The resulting mixture was warmed to reflux and stirred for 16 h before it was cooled to room temperature and diluted with water (100 mL). The resulting mixture was extracted with Et_2O (3 × 75 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl ether **43a** (433 mg, 88%) as an amorphous white solid.

(ii) To a stirred solution of phenol **43a** (obtained above) in CH_2Cl_2 (130 mL) at 0 °C was added *i*Pr_2NEt (0.33 mL, 1.89 mmol) followed by MOMCl (0.12 mL, 1.58 mmol). The resulting mixture was stirred for 2 h before it was warmed to room temperature and quenched

with water (80 mL). The resulting mixture was extracted with Et_2O (3 × 70 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl ether **43b** (416 mg, 85%) as an amorphous white solid. **43b**: R_f = 0.80 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3060, 2940, 1636, 1490, 806, 1002, 750 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.23 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.97–6.87 (m, 3H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.22 (s, 2H), 5.14 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.51 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.1, 149.0, 147.0, 146.4, 129.1, 124.1, 122.8, 121.6, 118.1, 117.7, 114.7, 111.2, 95.8, 70.4, 60.5, 56.2, 56.1 ppm; HRMS calcd. For $C_{17}H_{19}BrO_5Na^+$ $[M + Na]^+$ 405.0308, found 405.0309.

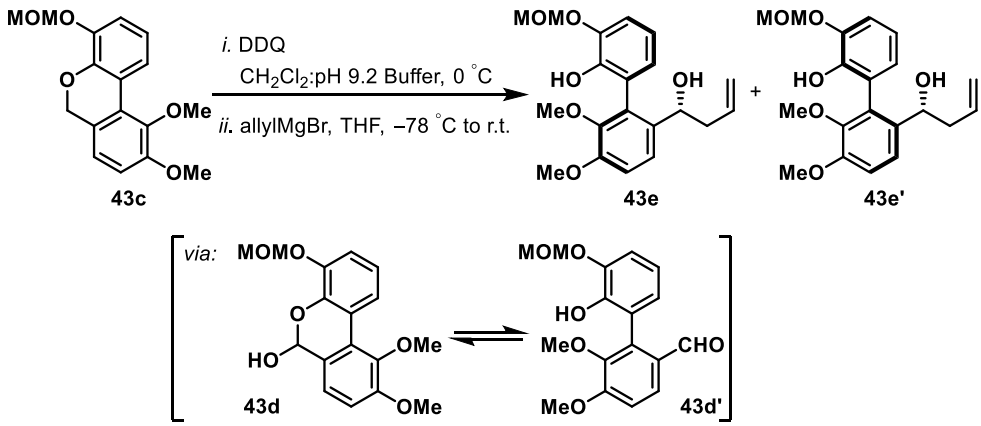
Tricycle 43c



To a stirred solution of biaryl ether **43b** (420 mg, 1.10 mmol) in dioxane (6.5 mL) at room temperature was added K_2CO_3 (454 mg, 3.28 mmol), $Pd(OAc)_2$ (36.9 mg, 0.16 mmol), Ph_3P (129 mg, 0.49 mmol) and PivOH (22.4 mg, 0.22 mmol). The resulting mixture was warmed to 110 ℃ and stirred for 16 h before it was cooled to room temperature and diluted with water (15 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricycle **43c** (235 mg, 71%) as an amorphous white solid. **43c**: R_f = 0.69 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3069, 2838, 1606, 1203, 1458, 1342, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.24 (s, 2H), 4.98 (s, 2H), 3.86 (s,

3H), 3.70 (s, 3H), 3.52 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.2, 146.3, 146.1, 145.4, 125.9, 123.3, 122.9, 121.7, 121.4, 120.0, 116.5, 111.2, 95.5, 68.8, 59.7, 56.1, 55.8 ppm; HRMS calcd. For $C_{17}H_{18}O_5Na^+$ $[M + Na]^+$ 325.1046, found 325.1047.

Alcohols 43e and 43e'

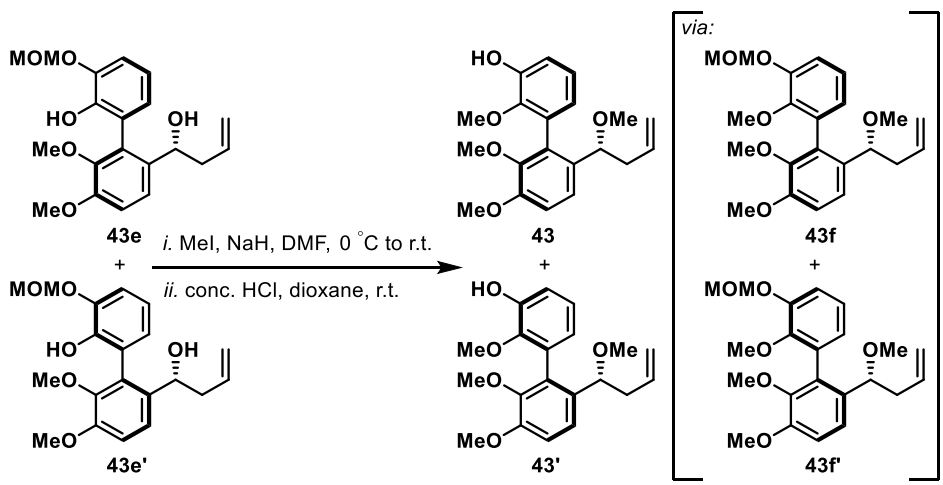


(i) To a stirred solution of biaryl ether **43c** (350 mg, 1.16 mmol) in CH_2Cl_2/pH 9.2 buffer (10:1, 12.1 mL) at 0 ℃ was added DDQ (315 mg, 1.39 mmol). The resulting mixture was stirred for 1.5 h before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed successively with water (until the aqueous layer became colorless), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure afforded crude mixture of hydroxy aldehyde **43d'** and hemiacetal **43d** (**43d'**:**43d~**1:1.4, 324 mg, 88%) as a pale amorphous yellow solid, which was used directly in the subsequent step without further purification.

(ii) To a stirred solution of hemiacetal-hydroxy aldehyde mixture (**43d**+**43d'**, obtained above) in THF (28 mL) at −78 ℃ was added allylmagnesium bromide (1.0 M in THF, 2.00 mL, 2.00 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alcohols **43e** and **43e'**

(~4:1 based on ^{1}H NMR analysis, 359 mg, 98% combined yield) as a clear amorphous solid. **43e**+**43e'**: R_f = 0.35, 0.10 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3126, 2990, 1573, 1421, 1262, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.85 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.31 (br s, 0.75H), 6.01 (br s, 0.25H), 5.70–5.52 (m, 1H), 5.17 (s, 2H), 4.98–4.88 (m, 2H), 4.43 (m, 0.25H), 4.39 (t, *J* = 6.8 Hz, 0.75H), 3.85 (s, 3H), 3.57 (s, 0.75H), 3.53 (s, 2.25H), 3.47 (s, 3H), 2.86 (br s, 0.75H), 2.45–2.22 ppm (m, 2.25H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9, 151.6, 146.2, 146.1, 144.5, 144.0, 143.1, 135.5, 135.4, 135.2, 134.8, 130.7, 130.3, 125.3, 124.5, 123.3, 123.1, 121.3, 119.7, 119.5, 117.2, 116.9, 114.8, 114.6, 112.1, 112.0, 95.9, 69.8, 60.4, 60.3, 56.3, 56.3, 55.6, 55.6, 42.5, 41.5 ppm; HRMS calcd. For $C_{20}H_{24}O_6Na^+$ $[M + Na]^+$ 383.1465, found 383.1464.

Phenols 43 and 43'



(i) To a stirred solution of alcohols **43e** and **43e'** (360 mg, 1.00 mmol) in DMF (13 mL) at 0 °C was added NaH (230 mg, 9.58 mmol) and MeI (0.18 mL, 2.89 mmol). The resulting mixture was warmed to room temperature and stirred for 10 h before it was quenched with MeOH (20 mL) and brine (20 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel,

hexane:EtOAc 6:1) afforded MOM ethers **43f** and **43f'** (~4:1 based on ^{1}H NMR analysis, 338 mg, 87% combined yield) as a yellow amorphous solid. **43f** + **43f'**: R_f = 0.65, 0.70 (silica gel, hexanes:EtOAc 2:1).

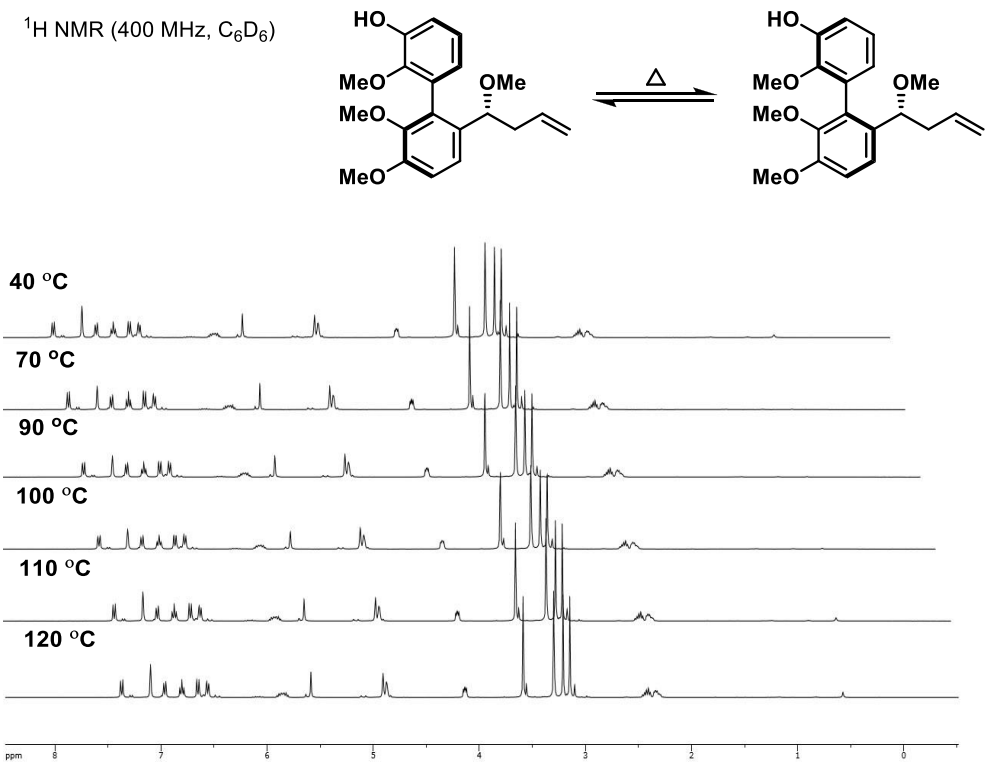
(ii) To a stirred solution of MOM ethers (**43f + 43f'**, obtained above) in dioxane (5.5 mL) was added HCl (0.1 M aq., 0.15 mL, 1.5 mmol). The resulting mixture was stirred for 2 h before it was carefully quenched with $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded phenols **43** (206 mg, 69%) and **43'** (52 mg, 17%) as a white amorphous solids.

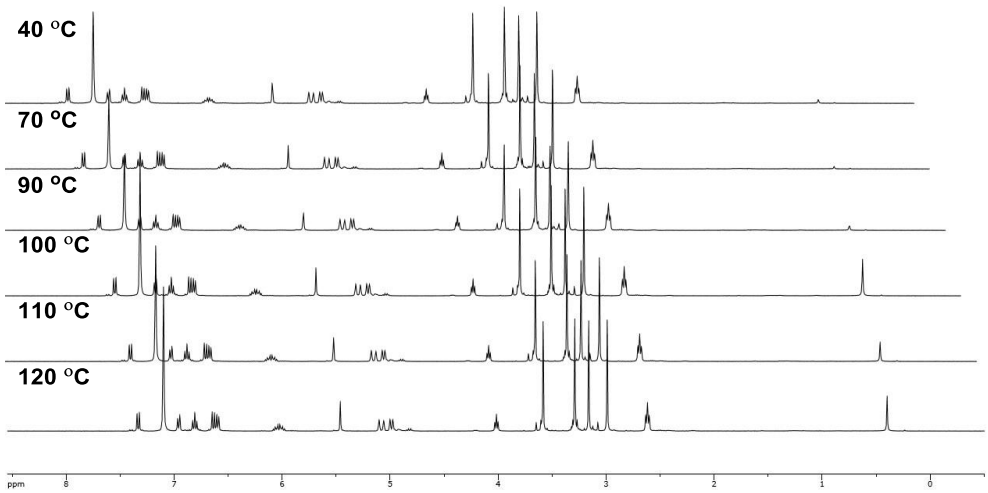
43 (relative stereochemistry arbitrarily assigned): R_f = 0.57 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3692, 3154, 2988, 1215, 908, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.9 Hz, 1H), 7.01–6.93 (m, 3H), 6.57 (d, *J* = 7.4 Hz, 1H), 5.99 (s, 0.75H), 5.94 (s, 0.25H), 5.66–5.54 (m, 1H), 4.86 (d, *J* = 10.1 Hz, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 3.94–3.85 (m, 4H), 3.68 (s, 3H), 3.48 (s, 3H), 3.17 (s, 3H), 2.23–2.12 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 148.8, 145.9, 143.9, 135.1, 133.7, 131.7, 128.6, 123.7, 123.2, 121.0, 116.3, 114.6, 111.9, 79.7, 60.7, 60.4, 56.5, 55.6, 42.3 ppm; HRMS calcd. For $C_{20}H_{24}O_5Na^+$ $[M + Na]^+$ 367.1516, found 367.1514.

43' (relative stereochemistry arbitrarily assigned): R_f = 0.60 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3523, 3052, 2988, 1267, 914, 765 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 7.39 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.15–6.02 (m, 1H), 5.52 (s, 1H), 5.14 (d, *J* = 16.7 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 1H), 3.64 (s, 3H), 3.35 (s, 3H), 3.22 (s, 3H), 3.05 (s, 3H), 2.68 ppm (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.7, 148.8, 145.7, 145.2, 135.8, 133.6, 132.5, 128.9, 123.8, 122.4, 121.8, 116.2, 114.5, 112.2, 79.2, 60.8, 60.5, 56.2, 55.7, 41.2 ppm; HRMS calcd. For $C_{20}H_{24}O_5Na^+$ $[M + Na]^+$ 367.1516, found 367.1517.

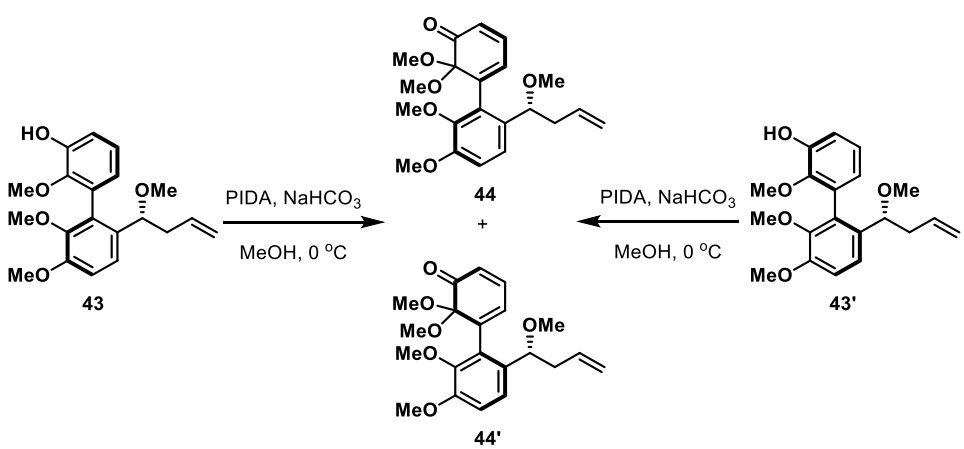
Atropisomer Thermal Stability Studies:

NMR samples of atropisomerically pure **43** and **43'** in C_6D_6 were subjected to heating (oil bath) at temperatures 40 ℃, 70 ℃, 90 ℃, 100 ℃, 110 ℃, 120 ℃ over 1 hour intervals. The samples were then cooled to room temperature after each incremental heating, and degree of atropisomerization analyzed by ^{1}H NMR analysis. Finally, heating was maintained at 120 ℃ until atropisomeric ratio remained constant.





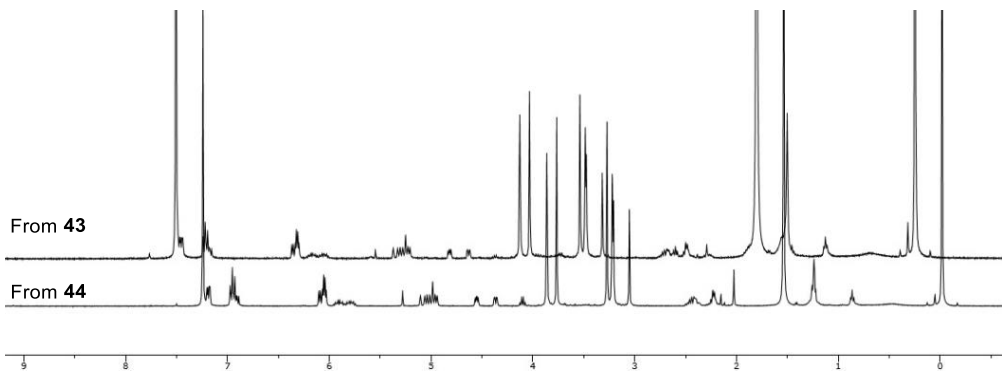
Dienone 44 and 44'



From 43: To a stirred solution of PIDA (34.8 mg, 10.8 mmol) and $NaHCO_3$ (76.0 mg, 0.90 mmol) in MeOH (3 mL) at 0 ℃ was added a solution of phenol **43** (31.0 mg, 90 μmol) in MeOH (1.5 mL) dropwise. The resulting mixture was stirred for 5 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (8 mL, sat. aq.) and water (8 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL), the combined organic layer was washed with $NaHCO_3$ (20 mL, sat. aq.), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexane:EtOAc 6:1) afforded dienones **44** and **44'** (28.0 mg, 83%) as an amorphous yellow solid.

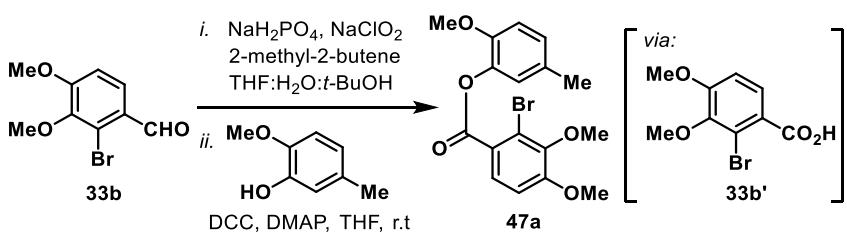
From 43': To a stirred solution of PIDA (4.5 mg, 14 μmol) and $NaHCO_3$ (9.8 mg, 0.12 mmol) in MeOH (0.5 mL) at 0 °C was added a solution of phenol **43'** (4.0 mg, 12 μmol) in MeOH (0.5 mL) dropwise. The resulting mixture was stirred for 5 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (3 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL), the combined organic layer was washed with $NaHCO_3$ (15 mL, sat. aq.), brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexane:EtOAc 6:1) afforded dienones **44** and **44'** (3.2 mg, 74%) as an amorphous yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$)



Preparation of biaryl phenol 47 and 47'

Biaryl Ester 47a

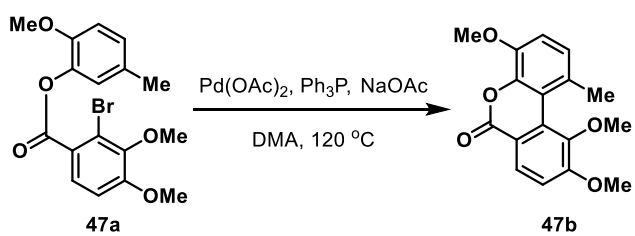


(i) To a stirred solution of aldehyde **33b** (390 mg, 1.59 mmol) in THF/H_2O/*t*BuOH (4:4:1, 36 mL) at room temperature was added NaH_2PO_4 (1.53 g, 12.8 mmol), $NaClO_2$ (576 mg, 6.37 mmol) and 2-methyl-2-butene (1.69 mL, 16.0 mmol). The resulting mixture was stirred for 3 h before it was diluted with EtOAc (30 mL). The resulting mixture was washed with HCl

(1.0 N, 3 × 35 mL), the organic layer was separated and dried (Na_2SO_4), and concentrated under reduced pressure afforded crude acid **33b'** (413 mg, 99%) as an amorphous white solid, which was sufficiently pure based on thin-layer-chromatography and ^{1}H NMR analysis and used directly in the subsequent step without further purification.

(ii) To a stirred solution of acid **33b'** (crude, obtained above) and 5-methylguaiacol (198 mg, 1.43 mmol) in THF (16 mL) at 0 ℃ was added DCC (360 mg, 1.74 mmol) and DMAP (20.0 mg, 0.16 mmol). The resulting mixture was warmed to room temperature and stirred for 10 h before it was filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl ester **47a** (343 mg, 57%) as an amorphous white solid. **47a**: R_f = 0.38 (silica gel, hexanes:EtOAc 3:1); IR (film) ν_{max} 3053, 2940, 1748, 1586, 1127, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.02–6.98 (m, 2H), 6.93 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 2.31 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 156.5, 148.8, 147.0, 139.2, 130.2, 128.4, 126.9, 123.7, 123.3, 118.9, 112.2, 110.2, 60.1, 55.9, 55.7, 20.2 ppm; HRMS calcd. For $C_{17}H_{17}BrO_5Na^+$ $[M + Na]^+$ 403.0152, found 403.0150.

Tricyclic Lactone 47b

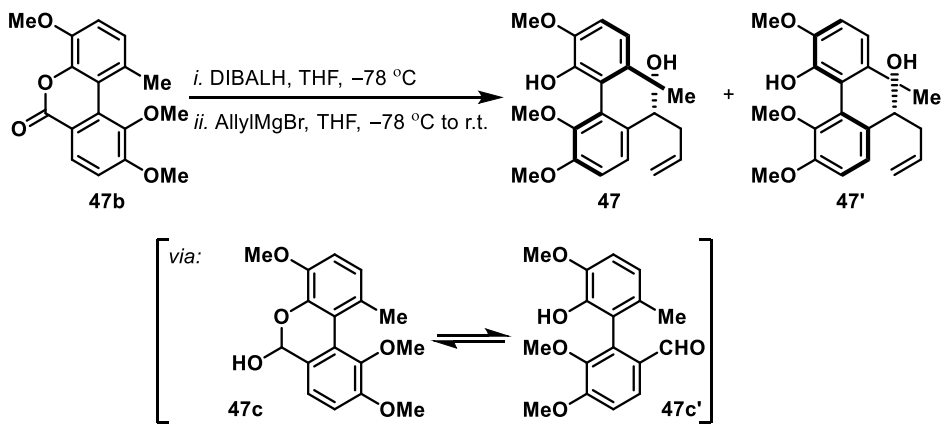


47a **47b**

To a stirred solution of biaryl ester **47a** (340 mg, 0.89 mmol) in DMA (10.5 mL) at room temperature was added NaOAc (146 mg, 1.78 mmol), $Pd(OAc)_2$ (31.4 mg, 0.14 mmol) and Ph_3P (70.2 mg, 0.27 mmol). The resulting mixture was warmed to 100 ℃ and stirred for 24 h before it was cooled to room temperature and diluted with water (30 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure.

Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic lactone **47b** (160 mg, 60%) as an amorphous white solid. **47b**: R_f = 0.30 (silica gel, hexanes:EtOAc 3:1); IR (film) ν_{max} 2992, 1732, 1566, 1257, 1173, 760 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 8.17 (d, *J* = 9.1 Hz, 1H), 7.18 (d, *J* = 9.1 Hz, 1H), 7.10 (d, *J* = 9.1 Hz, 1H), 7.00 (d, *J* = 9.1 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 3.48 (s, 3H), 2.40 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.8, 158.2, 145.3, 145.1, 140.6, 129.0, 128.8, 127.2, 126.6, 117.5, 117.1, 112.3, 112.2, 60.9, 56.3, 56.3, 22.7 ppm; HRMS calcd. For $C_{17}H_{16}O_5Na^+$ $[M + Na]^+$ 323.0890, found 323.0891.

Allylic Alcohols 47 and 47'



(i) To a stirred solution of lactone **47b** (40.0 mg, 0.13 mmol) in THF (3 mL) at −78 °C was added DIBAL-H (1.0 M in hexane, 0.27 mL, 0.27 mmol). The resulting mixture was stirred for 7 min before it was quenched with sodium potassium tartrate (5 mL, sat. aq.) and diluted with EtOAc (5 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 8 mL), the combined organic layer was washed with water (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude mixture of hydroxy aldehyde **47c'** and hemiacetal **47c** (18 mg, 45%) as an amorphous white solid, which was used directly in the subsequent step without further purification.

(ii) To a stirred solution of a hemiacetal hydroxy aldehyde mixture (**47c**+**47c'**, obtained above) in THF (1.0 mL) at −78 °C was added allylmagnesium bromide (1.0 M in Et_2O, 71 μL, 71 μmol). The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alcohols **47** (8.5 mg, 41%) and **47'** (7.5 mg, 37%) as a yellow amorphous solid.

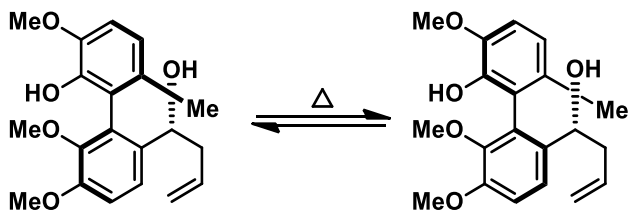
47 (relative stereochemistry arbitrarily assigned): R_f = 0.39 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3151, 2986, 1731, 1266, 1139, 757 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.46 (d, *J* = 8.2 Hz, 1H), 6.71 (t, *J* = 9.2 Hz, 2H), 6.42 (d, *J* = 8.2 Hz, 1H), 5.80–5.68 (m, 1H), 5.60 (s, 1H), 4.90 (d, *J* = 17.0 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 4.67 (t, *J* = 6.1 Hz, 1H), 3.53 (s, 3H), 3.28 (s, 3H), 3.17 (s, 3H), 2.74–2.57 (m, 2H), 2.12 ppm (s, 3H); ^{13}C NMR (101 MHz, C_6D_6): δ 152.8, 147.0, 144.7, 143.0, 135.9, 135.6, 131.3, 130.9, 123.5, 122.1, 121.0, 117.0, 112.7, 109.8, 70.8, 60.2, 55.2, 41.3, 20.0 ppm; HRMS calcd. For $C_{20}H_{24}O_5Na^+$ $[M + Na]^+$ 367.1516, found 367.1517.

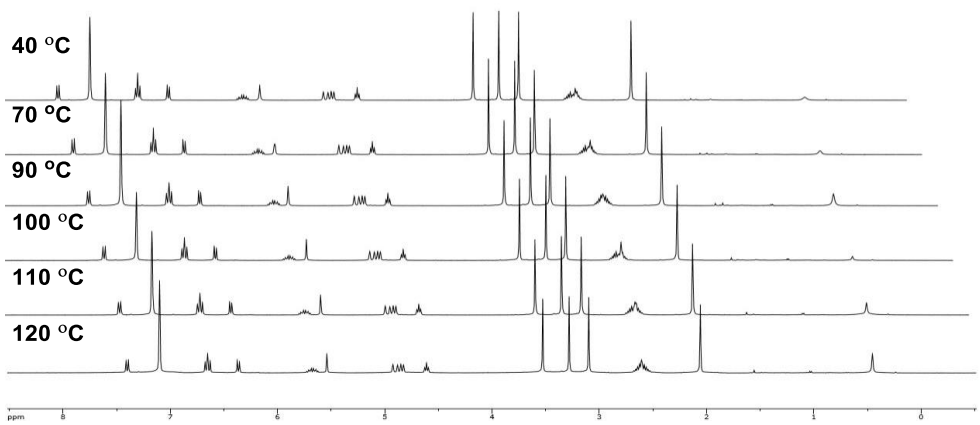
47' (relative stereochemistry arbitrarily assigned): R_f = 0.48 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3054, 2986, 1730, 1266, 1165, 763 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 7.47 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.2, 3.9 Hz, 2H), 6.45 (d, *J* = 8.1 Hz, 1H), 5.80–5.70 (m, 1H), 5.52 (s, 1H), 4.93 (d, *J* = 17.1 Hz, 1H), 4.88 (d, *J* = 9.4 Hz, 1H), 4.51 (dd, *J* = 8.3, 3.4 Hz, 1H), 3.69 (s, 3H), 3.36 (s, 3H), 3.19 (s, 3H), 2.69–2.63 (m, 1H), 2.50–2.41 (m, 1H), 2.10 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1, 146.1, 144.5, 142.9, 135.4, 135.3, 129.8, 129.4, 122.4, 121.6, 120.6, 117.8, 112.0, 110.0, 70.1, 60.4, 56.0, 55.7, 42.9, 19.5 ppm; HRMS calcd. For $C_{20}H_{24}O_5Na^+$ $[M + Na]^+$ 367.1516, found 367.1516.

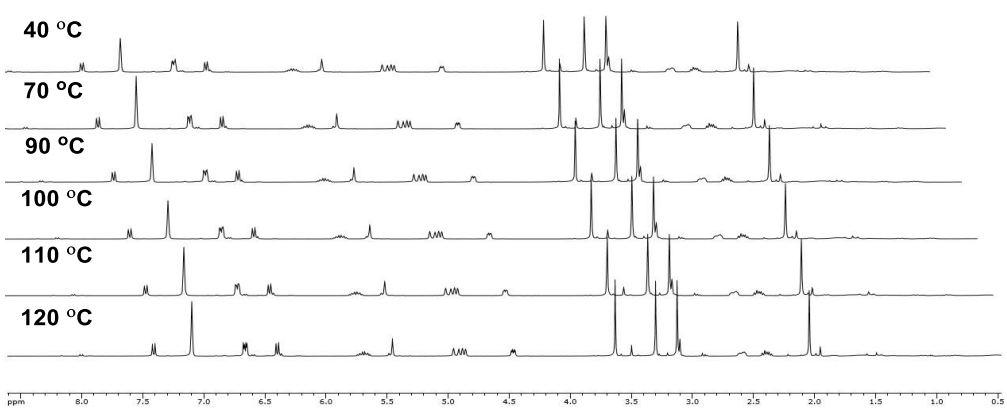
Atropisomer Thermal Stability Studies:

NMR samples of atropisomerically pure **47** and **47'** in C_6D_6 were subjected to heating (oil bath) at temperatures 40 ℃, 70 ℃, 90 ℃, 100 ℃, 110 ℃, 120 ℃ over 1 hour intervals. The samples were then cooled to room temperature after each incremental heating, and degree of atropisomerization analyzed by ^{1}H NMR analysis. Finally, heating was maintained at 120 ℃ until atropisomeric ratio remained constant.

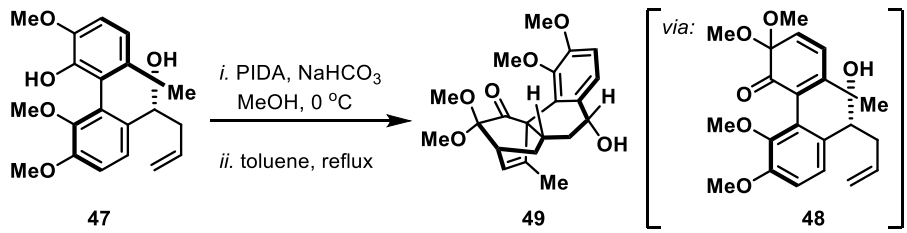
^{1}H NMR (400 MHz, C_6D_6)







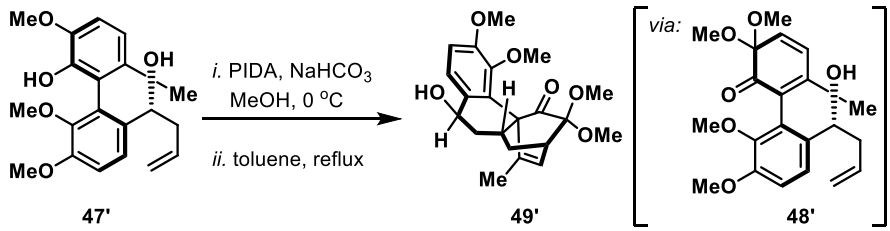
Tetracycle 49



(i) To a stirred solution of PIDA (9.5 mg, 29 μmol) and $NaHCO_3$ (24.9 mg, 0.30 mmol) in MeOH (1.0 mL) at 0 °C was added a solution of phenol **47** (8.5 mg, 25 μmol) in MeOH (0.2 mL) dropwise. The resulting mixture was stirred for 5 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (3 mL). The resulting mixture was extracted with Et_2O (3 × 8 mL), the combined organic layer was washed with $NaHCO_3$ (12 mL, sat. aq.), brine (12 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded dienone **48** as an amorphous yellow solid.

ii) A solution of dienone **48** (obtained above) in toluene (1.0 mL) was warmed to reflux and stirred for 4 h before it was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tetracycle **49** (6.5 mg, 70% over two steps) as an amorphous yellow solid. **49'** (relative stereochemistry arbitrarily assigned): R_f = 0.48 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3478, 2957, 1747, 1467, 1239, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.20 (d, *J* = 6.7 Hz, 1H), 4.78–4.67 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.37 (s, 6H), 3.00 (d, *J* = 7.7 Hz, 1H), 2.26 (t, *J* = 9.6 Hz, 1H), 2.15–2.08 (m, 1H), 2.02–1.97 (m, 1H), 1.69 (d, *J* = 7.7 Hz, 1H), 1.53 (s, 3H), 1.30 (q, *J* = 12.5, 1H), 1.01–0.96 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.5, 151.4, 146.8, 137.1, 134.3, 126.5, 125.1, 121.3, 113.0, 94.9, 69.3, 59.9, 59.2, 55.8, 50.8, 49.2, 38.4, 37.5, 36.5, 29.1, 21.0 ppm; HRMS calcd. For $C_{21}H_{26}O_6Na^+$ $[M + Na]^+$ 397.1622, found 397.1624.

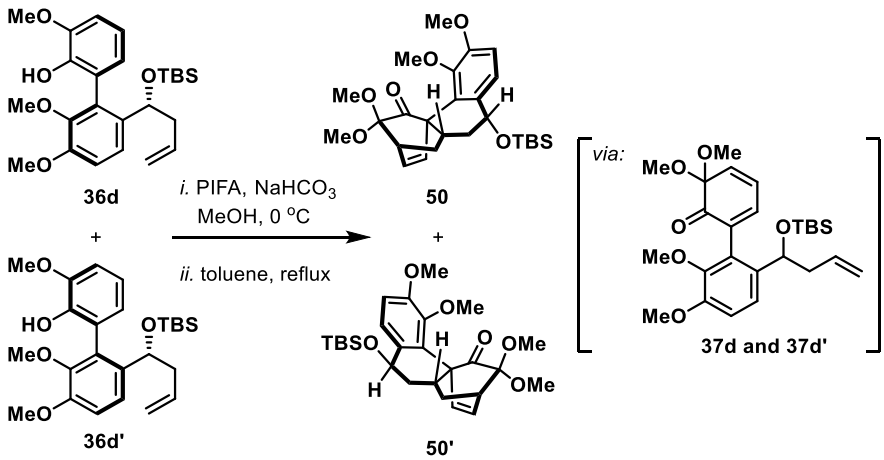
Tetracycle 49'



(i) To a stirred solution of PIDA (8.4 mg, 26 μmol) and $NaHCO_3$ (18.3 mg, 0.22 mmol) in MeOH (1.0 mL) at 0 °C was added a solution of phenol **47'** (7.5 mg, 22 μmol) in MeOH (0.2 mL) dropwise. The resulting mixture was stirred for 5 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (3 mL, sat. aq.) and water (3 mL). The resulting mixture was extracted with Et_2O (3 × 6 mL), the combined organic layer was washed with $NaHCO_3$ (10 mL, sat. aq.), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded dienone **48'** as an amorphous yellow solid.

ii) A solution of dienone **48'** (obtained above) in toluene (1.0 mL) was warmed to reflux and stirred for 4 h before it was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tetracycle **49'** (5.0 mg, 61% over two steps) as an amorphous yellow solid. **49'** (relative stereochemistry arbitrarily assigned): R_f = 0.49 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3469, 2956, 1747, 1464, 1239, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.20 (d, *J* = 7.4 Hz, 1H), 4.69 (br s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.38 (s, 6H), 3.04–3.01 (m, 1H), 2.57–2.46 (m, 1H), 2.28 (t, *J* = 11.9 Hz, 1H), 1.87 (d, *J* = 13.5 Hz, 1H), 1.77 (m, 1H), 1.51 (s, 3H), 1.53–1.46 (m, 1H) 1.00–0.95 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5, 152.3, 147.3, 135.9, 132.1, 127.1, 125.4, 125.0, 113.0, 95.0, 67.8, 59.9, 58.8, 55.8, 50.8, 49.2, 37.6, 36.2, 32.2, 28.7, 20.8 ppm; HRMS calcd. For $C_{21}H_{26}O_6Na^+$ $[M + Na]^+$ 397.1622, found 397.1623.

Tetracycles 50 and 50'



(i) To a stirred solution of phenol **36d** and **36d'** (8.50 g, 19.1 mmol) in MeOH (300 mL) at 0 °C was added PIFA (9.40 g, 21.9 mmol) and $NaHCO_3$ (15.0 g, 179 mmol). The resulting mixture was stirred for 15 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (100 mL, sat. aq.) and water (100 mL). The resulting mixture was extracted with Et_2O (3 × 75 mL), the combined organic layer was washed with $NaHCO_3$ (100 mL, sat. aq.), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienones **37d** and **37d'** as an orange amorphous solid.

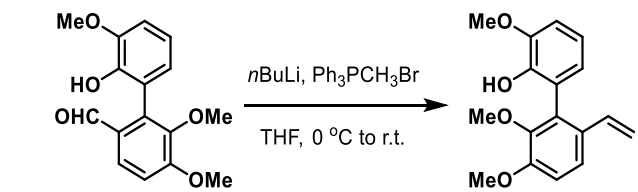
(ii) Dienones **37d** and **37d'** (obtained above) was redissolved in toluene (550 mL), and warmed to reflux and stirred for 1 h before it was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded tetracycles **50** and **50'** (~1:1 based on ^{1}H NMR analysis, 6.57 g, 72% over two steps) as an amorphous yellow solid. **50**+**50'**: R_f = 0.59 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3154, 2983, 1702, 1210, 1052, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.6 Hz, 0.5H), 6.92–6.85 (m, 1.5H), 6.42–6.38 (m, 1H), 5.82 (d, *J* = 8.1 Hz, 0.4H), 5.73 (d, *J* = 8.1 Hz, 0.6H), 4.76–4.66 (m, 1H), 3.86 (s, 1.8H), 3.85 (s, 1.2H), 3.81 (s, 1.8H), 3.79 (s, 1.2H), 3.39 (s, 3.6H), 3.38 (s, 2.4H), 3.10 (br s, 1H), 2.74–2.66 (m, 1H), 2.27–2.25 (m, 1H), 2.22–2.13 (m, 1H), 1.88–1.80 (m, 0.4H), 1.73 (dt, *J* = 13.4, 2.7

Hz, 0.6H), 1.54–1.45 (m, 1H), 0.95 (s, 3.6H), 0.84 (s, 5.4H), 0.18 (s, 1.2H), 0.12 (s, 1.2H), 0.05 (s, 1.8H), 0.00 ppm (s, 1.8H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.7, 199.5, 151.9, 151.4, 147.0, 146.7, 134.6, 132.2, 131.4, 131.2, 130.8, 129.1, 128.9, 128.5, 128.2, 125.0, 121.1, 112.6, 112.1, 94.7, 94.7, 70.0, 68.2, 60.2, 60.1, 55.9, 55.8, 55.7, 55.4, 50.8, 50.7, 49.3, 49.3, 38.2, 37.9, 37.8, 37.6, 34.5, 31.6, 29.7, 28.5, 28.2, 25.9, 25.8, 22.6, 18.2, 18.0, 14.1, –4.1, –4.2, –4.4, –4.8 ppm; HRMS calcd. For $C_{26}H_{38}O_6SiNa^+$ $[M + Na]^+$ 497.2330, found 497.2333.

Section 1.4

Preparation of biaryl phenol 51 and 51'

Alkene 51a

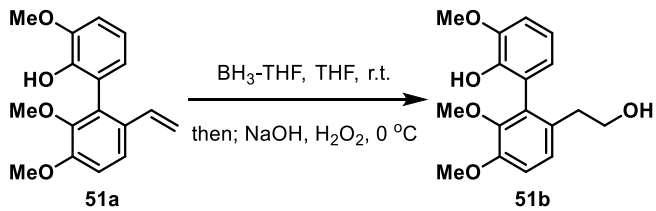


27 (mixture with hemiacetal **27'**) **51a**

To a stirred solution of methyltriphenylphosphonium bromide (dried over P_2O_5, 10.0 g, 30.0 mmol) in THF (150 mL) at 0 ℃ was added *n*BuLi (2.5 M in hexanes, 8.90 mL, 22.3 mmol). The resulting mixture was stirred for 15 min before a solution of hemiacetal-hydroxy aldehyde mixture (**27'**+**27**, 1.60 g, 5.55 mmol) in THF (30 mL) was added. The resulting mixture was stirred for 1 h before it was warmed to room temperature and quenched with NH_4Cl (40 mL, sat. aq.) and water (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL), the combined organic layer was washed with water (80 mL), brine (80 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alkene **51a** (1.13 g, 71%) as an amorphous white solid. **51a**: R_f = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3533, 3086, 3009, 1621, 1594, 1471, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.93–6.89 (m, 2H), 6.76–6.72 (m, 1H), 6.37 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.68 (s, 1H), 5.56 (d, *J* = 17.5 Hz, 1H), 5.01 (d, *J* = 10.9 Hz, 1H), 3.93 (s, 3H),

3.91 (s, 3H), 3.62 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.3, 146.7, 146.6, 143.1, 134.6, 131.0, 130.3, 123.7, 122.7, 120.6, 119.3, 112.7, 112.0, 109.9, 60.6, 60.6, 55.8 ppm; HRMS calcd. For $C_{17}H_{18}O_4Na^+$ $[M + Na]^+$ 309.1097, found 309.1095.

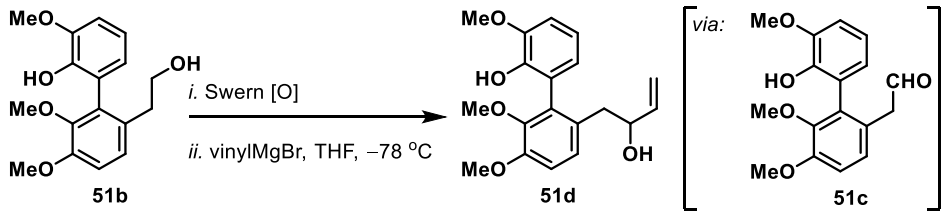
Alcohol 51b



51a **51b**

To a stirred solution of alkene **51a** (1.10 g, 3.84 mmol) in THF (100 mL) at –78 °C was added borane tetrahydrofuran complex (1.0 M in THF, 38.4 mL, 38.4 mmol). The resulting mixture was warmed to room temperature and stirred for 4 h before it was cooled to 0 °C and treated with NaOH (2.0 N aq., 5.16 mL, 10.3 mmol) and H_2O_2 (34.5% aq., 5.16 mL, 52.3 mmol). The resulting mixture was stirred for 4 h before it was quenched with NH_4Cl (80 mL, sat. aq.) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded alcohol **51b** (1.02 g, 87%) as an amorphous white solid. **51b**: R_f = 0.19 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3620, 3233, 3004, 1620, 1459, 946 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): δ 6.94 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.76 (t, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 7.9 Hz, 1H), 3.68 (s, 3H), 3.65–3.59 (m, 2H), 3.37 (s, 3H), 3.15 (s, 3H), 2.78–2.61 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 147.7, 146.7, 142.8, 132.3, 130.1, 124.9, 123.4, 123.3, 119.5, 112.0, 109.8, 63.1, 60.5, 55.8, 55.8, 35.8 ppm; HRMS calcd. For $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$ 327.1203, found 327.1203.

Allylic Alcohol 51d

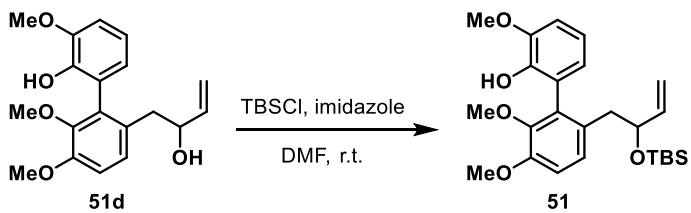


(i) To a stirred solution of oxalyl chloride (0.43 mL, 5.01 mmol) in CH_2Cl_2 (13.0 mL) at –78 °C was added DMSO (0.70 mL, 9.86 mmol) dropwise. The resulting mixture was stirred for 15 min before a solution of alcohol **51b** (150 mg, 0.49 mmol) in CH_2Cl_2 (13.0 mL) was added. The resulting mixture was stirred for 1 h before Et_3N (2.10 mL, 14.8 mmol) was added, and the resulting mixture was stirred for 1 h before it was warmed to room temperature and quenched with NH_4Cl (80 mL, sat. aq.) and water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford crude aldehyde **51c** (112 mg, 75%) as an amorphous yellow solid, which was used directly in the following step without further purification.

(ii) To a stirred solution of crude aldehyde (**51c**, obtained via above procedure, 380 mg, 1.26 mmol) in THF (50.0 mL) at –78 °C was added vinyl magnesium bromide (1.0 M in THF, 7.54 mL, 7.54 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 150 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded allylic alcohol **51d** (370 mg, 89%) as an amorphous yellow solid. **51d**: R_f = 0.30 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3690, 3528, 3054, 1602, 1264, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of atropisomers): δ 7.06 (t, J = 7.9 Hz, 1H), 6.97–6.84 (m, 3H), 6.75–6.73 (m, 1H), 5.84 (s, 1H), 5.78–5.67 (m, 1H), 5.12–4.94 (m, 2H), 4.17–4.03 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.60 (s, 1.5H), 3.58 (s, 1.5H), 2.74–2.68 (m, 1H), 2.59–2.49 (m, 1H),

1.74 ppm (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of atropisomers): δ 151.4, 151.4, 147.1, 147.0, 146.8, 146.7, 143.0, 142.5, 140.5, 132.4, 132.2, 129.7, 129.5, 125.9, 125.2, 123.5, 123.4, 123.4, 123.2, 119.6, 119.5, 114.3, 114.0, 112.0, 111.7, 109.9, 109.8, 73.4, 72.3, 60.5, 60.4, 55.9, 55.8, 55.8, 55.7, 41.0, 40.6 ppm; HRMS calcd. For $C_{19}H_{22}O_5Na^+$ $[M + Na]^+$ 353.1359, found 353.1362.

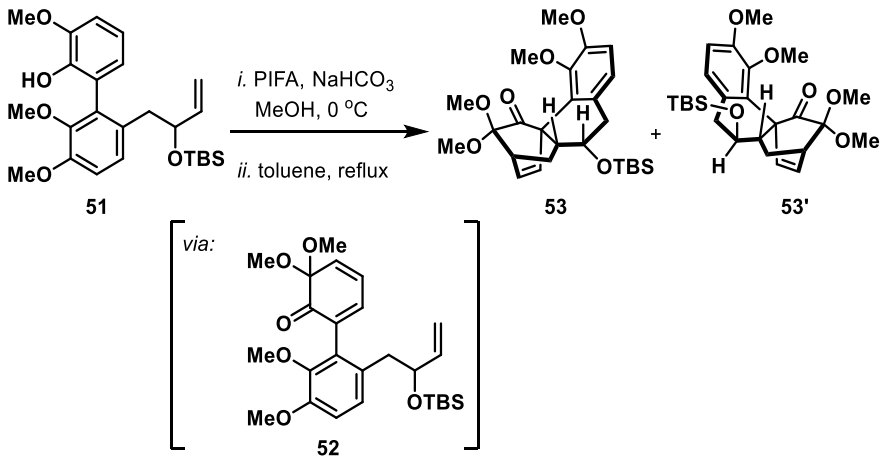
TBS Ether 51



51d **51**

To a stirred solution of alcohol **51d** (134 mg, 0.41 mmol) in DMF (5.0 mL) at room temperature was added TBSCl (183 mg, 1.21 mmol) and imidazole (82.8 mg, 1.22 mmol). The resulting mixture was stirred for 24 h before it was quenched with NH_4Cl (10 mL, sat. aq.) and water (10 mL). The resulting mixture was extracted with Et_2O (3 × 20 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded TBS ether **51** (127 mg, 70%) as an amorphous solid. **51**: R_f = 0.37 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3622, 3460, 3155, 2987, 1590, 1280, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.4 Hz, 1H), 6.95–6.84 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 5.69–5.58 (m, 2H), 4.98–4.82 (m, 2H), 4.10–3.92 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.58 (s, 3H), 2.66 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.53–2.48 (m, 1H), 0.80 (s, 9H), –0.18 (s, 3H), –0.26 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 151.2, 146.9, 146.8, 146.8, 142.9, 142.8, 141.2, 141.2, 132.0, 131.8, 130.4, 130.2, 126.9, 126.6, 123.8, 123.5, 123.4, 119.3, 119.3, 113.3, 113.2, 111.5, 109.8, 73.7, 73.5, 60.5, 55.9, 55.8, 55.8, 42.3, 42.2, 25.8, 25.8, 18.1, –5.1, –5.1, –5.3, –5.4 ppm; HRMS calcd. For $C_{25}H_{36}O_5SiNa^+$ $[M + Na]^+$ 467.2224, found 467.2226.

Tetracycle 53 and 53'



(i) To a stirred solution of phenol **51** (135 mg, 0.30 mmol) in MeOH (20.0 mL) at 0 °C was added PIFA (137 mg, 0.32 mmol) and $NaHCO_3$ (860 mg, 10.2 mmol). The resulting mixture was stirred for 15 min before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (20 mL, sat. aq.) and water (10 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), the combined organic layer was washed with $NaHCO_3$ (50 mL, sat. aq.), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:Et_2O 15:1) afforded dienone **52** as an orange amorphous solid.

(ii) Dienone **52** (obtained above) was redissolved in toluene (30.0 mL), and warmed to reflux and stirred for 1 h before it was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded tetracycles **53** and **53'** (~4:1 based on ^{1}H NMR analysis, 79.6 mg, 55% over two steps) as an amorphous yellow solid. **53**+**53'**: R_f = 0.37 (silica gel, hexanes:EtOAc 4:1); IR (film) ν_{max} 3105, 3000, 1710, 1468, 808, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–6.68 (m, 2H), 6.43 (t, *J* = 7.6 Hz, 0.7H), 6.16 (t, *J* = 7.6 Hz, 0.3H), 5.77 (d, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.60–3.50 (m, 1H), 3.39 (s, 6H), 3.18–3.05 (m, 1H), 2.92–2.80 (m, 1H), 2.80–2.68 (m, 1H), 2.22–2.10 (m, 2H), 1.42–1.30 (m, 1H), 0.90 (s, 7.2H), 0.71 (s, 1.8H), 0.07 (s, 2.2H), 0.05 (s, 2.2H), 0.00 (s, 0.9H), –0.08 ppm (s, 0.7H); ^{13}C NMR (101 MHz, $CDCl_3$): δ

199.3, 150.9, 147.3, 132.1, 131.3, 128.9, 128.0, 123.6, 113.0, 94.7, 71.3, 60.2, 57.0, 55.9, 50.7, 49.4, 44.4, 40.3, 37.7, 25.8, 25.6, 18.0, –3.9, –4.7 ppm; HRMS calcd. For $C_{26}H_{38}O_6SiNa^+$ $[M + Na]^+$ 497.2330, found 497.2327.

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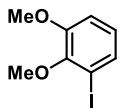
^{1}H NMR (400 MHz, $CDCl_3$)



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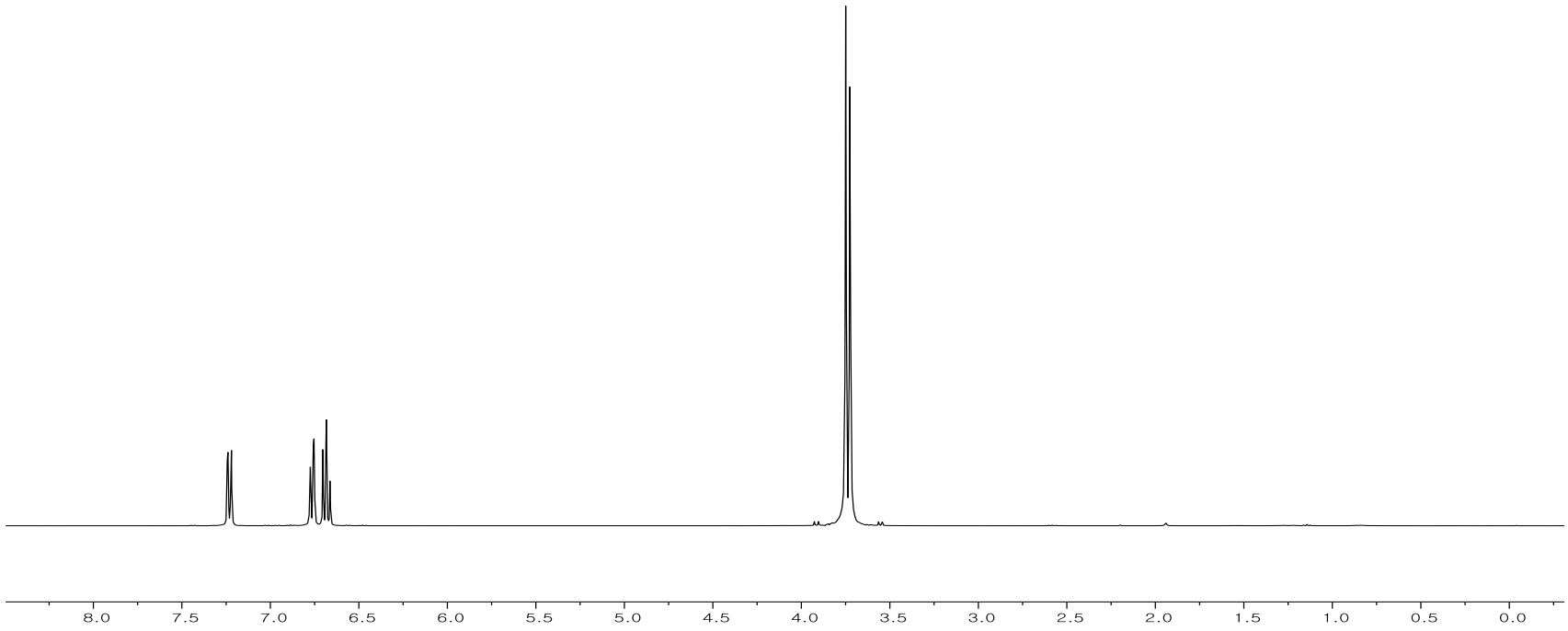
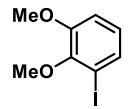


^{13}C NMR (101 MHz, $CDCl_3$)



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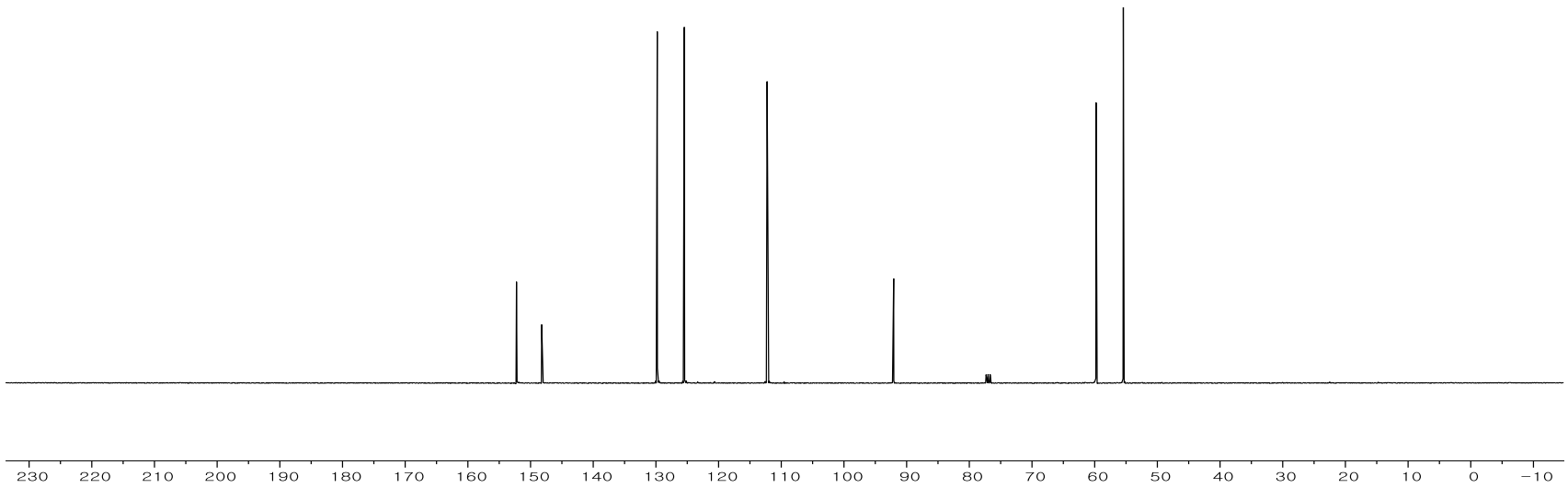
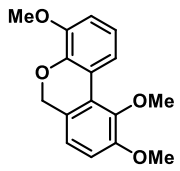


^{1}H NMR (499 MHz, $CDCl_3$)



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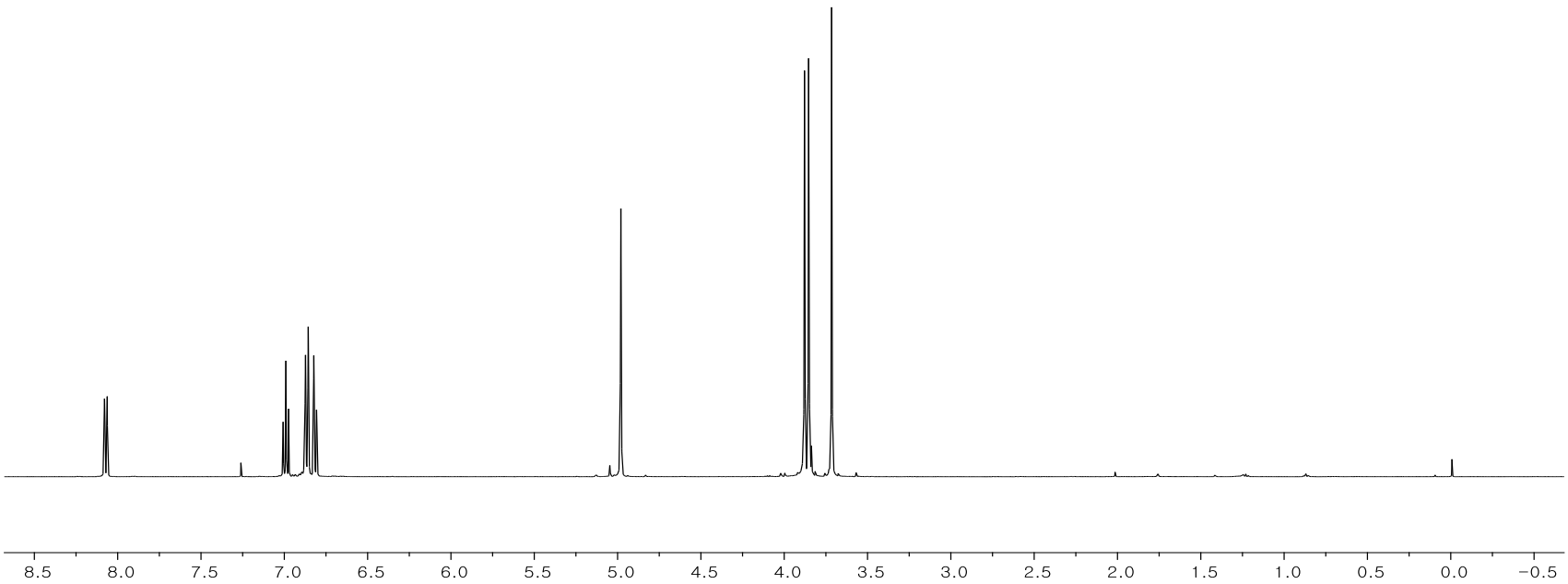
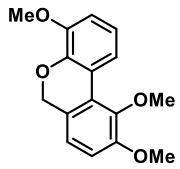


^{13}C NMR (126 MHz, $CDCl_3$)



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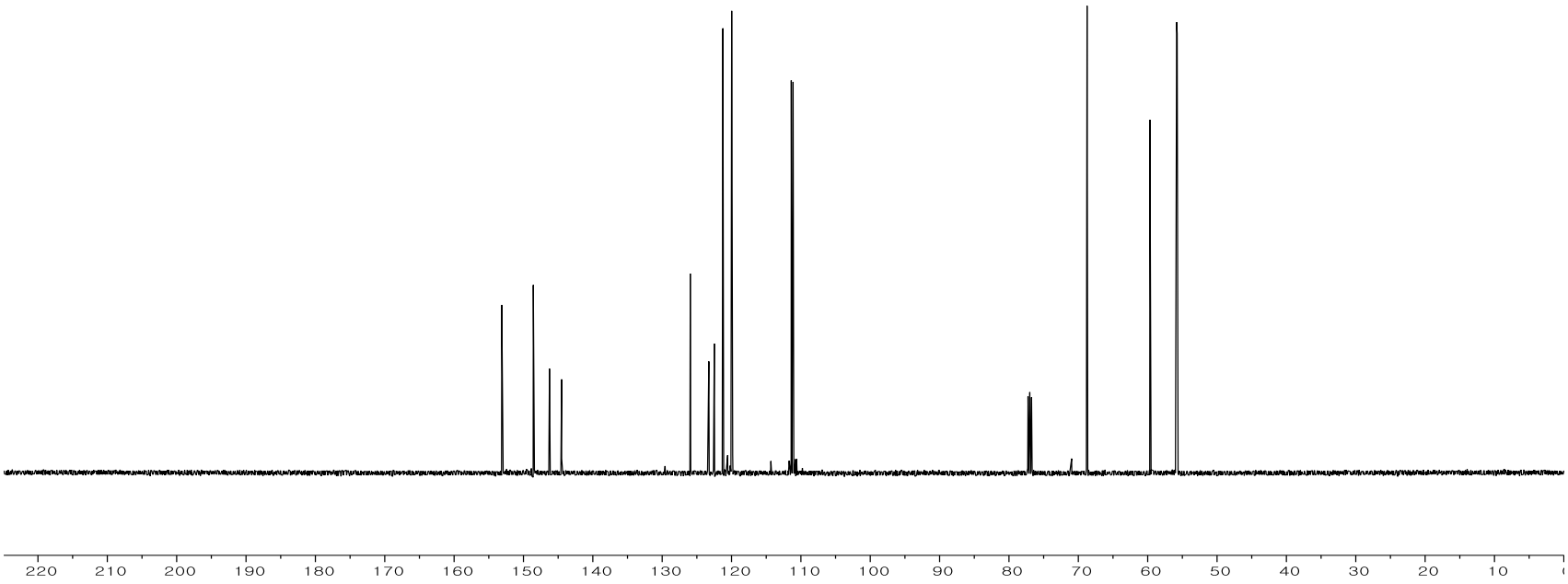
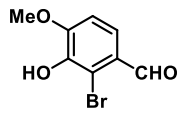
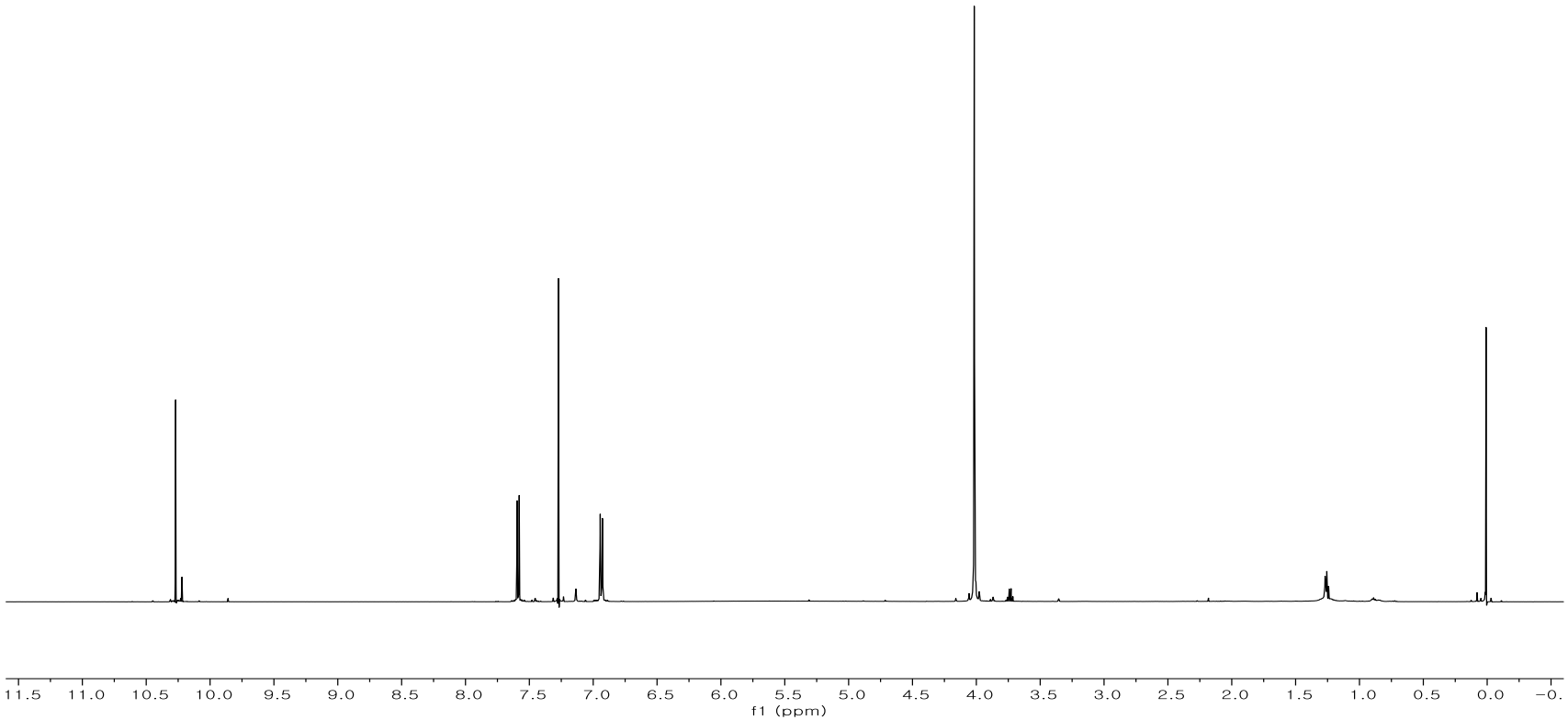


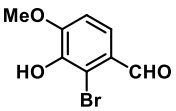
^{1}H NMR (499 MHz, $CDCl_3$)



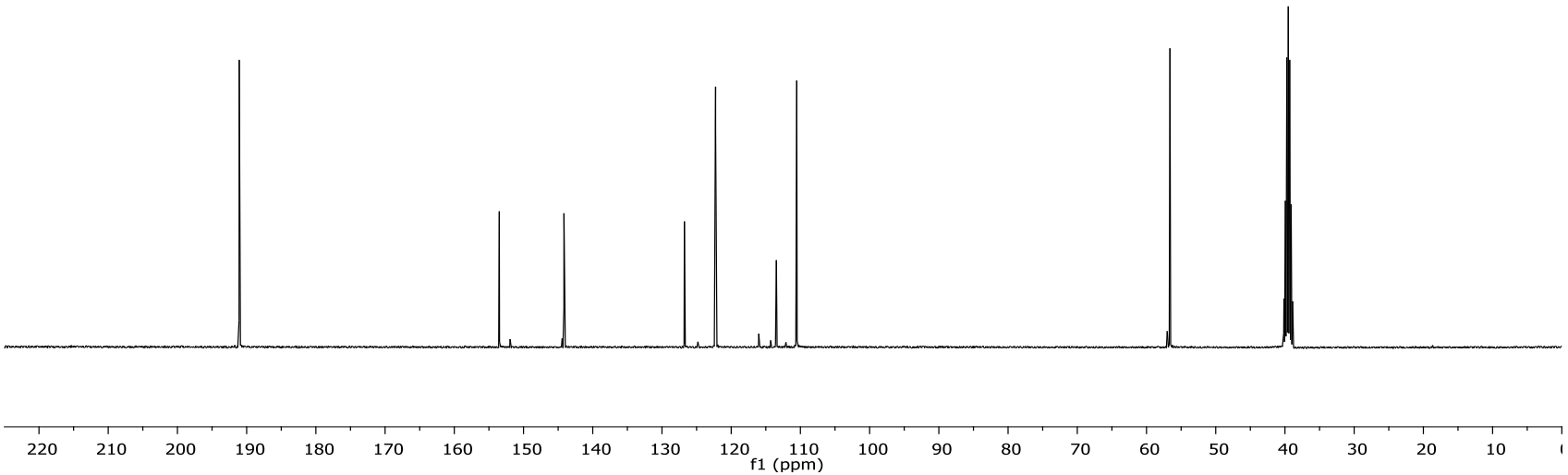
33a



^{13}C NMR (101 MHz, DMSO)

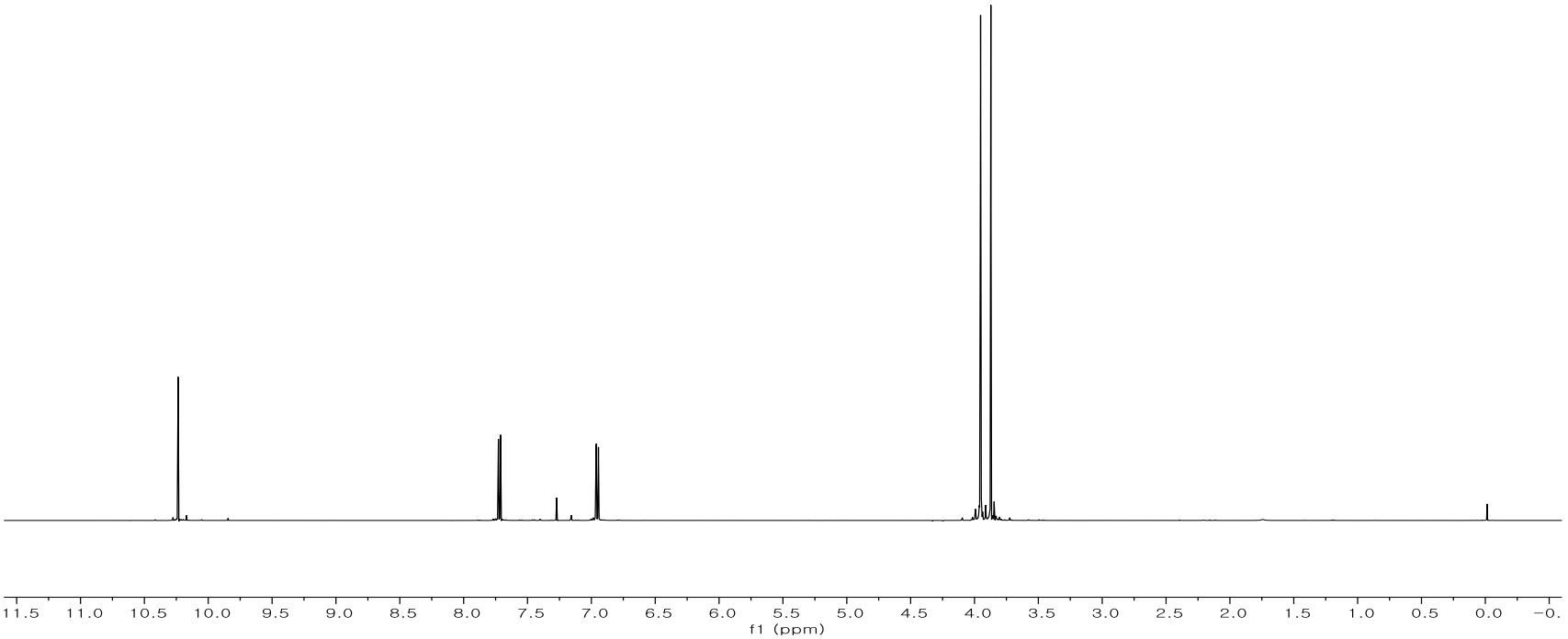


33a



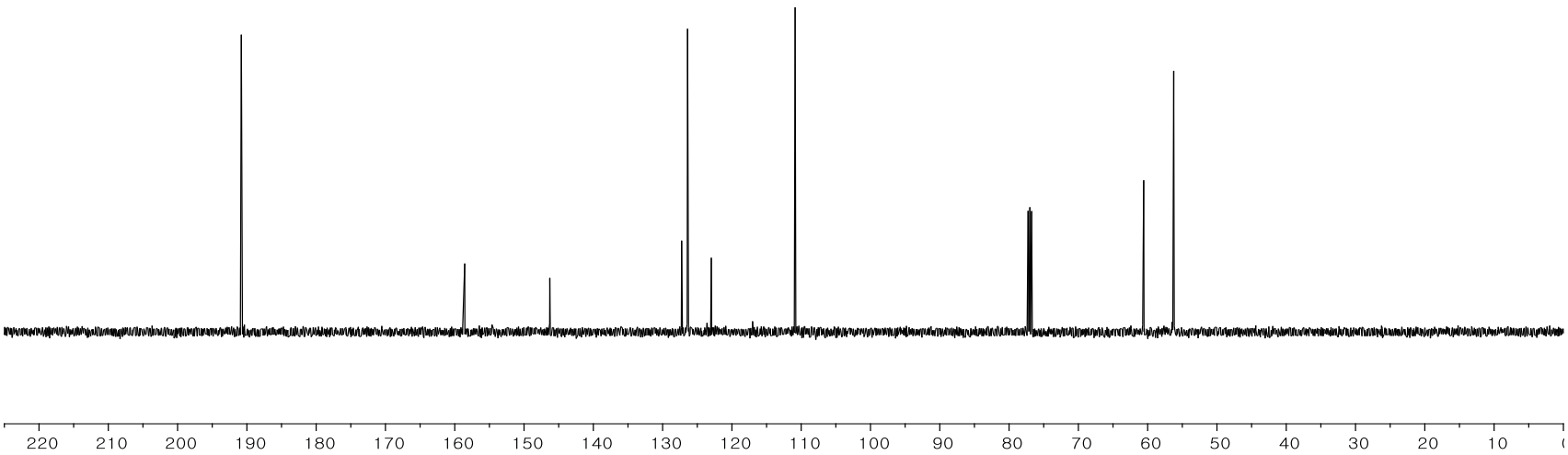
^{1}H NMR (499 MHz, $CDCl_3$)

33b

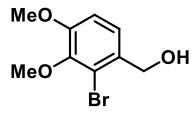


^{13}C NMR (126 MHz, $CDCl_3$)

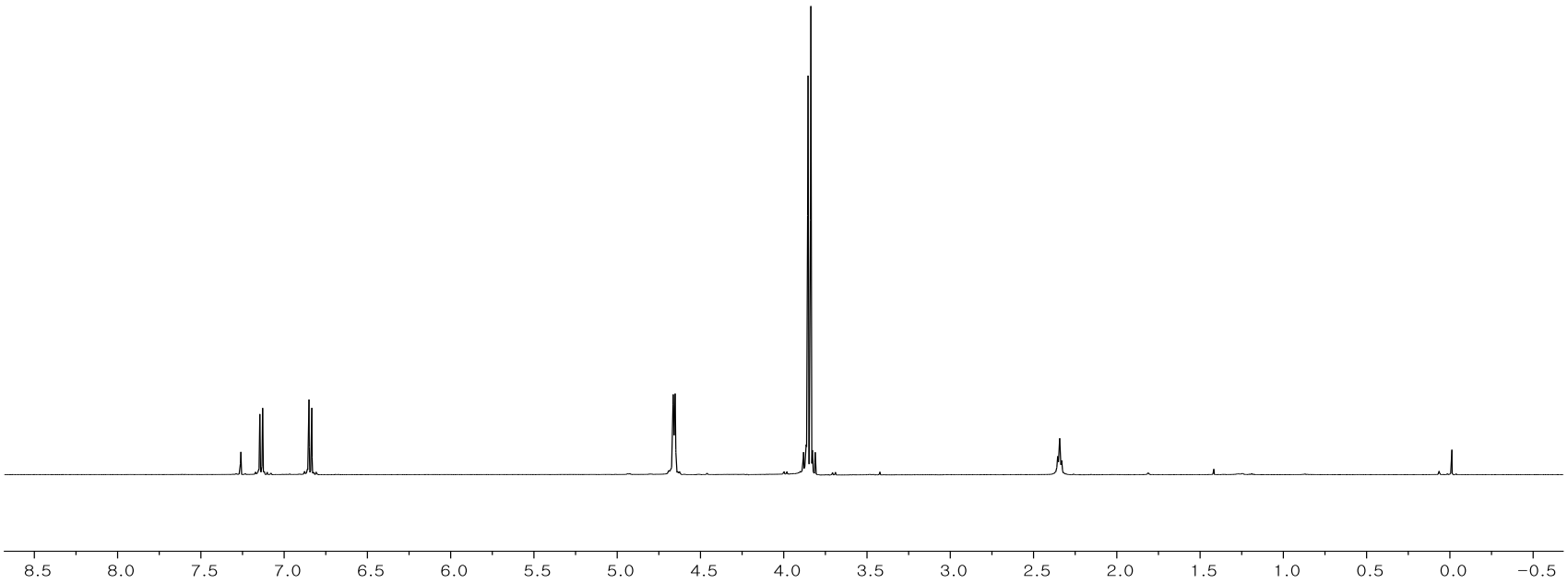
33b



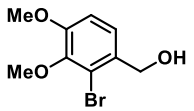
^{1}H NMR (499 MHz, $CDCl_3$)



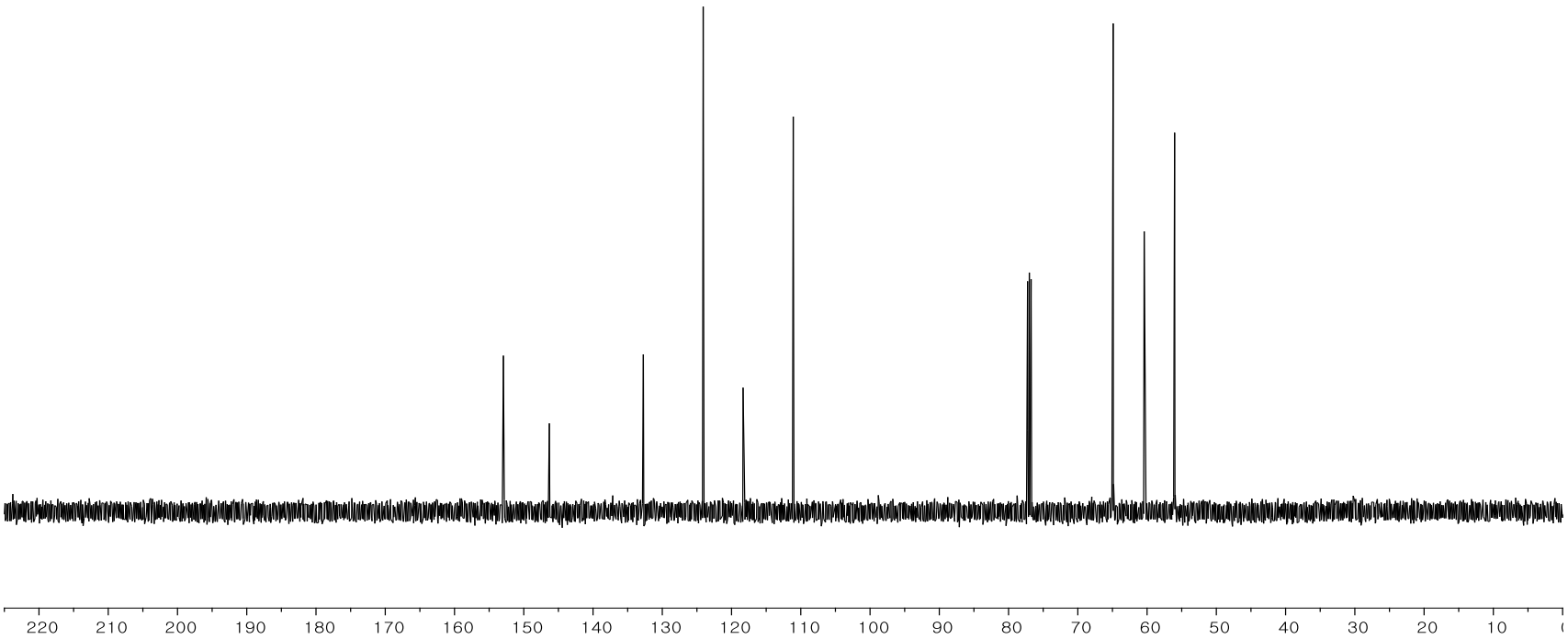
33c



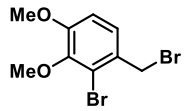
^{13}C NMR (126 MHz, $CDCl_3$)



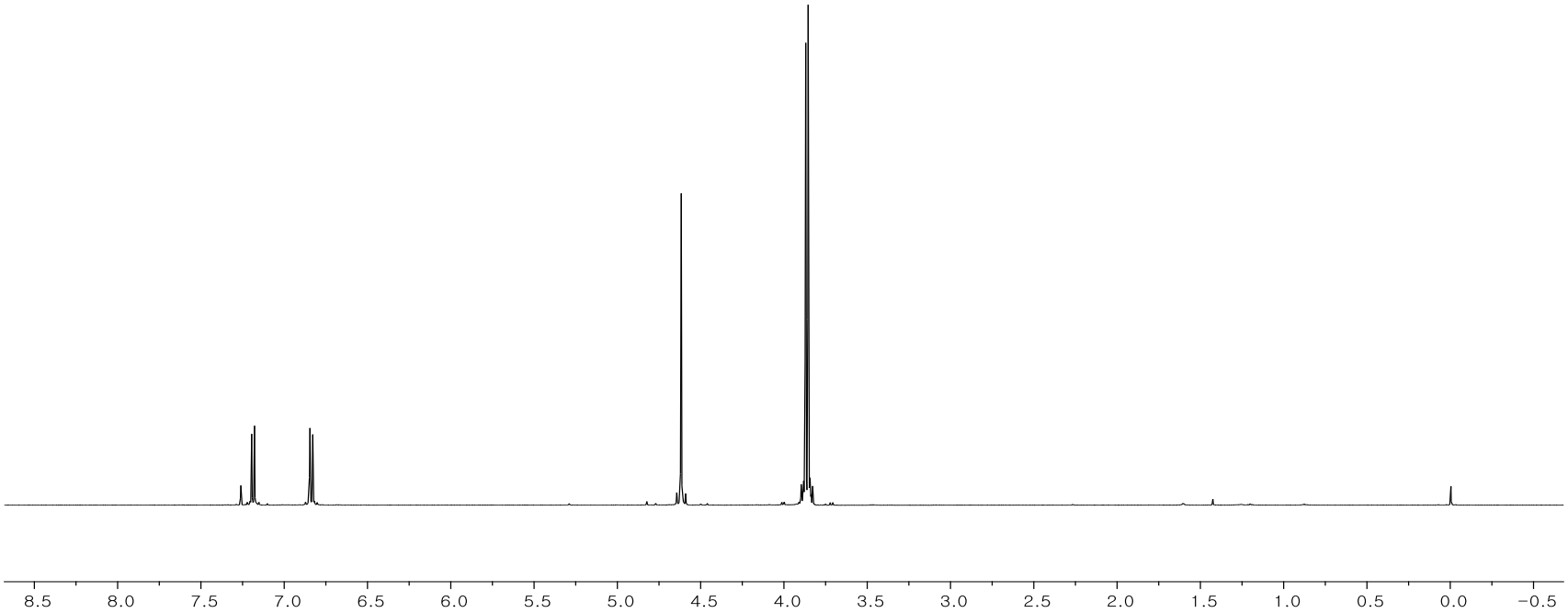
33c



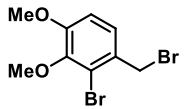
^{1}H NMR (499 MHz, $CDCl_3$)



33d

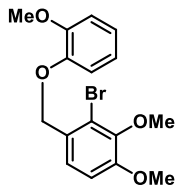


^{13}C NMR (126 MHz, $CDCl_3$)



33d

^{1}H NMR (499 MHz, $CDCl_3$)



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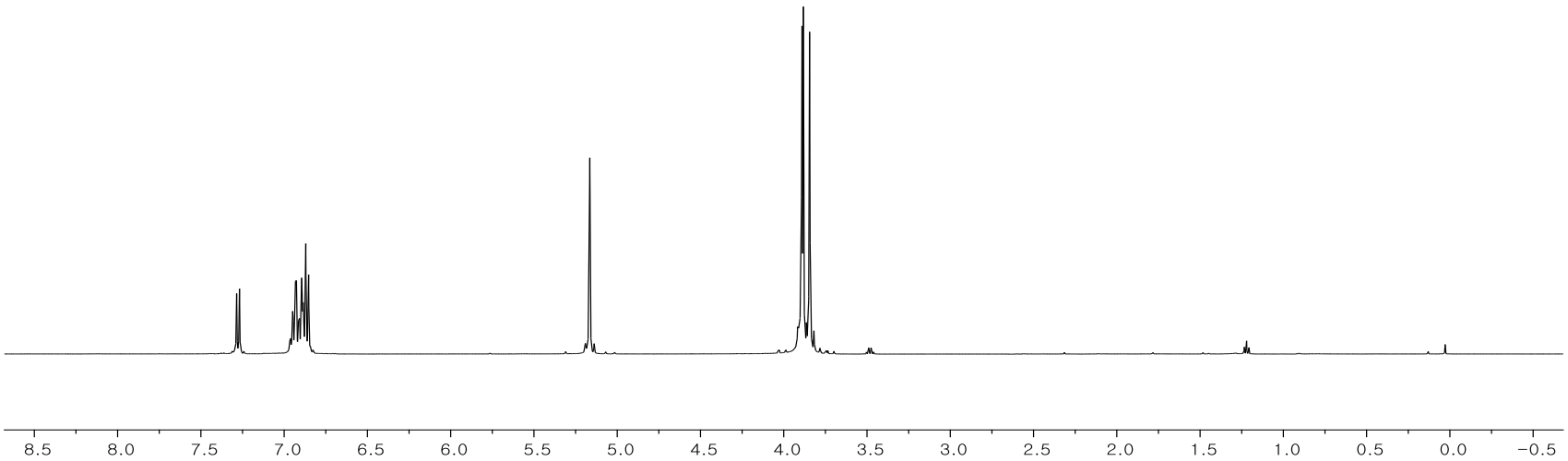
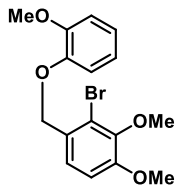


^{13}C NMR (101 MHz, $CDCl_3$)



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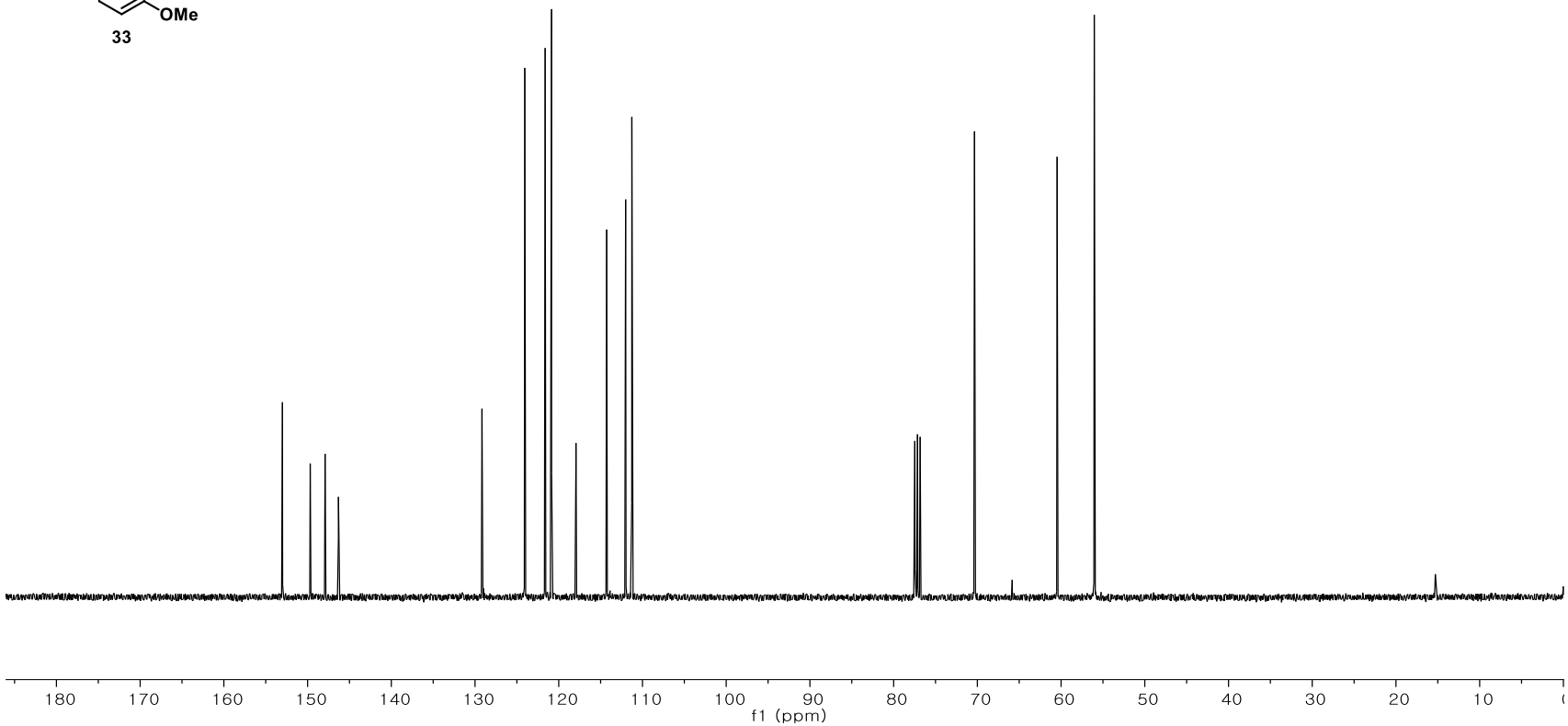
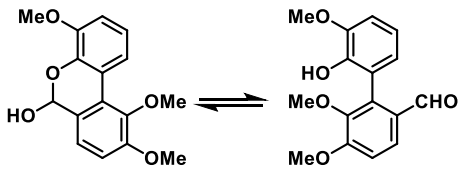
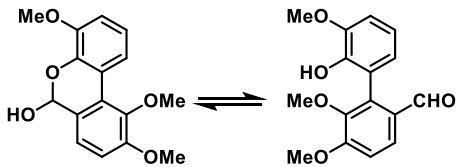


^{1}H NMR (499 MHz, $CDCl_3$)



27' **27**

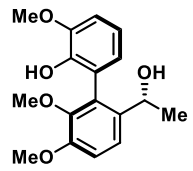
^{13}C NMR (101 MHz, DMSO)



27'

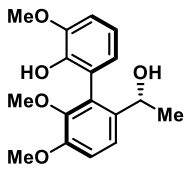
27

^{1}H NMR (400 MHz, C_6D_6)

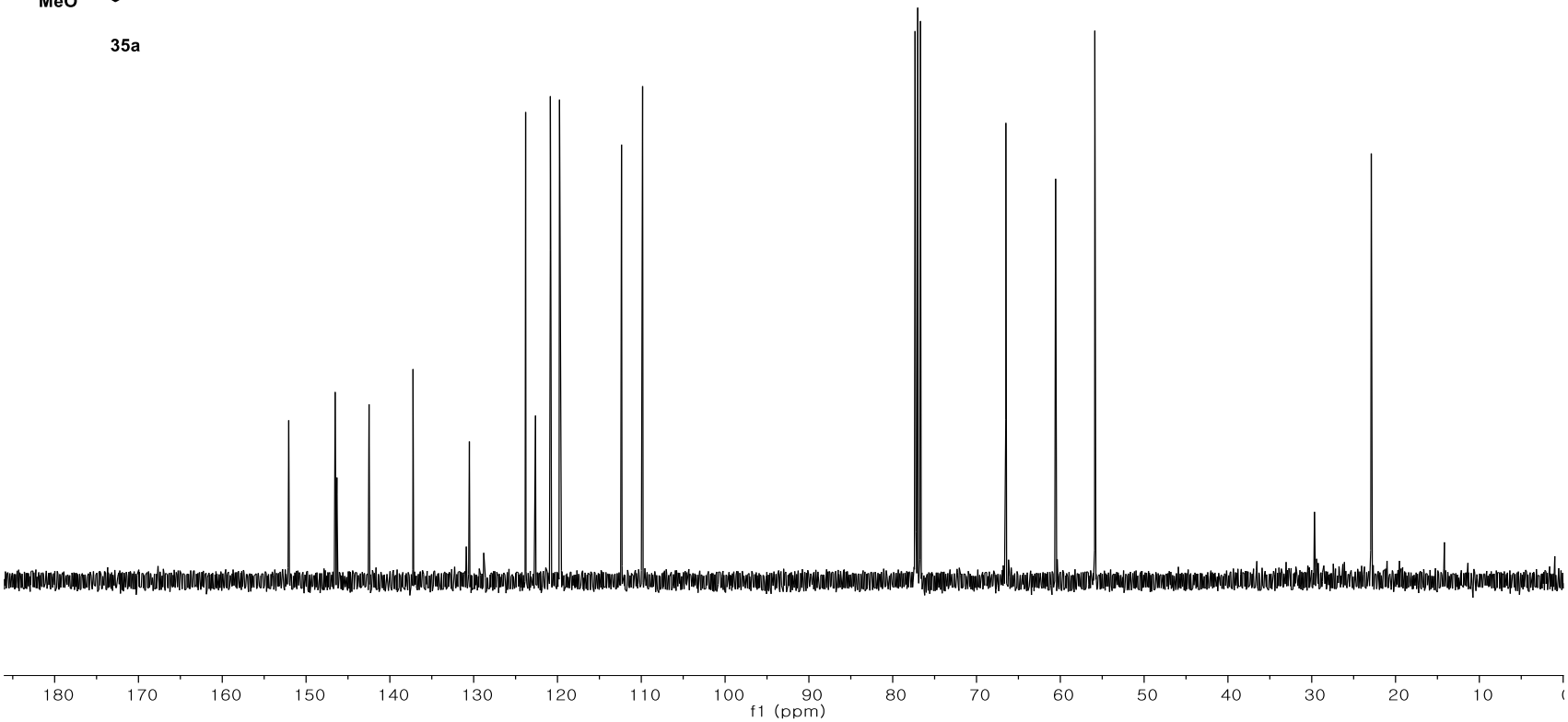


35a

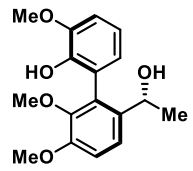
^{13}C NMR (101 MHz, $CDCl_3$)



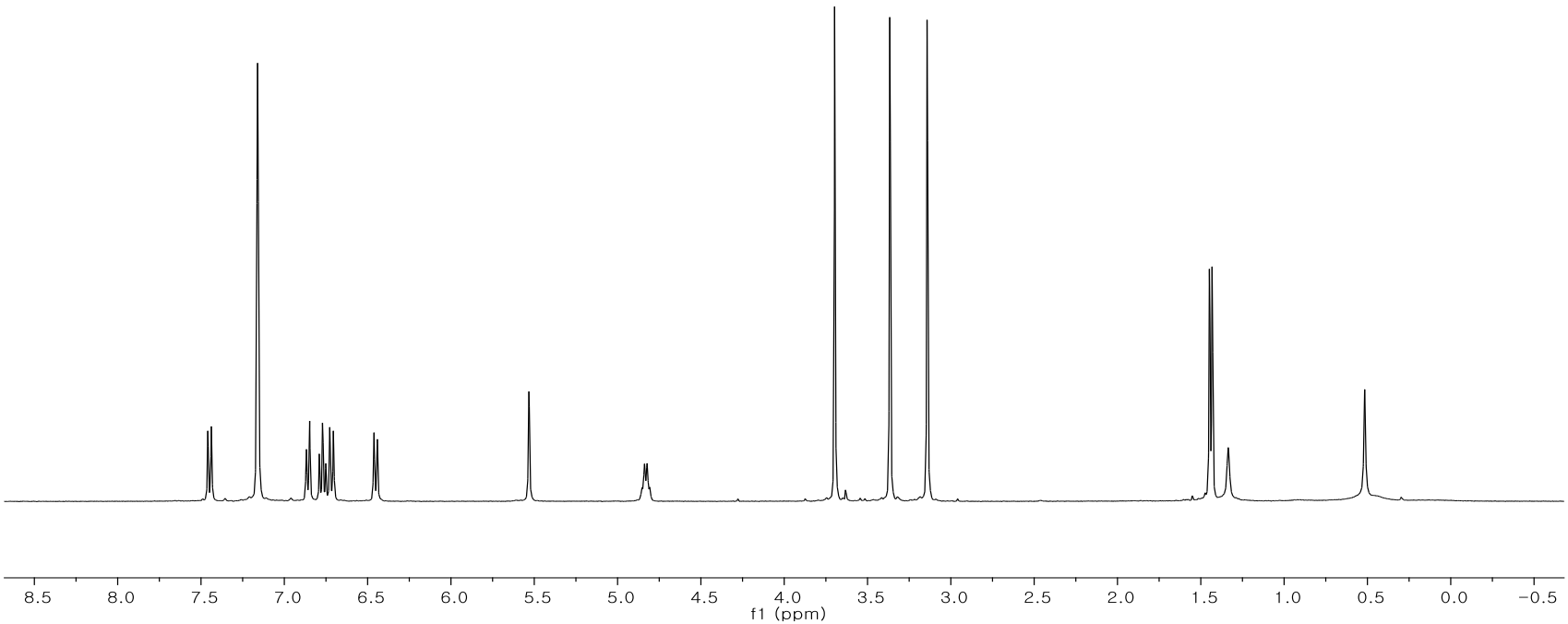
35a



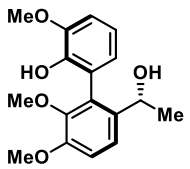
^{1}H NMR (400 MHz, C_6D_6)



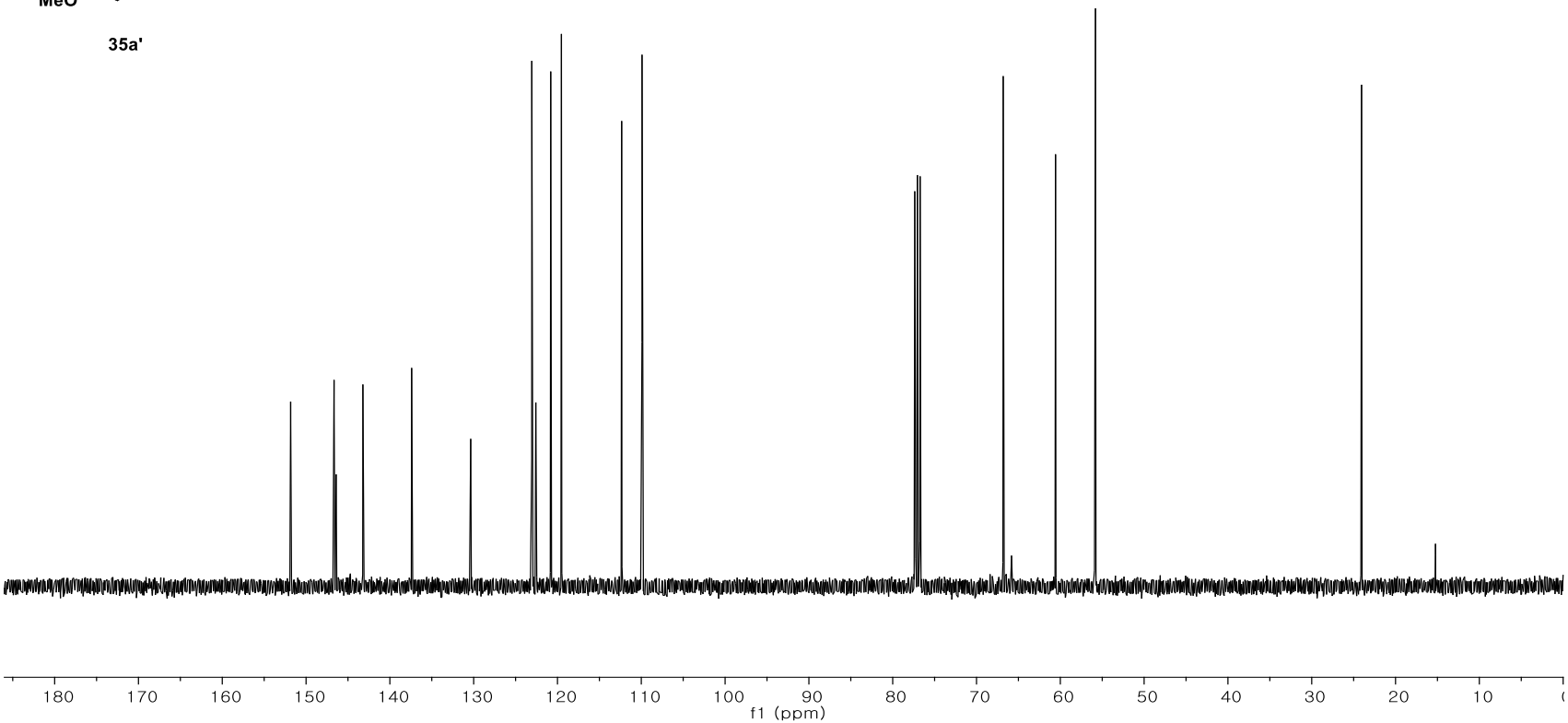
35a'



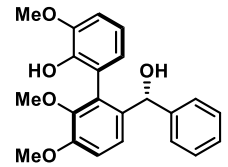
^{13}C NMR (101 MHz, $CDCl_3$)



35a'

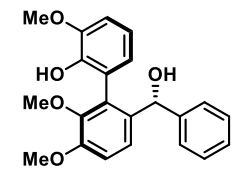


^{1}H NMR (400 MHz, C_6D_6)



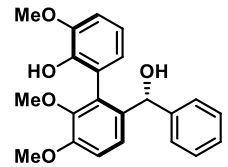
35b

^{13}C NMR (126 MHz, C_6D_6)

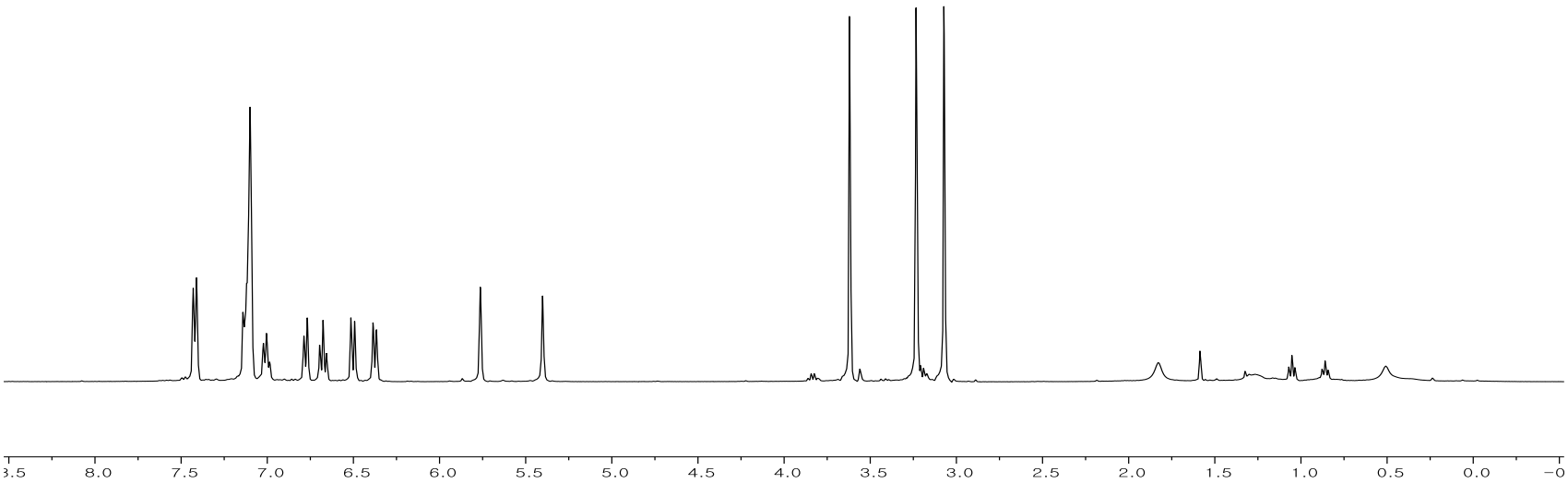


35b

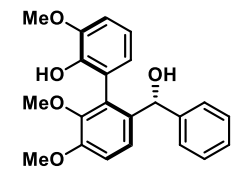
^{1}H NMR (400 MHz, C_6D_6)



35b'

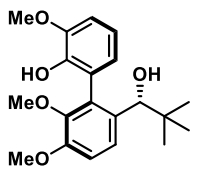


^{13}C NMR (101 MHz, C_6D_6)



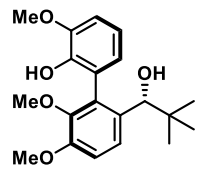
35b'

^{1}H NMR (499 MHz, $CDCl_3$)



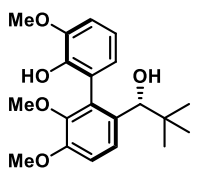
35c

^{13}C NMR (101 MHz, $CDCl_3$)



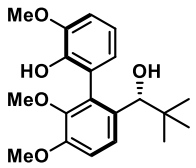
35c

^{1}H NMR (499 MHz, $CDCl_3$)



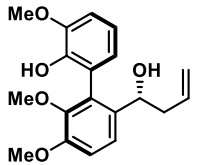
35c'

^{13}C NMR (101 MHz, $CDCl_3$)

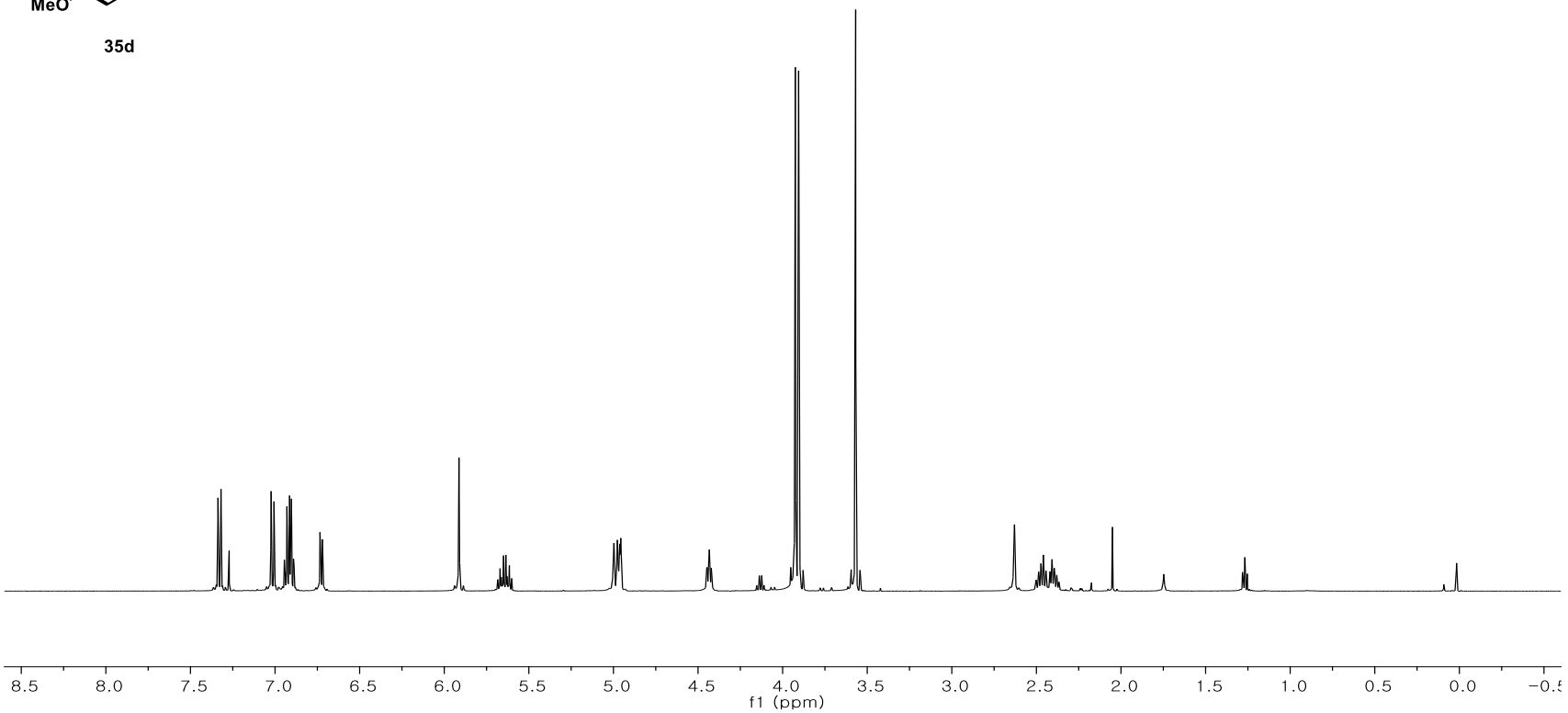


35c'

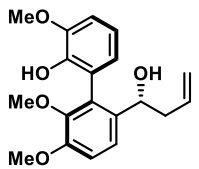
^{1}H NMR (400 MHz, $CDCl_3$)



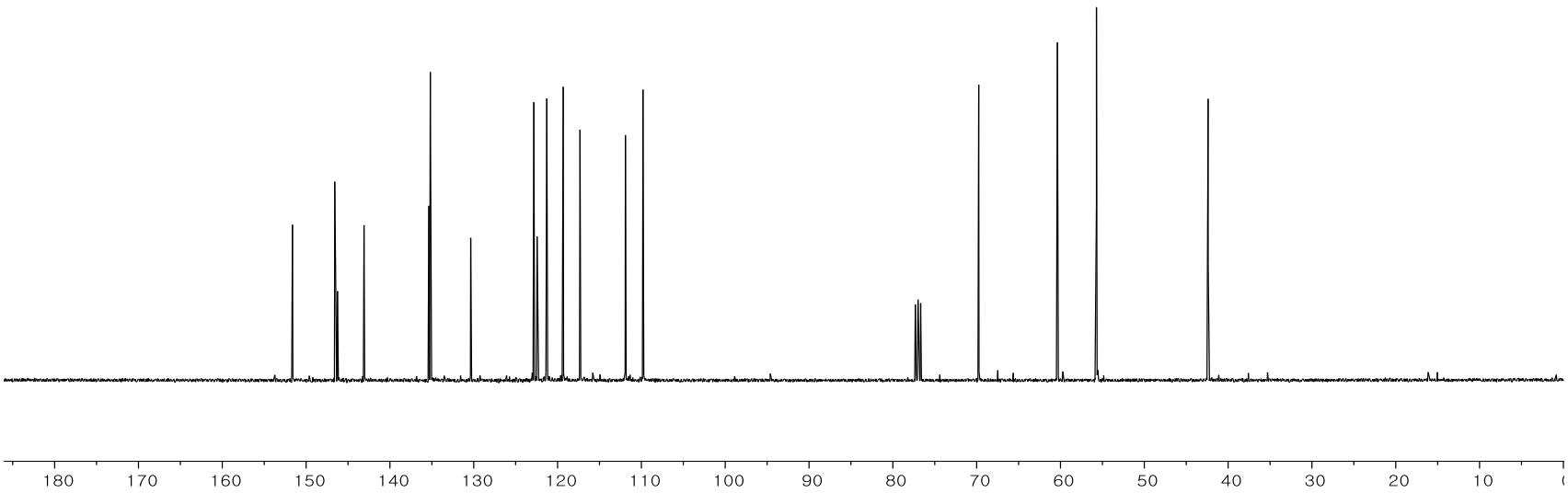
35d



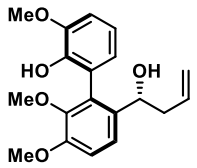
^{13}C NMR (101 MHz, $CDCl_3$)



35d

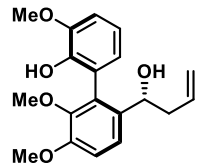


^{1}H NMR (400 MHz, $CDCl_3$)

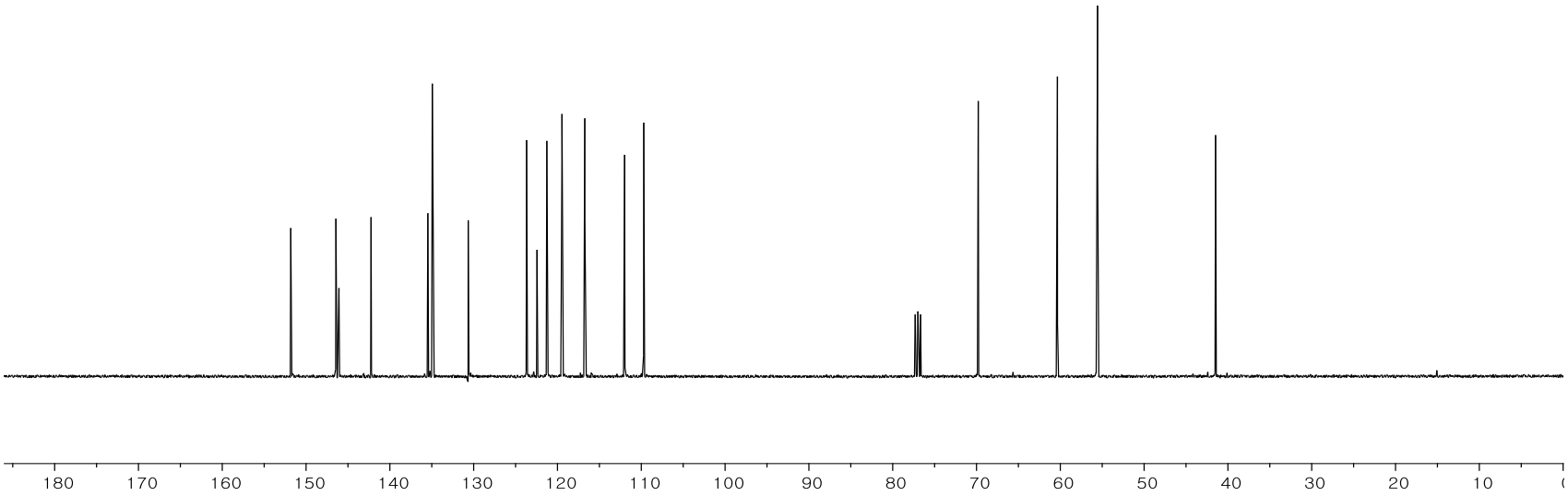


35d'

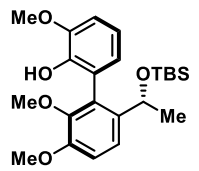
^{13}C NMR (101 MHz, $CDCl_3$)



35d'

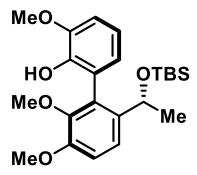


^{1}H NMR (499 MHz, $CDCl_3$)



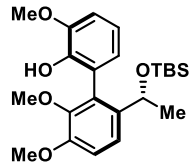
36a

^{1}H NMR (101 MHz, $CDCl_3$)



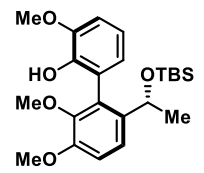
36a

^{1}H NMR (499 MHz, $CDCl_3$)

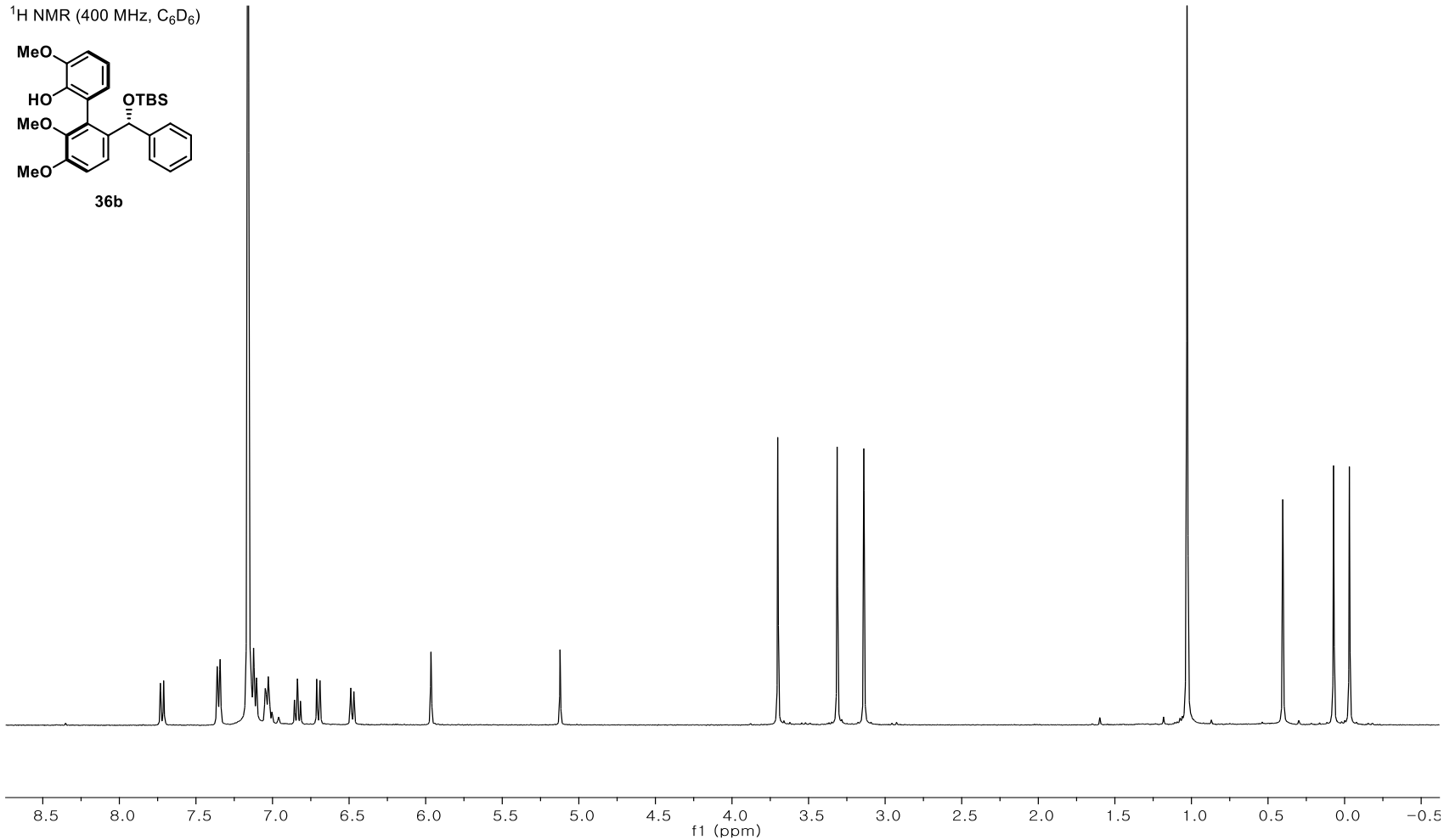


36a'

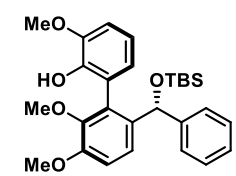
^{13}C NMR (101 MHz, $CDCl_3$)



36a'

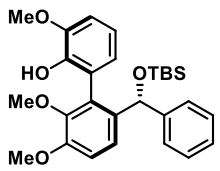

^{1}H NMR (400 MHz, C_6D_6)
MeO
HO
OTBS
MeO
MeO
36b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)

^{13}C NMR (101 MHz, C_6D_6)

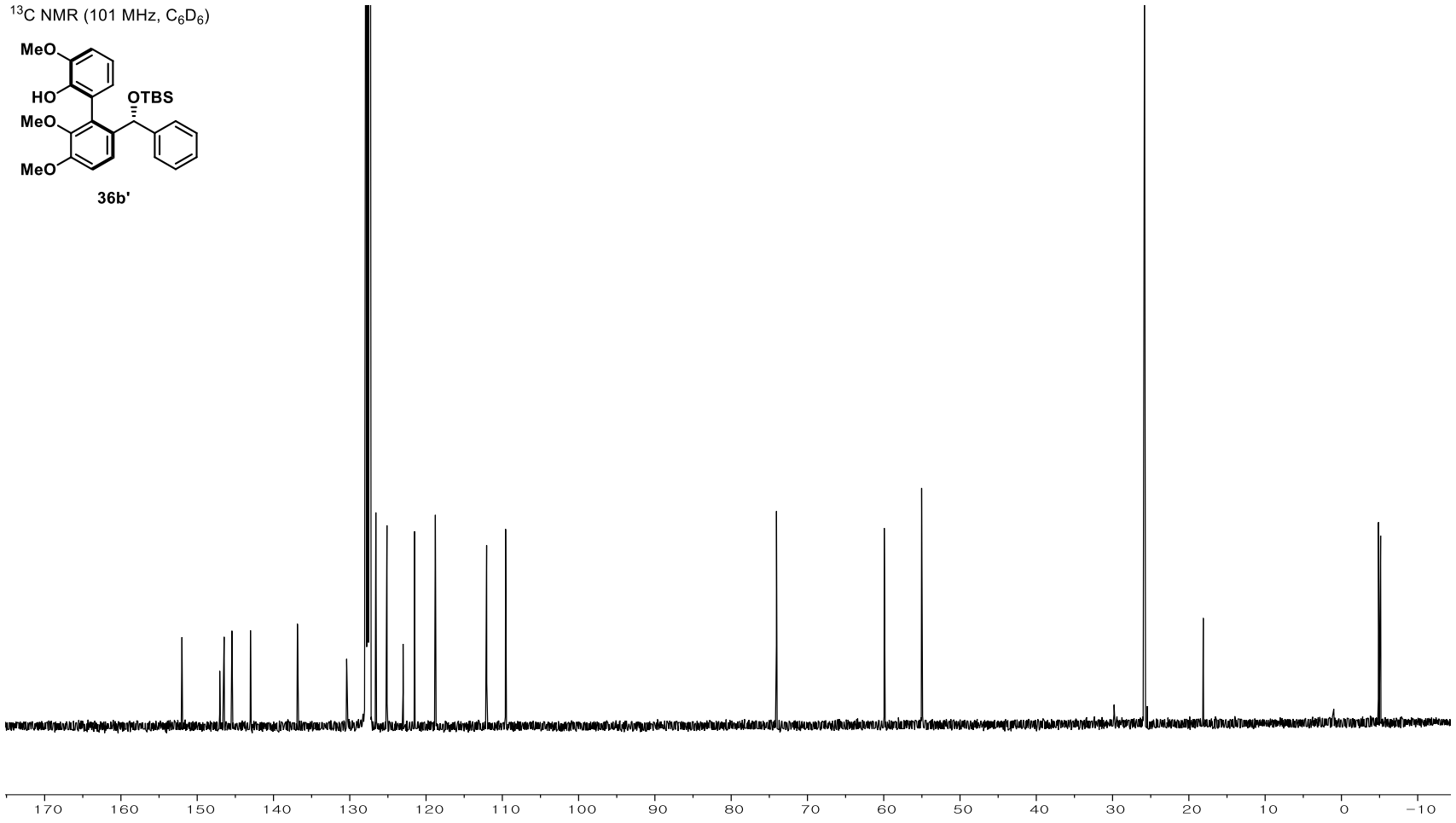


36b

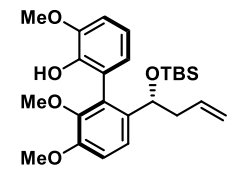
^{1}H NMR (400 MHz, C_6D_6)



36b'

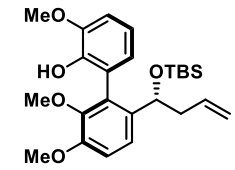

^{13}C NMR (101 MHz, C_6D_6)
MeO
HO
OTBS
MeO
MeO
36b'
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10

^{1}H NMR (499 MHz, $CDCl_3$)

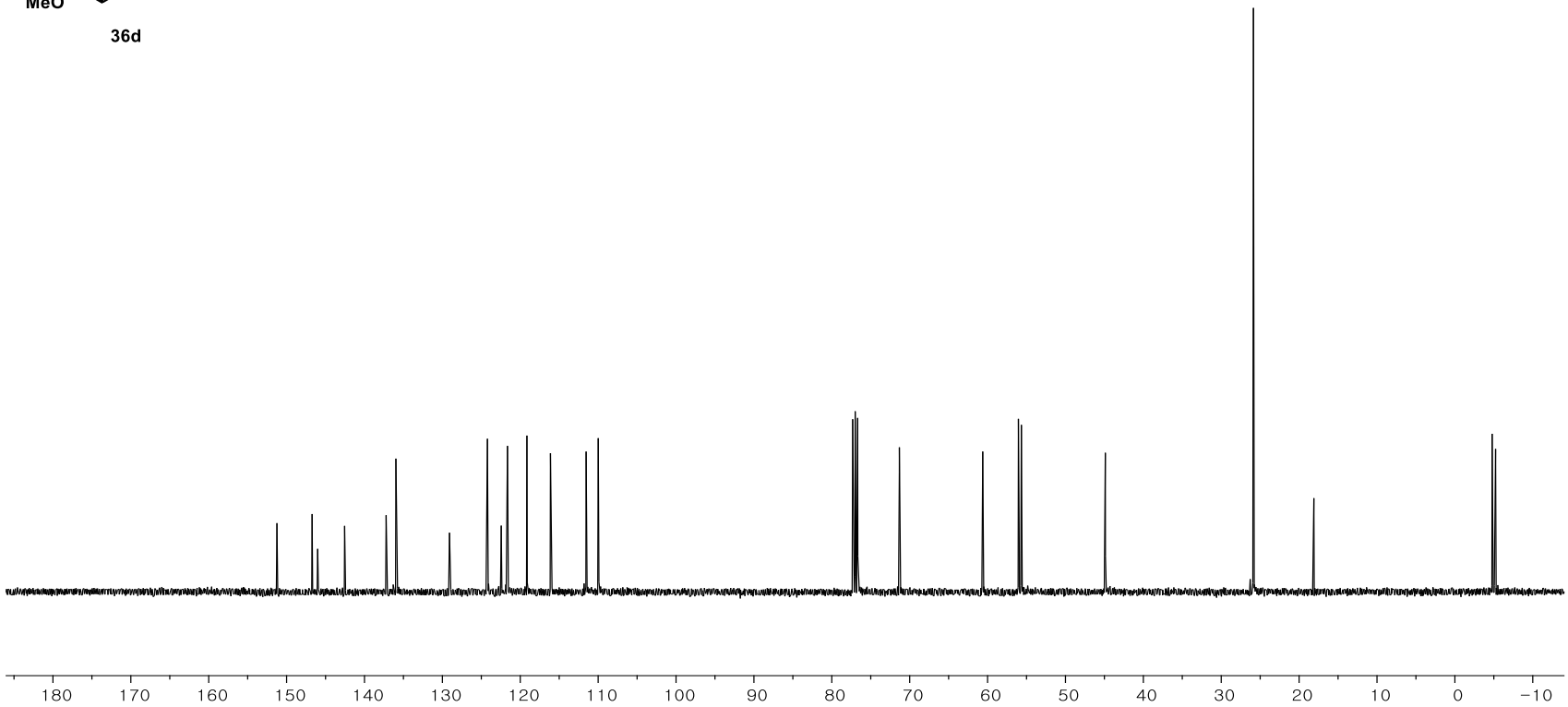


36d

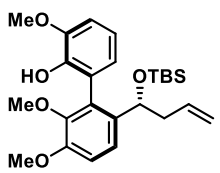
^{13}C NMR (101 MHz, $CDCl_3$)



36d

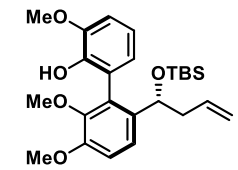


^{1}H NMR (499 MHz, $CDCl_3$)



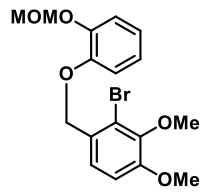
36d'

^{13}C NMR (101 MHz, $CDCl_3$)

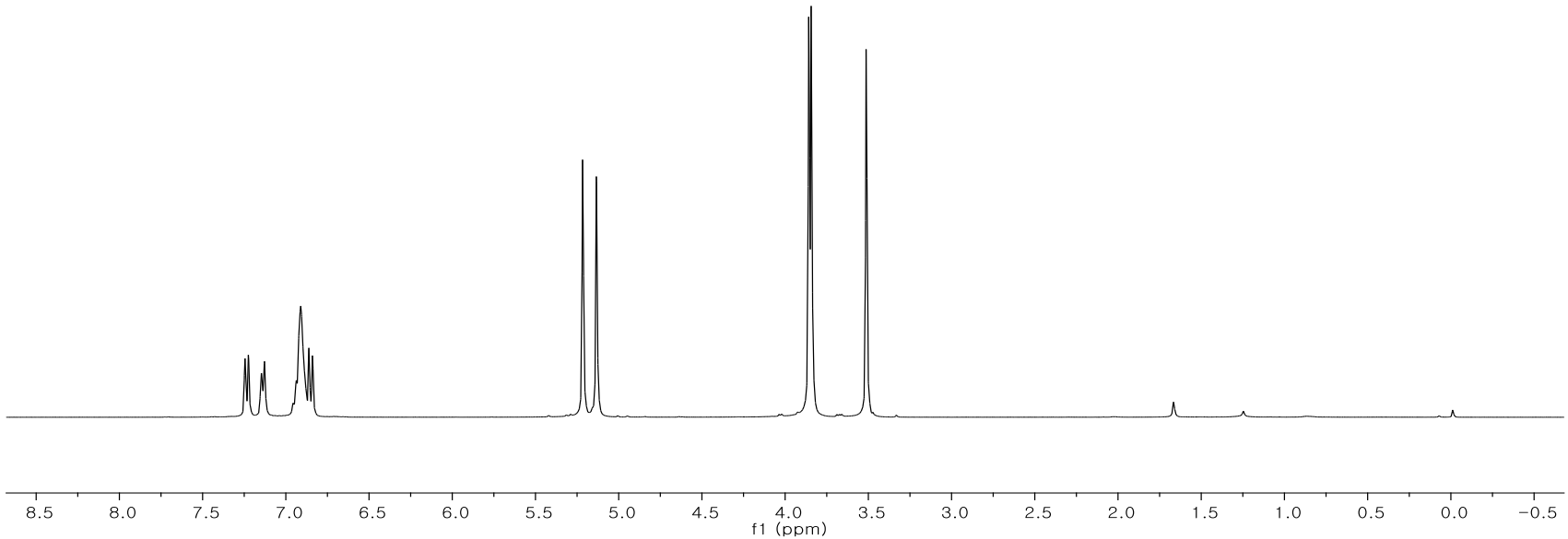


36d'

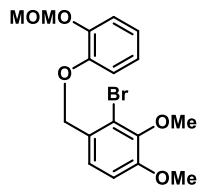
^{1}H NMR (499 MHz, $CDCl_3$)



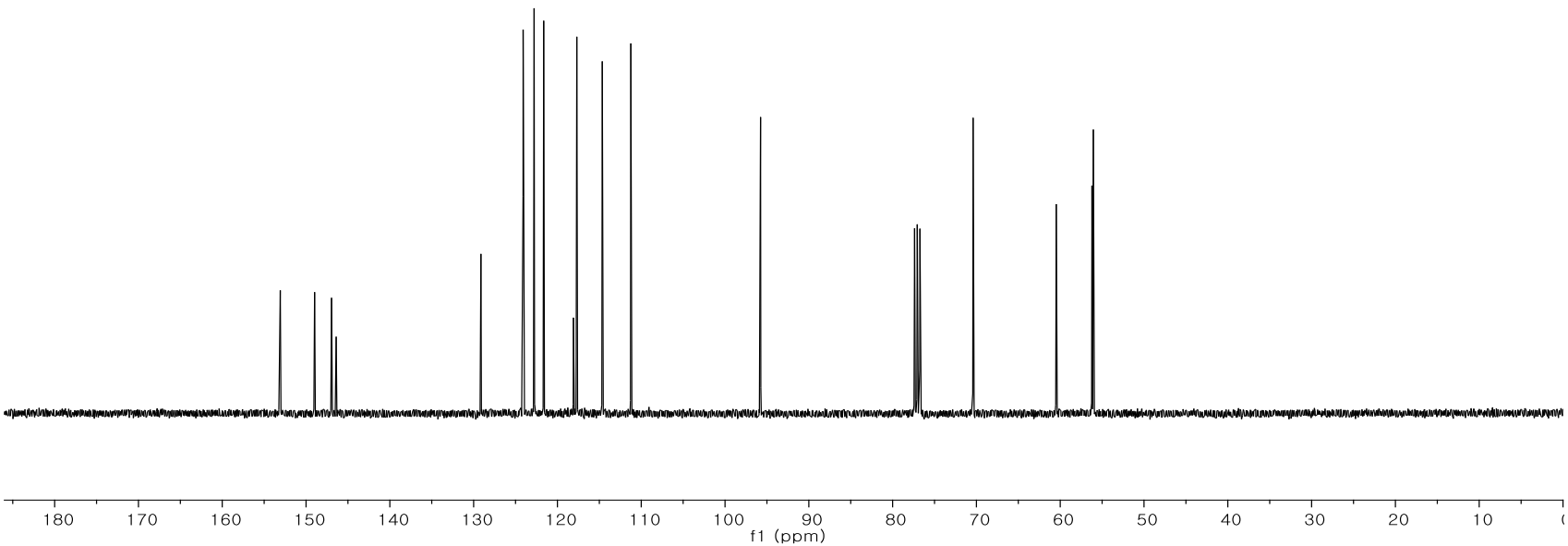
43b



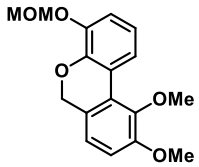
^{13}C NMR (101 MHz, $CDCl_3$)



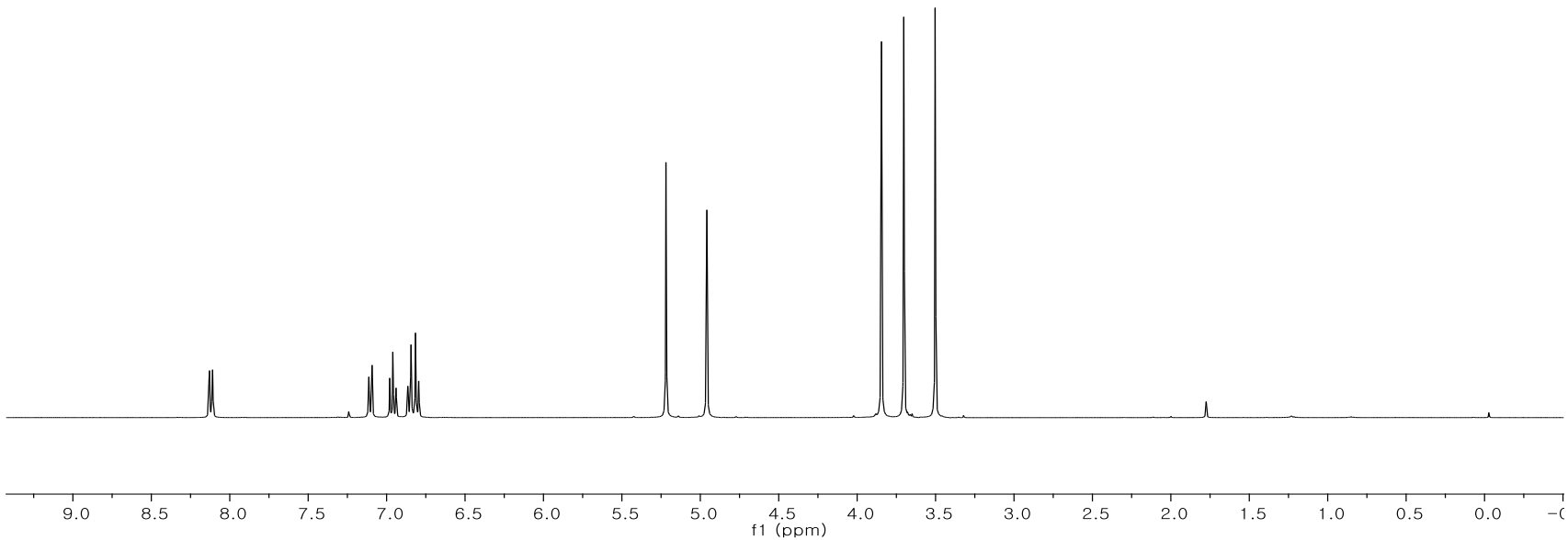
43b



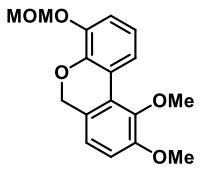
^{1}H NMR (400 MHz, $CDCl_3$)



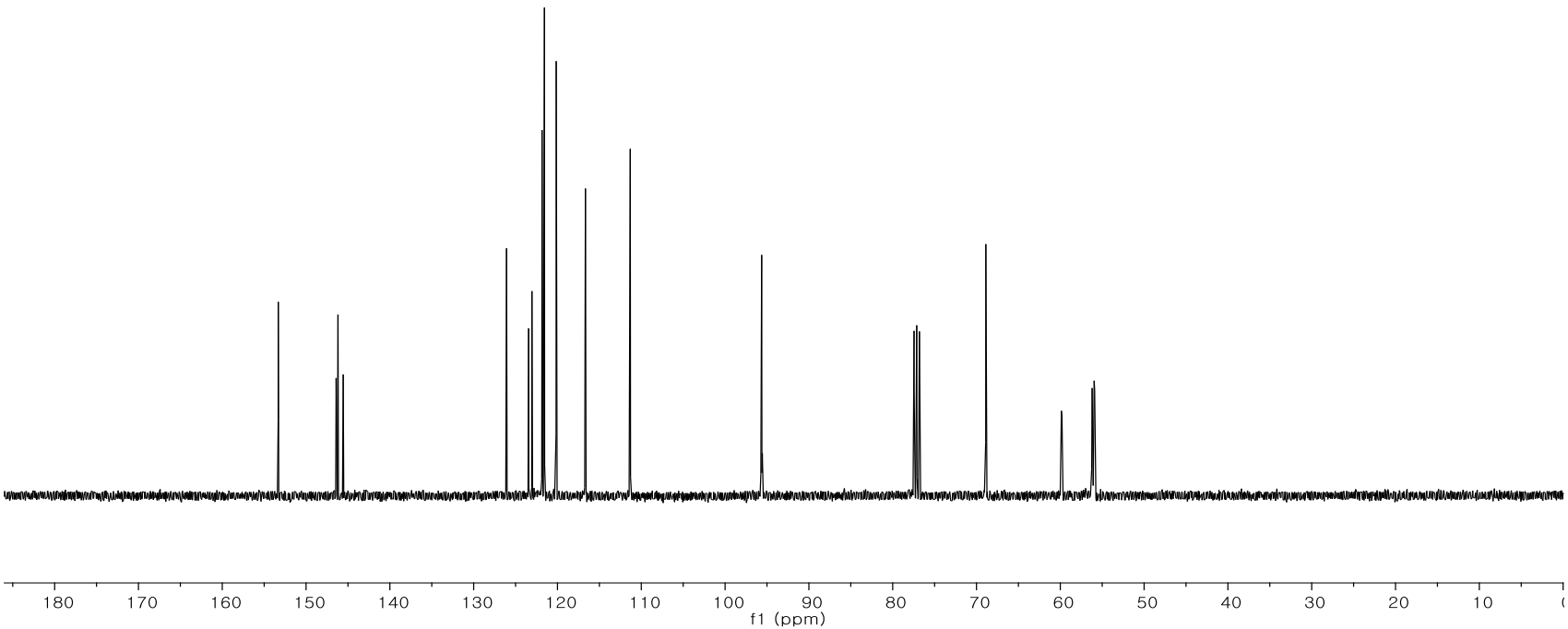
43c



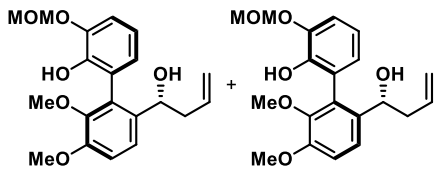
^{13}C NMR (101 MHz, $CDCl_3$)



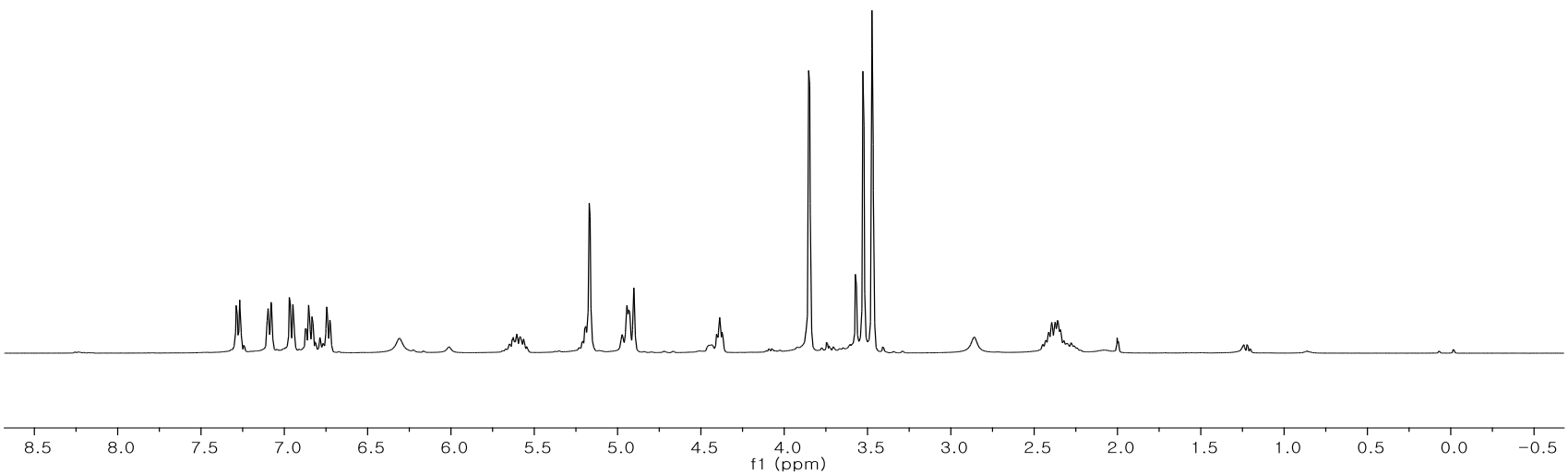
43c



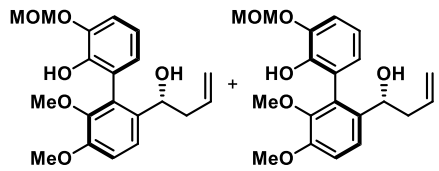
^{1}H NMR (400 MHz, $CDCl_3$)



43e **43e'**



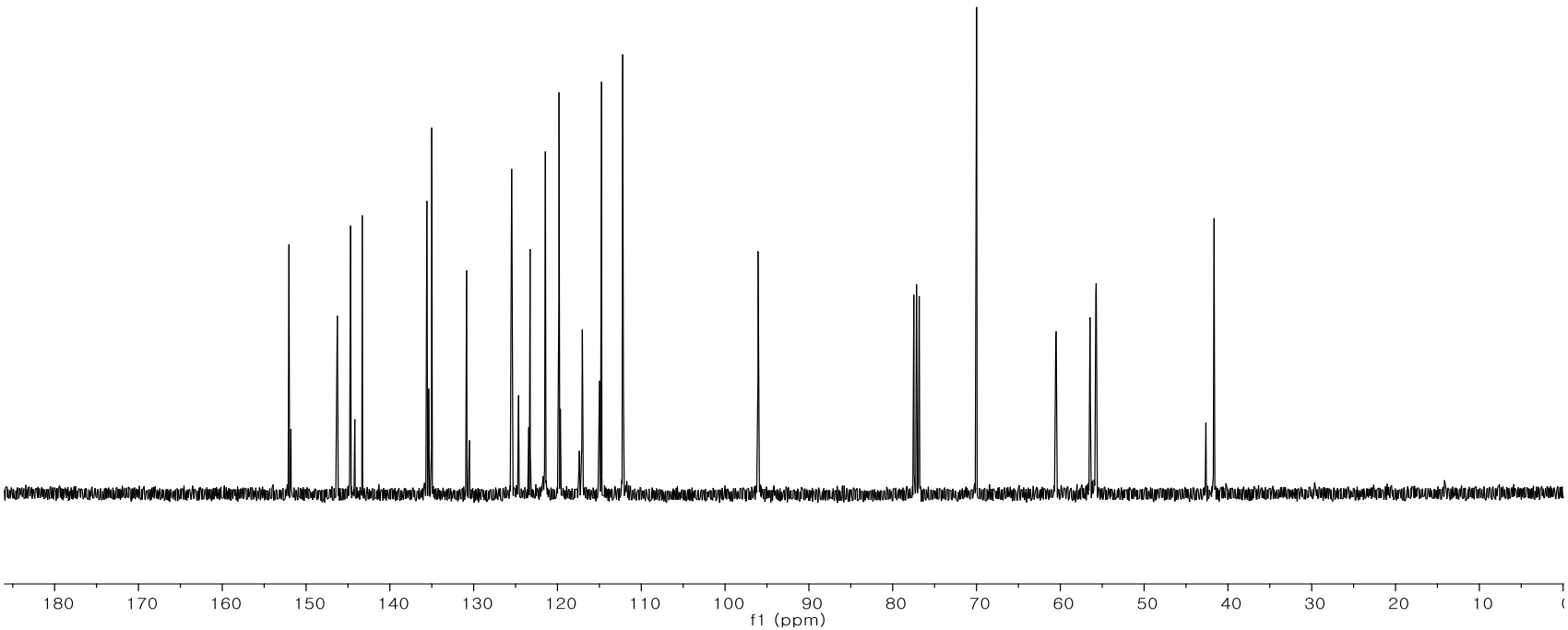
^{13}C NMR (101 MHz, $CDCl_3$)



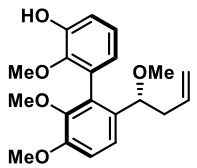
43e

+

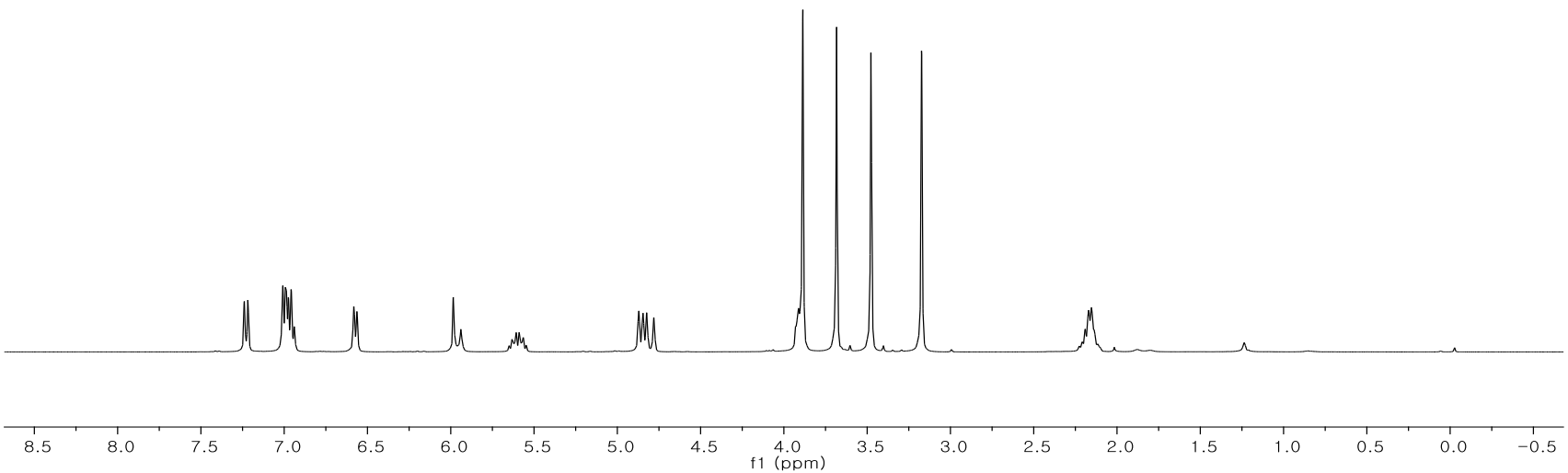
43e'



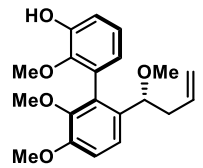
^{1}H NMR (400 MHz, $CDCl_3$)



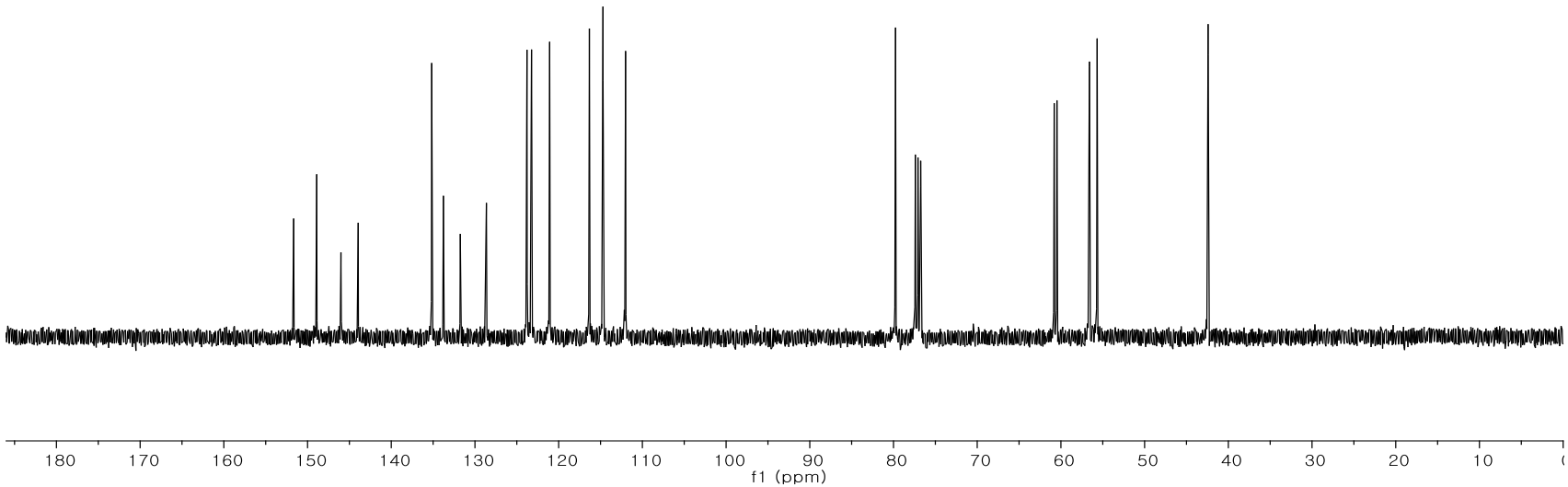
43



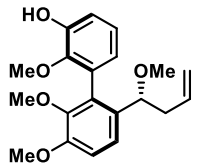
^{13}C NMR (101 MHz, $CDCl_3$)



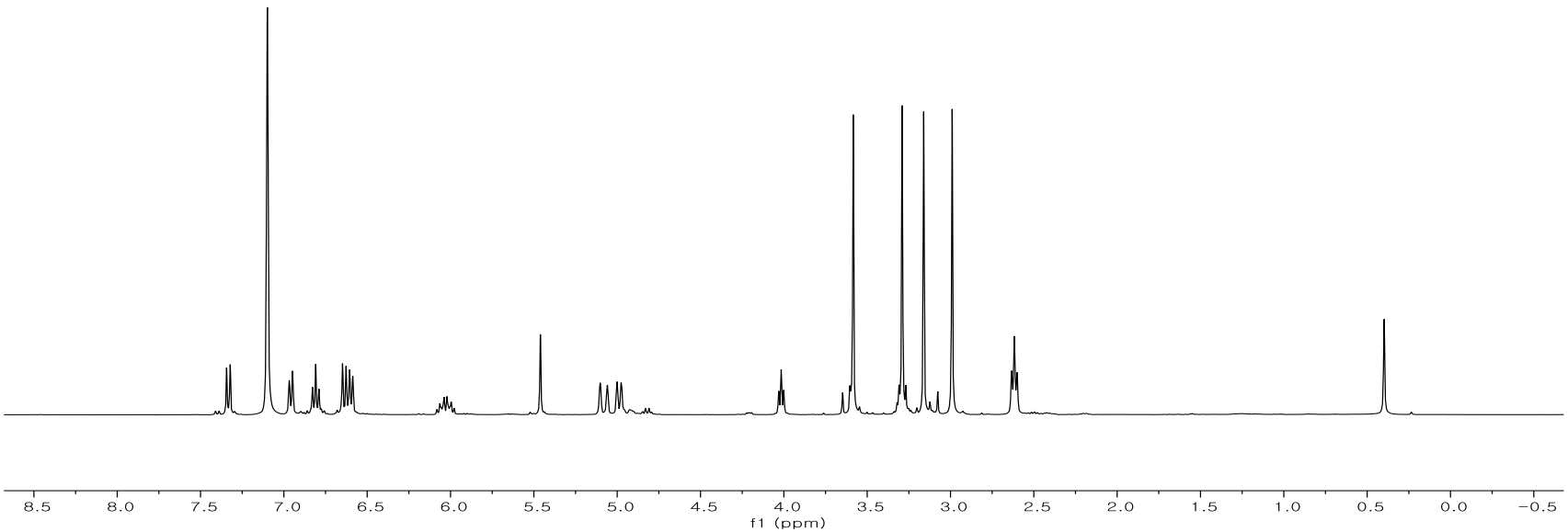
43



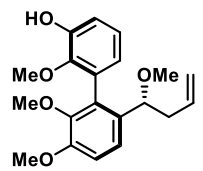
^{1}H NMR (400 MHz, C_6D_6)



43'

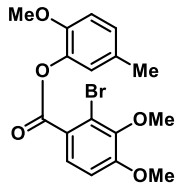


^{13}C NMR (101 MHz, $CDCl_3$)

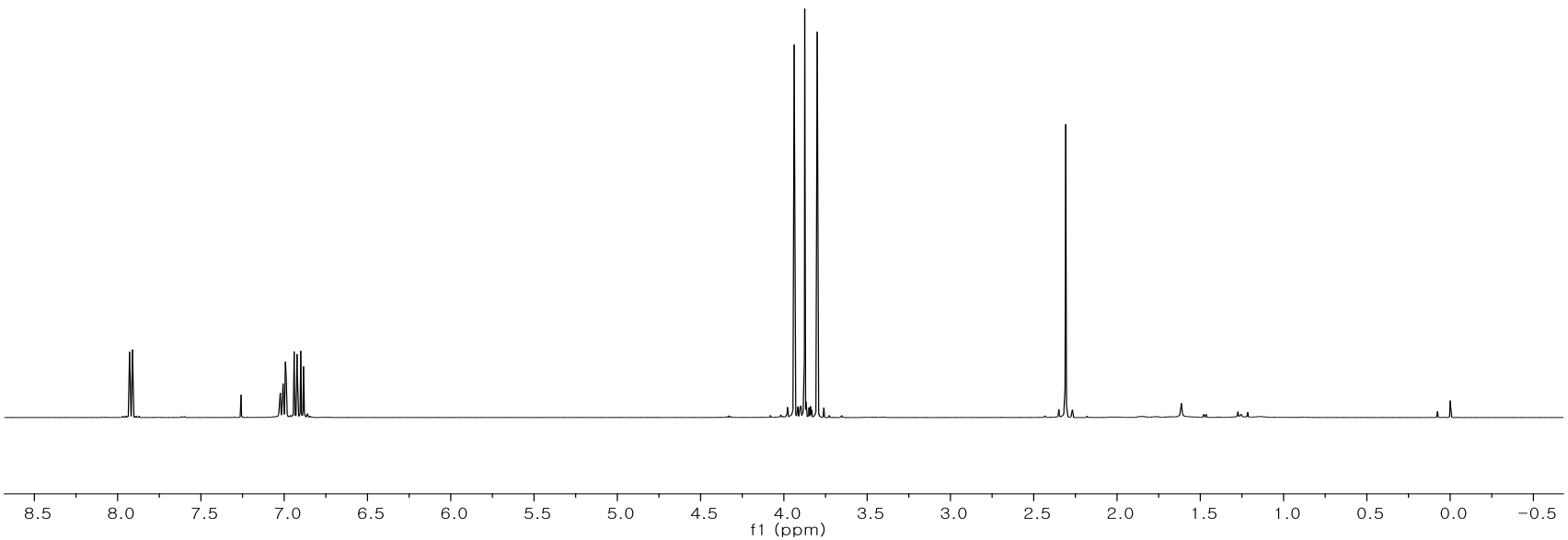


43'

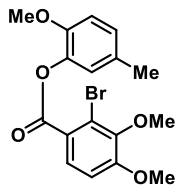
^{1}H NMR (499 MHz, $CDCl_3$)



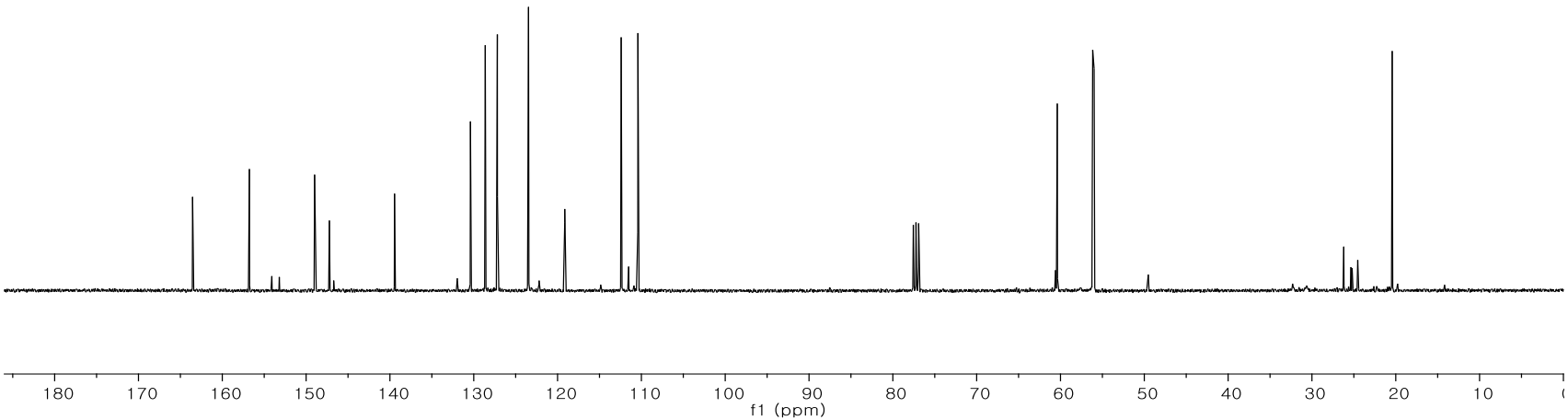
47a



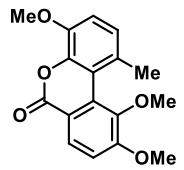
^{13}C NMR (101 MHz, $CDCl_3$)



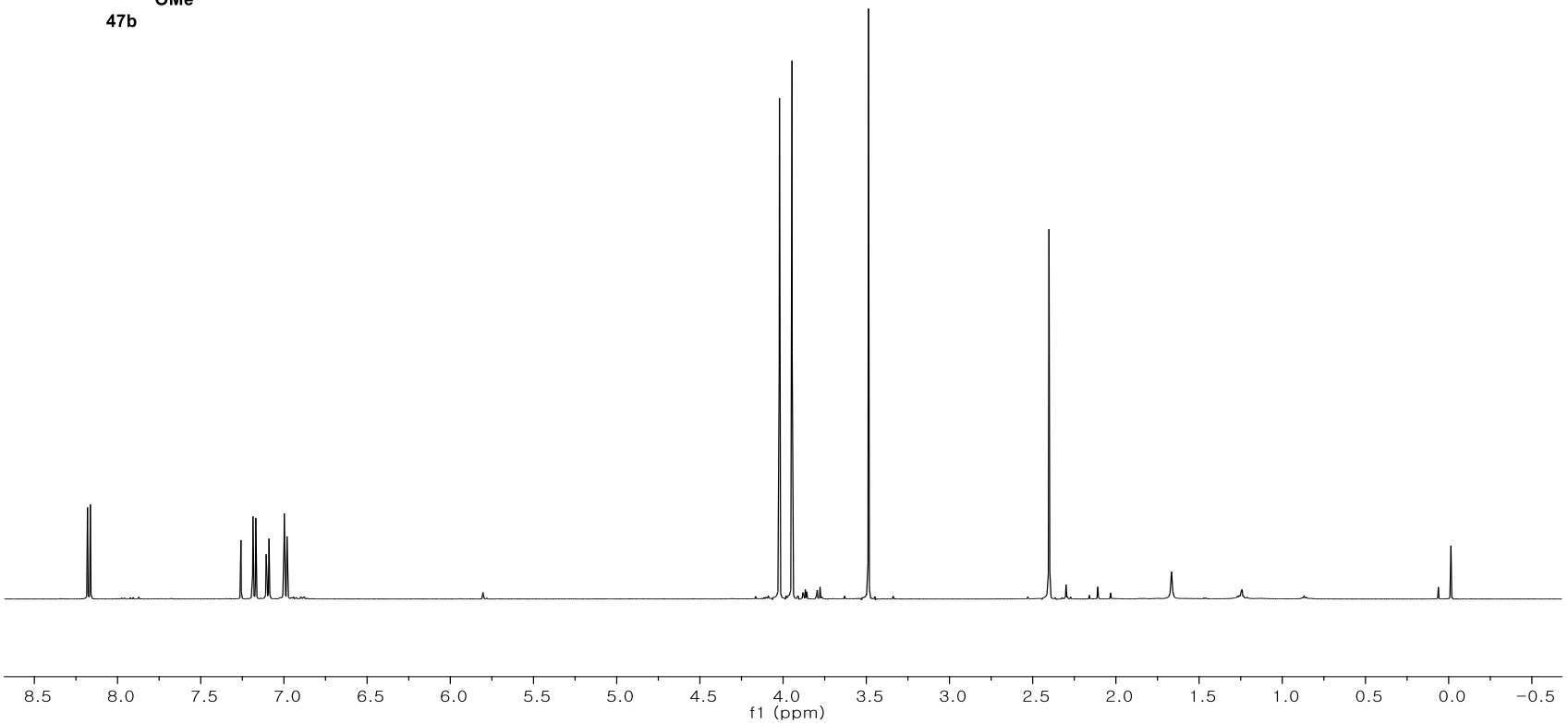
47a



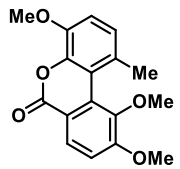
^{1}H NMR (499 MHz, $CDCl_3$)



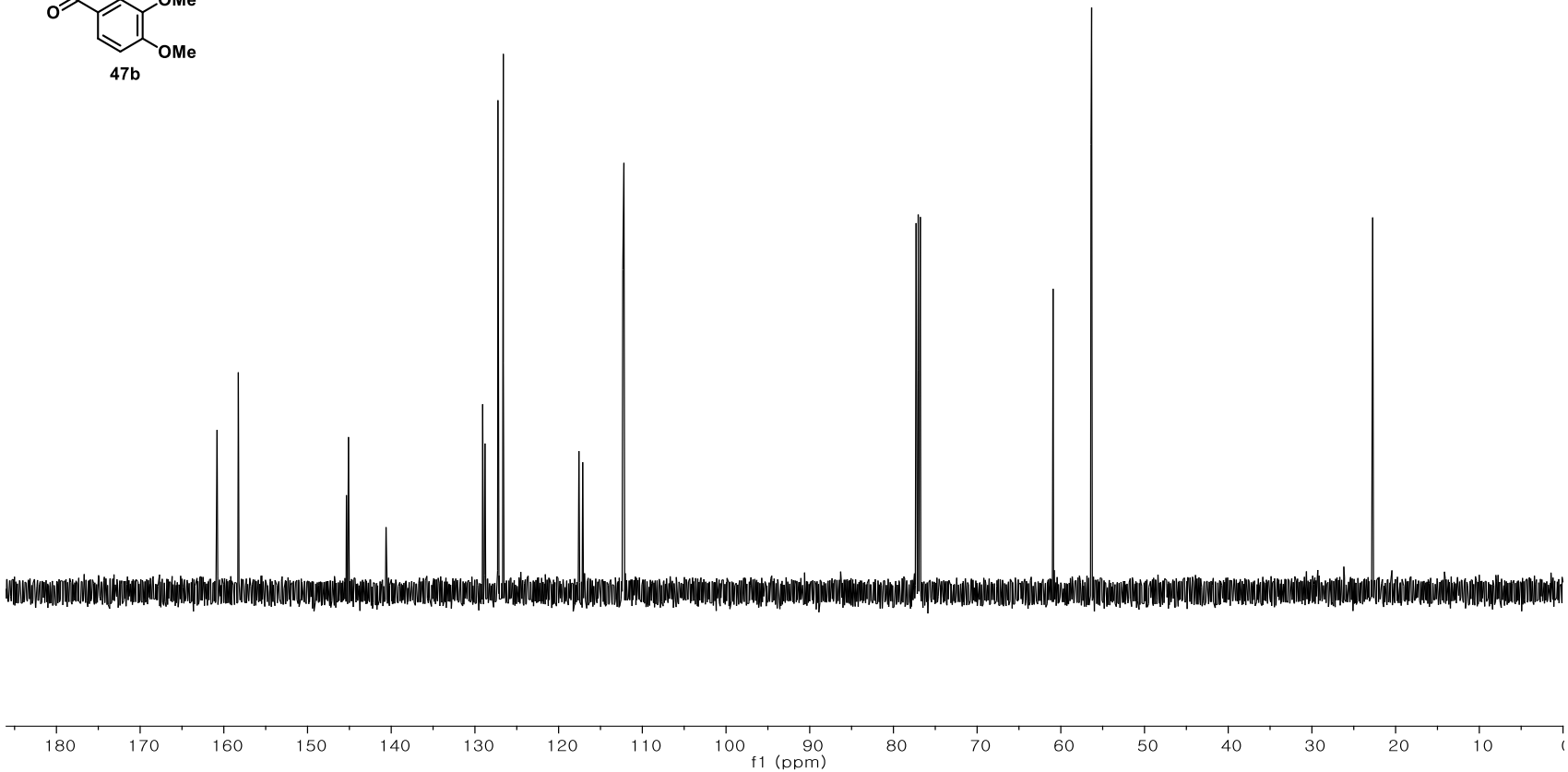
47b



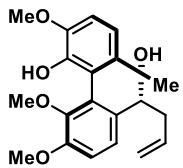
^{13}C NMR (126 MHz, $CDCl_3$)



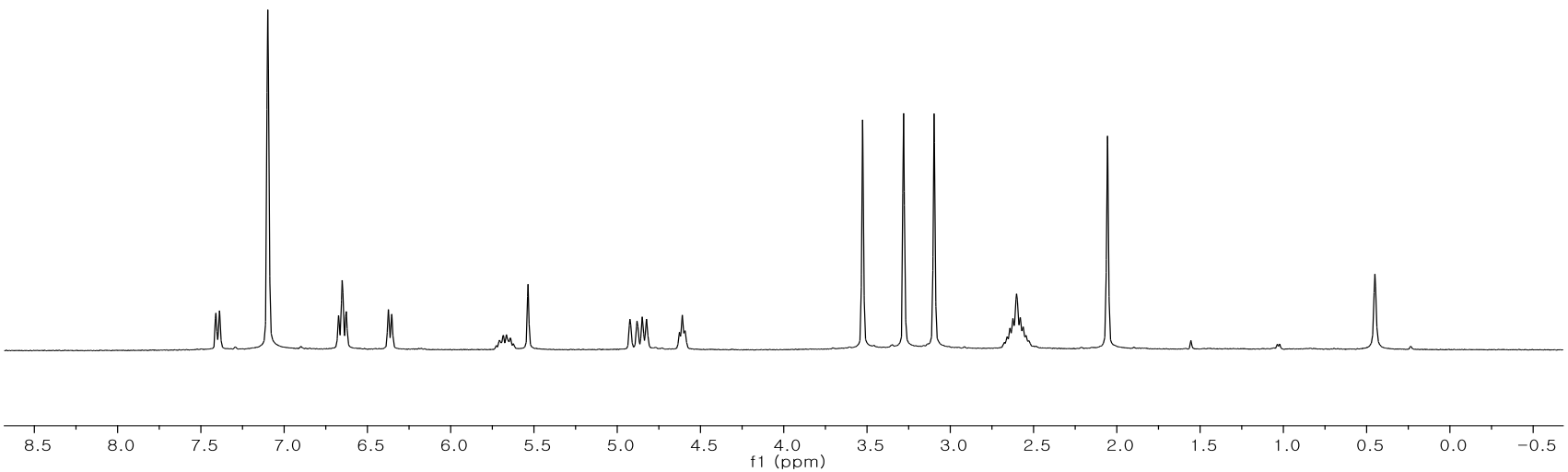
47b



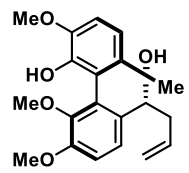
^{1}H NMR (400 MHz, C_6D_6)



47

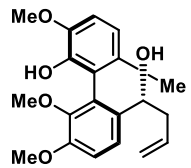


^{13}C NMR (101 MHz, C_6D_6)

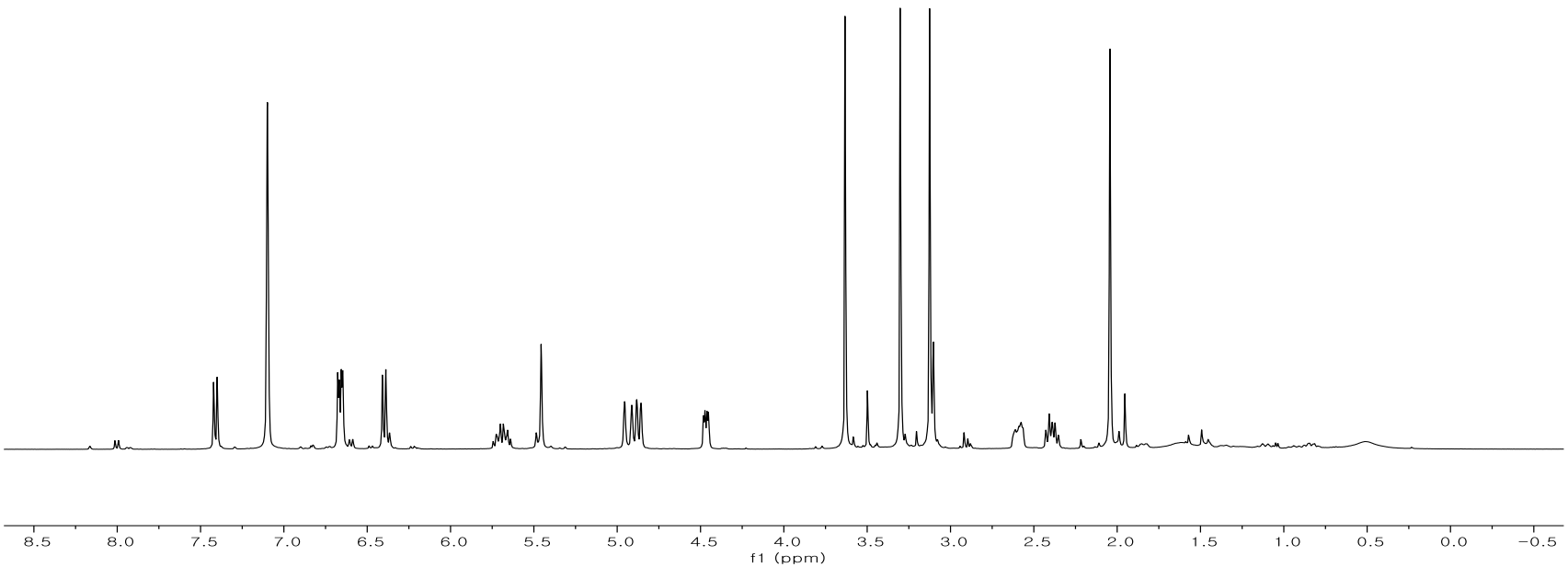


47

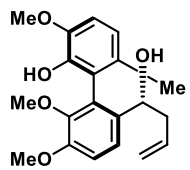
^{1}H NMR (400 MHz, $CDCl_3$)



47'



^{13}C NMR (101 MHz, $CDCl_3$)



47'

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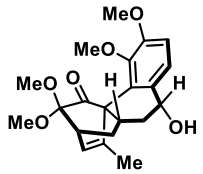

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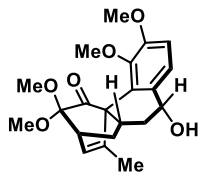

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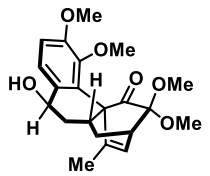

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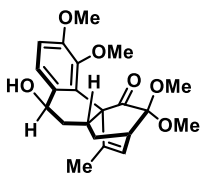

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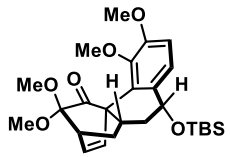

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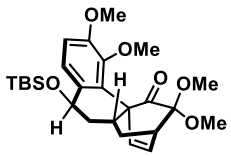

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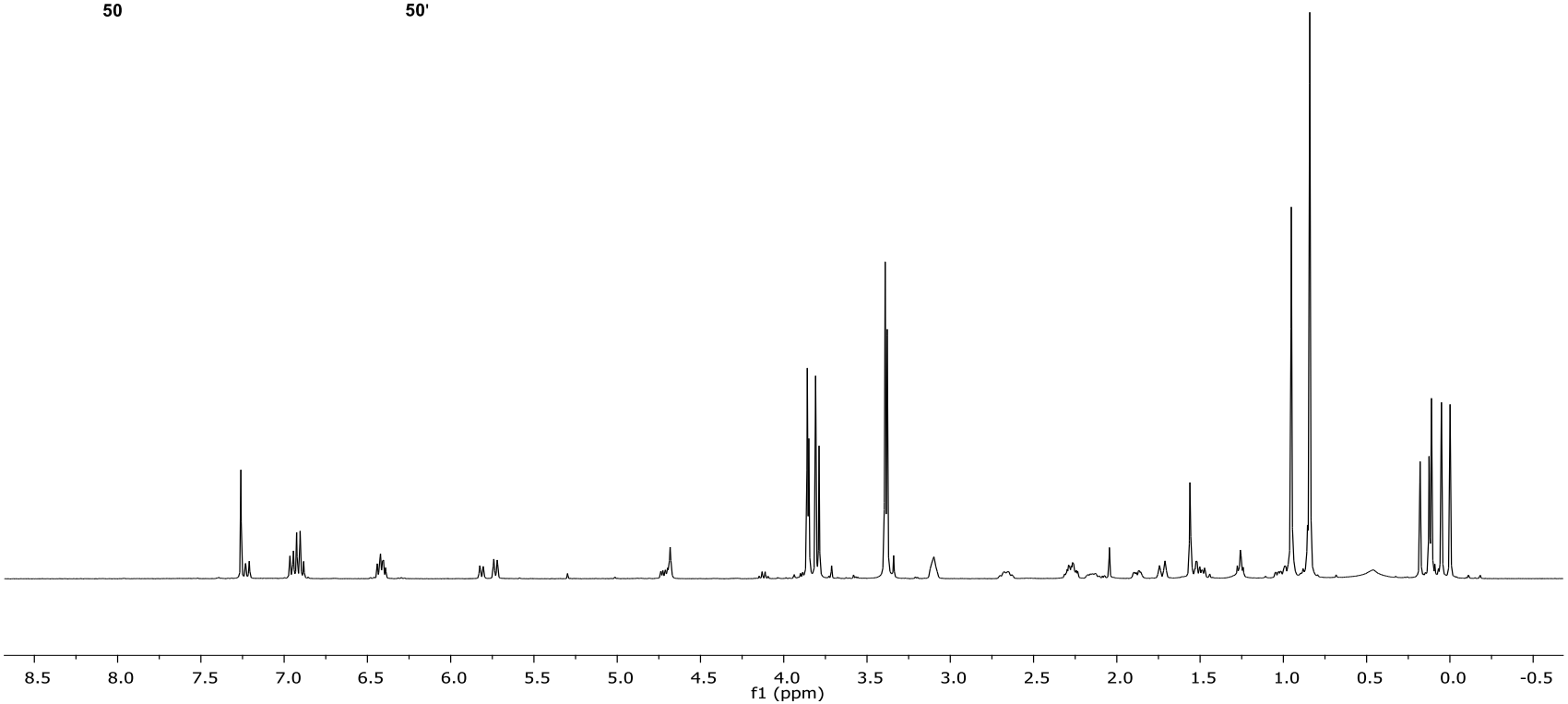

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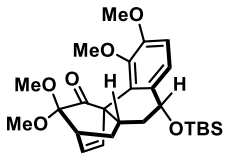

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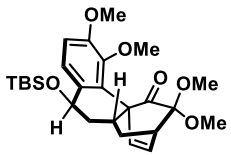

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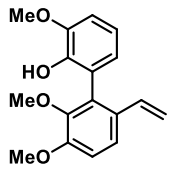

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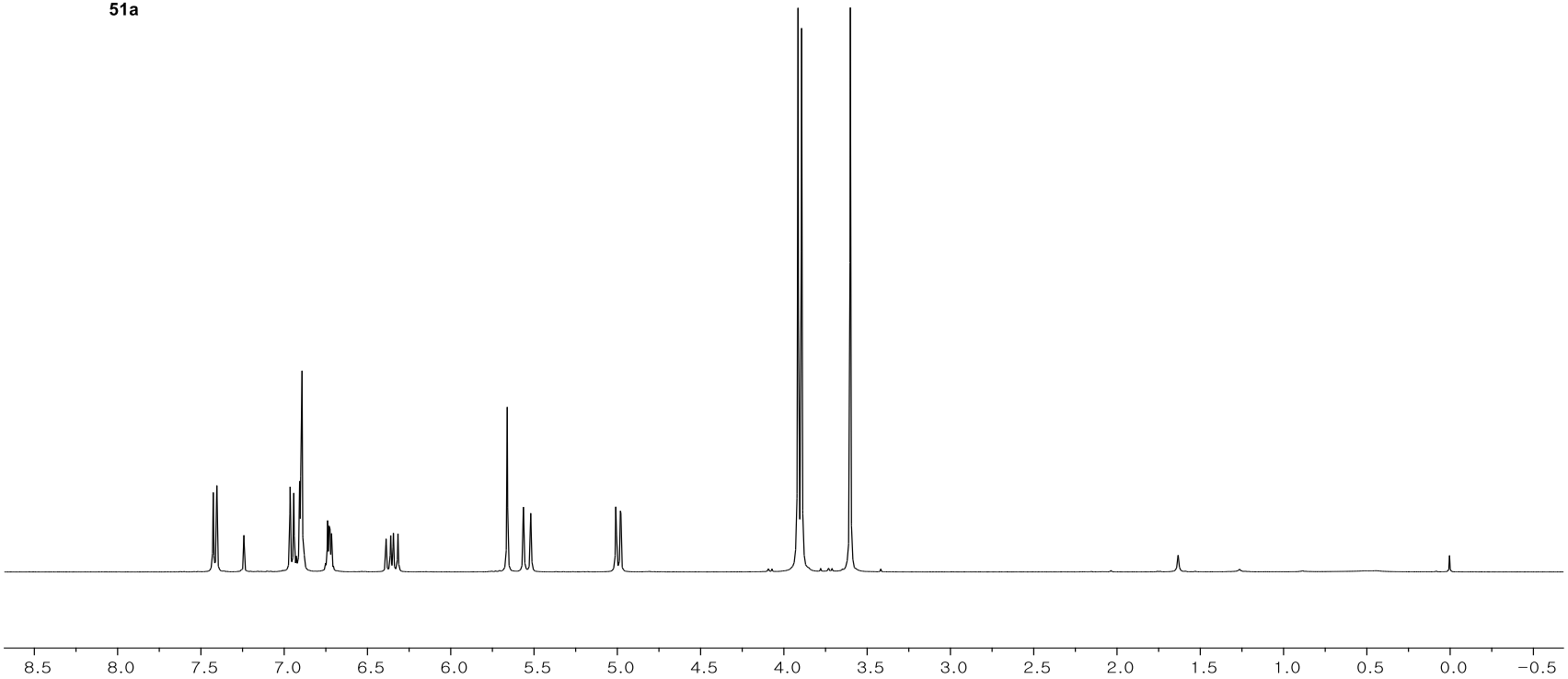

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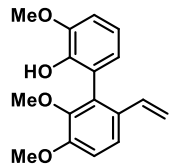

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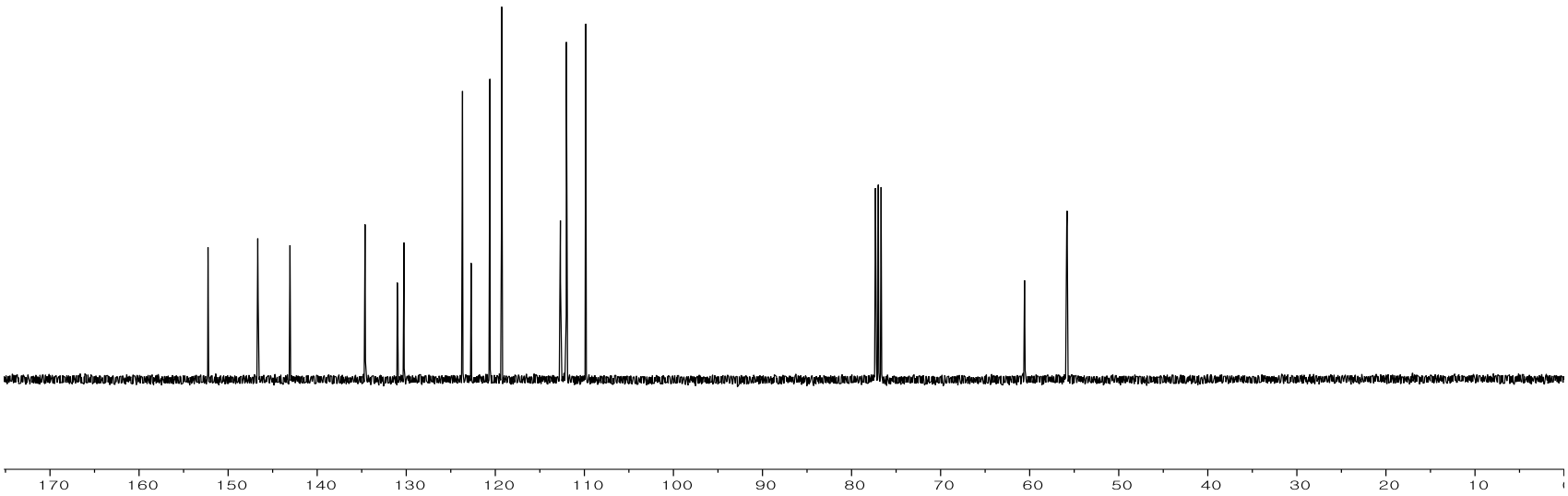

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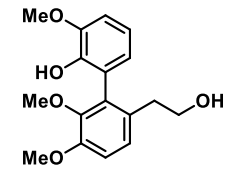

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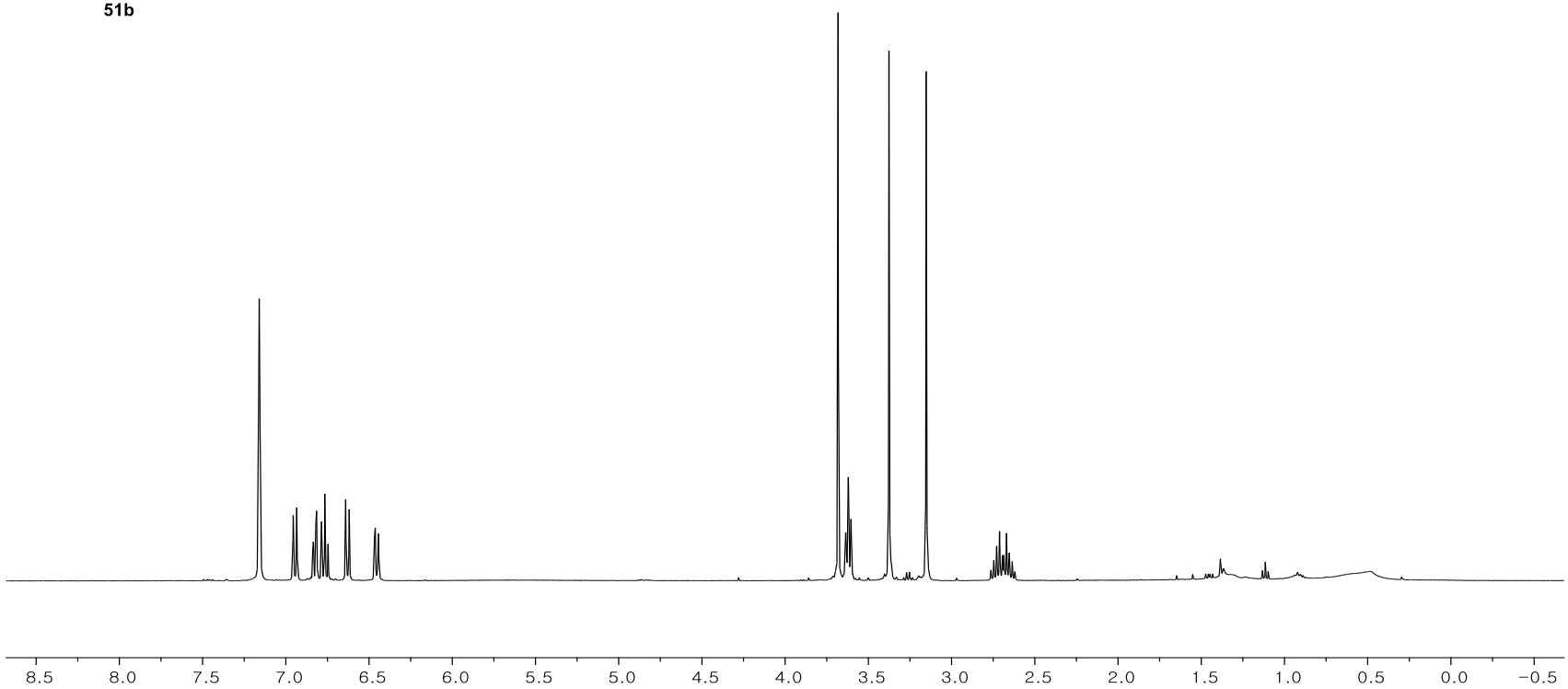
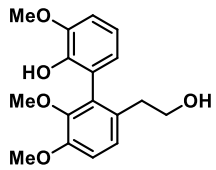


^{13}C NMR (101 MHz, $CDCl_3$)



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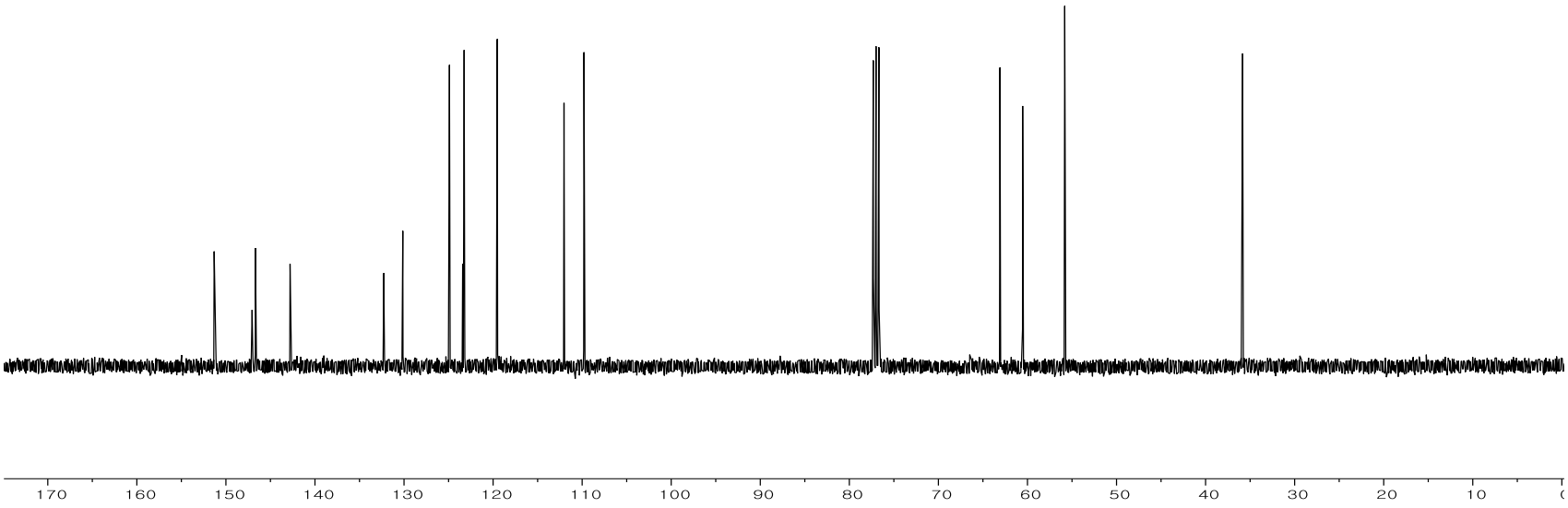

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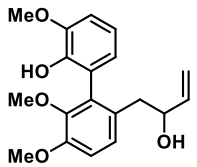

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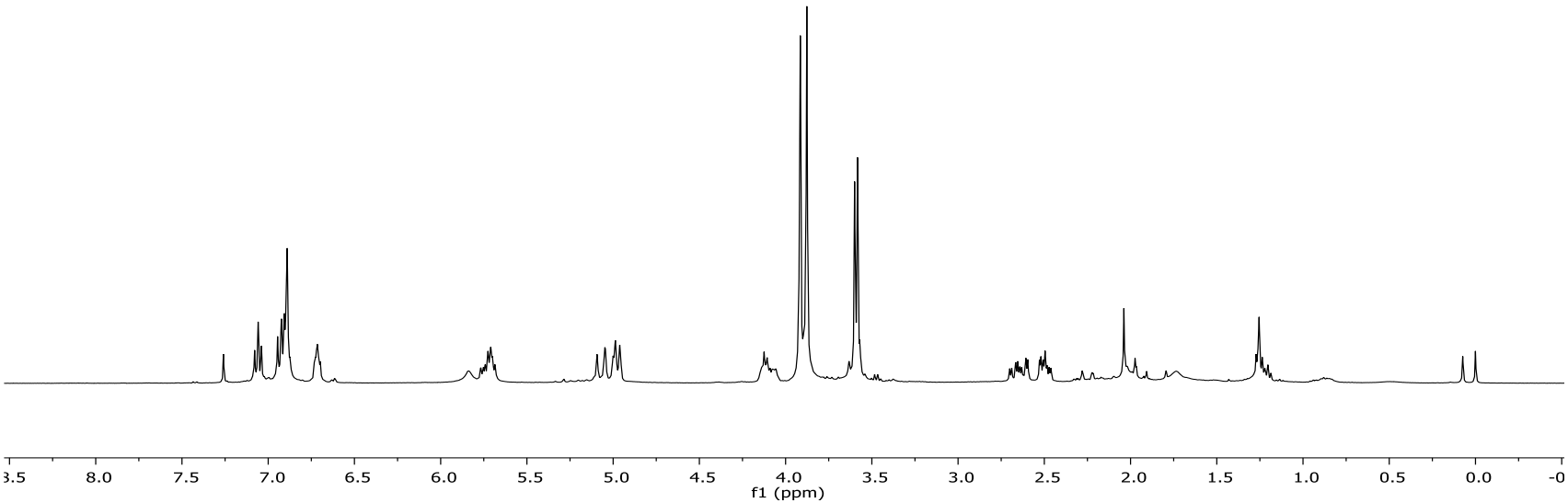

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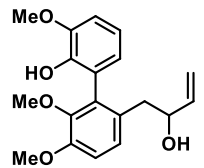

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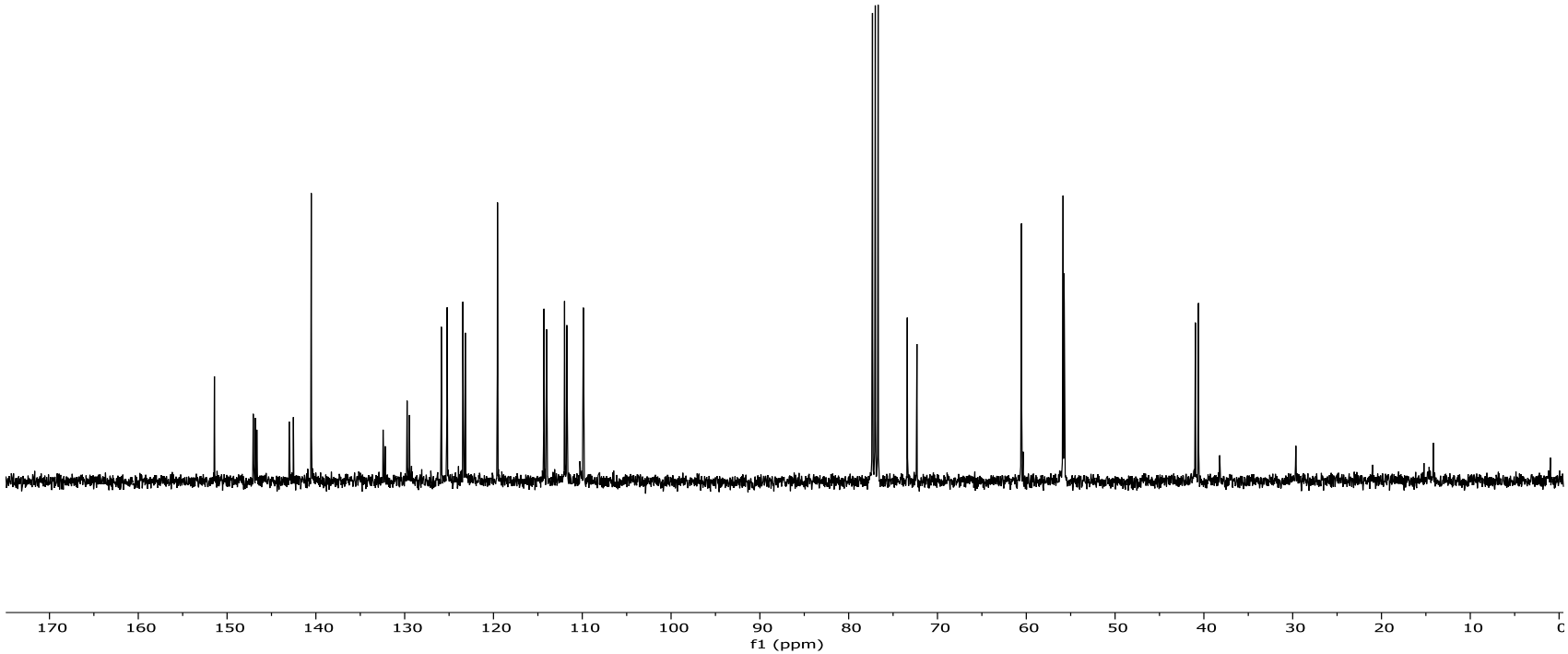
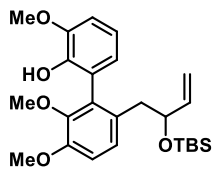


^{1}H NMR (400 MHz, $CDCl_3$)



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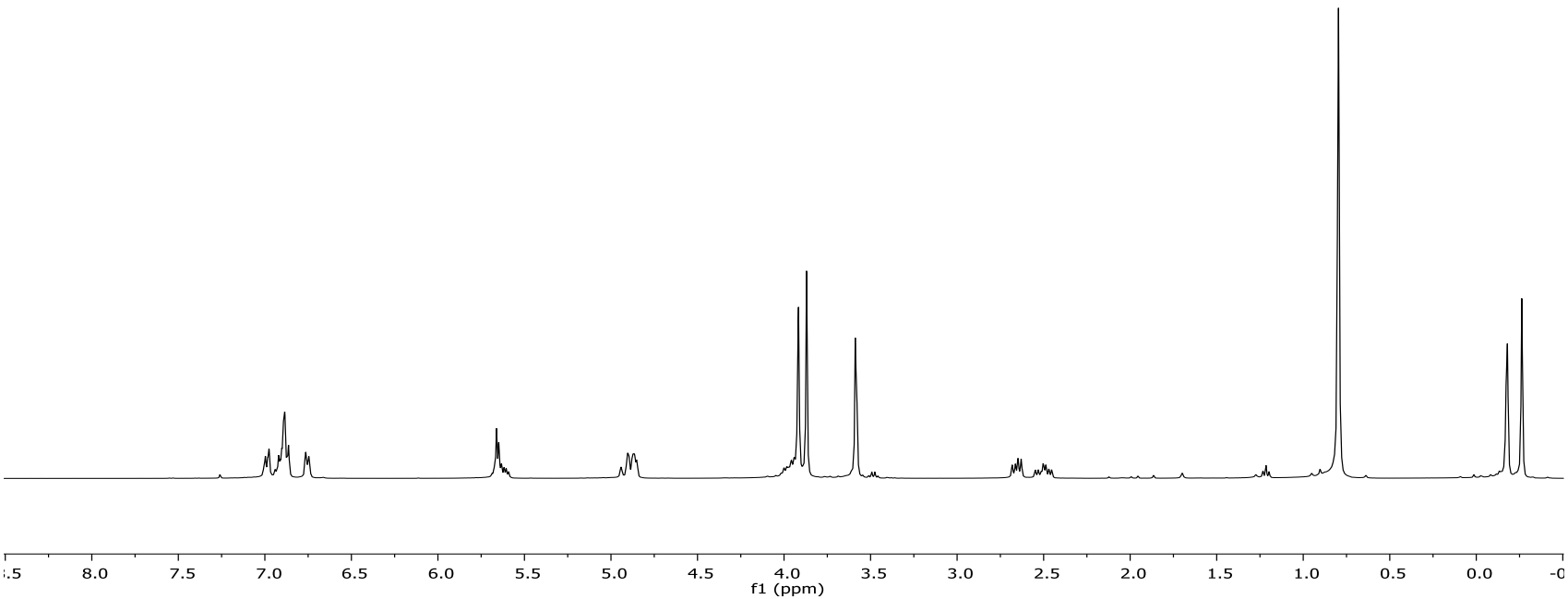
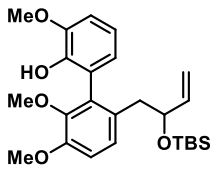


^{13}C NMR (101 MHz, $CDCl_3$)



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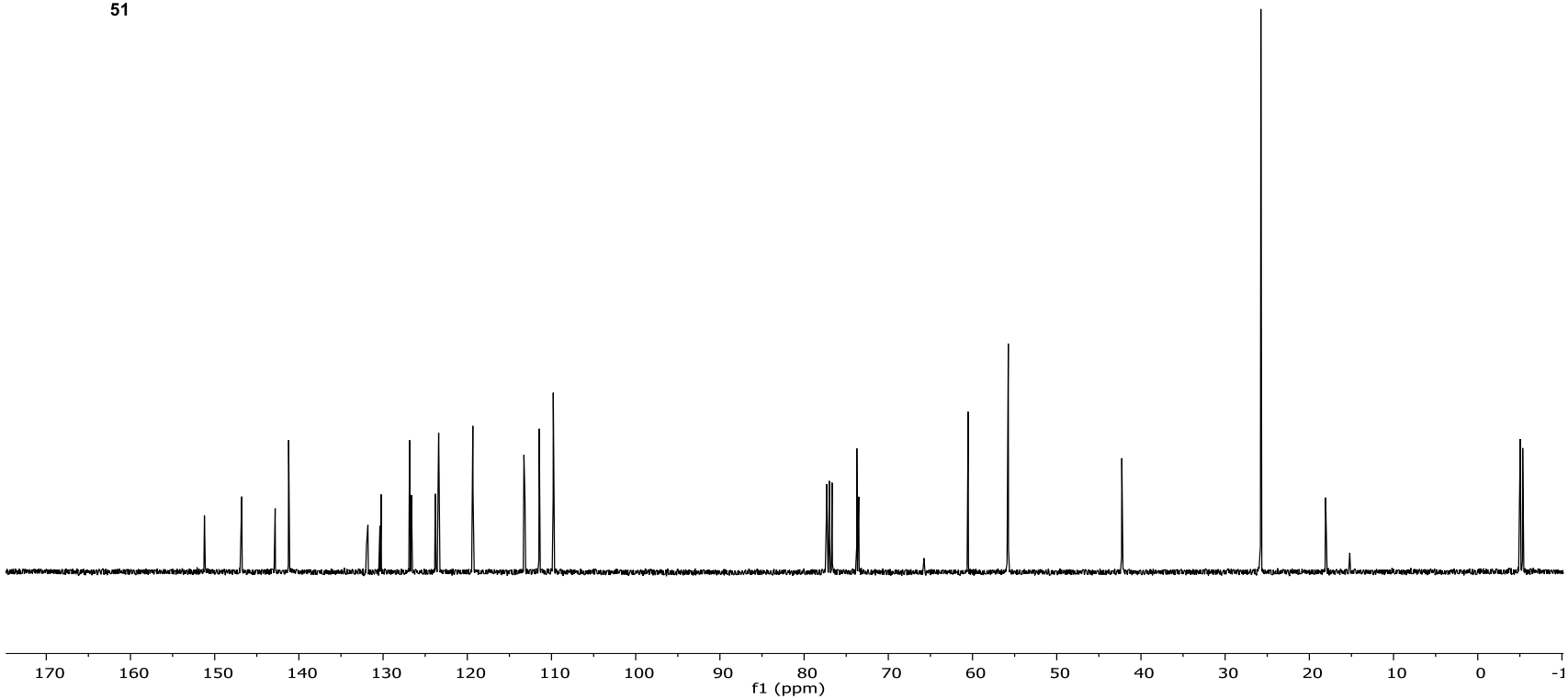

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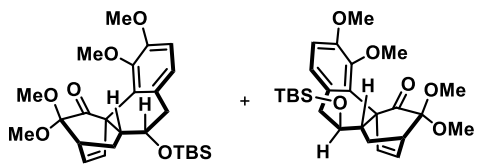

53

+

53'

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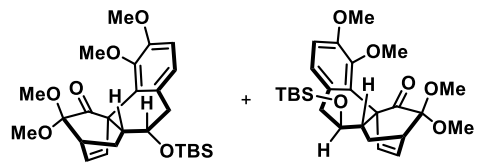
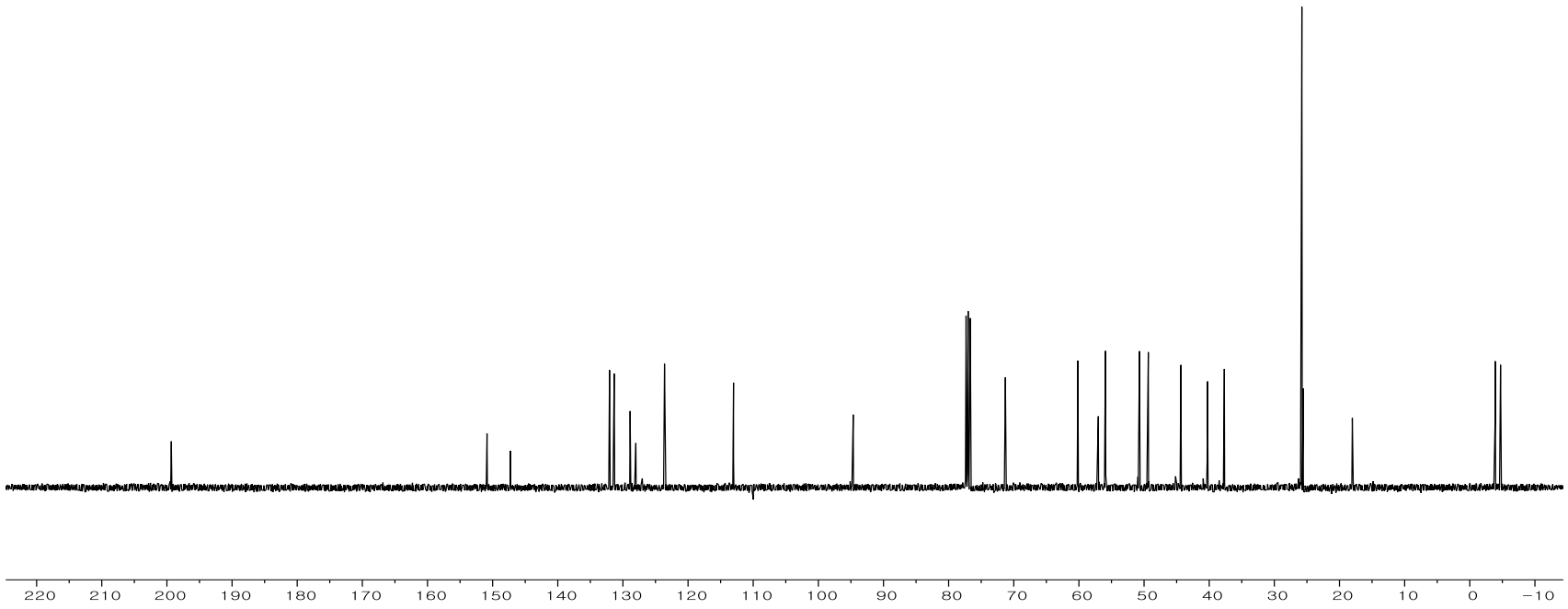


53

+

53'

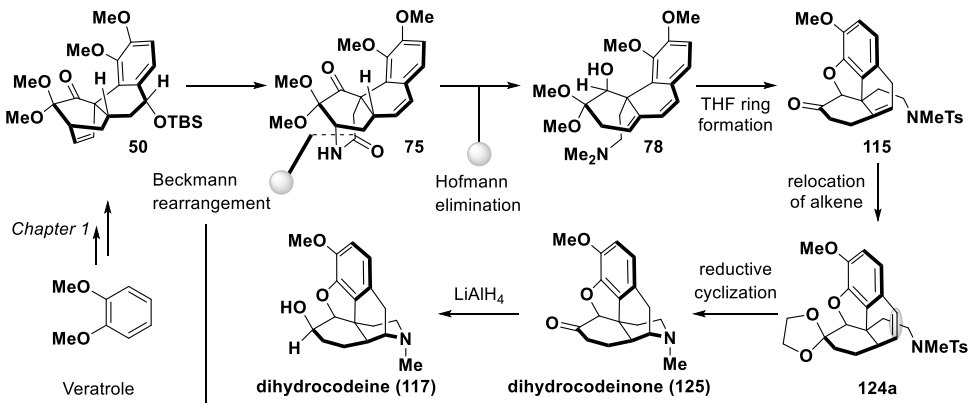


CHAPTER TWO

Synthetic Application of a Quaternary Center Containing Tetracyclic Intermediate in the Total Synthesis of Dihydrocodeinone and Dihydrocodeine

ABSTRACT

In this Chapter, chemical elaborations of the highly functionalized tetracycle **50** leading to the total synthesis of two morphinan alkaloids dihydrocodeinone (**125**) and dihydrocodeine (**117**), are described. The developed synthetic pathway featured a sequential Beckmann rearrangement and Hofmann elimination to rupture the [2.2.2]-bicyclic domain within tetracycle **50**, and a late-stage reductive cyclization to cast the core structure of the synthetic targets.

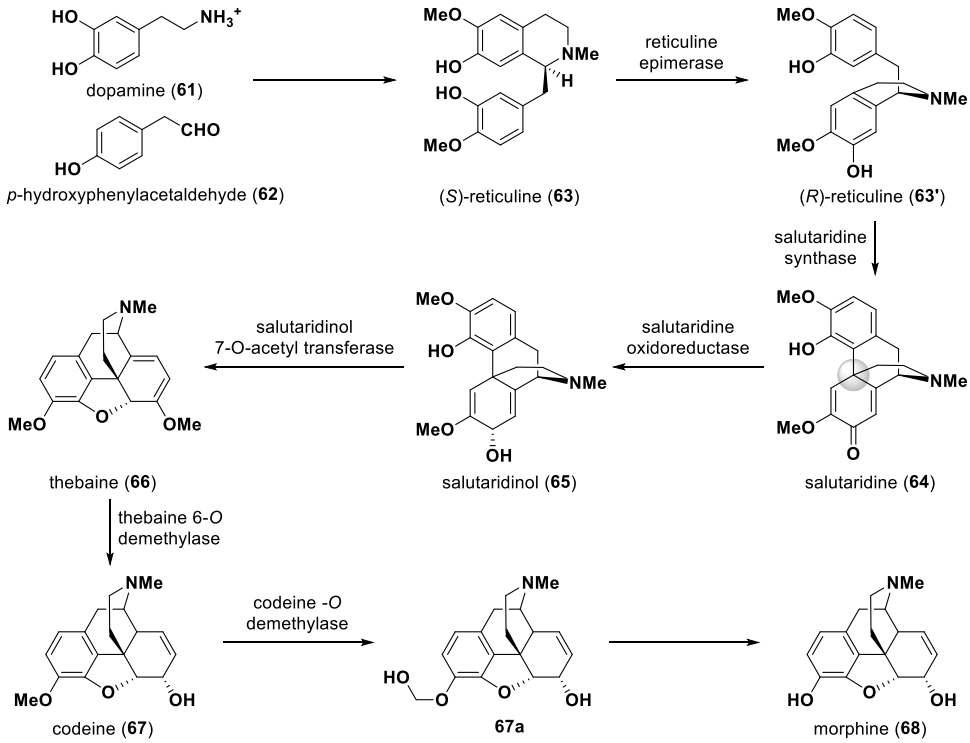


Keywords: bond cleavage, dihydrocodeinone, dihydrocodeine, morphinan, reductive cyclization, total synthesis

Student Number: 2014-22396

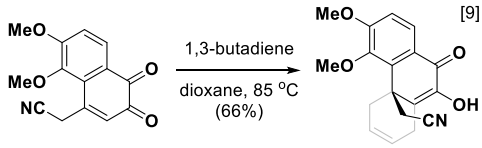
INTRODUCTION

Naturally occurring and synthetic morphinans are characterized by their powerful euphoric and analgesic properties, and has a long-standing history in both medicinal applications and illicit recreational usage.[1] Morphine (**68**), the most recognized member of the morphinan family isolated from the opium poppy plant *Papaver Somniferum* together with its congeners, was structurally elucidated by Sir Robert Robinson after extensive degradation studies more than ninety years ago.[2] Notwithstanding its rich history, the chemical[3] and biological investigations[4] of the morphinans remain vibrant today and have culminated in the discovery of numerous efficacious therapeutic agents with clinical successes.[5] This exercise is primarily based on the chemical modifications of naturally occurring substances, where large-scale cultivation and harvesting of natural morphinans continue to be the most practical and cost-effective protocol.[6] Biosynthetically, the natural origin of the morphinans has been fully established together with the identification of the responsible intervening enzymes.[7] As shown in Scheme 1, the elementary steps in the biosynthesis of morphine (**68**) involved an enzyme-mediated Pictet-Spengler reaction (**61** + **62** → **63**), an epimerization (**63** → **63'**), an oxidative biaryl couping (**63'** → **64**), and an intramolecular S_N2' displacement (**65** → **66**). More recently, the enzymes responsible for the demethylation of thebaine (**66**) leading to the sequential generation of codeine (**67**) and morphine (**68**) have also been identified.[8] This biosynthetic blueprint not only provided an overview of the intertwining relationship between the various secondary metabolites, but also presented valuable clues for the development of laboratory variants of these biological processes (*vide infra*).



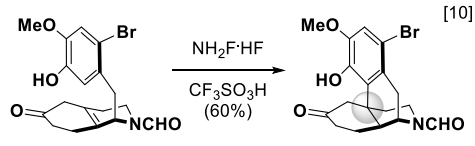
Scheme 1: Biosynthesis of Morphine (68).

On the other hand, the chemical synthesis of morphinans has witnessed remarkable methodological and strategic advances since Gates' landmark achievement in 1952 and remains active to date (Scheme 2). While these chemical advances are yet to surpass the efficiency and practicality of *Nature's* biosynthetic machinery, the ability to access a diverse array of designed morphinans with more superior pharmacological properties cannot be overstated.



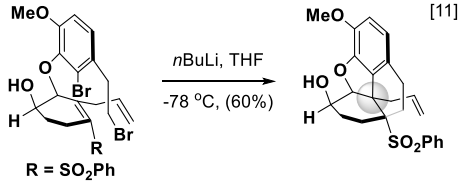
[9]

Gates (1952)
Diels-Alder



[10]

Rice (1980)
Grewe Cyclization



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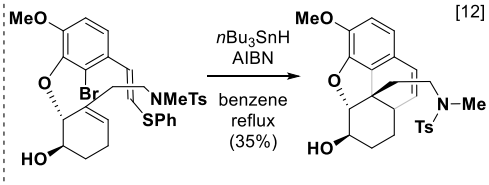
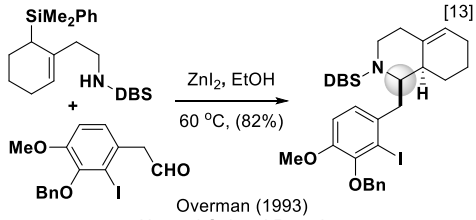
Fuch (1987)
Tandem Cojugate Additon/Alkylation



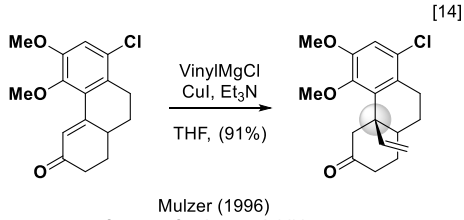
[12]

Parker (1992)
Tandem Radical Cyclization



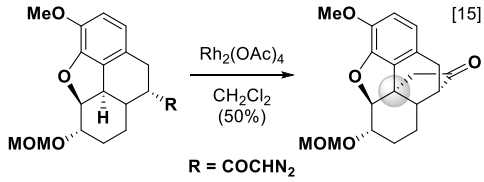
[13]

Overman (1993)
Hosomi-Sakurai Reaction



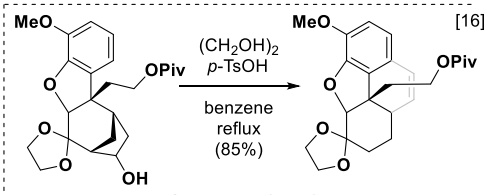
[14]

Mulzer (1996)
Cuprate Conjugate Addition



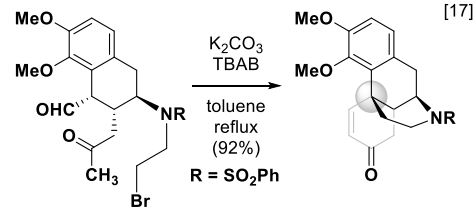
[15]

White (1999)
Carbenoid C-H Insertion



[16]

Ogasawara (2001)
Oxonium Mediated Cyclization



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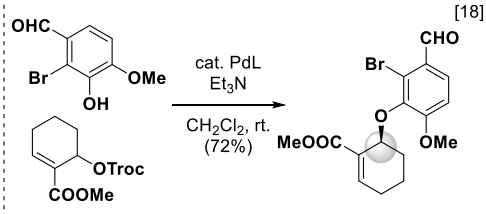
Taber (2002)
Tandem Alkylation/Aldol



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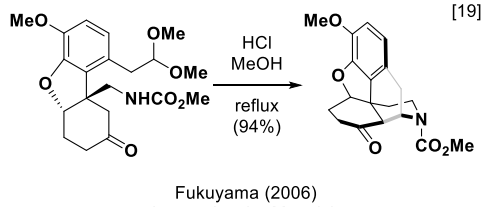
Trost (2002)
Asymmetric Allylic Alkylation



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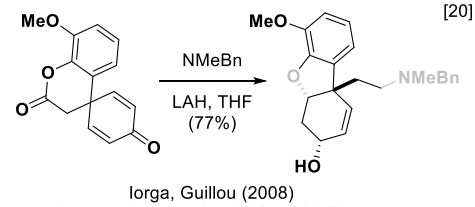
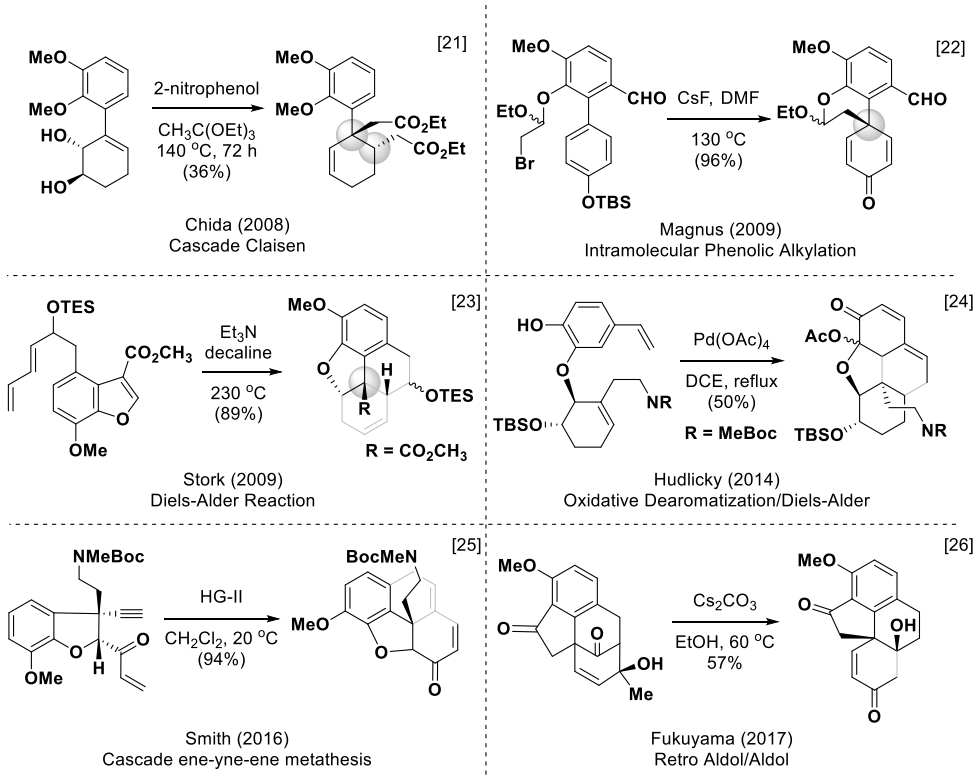
Fukuyama (2006)
Intramolecular Mannich



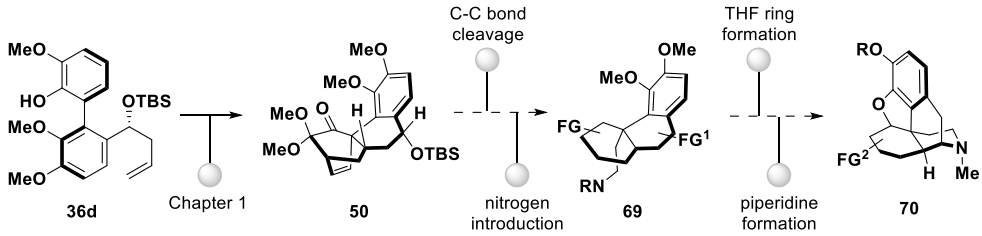
[20]

Iorga, Guillou (2008)
Lactone ring opening Michael Addition



Scheme 2: Representative Past Work of Morphinan.

In Chapter One, a stereocontrolled preparation of the highly functionalized tetracycle **50** was demonstrated that featured several thoughtfully orchestrated stereochemical induction events. Recognizing the structural similarity between the fused-tricycle domain within **50** and the characteristic phenanthrene backbone of the morphinan family of natural products, a synthetic plan was put forward to demonstrate the utility of tetracycle **50** in target-oriented synthesis. As illustrated in Scheme 3, bond cleavage of the [2.2.2]-bicyclic moiety within tetracycle **50** together with the introduction of a nitrogen atom is expected to generate a hypothetical quaternary center containing phenanthrene system **69**. Further synthetic elaborations of the hypothetical intermediate **69** involving two intramolecular cyclizations for the formation of the tetrahydrofuran and the piperidine rings are expected to cast the core structure of the morphinans, and the so-obtained late-stage intermediate may provide an access a variety of naturally occurring and designed morphinans.

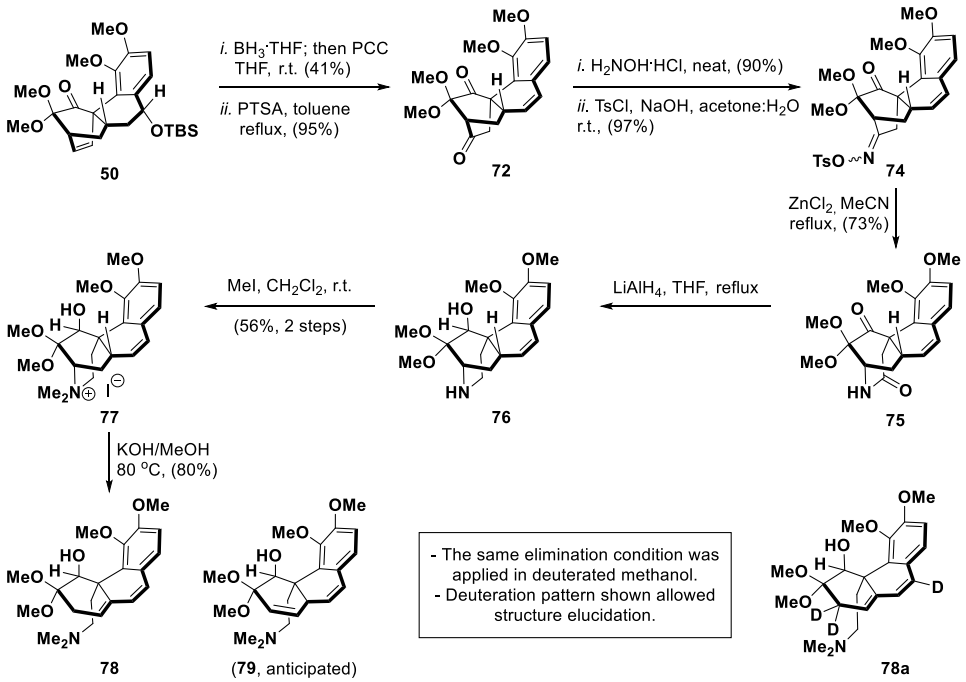


Scheme 3: Proposed Synthetic Strategy Toward Morphinan.

RESULTS AND DISCUSSION

The synthetic investigations toward the morphinan core structure commenced with the rupture of the [2.2.2]-bicyclic domain within tetracycle **50** while preserving its quaternary stereocenter. After contemplating several plausible carbon-carbon bond cleavage processes, a Beckmann rearrangement[27] with concomitant introduction of a nitrogen atom appeared most attractive for the synthesis of the morphinans. In this context, regioselective hydroboration of tetracycle **50** and oxidative workup of the intermediate organoborane with PCC afforded the corresponding ketone, which on treatment under acidic conditions underwent elimination of the benzylic TBS ether to afford diketone **72** (39%, two steps). In preparation for the proposed Beckmann rearrangement, the sterically more accessible ketone within **72** was converted to a geometric mixture of oximes (*E*/*Z*)-**73**. Interestingly, the mixture of oximes (*E*/*Z*)-**73** could be funneled to a single geometric isomer **73** upon heating in the absence of solvent ($H_2NOH{\cdot}HCl$, 90%). After several unsuccessful attempts of Beckmann rearrangements on oxime **73**, the attention was turned to its tosylated derivative **74** (TsCl, NaOH, acetone:H_2O, 97%) and further examined under a variety of conditions. Ultimately, $ZnCl_2$[28] was identified as the activating agent of choice to afford lactam **75** as a single regioisomer (Scheme 4), albeit additional $ZnCl_2$ was frequently required to drive the reaction to completion ($ZnCl_2$, MeCN, 73%). With lactam **75** in hand, further carbon-nitrogen bond cleavage and in doing so revealing the targeted quaternary centering bearing phenanthrene system was realized through a Hofmann elimination.[29] In preparation for this transformation, lactam **75** underwent exhaustive reduction followed by methylation to afford quaternary ammonium salt **77** through the intermediacy of amino alcohol **77a** [(i) $LiAlH_4$, THF, (ii) MeI, CH_2Cl_2, 56% for two steps]. Treatment of ammonium salt **77** under basic conditions smoothly delivered a diene product **78** (20% methanolic KOH, 80%) (Scheme 4) based on NMR analysis, however, the position of the newly generated olefin was inconsistent with the originally expected Hofmann elimination product **79**. This discrepancy can be

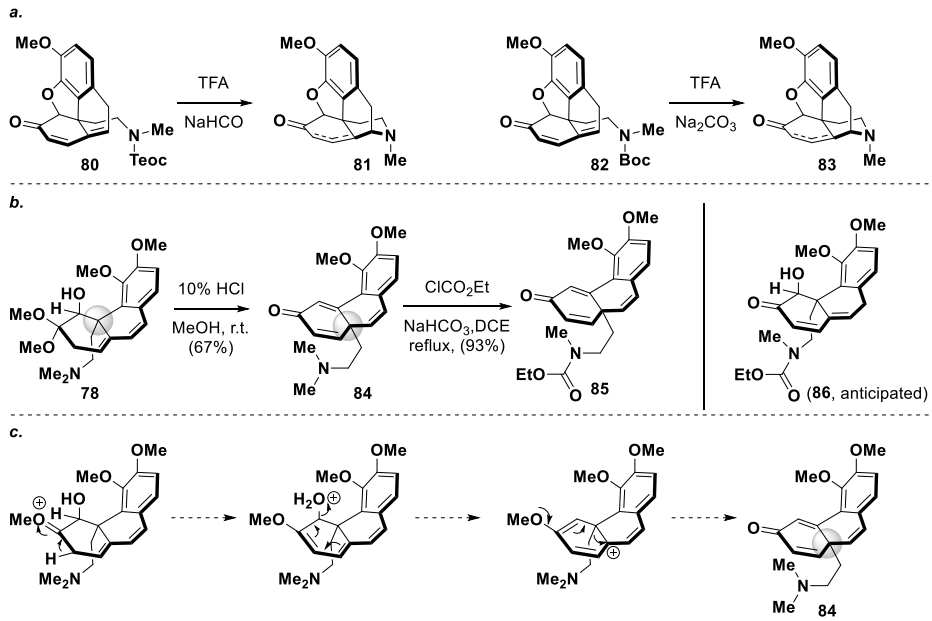
attributed to the formation of the thermodynamically more stable conjugated diene **78**, and further supported through an independent experiment performed in the presence of CD_3OD to afford deuterated diene **78a** through a series of deprotonation/protonation processes (Scheme 4).



Scheme 4: Synthesis of Tricyclic Diene 78.

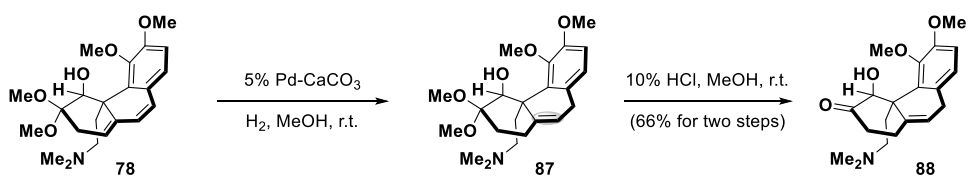
Realization of the sequential Beckmann rearrangement and Hofmann elimination ushered the synthetic investigation to the next phase. In particular, the successful preparation of conjugated diene **78** presented an enticing opportunity to explore an intramolecular 1,6-addition that was pioneered by Fuchs[11] and very recently also demonstrated by the Smith group (Scheme 5a).[25] To this end, it was anticipated that deprotection of dimethoxy ketal in **78** would lead to the formation of a conjugated dienone system **86** closely resemble the late-stage intermediates reported by Fuchs and Smith. Unfortunately, treatment of dimethoxy ketal **78** under acidic conditions led to the formation of an unexpected product **84** with its structure confirmed by extensive NMR analysis of the carbamate derivative **85** [HCl (aq), MeOH; then ethyl chloroformate, $NaHCO_3$, DCE, 62% for two steps], (Scheme 5b)

Mechanistically (Scheme 5c) the formation of dienone **84** could be attributed to a 1,2-migratory process closely related to a documented transformation.[30]



Scheme 5: ***a.*** **1,6-Addition of Cojugated dienone 80 and 82 Demonstrated by Fuchs and Smith, respectively;** ***b.*** **Synthesis of unexpected amine 84 and Carbamate 85;** ***c.*** **Proposed Mechanism for the Formation of Dienone 84.**

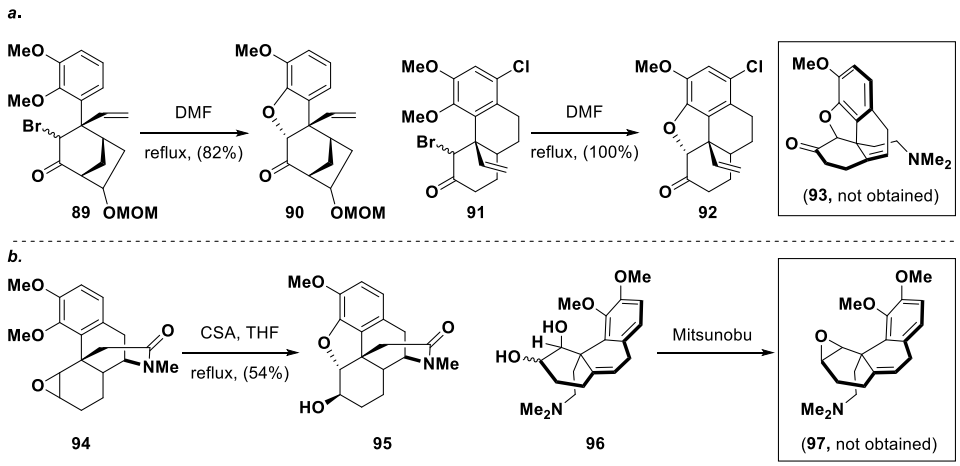
This mechanistic proposal also provided clues to a possible solution, in which a partially saturated diene system should prevent the 1,2-migratory process taking place. Indeed, partial reduction of diene **78** under carefully controlled hydrogenation conditions afforded a 1,4-migratory reduction product **87**, which on treatment under acidic conditions smoothly delivered ketone **88** [Pd-$CaCO_3$, H_2, MeOH; then HCl (aq), MeOH, 66% for two steps] (Scheme 6).



Scheme 6: Synthesis of Hydroxy Ketone 88.

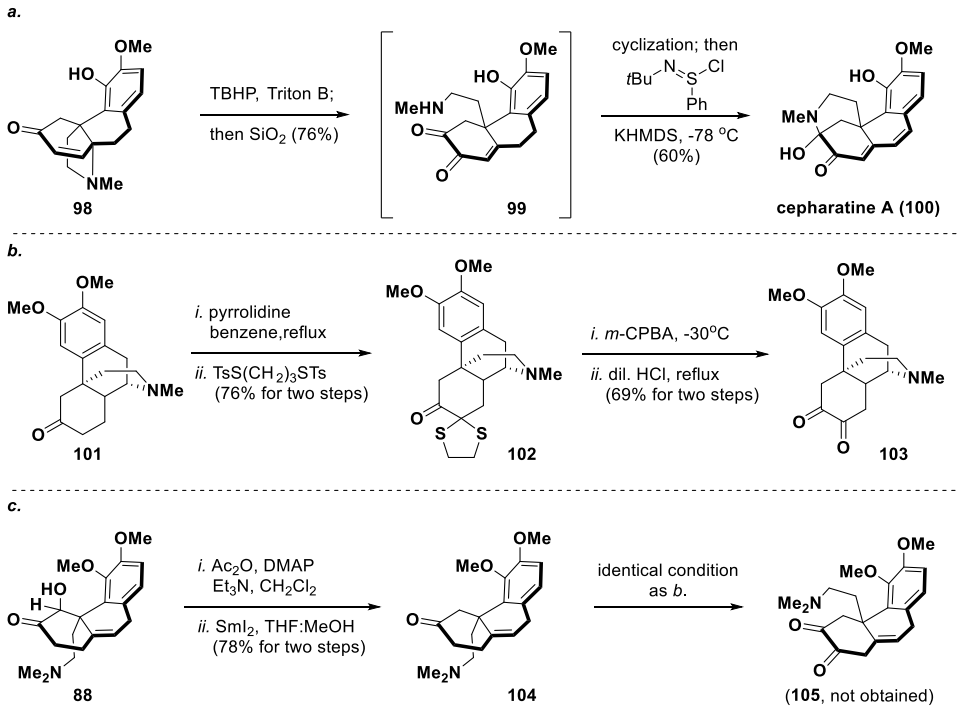
With hydroxy ketone **88** in hand, its unprotected alcohol presented an opportunity to explore the formation of the tetrahydrofuran moiety found in many of the morphinans.

Furthermore, tetrahydrofuran formation directly from a methylated phenol was particularly enticing which have been demonstrated by Ogasawara,[16] Mulzer,[14] and Hudlicky groups (Scheme 7).[31] To this end, several "activated hydroxyl" substrates were considered and prepared, but unfortunately synthetic efforts in this direction did not prevail (Scheme 7).



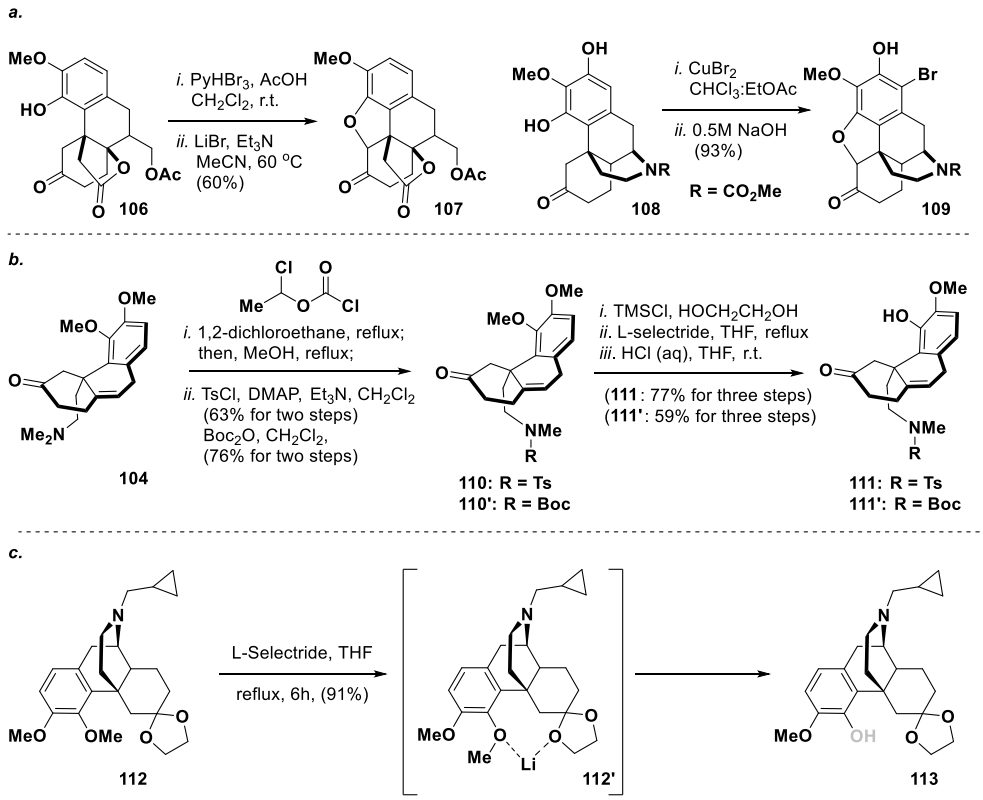
Scheme 7: ***a.*** **THF Formation from Phenolic Methyl Ether 89 and 91 Demonstrated by Ogasawara and Mulzer, respectively and Attempted Formation of Tetracycle 93;** ***b.*** **THF formation from Epoxide 94 Demonstrated by Hudlicky. Attempted Formation of Epoxide 97.**

As shown in Scheme 8, continued exploration of hydroxy ketone **88** presented an additional opportunity that detoured from the originally targeted morphinans. In this context, the cepharatine family of natural products displayed close structural resemblance with tricycle **88** with the most notable difference being the oxygenation pattern. Furthermore, several redox transformations reported by the Reisman[32] and Ogasawara[33] groups suggested the conversion from tricycle **88** to the cepharatines could be feasible. Therefore, tricycle **88** was first deoxygenated through the reductive action of samarium iodide to afford ketone **104** uneventfully [(i) Ac_2O, DMAP, Et_3N, CH_2Cl_2, (ii) SmI_2, THF:MeOH, 78% for two steps]. Unfortunately, despite numerous attempts to oxygenate ketone **104** under the conditions reported by Ogasawara, the anticipated diketone **105** was not obtained (Scheme 8c).



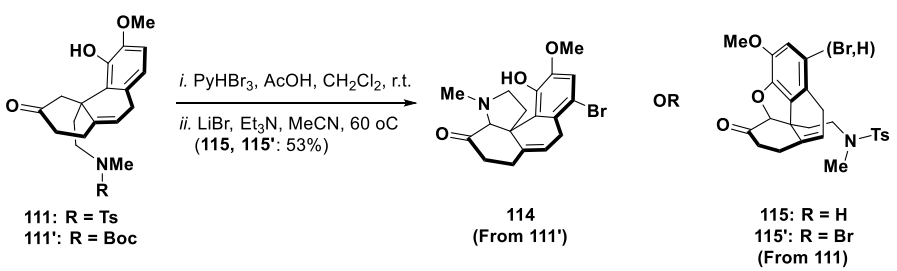
Scheme 8: *a*. Synthesis of Cepharatine A (100) from Amine 98 Demonstrated by Reisman; *b*. Synthesis of Diketone 103 from Amine 101 Demonstrated by Ogasawara; *c*. Attempted Synthesis of Diketone 105.

Although the synthetic explorations towards the cepharatines ended prematurely, the deoxygenated ketone **104** presented an opportunity to continue the synthetic endeavors toward the morphinans. In this context, the Fukuyama[34] and Opatz[35] groups have previously demonstrated ketones **106** and **108** could undergo regioselective bromination in the presence of a free "inner" phenol, followed by the subsequent tetrahydrofuran formation (Scheme 9a). Implementation of this strategy required the initial conversion of the dimethylamine moiety within ketone **104** to a protected methylamine, followed by a selective phenol demethylation (Scheme 9b). While the former objective was readily accomplished, the latter required the dioxolane-directed demethylation developed by Coop and coworkers (Scheme 9c).[36]



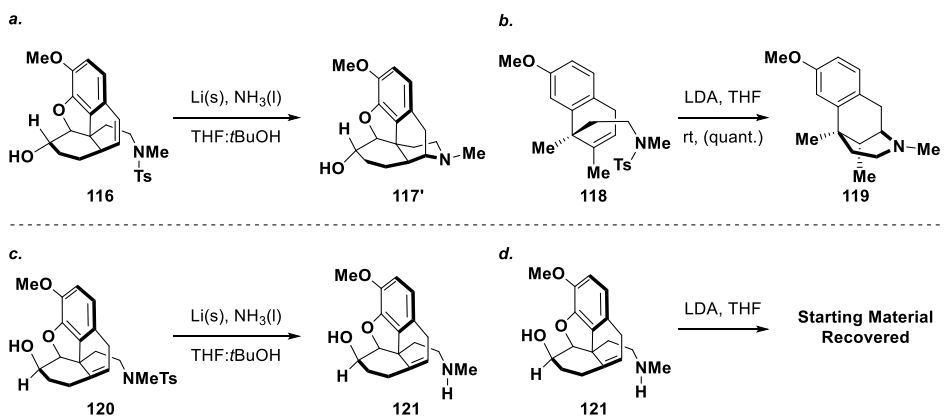
Scheme 9: *a*. Hydroxyl Directed Bromination/Cyclization of Phenolic Ketone 106 and 108 Demonstrated by Fukuyama and Opatz, respectively; *b*. Synthesis of Phenolic Ketone 111, 111'; *c*. Dioxolane Directed Demethylation of Amine 112 Demonstrated by Coop.

With phenolic ketone **111'** in hand, application of the reaction conditions developed by Fukuyama[34] and coworkers unexpectedly afforded a speculated tetracyclic compound **114**. Fortunately, revision of the nitrogen protecting group provided an easy solution and the targeted tetrahydrofuran systems **115** and **115'** were obtained as an inconsequential mixture (the aryl bromide was expected to undergo reductive cleavage later in the synthetic sequence, *vide supra*).



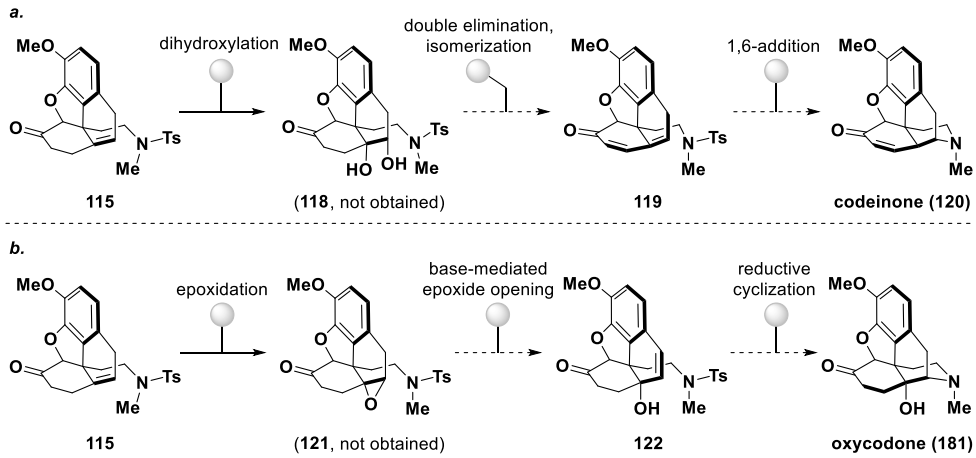
Scheme 10: Hydroxyl Directed Bromination/Cyclization of Phenolic Ketone 111 and 111'.

With tetracyclic tosyl amide **115** in hand, the final structural feature of the morphinan to be installed is the piperdine ring. In particular, a direct carbon-nitrogen bond formation without prior manipulations of the trisubstituted olefin in **115** was first considered. A cursory literature survey of the past morphinan syntheses presented two immediate options to be examined, namely the reductive cyclization pioneered by Parker group[12] and the base-promoted hydroamination reported by Trost laboratory (Scheme 11a, 11b).[37] Unfortunately and to some degree of surprise, treatment of tosylamide **120** under the Birch-type conditions developed by Parker and methylamine **121** under the LDA conditions reported by Trost both failed to deliver the morphinan piperidine ring (Scheme 11c, 11d). Presumably, radical stabilization at the tertiary position was less favorable compared to the benzylic stabilization in the substrate reported by Parker, whereas Trost suggested the electronic nature of the aryl system is critical for the LDA-mediated hydroamination.[37]



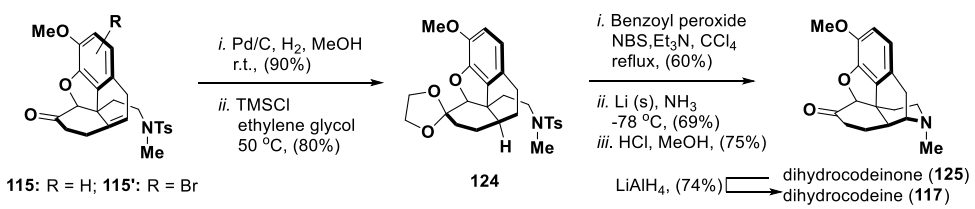
Scheme 11: *a*. Reductive Cyclization of Tosyl Amide 116 Demonstrated by Parker; *b*. Base Promoted Hydroamination of Tosyl Amide 118 Demonstrated by Trost; *c*. Attempted Reductive Cyclization of Tosyl Amide 120; *d*. Attempted Base Promoted Hydroamination of Amine 121.

With this minor setback in mind, several attempts to isomerize the trisubstituted alkene in **115** to the styrene position also met with failure.[38] Last but not least, oxidative transformations of alkene **115** to the corresponding epoxide **121** or diene **119** (for 1,6-addition approach, *vide supra*) also proved challenging (Scheme 12).



Scheme 12: *a.* Attempted Dihydroxylation of Tetracyclic Tosylamide 115; *b.* Attempted Epoxidation of Tetracyclic Tosylamide 115.

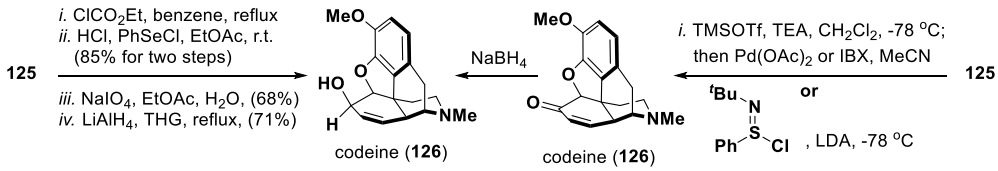
Finally, the successful piperdine formation took advantage of the protocol developed by Mulzer and co-workers.[14] To this end, relocation of the bridgehead alkene in **115/115'** to the styrene position was realized through a redox process involving an initial hydrogenation followed by a subsequent benzylic bromination/elimination. With the styrene system established, piperdine formation under the Birch-type conditions described Parker took place uneventfully.[12] Two signature morphinans dihydrocodeinone (**125**) and dihydrocodeine (**117**) were readily obtained after dioxolane deprotection and ketone reduction, respectively (Scheme 13).



Scheme 13: Successful Synthesis of Dihydrocodeine (117), Dihydrocodeinone (125)

With dihydrocodeinone (**125**) in hand, the preparation of codeine (**126**) was attempted through Saegusa,[39] Mukaiyama[40] and IBX[41] dehydrogenation chemistry. Although trace amounts of the desired compound could be identified by NMR and LCMS analysis, this transformation has not demonstrated synthetic utility up to this point. It is with

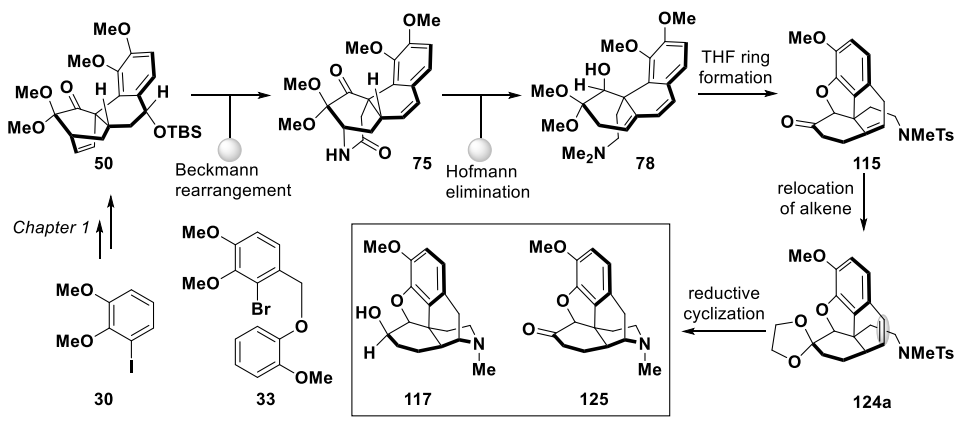
much anticipation this two-step transformation could be realized as a more efficient alternative compared to the well-documented four-step procedure.[42]



Scheme 14: Reported Protocol for the Conversion of Dihydrocodeinone (125) to Codeine (126) and Attempted Conversion of Dihydrocodeinone (125) to Codeine (126).

CONCLUSION

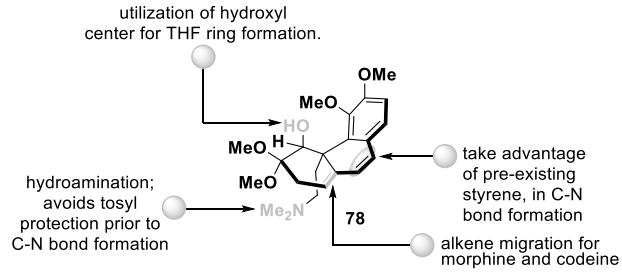
In this chapter, the total syntheses of morphinans dihydrocodeinone (**125**) and dihydrocodeine (**117**) were successfully achieved from tetracycle **50**. The successful synthetic pathway featured a sequential Beckmann rearrangement and Hofmann elimination to rupture the [2.2.2]-bicyclic domain within tetracycle **50**, followed by a bromination/cyclization to construct the tetrahydrofuran and a late-stage reductive Birch-type cyclization to cast the piperidine ring (Scheme 15).



Scheme 15: Synthesis of Dihydrocodeinone (125) and Dihydrocodeine (117) from Tetracyclic 50.

Although the rupture of the [2.2.2]-bicyclic system within tetracycle **50** proceeded as planned, the final solution devised for the construction of the tetrahydrofuran and the piperidine rings proved less ideal. As a result, several redox redundant steps were implemented and consequently a substantially lengthened synthetic sequence was resulted. Although a "diversity" argument could be put forward to justify this develop synthetic pathway, more efforts are needed to render a more efficient solution. Specifically, several redox adjustments were made along the phenanthrene backbone to circumvent any undesired side reactions and to facilitate the piperidine formation. Furthermore, the hydroxyl group which was poised for the tetrahydrofuran formation was removed and later re-generated in the form of a bromide. In retrospect, the Hofmann elimination product **78** with its rich array of functional groups is an ideal starting point for more extensive investigations. In doing so,

not only the synthesis of morphinans will be greatly improved, but structurally related alkaloids could also be accessed in a “collective” manner (Scheme 16).



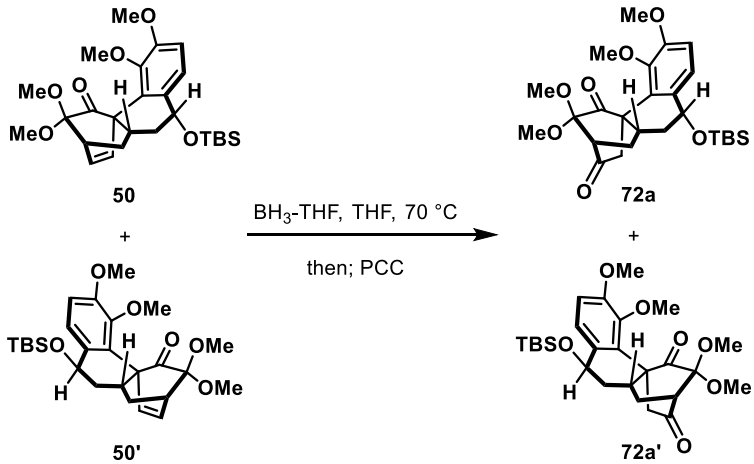
Scheme 16: Proposed Improvement of Synthesis of Morphinan from Diene 78.

EXPERIMENTAL

General Procedures

Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2) and toluene were dried and distilled according to the standard protocols. Benzene and acetonitrile (CH_3CN) were purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc), Et_2O, CH_2Cl_2, hexanes and water were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F−254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde or potassium permanganate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer and IRTracer-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

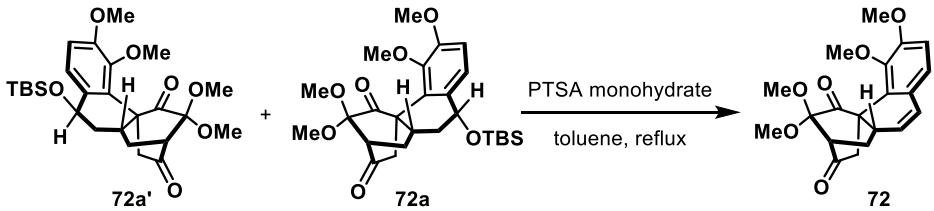
Ketones 72a and 72a'



To a stirred solution of alkenes **50** and **50'** (98.0 mg, 0.21 mmol) in THF (2.0 mL) at –78 °C was added borane tetrahydrofuran complex (1.0 M in THF, 1.03 mL, 1.03 mmol). The resulting mixture was warmed to 70 °C and stirred for 4 h before it was cooled to room temperature and treated with PCC (223 mg, 1.03 mmol). The resulting mixture was stirred for 5 h before it was filtered through Celite® and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:Et_2O 1:1) afforded ketones **72a** and **72a'** (42.0 mg, 41%) as an amorphous white solid. **72a**+**72a'**: R_f = 0.76 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3456, 3154, 2970, 1710, 1200, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.1 Hz, 0.5H), 6.91 (dd, *J* = 8.0 Hz, 0.5H), 6.92 (s, 1H), 4.72 (dd, *J* = 5.7 Hz, 0.5H), 4.67 (br t, *J* = 2.5 Hz, 0.5H), 3.86–3.76 (m, 4.5H), 3.70 (s, 1.2H), 3.56 (s, 0.3H), 3.43–3.37 (m, 6H), 3.30 (d, *J* = 20.5 Hz, 0.5H), 3.08 (br s, 0.25H), 3.06–2.96 (m, 0.25H), 2.91 (d, *J* = 19.3 Hz, 0.25H), 2.79 (br s, 0.25H), 2.71 (d, *J* = 20.6 Hz, 0.5H), 2.51–2.24 (m, 2H), 2.02–1.92 (m, 1H), 1.88–1.76 (m, 1H), 1.50–1.42 (m, 1H), 1.35–1.24 (m, 1H), 0.94 (s, 5H), 0.80 (s, 4H), 0.17 (s, 1.7H), 0.11 (s, 1.7H), 0.10 (s, 1.3H), 0.03 ppm (s, 1.3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.9, 204.3, 201.4, 196.0, 151.4, 147.0, 146.0, 133.6, 132.2, 126.6, 124.9, 123.1, 121.8, 113.0, 112.9, 100.0, 97.5, 96.7, 80.0, 69.5, 68.9, 67.5, 60.0, 59.8, 58.4, 55.8, 55.7, 51.9, 51.5, 50.7, 50.0, 49.9, 49.6, 41.7, 40.9, 36.6, 36.1, 34.3, 33.8, 31.3, 28.3, 25.9,

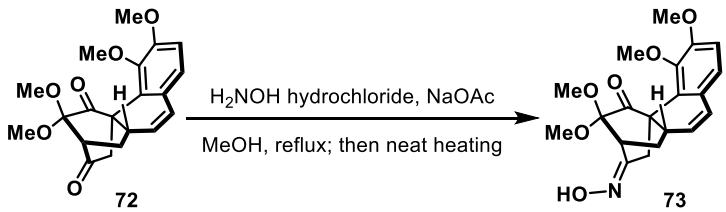
25.8, 24.9, 18.2, 17.9, –0.01, –4.1, –4.5, –4.8 ppm; HRMS calcd. For $C_{26}H_{38}O_7SiNa^+$ [M + Na]$^+$ 513.2279, found 513.2281.

Alkene 72



To a stirred solution of TBS ethers **72a** and **72a'** (4.20 g, 8.56 mmol) in toluene (350 mL) at room temperature was added *p*-toluenesulfonic acid monohydrate (1.63 g, 8.57 mmol). The resulting mixture was warmed to reflux and stirred for 20 min before it was cooled to room temperature and quenched with $NaHCO_3$ (40 mL, sat. aq.) and water (40 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 80 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 9:1) afforded alkene **72** (2.90 g, 95%) as an amorphous white solid. **72**: R_f = 0.48 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3455, 3154, 2924, 1704, 1597, 722 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 6.82–6.70 (m, 2H), 6.37 (d, *J* = 9.4 Hz, 1H), 5.43 (d, *J* = 9.3 Hz, 1H), 3.85 (s, 6H), 3.42 (s, 3H), 3.39 (s, 3H), 3.14–3.04 (m, 2H), 2.77 (d, *J* = 19.5 Hz, 1H), 2.67 (d, *J* = 21.1 Hz, 1H), 2.53–2.49 (m, 1H), 1.77–1.66 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.3, 202.8, 152.9, 145.9, 128.0, 126.8, 125.7, 125.6, 123.1, 111.8, 97.5, 59.8, 55.7, 52.4, 51.9, 51.1, 49.3, 38.6, 37.4, 24.7 ppm; HRMS calcd. For $C_{20}H_{22}O_6Na^+$ [M + Na]$^+$ 381.1309, found 381.1308.

Oxime 73



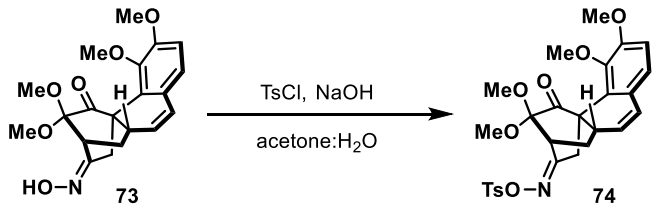
To a stirred solution of alkene **72** (3.20 g, 8.93 mmol) in MeOH (28.0 mL) at room temperature was added hydroxylamine hydrochloride (1.86 g, 26.8 mmol) and NaOAc (2.20 g, 26.8 mmol). The resulting mixture was warmed to reflux and gradually allow the reaction mixture to evaporate to dryness, and the resulting solid residue was heated for 16 h before it was cooled to room temperature and quenched with $NaHCO_3$ (40 mL, sat. aq.) and MeOH (40 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded oxime **73** (3.0 g, 90%) as an amorphous yellow solid. Performing the reaction without "neat-heating" gave rise to a mixture of oxime **73** and its geometric isomer **73'**.

73: R_f = 0.24 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3707, 3456, 2926, 1705, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 6.81 (s, 2H), 6.35 (d, *J* = 9.3 Hz, 1H), 5.43 (d, *J* = 9.4 Hz, 1H), 3.85 (s, 6H), 3.41 (s, 6H), 3.20–3.15 (m, 1H), 3.01–2.95 (m, 1H), 2.85 (s, 2H), 2.45 (t, *J* = 12.1 Hz, 1H), 1.70–1.64 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7, 157.9, 152.9, 146.3, 127.7, 127.1, 126.6, 126.2, 122.9, 111.8, 97.7, 59.8, 55.7, 51.3, 50.9, 49.4, 41.6, 37.6, 26.5, 26.3 ppm; HRMS calcd. For $C_{20}H_{23}NO_6Na^+$ $[M + Na]^+$ 396.1418, found 396.1416.

73': R_f = 0.37 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3705, 3457, 2926, 1702, 733 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 7.41 (s, 1H), 6.82 (dd, *J* = 2.5, 0.9 Hz, 2H), 6.36 (dd, *J* = 9.3, 2.2 Hz, 1H), 5.46 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.17 (t, *J* = 3.0 Hz, 1H), 3.86 (s, 6H), 3.45

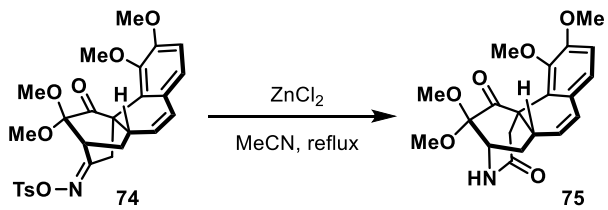
(s, 3H), 3.44 (s, 3H), 3.12–2.99 (m, 1H), 2.84 (d, *J* = 18.0 Hz, 1H), 2.66 (d, *J* = 17.4 Hz, 1H), 2.43–2.38 (m, 1H), 1.70–1.60 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.1, 156.8, 152.9, 146.3, 127.7, 127.2, 126.5, 126.5, 123.0, 111.7, 98.1, 59.9, 55.7, 51.7, 51.2, 49.5, 37.7, 35.5, 28.7, 25.5 ppm; HRMS calcd. For $C_{20}H_{23}NO_6Na^+$ $[M + Na]^+$ 396.1418, found 396.1416.

Tosylate 74



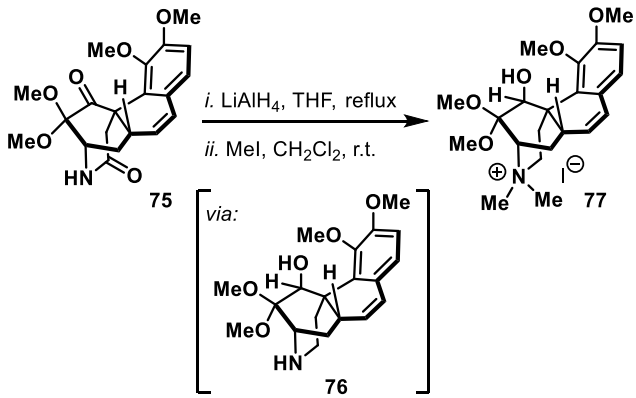
To a stirred solution of oxime **73** (5.10 g, 13.7 mmol) in acetone/H_2O (1:1, 260 mL) at room temperature was added NaOH (1.37 g, 34.3 mmol) and TsCl (3.91 g, 20.5 mmol). The resulting mixture was stirred for 2 h before it was quenched with $NaHCO_3$ (100 mL, sat. aq.) and water (60 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), the combined organic layer was washed with water (70 mL), brine (70 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 10:1) afforded tosylate **74** (7.02 g, 97%) as an amorphous yellow solid. **74**: R_f = 0.43 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3695, 3457, 3154, 2918, 1704, 723 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.82 (s, 2H), 6.34 (dd, *J* = 9.3, 3.3 Hz, 1H), 5.33 (dd, *J* = 9.3, 2.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.39 (s, 3H), 3.24 (s, 3H), 3.23–3.20 (m, 1H), 3.08–2.98 (m, 1H), 2.85 (d, *J* = 3.4 Hz, 2H), 2.49–2.40 (m, 1H), 2.48 (s, 3H), 1.57–1.51 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 167.3, 153.0, 146.2, 144.7, 132.9, 129.5, 128.6, 128.0, 126.9, 125.4, 125.4, 123.2, 112.1, 97.1, 59.8, 55.8, 50.6, 50.6, 49.8, 41.8, 37.2, 27.5, 26.0, 21.7 ppm; HRMS calcd. For $C_{27}H_{29}NO_8SNa^+$ $[M + Na]^+$ 550.1506, found 550.1503.

Lactam 75



To a stirred solution of tosylate **74** (388 mg, 0.74 mmol) in MeCN (14.4 mL) at room temperature was added $ZnCl_2$ (200 mg, 1.47 mmol). The resulting mixture was warmed to reflux and stirred for 4 h before additional $ZnCl_2$ (200 mg, 1.47 mmol) was added. The resulting mixture was refluxed for further 4 h before it was cooled down to room temperature, quenched with sodium potassium tartrate (30 mL, sat. aq.) and diluted with EtOAc (30 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The combined organic layer was washed with water (70 mL), brine (70 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:MeOH 10:1) afforded lactam **75** (200 mg, 73%) as a brown amorphous solid. **75**: R_f = 0.32 (silica gel, EtOAc); IR (film) ν_{max} 3695, 3457, 3154, 2918, 1704, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 7.6 Hz, 1H), 6.86–6.76 (m, 2H), 6.38 (dd, *J* = 9.4, 2.5 Hz, 1H), 5.48 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.72–3.69 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.09–2.97 (m, 1H), 2.93–2.78 (m, 2H), 2.72–2.68 (m, 1H), 2.10–2.04 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.5, 174.2, 153.1, 147.1, 128.1, 128.0, 126.7, 123.6, 122.5, 112.2, 98.9, 60.3, 55.8, 54.1, 50.8, 49.8, 49.3, 37.3, 37.1, 32.4 ppm; HRMS calcd. For $C_{20}H_{23}NO_6Na^+$ $[M + Na]^+$ 396.1418, found 396.1417.

Ammonium salt 77

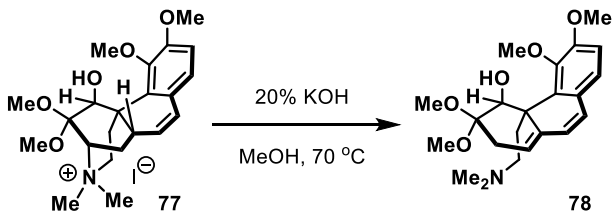


(i) To a stirred solution of $LiAlH_4$ (122 mg, 3.20 mmol) in THF (20 mL) at 0 ℃ was added a solution of lactam **75** (120 mg, 0.32 mmol) in THF (15 mL). The resulting mixture was warmed to reflux and stirred for 8 h before it was cooled to room temperature, quenched with sodium potassium tartrate (30 mL, sat. aq.) and diluted with EtOAc (30 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure.

(ii) To a stirred solution of crude amine **76** (obtained above) in CH_2Cl_2 (2.0 mL) at room temperature was added MeI (0.28 mL, 4.40 mmol). The resulting mixture was stirred for 10 h before it was concentrated under reduced pressure afforded crude ammonium salt **77** (70.3 mg, 42% over two steps) as a brown solid, which was used directly without further purification. **77**: R_f = 0.05 (silica gel, EtOAc:MeOH 1:1); IR (film) ν_{max} 3287, 2824, 1457, 1257, 1060, 710 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 6.88 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 9.5 Hz, 1H), 5.49 (d, *J* = 9.5 Hz, 1H), 5.23 (s, 1H), 4.12 (m, 1H), 4.01 (s, 3H), 3.84 (s, 3H), 3.68 (td, *J* = 14.0, 3.4 Hz, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 3.44 (s, 3H), 3.28–3.26 (m, 1H), 3.22 (s, 3H), 3.16–3.05 (m, 1H), 2.51–2.42 (m, 2H), 2.17 (dd, *J* = 17.4, 9.0 Hz, 1H), 1.71 ppm (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD): δ 154.3,

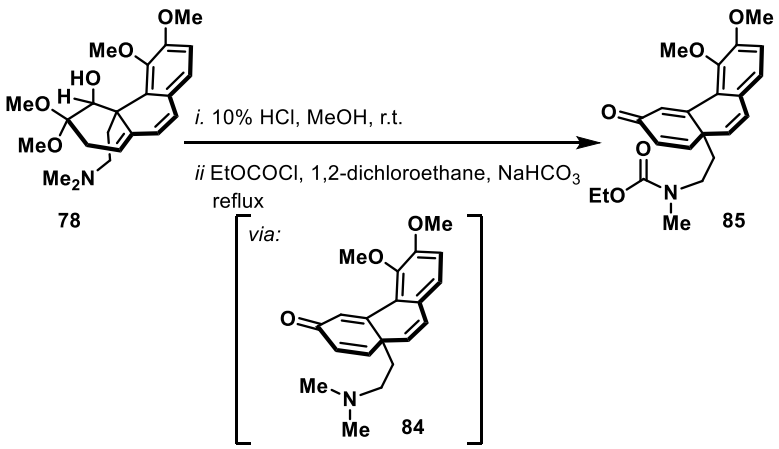
147.8, 134.1, 128.6, 128.4, 127.2, 123.9, 112.4, 101.6, 73.8, 71.3, 61.0, 60.6, 58.1, 56.3, 53.8, 50.6, 50.1, 48.5, 31.1, 28.5, 27.8 ppm; HRMS calcd. For $C_{22}H_{32}NO_5^+$ $[M]^+$ 390.2275, found 390.2274.

Diene 78



A stirred solution of ammonium salt **77** (0.100 g, 0.19 mmol) in KOH (20% in MeOH, 5.8 mL) was warmed to 70 °C and stirred for 10 h before it was cooled to room temperature and diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:MeOH 4:1) afforded diene **78** (60.0 mg, 80%) as a brown amorphous solid. **78**: R_f = 0.38 (silica gel, EtOAc:MeOH 1:1); IR (film) ν_{max} 3345, 3043, 1648, 1386, 1123, 822 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 6.82 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.13–6.07 (m, 2H), 5.56 (t, *J* = 4.2 Hz, 1H), 5.09 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.28 (s, 3H), 3.31 (s, 3H), 2.65 (dd, *J* = 21.1, 4.3 Hz, 1H), 2.44 (dd, *J* = 20.0, 4.7 Hz, 1H), 2.36–2.30 (m, 1H), 2.18 (td, *J* = 11.8, 4.1 Hz, 1H), 2.05–2.00 (m, 1H), 2.00 (s, 6H), 2.08 ppm (td, *J* = 11.1, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4, 147.6, 138.9, 130.7, 128.5, 127.2, 125.1, 123.0, 122.4, 110.6, 100.9, 70.6, 60.2, 55.6, 55.3, 49.0, 48.3, 48.1, 45.4, 45.4, 37.2, 31.4 ppm; HRMS calcd. For $C_{22}H_{32}NO_5^+$ $[M]^+$ 390.2275, found 390.2277.

Ethyl Carbamate 85

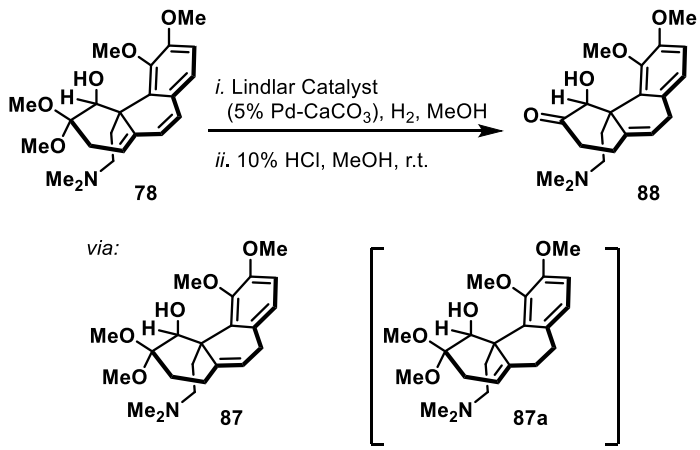


(i) To a stirred solution of dimethyl ketal **78** (220 mg, 0.56 mmol) in MeOH (5.0 mL) at room temperature was added HCl (10% aq., 20 mL). The resulting mixture was stirred for 1 h before it was slowly quenched with $NaHCO_3$ (40 mL, sat. aq.) and water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude dienone **84 (**124 mg, 67%) as a dark purple solid, which was used directly without further purification.

(ii) To a stirred solution of crude dienone **84** (obtained above) in 1,2-dichloroethane (10.0 mL) at room temperature was added $NaHCO_3$ (640 mg, 7.62 mmol) followed by ethyl chloroformate (0.18 mL, 1.89 mmol). The resulting mixture was warmed to reflux and stirred for 2 h before it was cooled to room temperature and quenched with $NaHCO_3$ (40 mL, sat. aq.) and water (30 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 80 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 5:1) afforded ethyl carbamate **85** (136 mg, 93%) as an amorphous yellow solid. **85**: R_f = 0.58 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3054, 2987, 1693, 1659, 1422, 909, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (br s, 1 H), 6.91–6.77 (m, 3H), 6.39 (d, *J* = 9.8 Hz, 2H), 5.87 (d, *J* = 9.4 Hz, 1H), 4.01 (br s, 2H), 3.89 (s, 6H), 3.26–2.99 (m, 2H), 2.70 (br s, 3H), 2.09–1.76 (m, 2H), 1.27–1.03 ppm (m,

3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.6, 156.1, 155.7, 153.4, 150.6, 130.1, 130.0, 129.1, 126.7, 126.5, 124.3, 122.7, 113.3, 61.2, 60.8, 55.9, 45.3, 37.4, 37.1, 34.6, 34.1, 14.4 ppm; HRMS calcd. For $C_{22}H_{32}NO_5^+$ $[M]^+$ 406.1625, found 406.1627.

Ketone 88

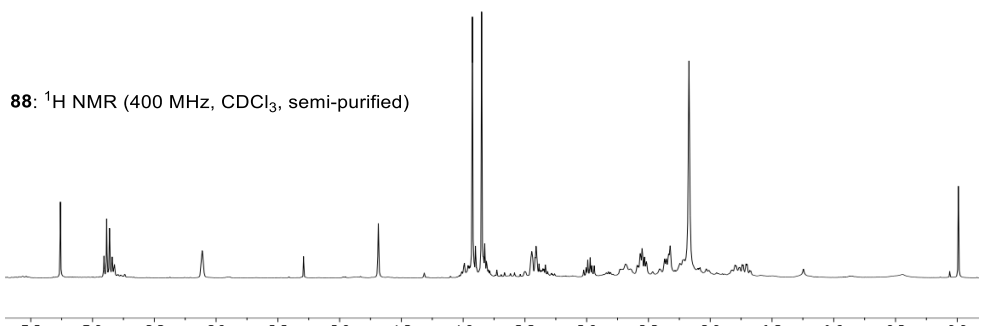


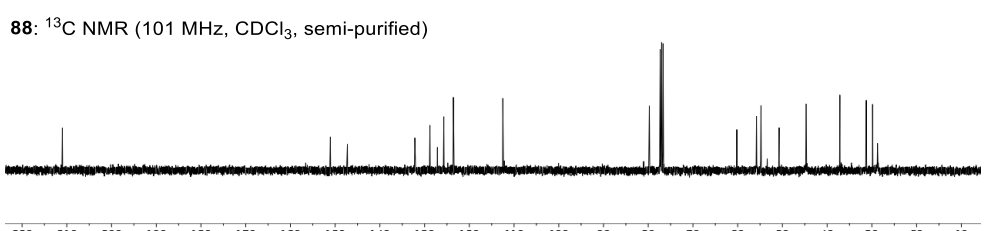
(i) To a stirred solution of diene **78** (168 mg, 0.43 mmol) in MeOH (10 mL) at room temperature was added 5% Pd–$CaCO_3$ (916 mg, 0.43 mmol). The resulting mixture was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H_2 (balloon) for 16 h. The resulting mixture was filtered through Celite® and eluted with MeOH (3 × 8 mL), and concentrated under reduced pressure to afford crude alkene **87** (as a ~5:1 mixture with 1,2-hydrogenated product **87a** based on ^{1}H NMR analysis, 154 mg, 91% combined yield) as an amorphous yellow solid, which was used directly without further purification. R_f = 0.18 (silica gel, EtOAc:MeOH 1:1)

(ii) To a stirred solution of the crude alkene **87** (**87**:**87a**~5:1, obtained above) in MeOH (5 mL) at room temperature was added HCl (10% aq., 10 mL). The resulting mixture was stirred for 1 h before it was slowly quenched with $NaHCO_3$ (15 mL, sat. aq.) and water (15 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:MeOH 4:1) afforded ketone **88** (98.0 mg, 72%) as an amorphous yellow solid. *Note: Due the highly polar nature of dimethylamine ketone **88**, this compound was*

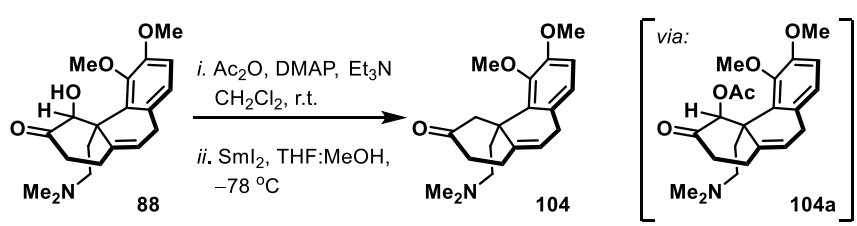
semi-purified by flash column chromatography and subjected directly to the following reaction.

88: R_f = 0.15 (silica gel, EtOAc:MeOH 1:1); IR (film) ν_{max} 3690, 3053, 3005, 1721, 1458, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.11 (br s, 1H), 4.69 (s, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.43 (d, *J* = 13.9 Hz, 2H), 3.03–2.92 (m, 1H), 2.74–2.62 (m, 1H), 2.60–2.50 (m, 2H), 2.38–2.30 (m, 2H), 2.17 (s, 6H), 1.85–1.65 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.0, 151.1, 147.3, 132.2, 128.8, 127.2, 125.7, 123.6, 112.5, 79.8, 60.2, 55.8, 54.8, 50.7, 44.7, 37.2, 31.3, 29.9, 28.8 ppm; HRMS calcd. For $C_{20}H_{28}NO_4^+$ $[M]^+$ 346.2013, found 346.2011.





Ketone 104

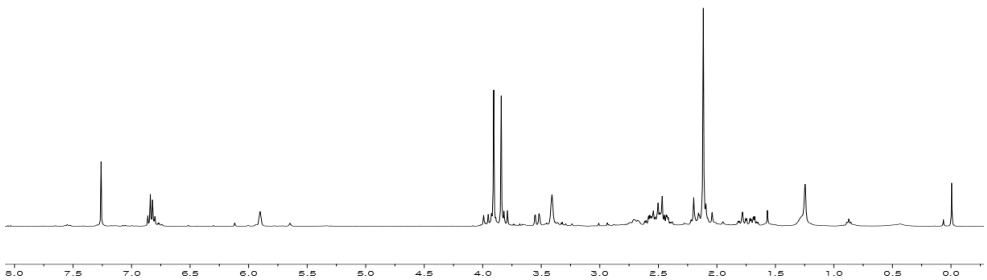


(i) To a stirred solution of ketone **16** (254 mg, 0.74 mmol) in CH_2Cl_2 (5.0 mL) at room temperature was added acetic anhydride (0.70 mL, 7.41 mmol), Et_3N (1.0 mL, 7.17 mmol) and DMAP (9.0 mg, 74 μmol). The resulting mixture was stirred for 4 h before it was quenched with $NaHCO_3$ (5.0 mL, sat. aq.). The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford crude acetate **16a** as a brown amorphous solid, which was used directly without further purification. R_f = 0.25 (silica gel, EtOAc:MeOH 1:1).

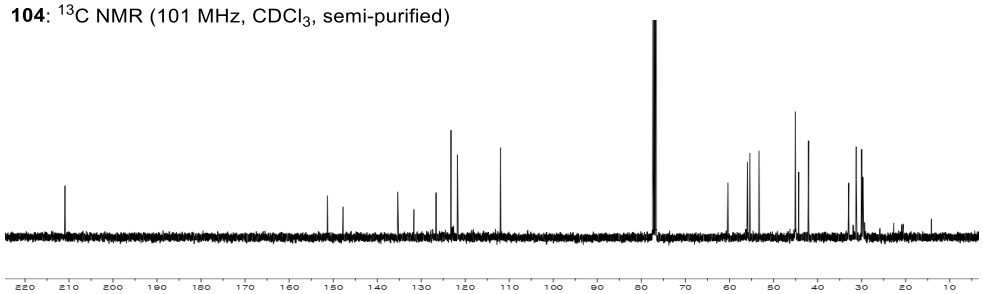
(ii) To a stirred solution of the crude acetate **16a** (obtained above) in anhydrous THF:MeOH (1:1, 10.0 mL) at –78 °C was added SmI_2 (0.1 M in THF) until a blue color persists (~30 mL, 3.0 mmol). The resulting mixture was stirred for 0.5 h before it was quenched with K_2CO_3 (10 mL, sat. aq.). The resulting mixture was extracted with CH_2Cl_2 (4 × 30 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:MeOH 4:1) afforded ketone **17** (189 mg, 78% over two steps) as an amorphous white solid. *Note: Due the highly polar nature of dimethylamine ketone **17**, this compound was semi-purified by flash column chromatography and subjected directly to the following reaction*.

17: R_f = 0.30 (silica gel, EtOAc:MeOH 1:1); IR (film) ν_{max} 3691, 3059, 1707, 1661, 1550, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.90 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.53 (d, *J* = 14.6 Hz, 1H), 3.41 (s, 2H), 2.77–2.65 (m, 2H), 2.63–2.52 (m, 2H), 2.48 (d, *J* = 14.6 Hz, 1H), 2.47–2.36 (m, 2H), 2.19 (s, 1H), 2.11 (s, 6H), 1.86–1.63 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.9, 151.3, 147.8, 135.3, 131.7, 126.6, 123.2, 121.7, 112.0, 60.3, 55.9, 55.4, 53.3, 45.1, 44.3, 42.0, 32.9, 31.2, 30.0, 29.7 ppm; HRMS calcd. For $C_{20}H_{28}NO_3^+$ $[M]^+$ 330.2064, found 330.2065.

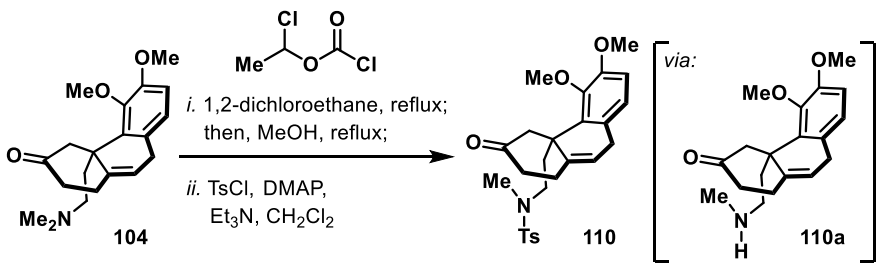
104: ^{1}H NMR (400 MHz, $CDCl_3$, semi-purified)



104: ^{13}C NMR (101 MHz, $CDCl_3$, semi-purified)



Ketone 110

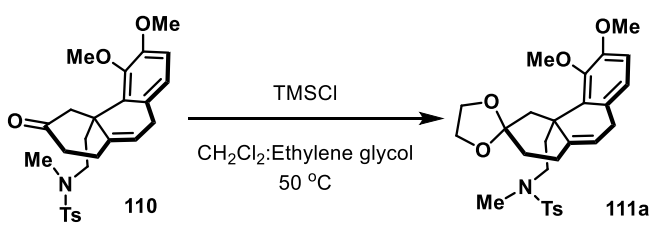


(i) To a stirred solution of dimethyl amine **104** (16.0 mg, 49 μmol) in 1,2-dichloroethane (3 mL) at room temperature was added $NaHCO_3$ (81.6 mg, 0.97 mmol) followed by 1-chloroethyl chloroformate (0.11 mL, 1.02 mmol). The resulting mixture was warmed to reflux and stirred for 2 h before it was cooled to room temperature and quenched with $NaHCO_3$ (2 mL, sat. aq.) and water (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude residue, which was dissolved in MeOH (3 mL) and warmed to reflux and heated for 1.5 h before it was cooled to room temperature

and concentrated under reduced pressure to afford crude amine **110a** (14.3 mg, 93%) as an amorphous yellow solid. **110a**: R_f = 0.10 (silica gel, EtOAc:MeOH 1:1).

(ii) To a stirred solution of crude amine **110a** (9.8 mg, 31 μmol) in CH_2Cl_2 (1.5 mL) at room temperature was added TsCl (11.8 mg, 62 μmol), DMAP (1.5 mg, 12 μmol) and Et_3N (0.10 mL, 0.72 mmol). The resulting mixture was stirred for 1.5 h before it was diluted with water (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded ketone **110** (10.0 mg, 69%) as an amorphous yellow solid. **110**: R_f = 0.68 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 2960, 1700, 1610, 1490, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 6.5 Hz, 2H), 7.23 (d, *J* = 6.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.93 (br s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.47 (d, *J* = 12.5 Hz, 1H), 3.40 (br s, 2H), 2.91 (dt, *J* = 12.8, 3.4 Hz, 1H), 2.56 (s, 3H), 2.47 (d, *J* = 12.4 Hz, 1H), 2.40 (s, 3H), 2.74–2.27 (m, 6H), 1.79 ppm (dt, *J* = 12.3, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.5, 151.4, 147.7, 143.1, 135.1, 134.8, 130.9, 129.5, 127.2, 126.6, 123.3, 122.2, 112.2, 60.4, 55.9, 53.1, 46.9, 44.0, 42.0, 34.7, 33.5, 31.1, 29.9, 21.5 ppm; HRMS calcd. For $C_{26}H_{31}NO_5SNa^+$ $[M + Na]^+$ 492.1815, found 492.1818.

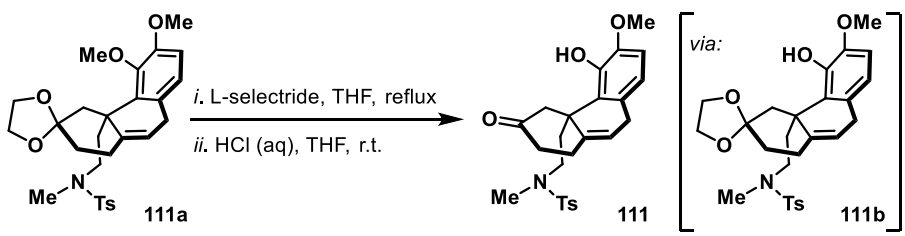
Dioxolane 111a



To a stirred solution of ketone **110** (18.0 mg, 38 μmol) in CH_2Cl_2/ethylene glycol (1:1, 3.0 mL) at room temperature was added TMSCl (10 μL, 79 μmol). The resulting mixture was warmed to 50 °C and stirred for 5 h before it was cooled to 0 °C and quenched with $NaHCO_3$ (3 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2

(3 × 3 mL), the combined organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded dioxolane **111a** (18.2 mg, 92%) as an amorphous yellow solid. **111a**: R_f = 0.45 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 2900, 1510, 1460, 1160, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 5.71 (br s, 1H), 4.09–4.01 (m, 1H), 4.01–3.95 (m, 1H), 3.88 (s, 3H), 3.93–3.84 (m, 2H), 3.82 (s, 3H), 3.32 (d, *J* = 22.8 Hz, 1H), 3.23 (d, *J* = 22.0 Hz, 1H), 2.99 (dd, *J* = 14.4, 1.7 Hz, 1H), 2.81–2.69 (m, 1H), 2.59 (s, 3H), 2.64–2.49 (m, 2H), 2.38 (s, 3H), 2.44–2.28 (m, 2H), 2.17 (td, *J* = 13.7, 3.9 Hz, 1H), 1.84 (d, *J* = 12.2 Hz, 1H), 1.64 (d, *J* = 14.2 Hz, 1H), 1.57 ppm (dt, *J* = 13.7, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 147.8, 142.7, 137.3, 134.9, 133.1, 129.3, 127.2, 126.7, 123.1, 119.8, 111.6, 109.0, 64.5, 63.6, 60.2, 55.8, 47.6, 45.0, 42.3, 36.2, 34.7, 32.7, 30.1, 29.9, 21.4 ppm; HRMS calcd. For $C_{28}H_{35}NO_6SNa^+$ $[M + Na]^+$ 536.2077, found 536.2079.

Phenolic Ketone 111

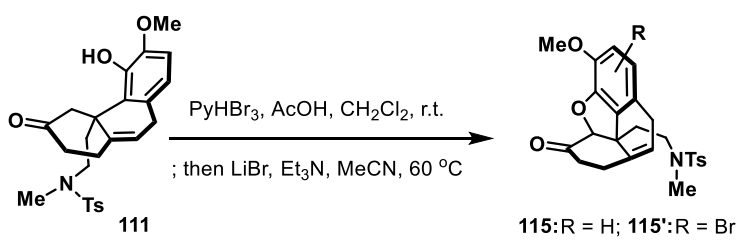


(i) To a stirred solution of dioxolane **111a** (22 mg, 43 μmol) in THF (1.5 mL) at room temperature was added L-selectride (1.0 M in THF, 0.21 mL, 0.21 mmol). The resulting mixture was warmed to reflux and stirred for 24 h before it was cooled to room temperature and quenched with sodium potassium tartrate (3 mL, sat. aq.) and diluted with EtOAc (5 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 8 mL), the combined organic layer was dried (Na_2SO_4) and

concentrated under reduced pressure to afford crude phenol **111b** as a clear amorphous solid, which was used directly in the subsequent step without further purification.

(ii) To a stirred solution of crude phenolic dioxolane **111b** (obtained above) in MeOH (1.5 mL) at room temperature was added HCl (4.0 N aq., 0.1 mL, 0.40 mmol). The resulting mixture was warmed to 45 °C stirred for 3 h before it was cooled to 0 °C quenched with $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded phenolic ketone **111** (15 mg, 77% over two steps) as a clear amorphous solid. **111**: R_f = 0.30 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3440, 2950, 1690, 1490, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.05 (s, 1H), 5.92 (br s, 1H), 3.88 (s, 3H), 3.65 (d, *J* = 13.6 Hz, 1H), 3.40 (br s, 2H), 2.98 (dt, *J* = 12.3, 4.8 Hz, 1H), 2.82 (dt, *J* = 12.3, 4.1 Hz, 1H), 2.67 (br t, *J* = 13.6 Hz 1H), 2.57 (s, 3H), 2.60–2.51 (m, 1H), 2.40 (s, 3H), 2.49–2.37 (m, 3H), 2.32 (dt, *J* = 12.3, 4.1 Hz, 1H), 1.70 ppm (dt, *J* = 12.3, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.6, 144.8, 143.1, 143.0, 135.3, 134.8, 129.5, 127.2, 126.9, 123.8, 122.1, 119.2, 109.5, 56.2, 51.9, 46.9, 43.5, 42.2, 34.5, 31.5, 31.0, 29.8, 21.5 ppm; HRMS calcd. For $C_{25}H_{29}NO_5SNa^+$ [M + Na]$^+$ 478.1659, found 478.1660.

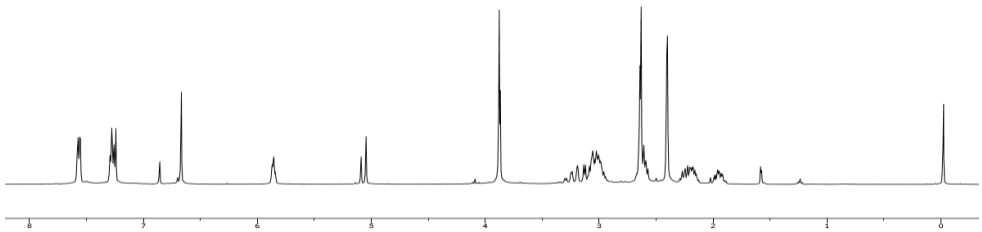
Tetracyclic Ketone 115 and 115'



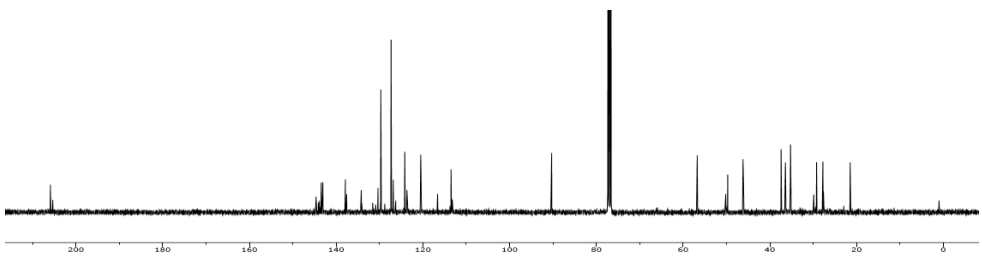
(i) To a stirred solution of phenolic ketone **111** (47 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) at room temperature was added a solution of pyridinium tribromide (freshly recrystallized, 66 mg, 0.20 mmol) in acetic acid (5.0 mL) dropwise. The resulting mixture was stirred for 30

min before it was diluted with toluene and concentrated under reduced pressure. The resulting residue was redissolved in CH_2Cl_2 (5 mL) and water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. To a stirred solution of the crude reaction mixture (obtained above) in MeCN (5.0 mL) at room temperature was added LiBr (44.8 mg, 0.52 mmol) and Et_3N (0.14 mL, 1.03 mmol). The resulting mixture was warmed to 60 ℃ and stirred for 20 min before it was cooled to room temperature and quenched with NH_4Cl (5 mL, sat. aq.) and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with water (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 7:1) afforded an inseparable mixture of tetracycles **115** and **115'** (25 mg, 53% over two steps) as an amorphous yellow solid. **115+115'**: R_f = 0.28 (silica gel, hexanes:EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.32–7.27 (m, 2H), 6.88 (s, 0.3H), 6.68 (s, 1.3H), 5.91–5.85 (m, 1H), 5.11 (s, 0.4H), 5.06 (s, 0.6H), 3.89 (s, 3H), 3.33–3.18 (m, 1H), 3.12 (dd, *J* = 5.6 Hz, 1H), 3.13–2.96 (m, 3H), 2.71–2.57 (m, 2H), 2.65 (s, 3H), 2.42 (s, 3H), 2.33–2.14 (m, 2H), 2.18 ppm (td, *J* = 12.0, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.9, 205.4, 144.6, 144.1, 143.9, 143.6, 143.5, 143.1, 137.9, 137.6, 134.2, 134.1, 131.6, 130.4, 129.8, 129.7, 127.3, 126.8, 126.3, 124.2, 123.7, 120.5, 116.6, 113.5, 113.2, 90.4, 90.3, 56.9, 56.8, 50.2, 49.7, 46.2, 46.1, 37.4, 37.4, 36.5, 36.4, 35.3, 35.2, 29.9, 29.2, 27.8, 27.6, 21.5 ppm; **115**: HRMS calcd. For $C_{25}H_{27}NO_5SNa^+$ $[M + Na]^+$ 476.1502, found 476.1505; **115'**: HRMS calcd. For $C_{25}H_{26}BrNO_5SNa^+$ $[M + Na]^+$ 554.0607, found 554.0604.

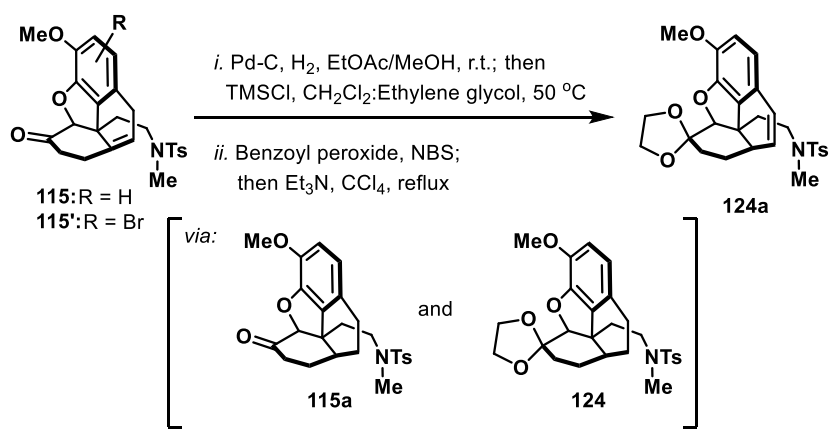
115+115': ^{1}H NMR (400 MHz, $CDCl_3$)



115+115': ^{13}C NMR (101 MHz, $CDCl_3$)



Pentacyclic Alkene 124a

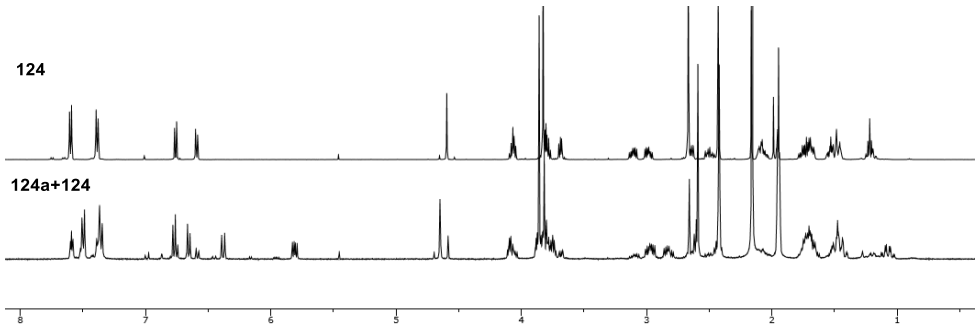


(i) To a stirred solution of tetracyclic ketone **115+115'** (14.0 mg, 31 μmol) in EtOAc/MeOH (1:3, 3.0 mL) at room temperature was added Pd/C (10% wt/wt, 6.6 mg, 6 μmol). The resulting mixture was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H_2 (balloon) for 1 h. The resulting mixture was filtered through Celite® and eluted with EtOAc (3 × 8 mL), and concentrated under reduced pressure. Flash column

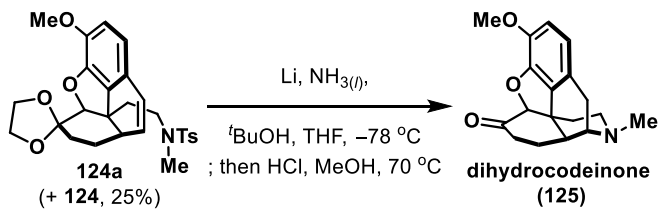
chromatography (silica gel, hexanes:EtOAc 3:1) afforded tetracyclic ketone **115a** (12.7 mg, 90%) as a clear amorphous solid. To a stirred solution of tetracyclic ketone **115a** (7.8 mg, 17 μmol) in CH_2Cl_2/ethylene glycol (1:1, 1.0 mL) at room temperature was added TMSCl (50 μL, 0.39 mmol). The resulting mixture was warmed to 50 ℃ and stirred for 5 h before it was cooled to 0 ℃ and quenched with $NaHCO_3$ (1 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layer was washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded dioxolane **124** (6.9 mg, 80%) as a clear amorphous solid.

(ii) To a stirred solution of pentacyclic dioxolane **124** (23.0 mg, 46 μmol) in carbon tetrachloride (freshly distilled, 3.6 mL) at room temperature was added benzoyl peroxide (freshly recrystallized, 5.6 mg, 23 μmol) and *N*-bromosuccinimide (8.6 mg, 48 mmol). The resulting mixture was warmed to reflux and stirred for 1 h before it was cooled to room temperature and added Et_3N (50 μL, 0.36 mmol). The resulting mixture was warmed to reflux and stirred for 15 min before it was cooled to room temperature. The resulting mixture was washed with $NaHCO_3$ (5 mL, sat. aq.), $Na_2S_2O_3$ (5 mL, sat. aq.), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded an inseparable mixture of alkene **124a** and starting material **124** (**124a**:**124** ~ 3:1, 18 mg, 60% yield for **124a** based on ^{1}H NMR calculation) as an amorphous solid. **124a**+**124**: R_f = 0.45 (silica gel, hexanes:EtOAc 2:1); ^{1}H NMR (400 MHz, CD_3CN, selected signals for **23**): δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 7.7 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.38 (d, *J* = 9.3 Hz, 1H), 5.81(dd, *J* = 12.7, 8.7 Hz, 1H), 4.65 (s, 1H), 4.14–4.02 (m, 1H), 3.90–3.72 (m, 3H), 3.86 (s, 3H), 3.03–2.92 (m, 1H), 2.88–2.77 (m, 1H), 2.64–2.57 (m, 1H), 2.59 (s, 3H), 2.42 (s, 3H), 1.80–1.62 (m, 3H), 1.56–1.38 (m, 2H), 1.08 ppm (qd, *J* = 12.7, 3.3 Hz, 1H).

^{1}H NMR (400 MHz, CD_3CN)



Dihydrocodeinone (125)



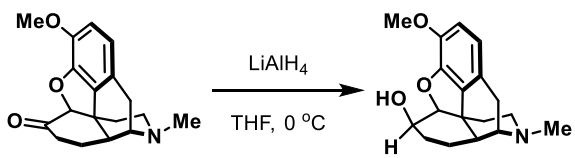
To a stirred solution liquid ammonia (10 mL), THF (1.0 mL) and ^{t}BuOH (0.1 mL) at –78 °C was added lithium metal (finely-cut, 30 mg) in small portions. The resulting solution was stirred for 15 min before a solution of tosylamide **124a** (ca. ~3:1 mixture with **124**, 8.0 mg, 16 μmol) in THF (1.5 mL) was added *via* a cannula. The resulting mixture was stirred for 10 min before it was quenched with NH_4Cl (10 mL, sat. aq.) and MeOH (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH 94:2:1) afforded hexacyclic dioxolane **125a** (3.8 mg, 69%) as an amorphous yellow solid.

To a stirred solution of dioxolane **125a** (obtained above, 3.8 mg, 11 μmol) in MeOH (3.0 mL) at room temperature was added HCl (4.0 N aq., 0.2 mL, 0.80 mmol). The resulting mixture was warmed to 70 °C stirred for 6 h before it was cooled to 0 °C quenched with $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure.

Flash column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH 94:2:1) afforded dihydrocodeinone (**125**) (2.5 mg, 75%) as a clear amorphous solid.

Dihydrocodeinone (125): R_f = 0.17 (silica gel, EtOAc:MeOH 1:1); IR (film) ν_{max} 3410, 2960, 1725, 1510, 1430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.68 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.64 (s, 1H), 3.89 (s, 3H), 3.16 (br s, 1H), 3.01 (d, *J* = 18.5 Hz, 1H), 2.61–2.50 (m, 2H), 2.47–2.38 (m, 2H), 2.41 (s, 3H), 2.31 (td, *J* = 14.2, 4.3 Hz, 1H), 2.17 (td, *J* = 11.8, 2.9 Hz, 1H), 2.05 (td, *J* = 12.2, 4.8 Hz, 1H), 1.89–1.78 (m, 2H), 1.24 ppm (qd, *J* = 13.1, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 145.4, 142.8, 127.2, 126.3, 119.8, 114.5, 91.4, 59.2, 56.7, 46.9, 46.8, 42.9, 42.7, 40.2, 35.6, 25.6, 20.0 ppm; HRMS calcd. For $C_{18}H_{22}NO_3^+$ $[M + H]^+$ 300.1594, found 300.1597.

Dihydrocodeine (117)



dihydrocodeinone (125) **dihydrocodeine (117)**

To a stirred solution of dihydrocodeinone (**125**) (2.5 mg, 8.4 μmol) in THF (1.0 mL) at 0 °C was added $LiAlH_4$ (10 mg, 0.26 mmol). The resulting mixture was stirred for 45 min before it was quenched with sodium potassium tartrate (3 mL, sat. aq.) and diluted with EtOAc (3 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 5 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH 94:2:1) afforded dihydrocodeine (1.9 mg, 74%) as a clear amorphous solid. **Dihydrocodeine (117)**: R_f = 0.23 (silica gel, EtOAc:MeOH 1:3); IR (film) ν_{max} 3470, 2950, 1510, 1250, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.59 (d, *J* = 5.2 Hz, 1H), 4.02 (br s, 1H), 3.86 (s, 3H), 3.06 (br s, 1H), 2.98 (d, *J* = 18.5 Hz, 1H), 2.49 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.39–2.30 (m, 1H), 2.38 (s, 3H),

2.27–2.13 (m, 2H), 1.83 (td, *J* = 12.0, 4.8 Hz, 1H), 1.68 (d, *J* = 12.5 Hz, 1H), 1.59–1.51 (m, 1H), 1.49–1.37 (m, 2H), 1.17–1.02 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): 146.2, 141.7, 130.0, 126.5, 119.2, 113.3, 90.3, 67.1, 60.0, 56.4, 47.0, 42.8, 41.9, 40.4, 37.0, 27.2, 20.2, 18.9 ppm; HRMS calcd. For $C_{18}H_{24}NO_3^+$ $[M + H]^+$ 302.1754, found 302.1751.

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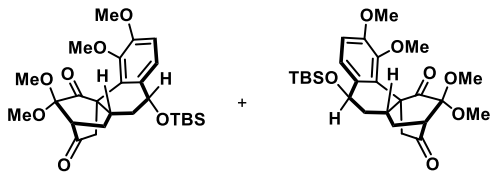
^{1}H NMR (400 MHz, $CDCl_3$)

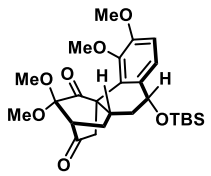


72a

+

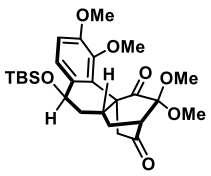
72a'

^{13}C NMR (126 MHz, $CDCl_3$)



72a

+



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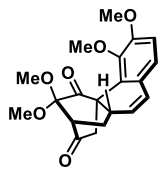

72

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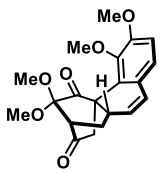

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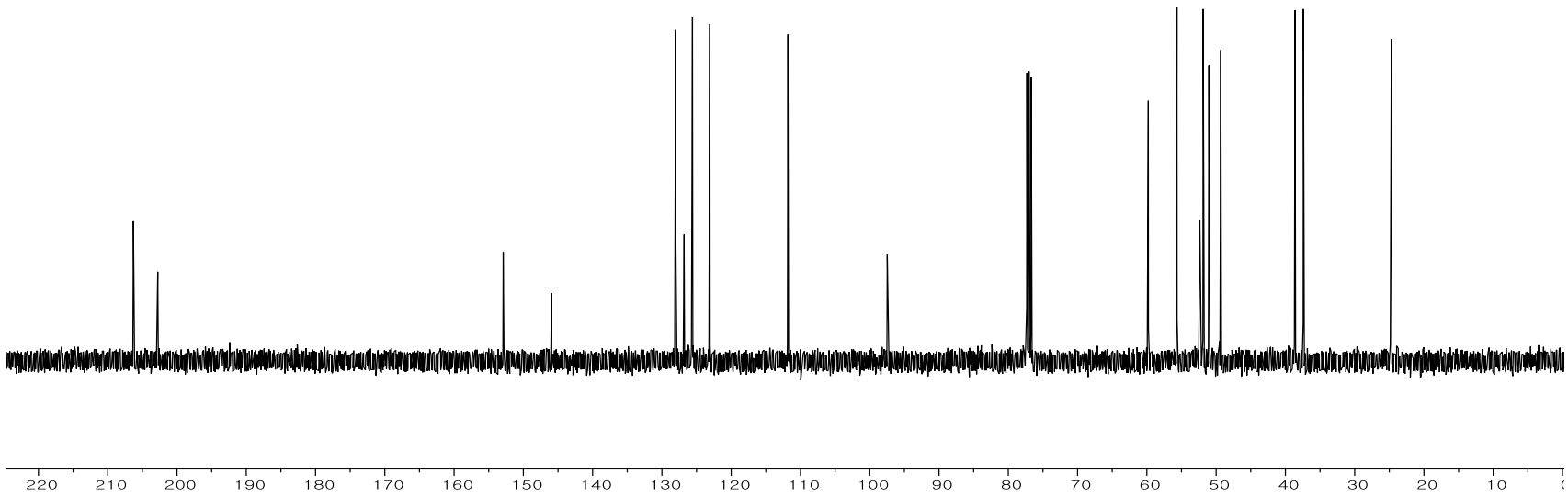

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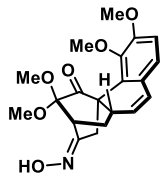

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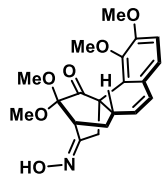

73

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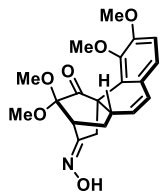

73'

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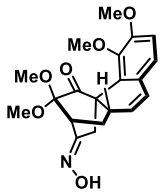
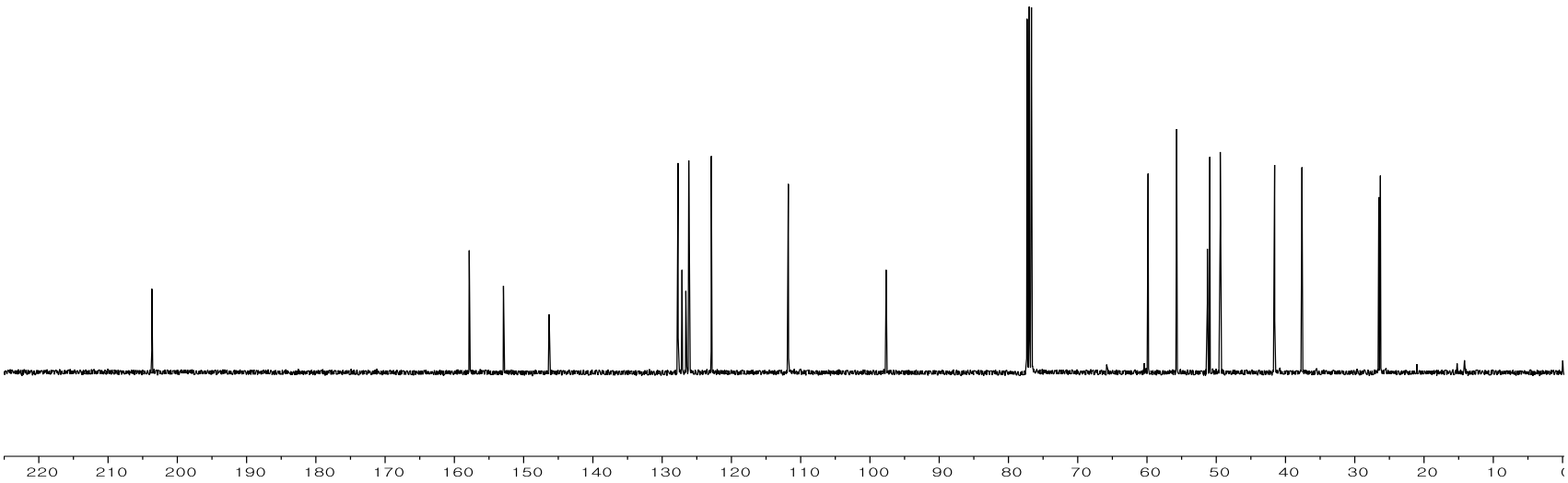
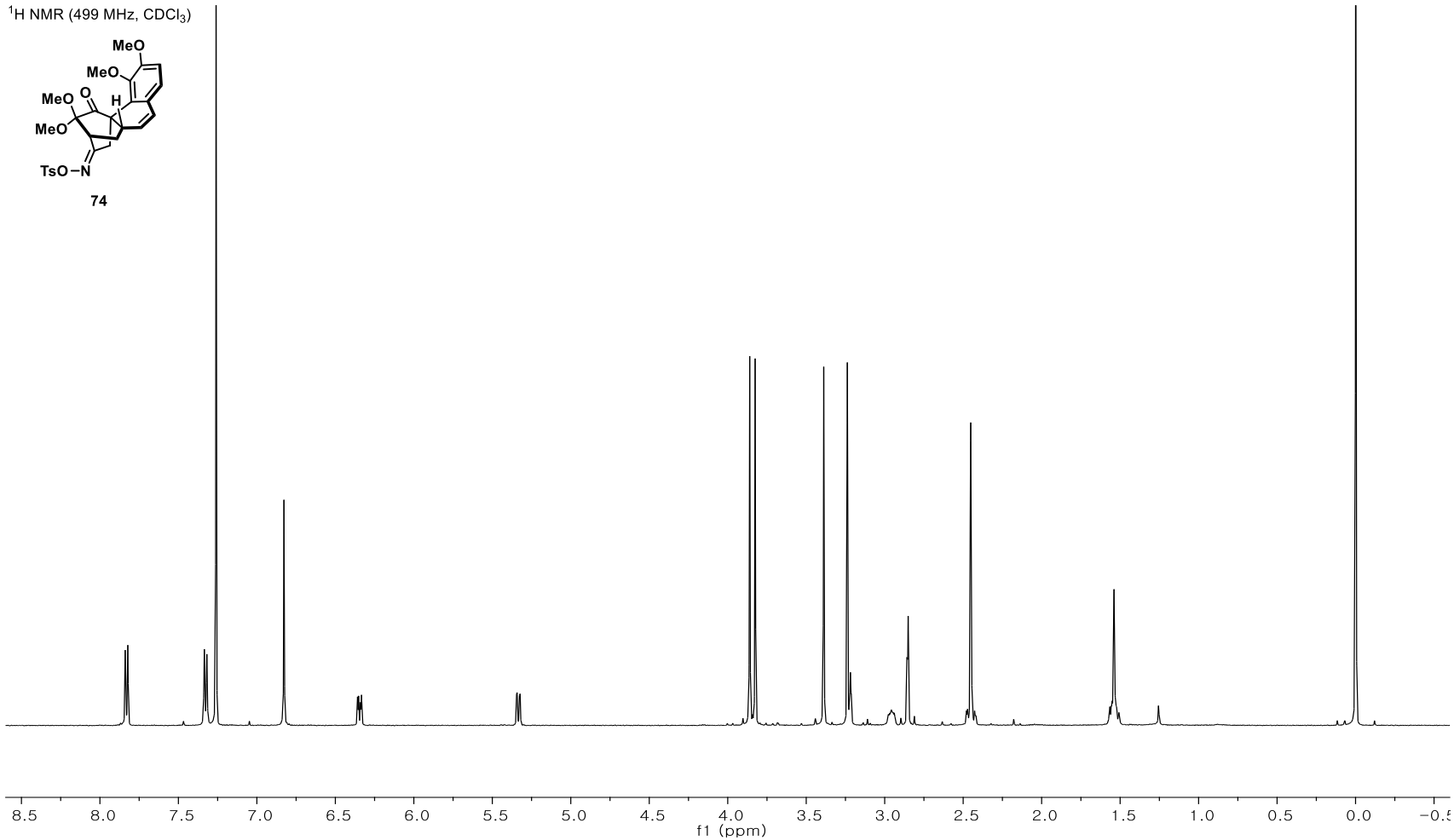
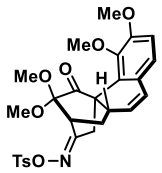


73'

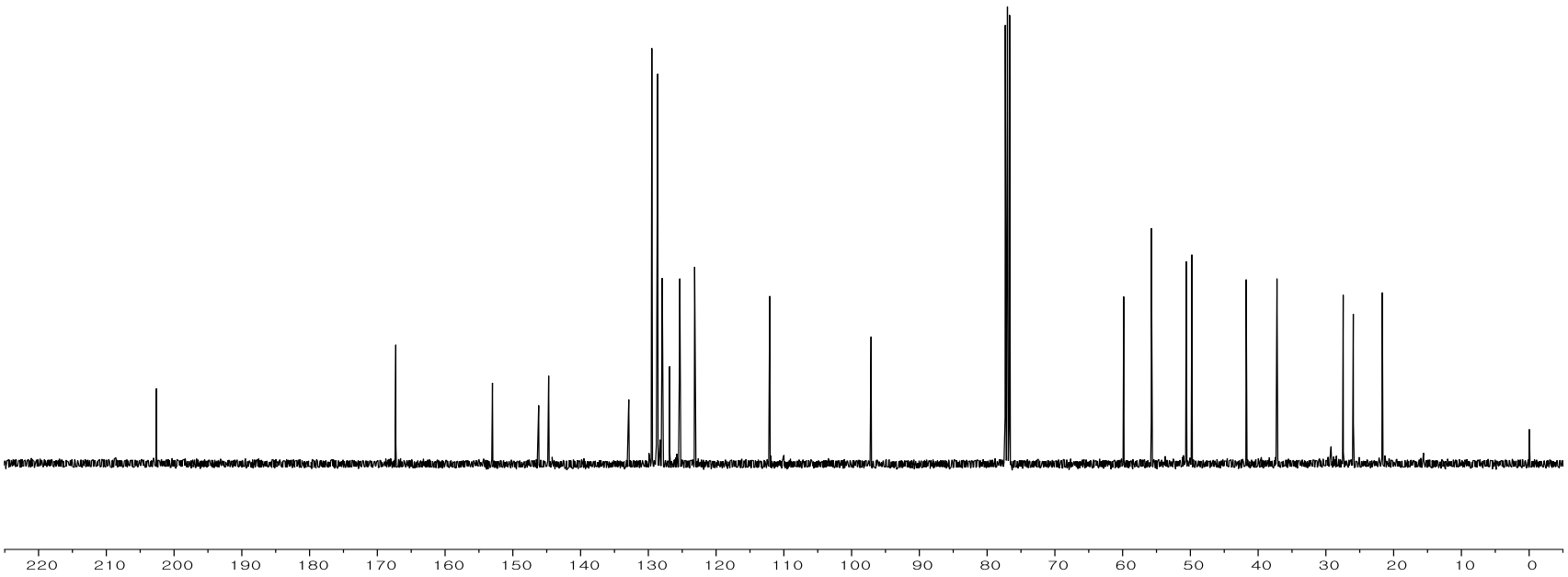



1H NMR (499 MHz, CDCl3)
MeO
MeO
MeO
MeO
O
H
TsO–N
74
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

^{13}C NMR (101 MHz, $CDCl_3$)



74



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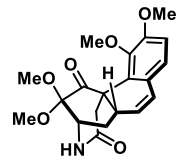

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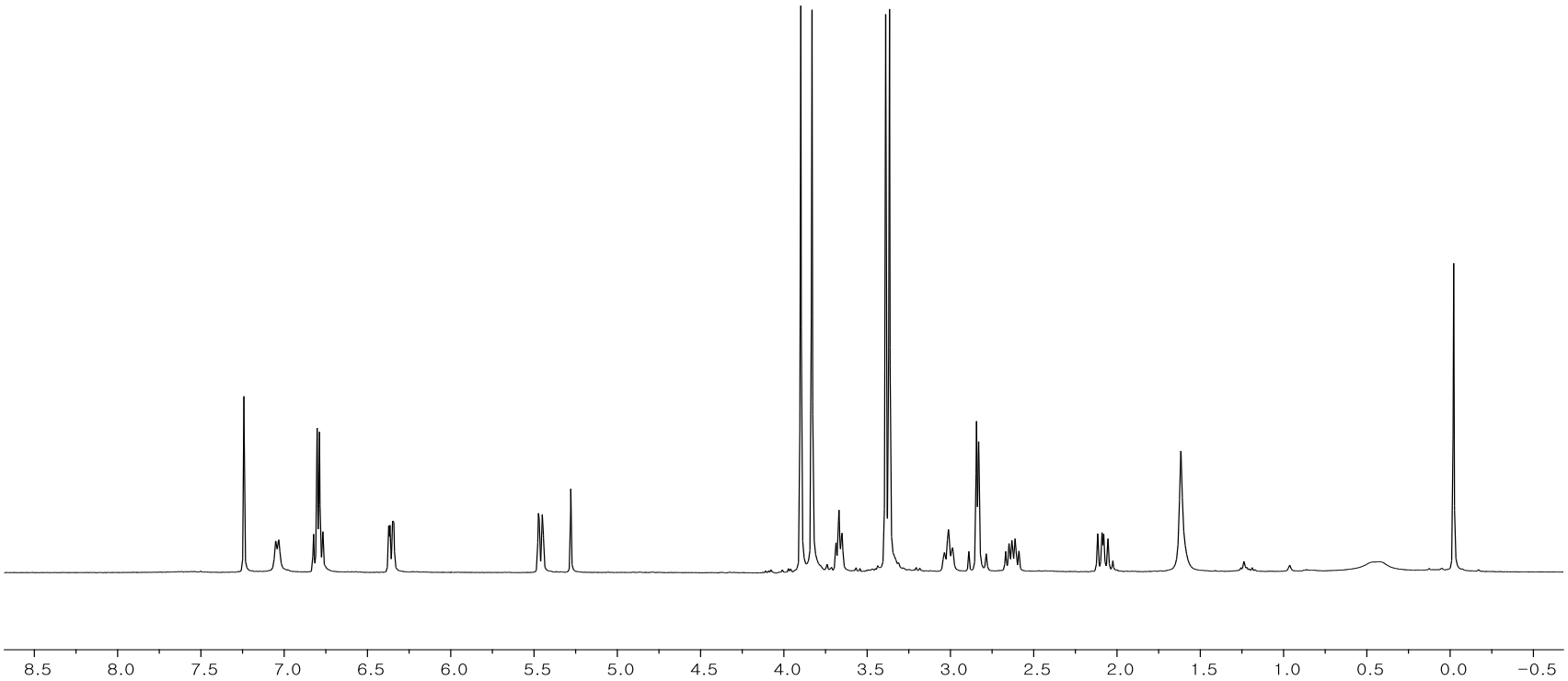
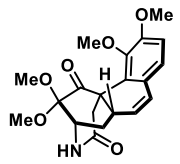


^{13}C NMR (126 MHz, $CDCl_3$)



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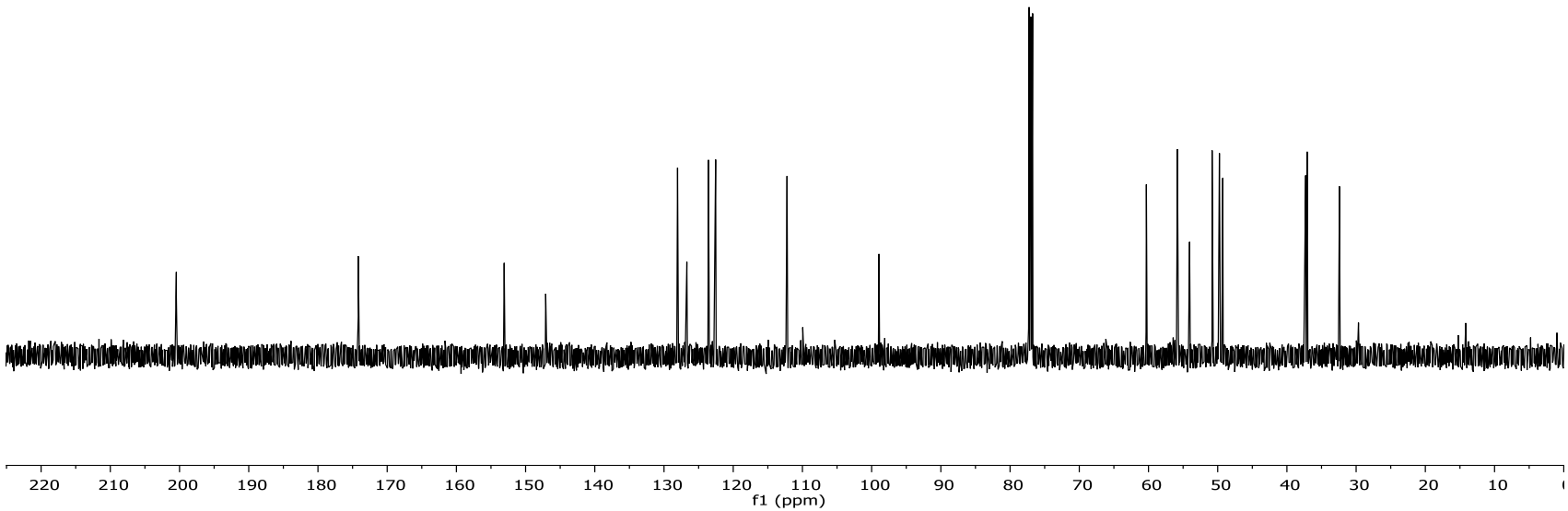

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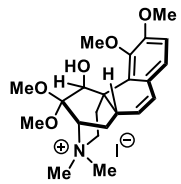

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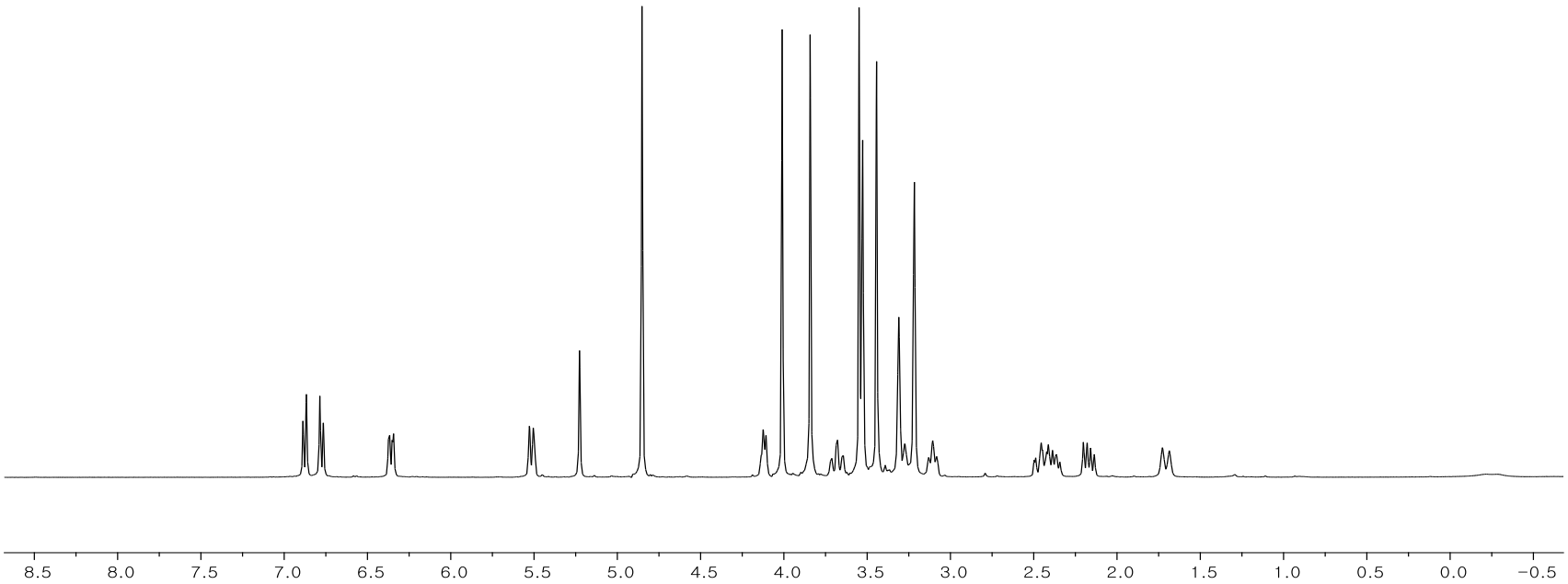

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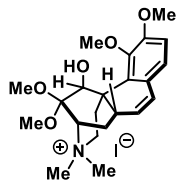

77

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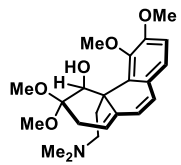
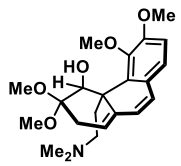


78

^{13}C NMR (101 MHz, $CDCl_3$)



78

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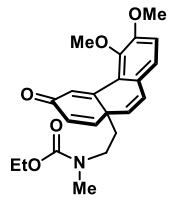

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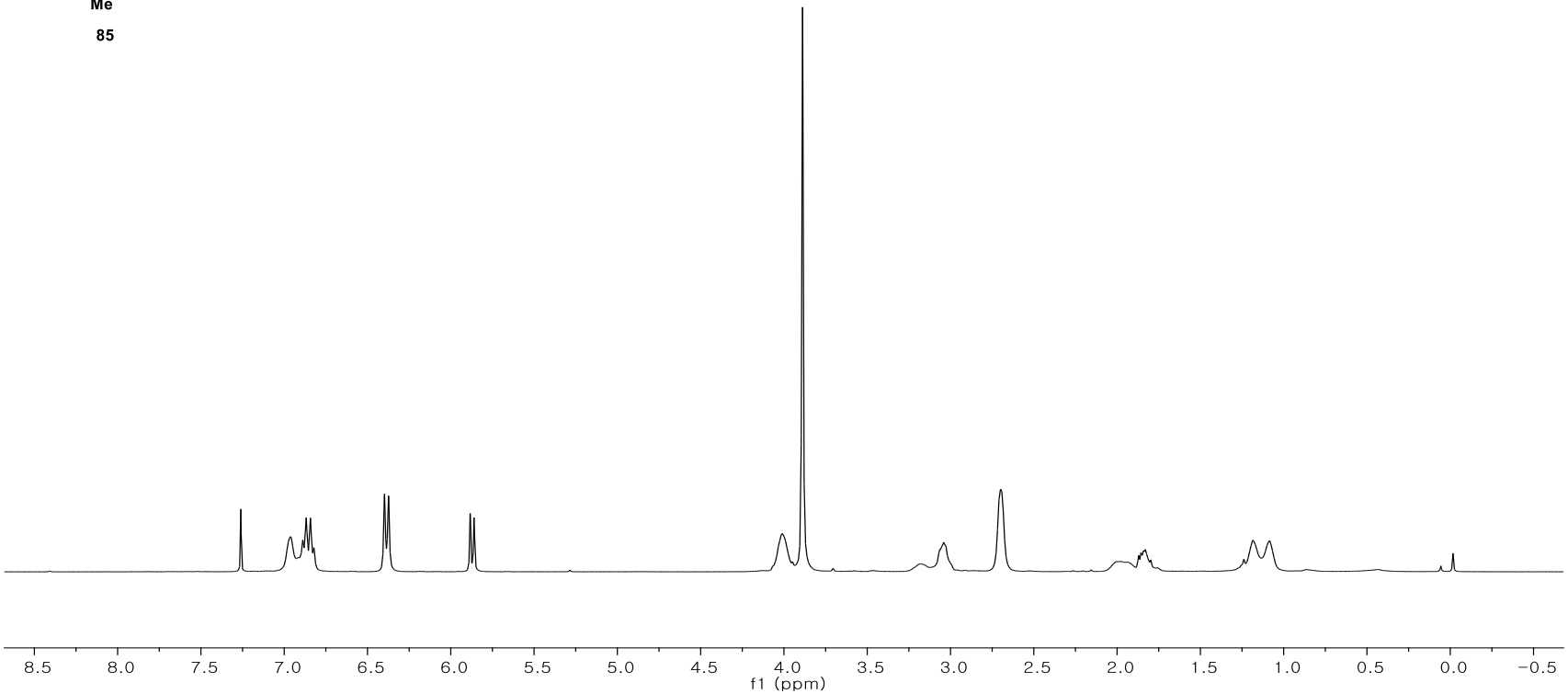

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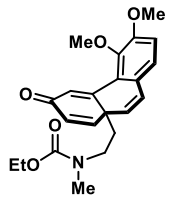

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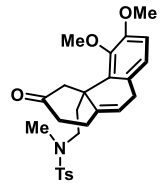

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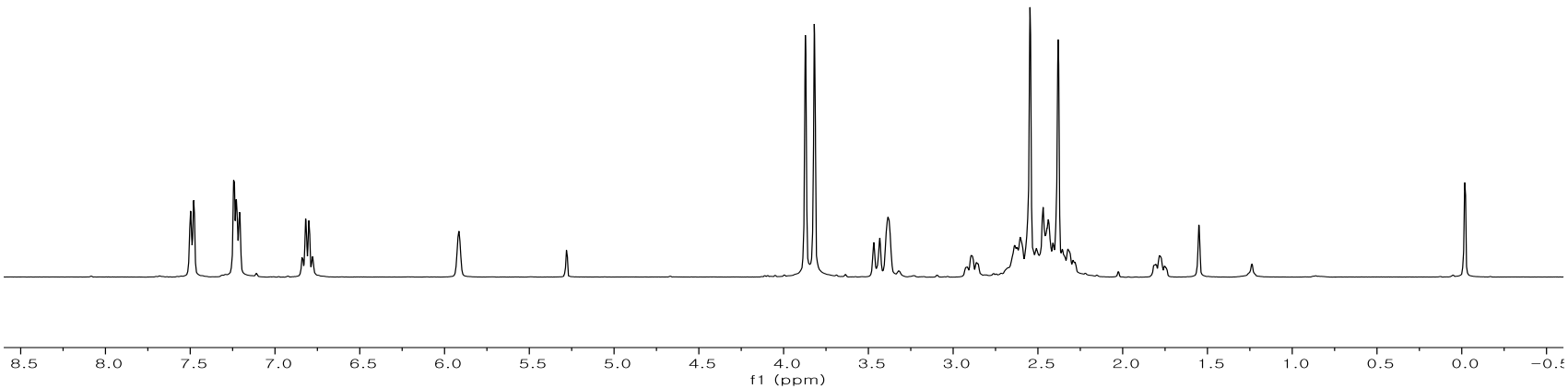

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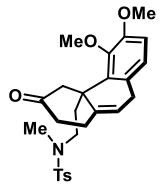

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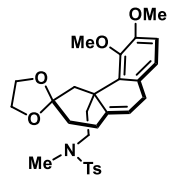

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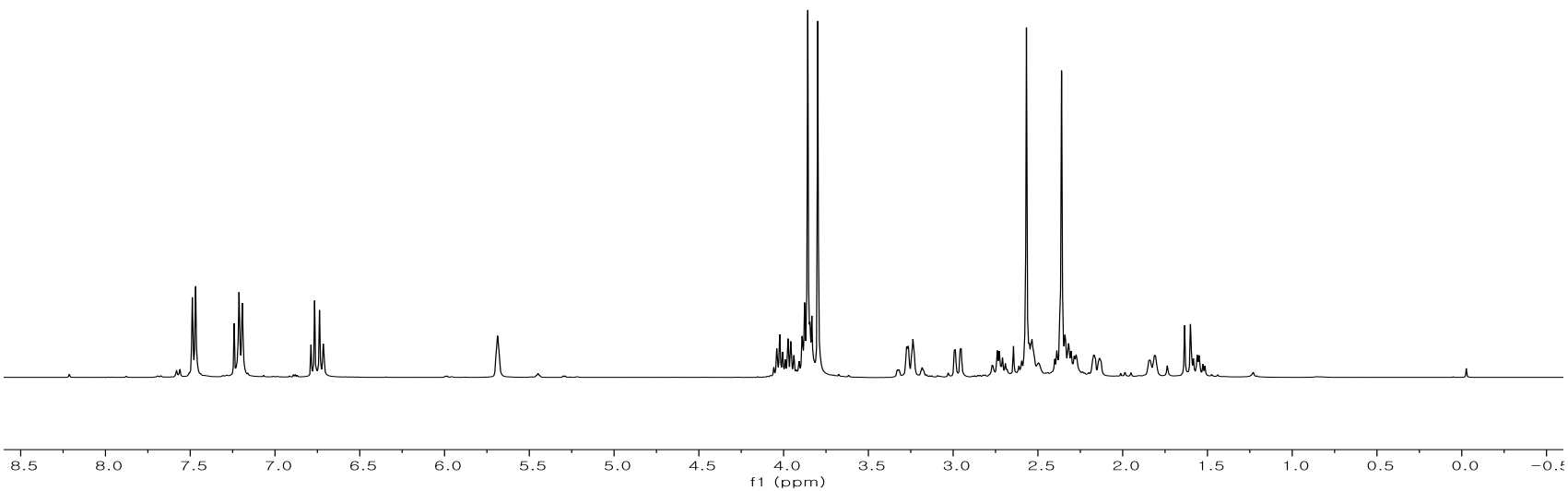

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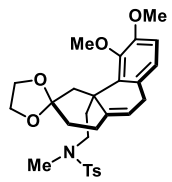

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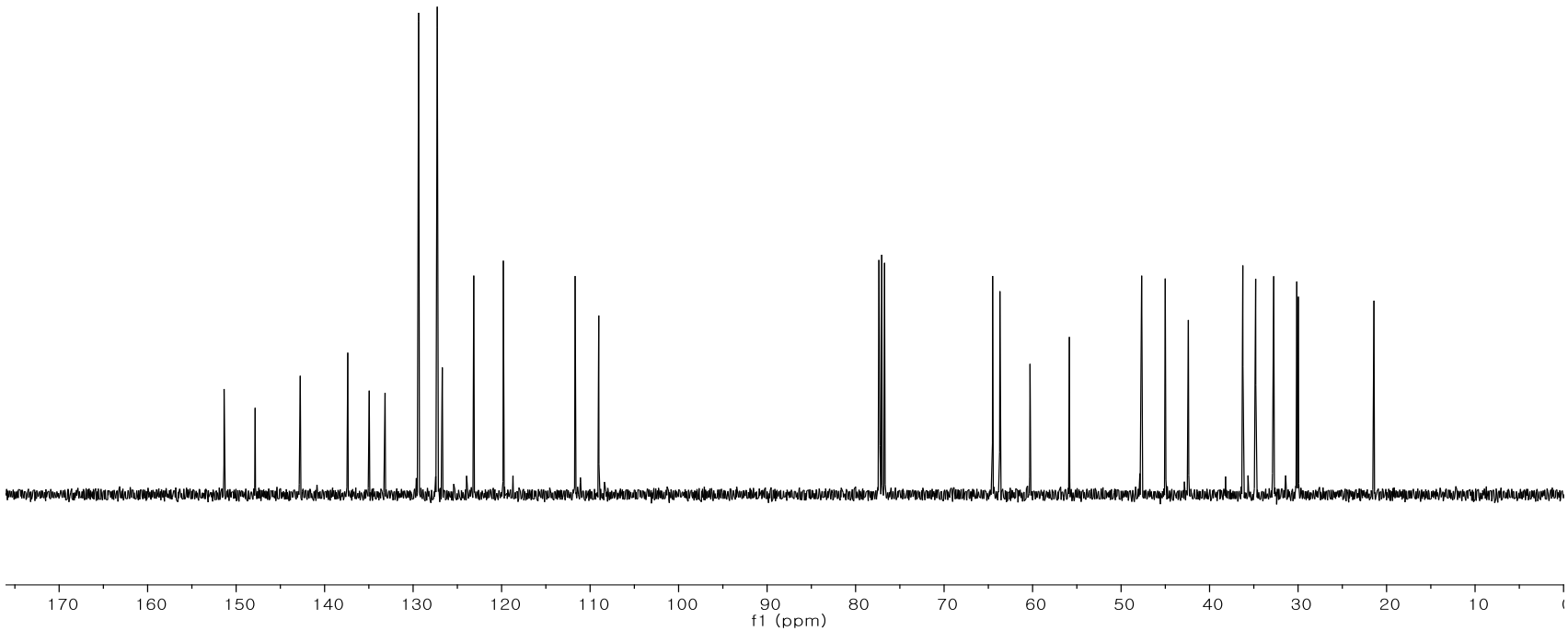

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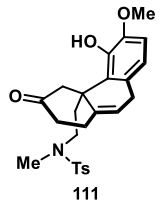

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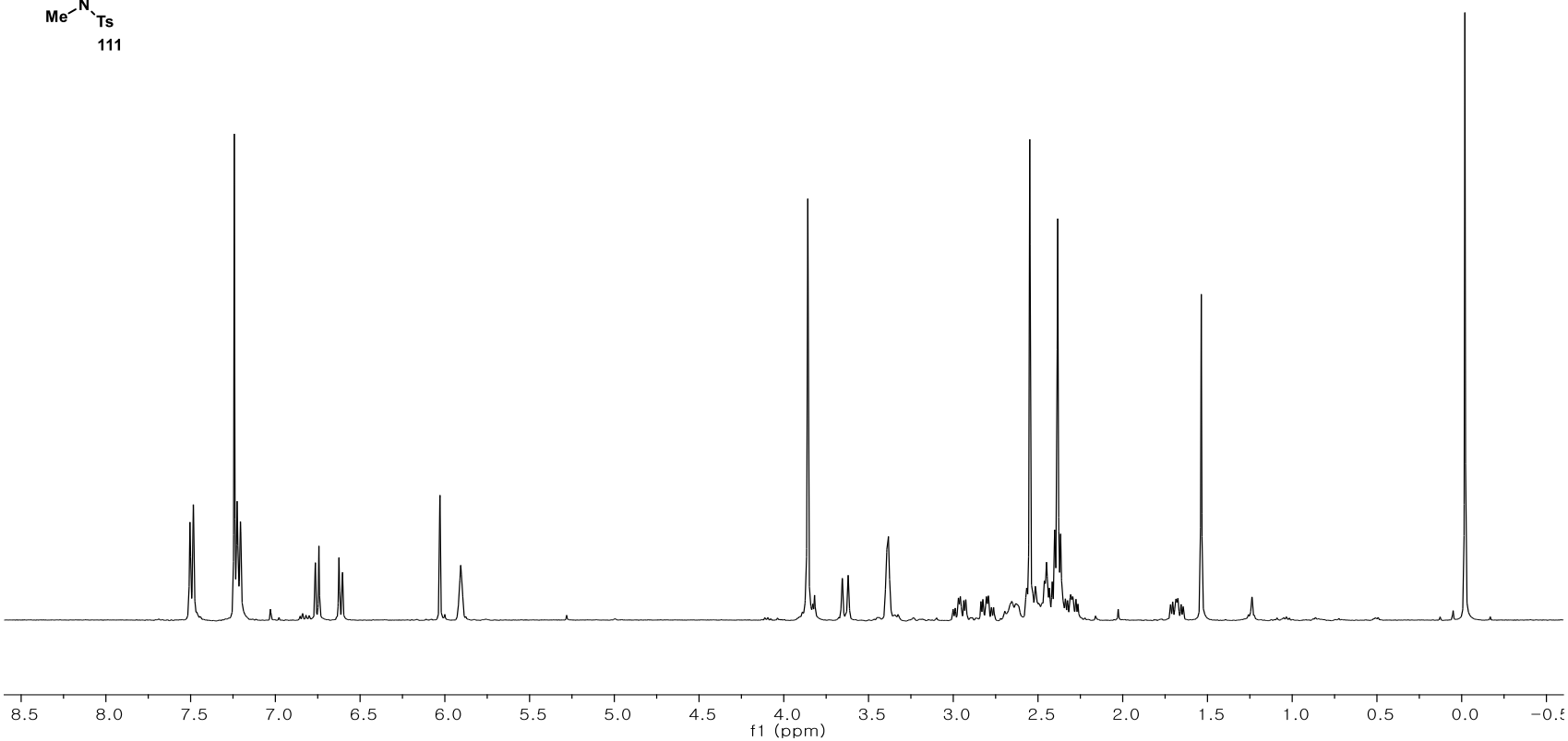

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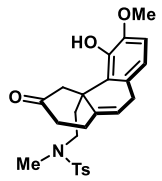

111

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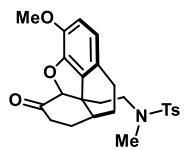
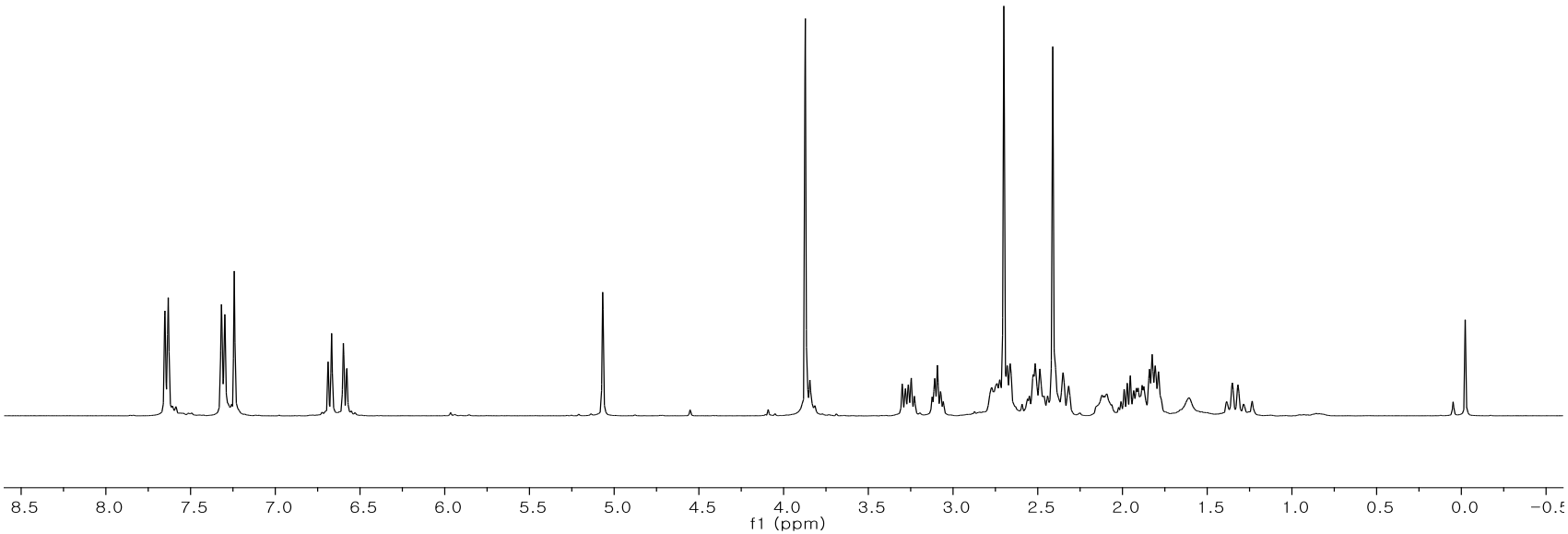


115a



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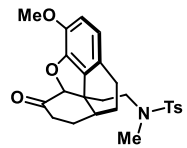

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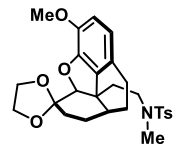
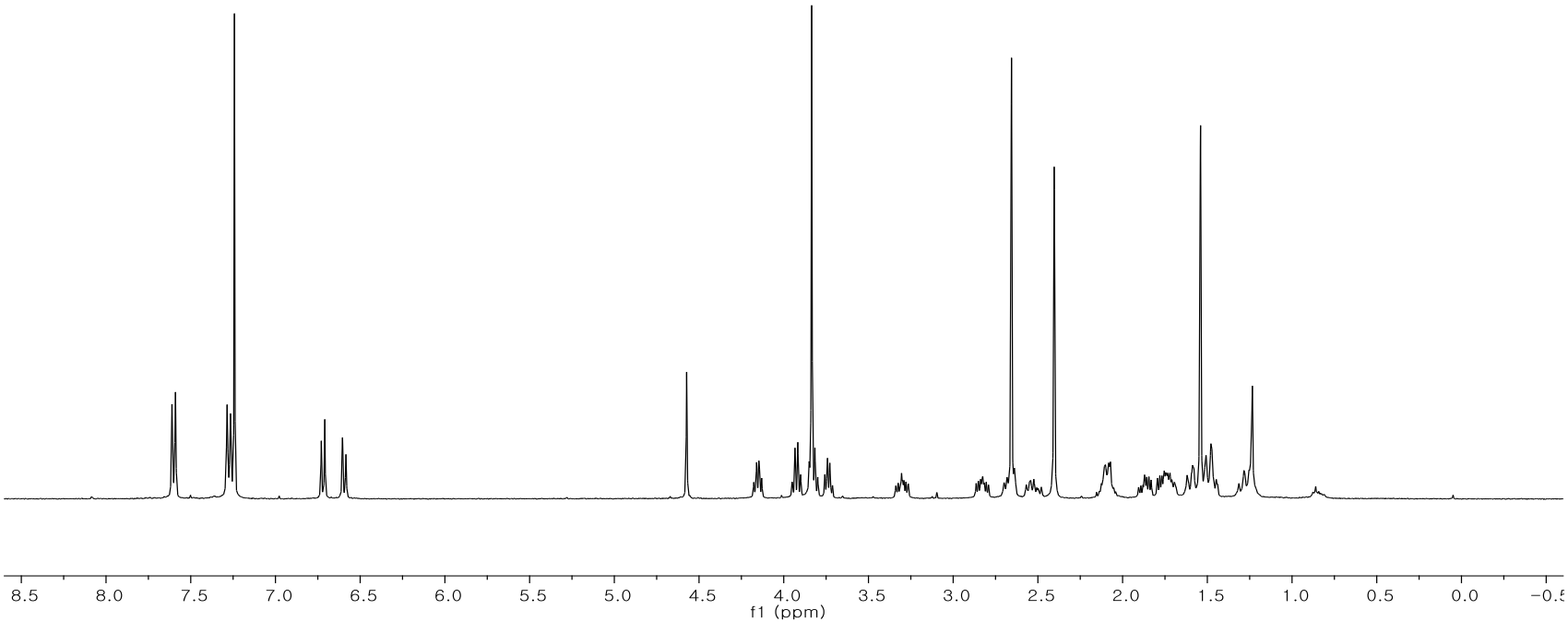
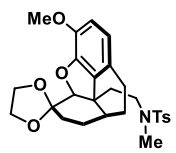


124

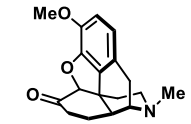


^{13}C NMR (101 MHz, $CDCl_3$)

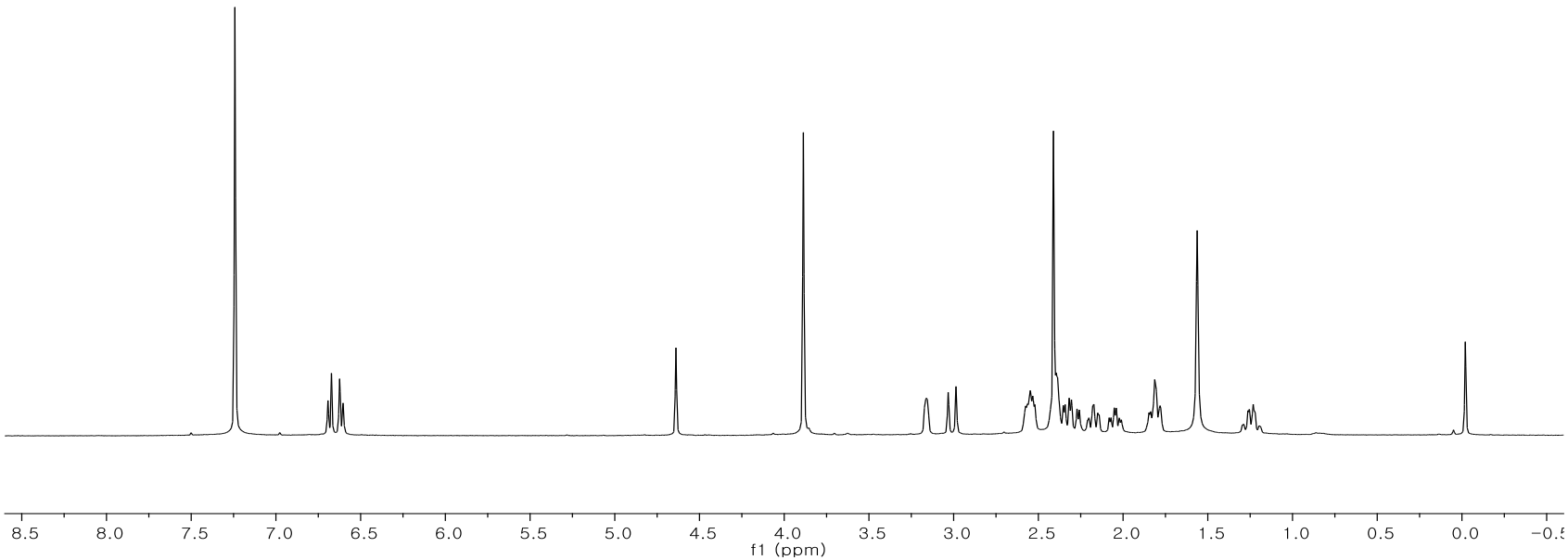


124

^{1}H NMR (400 MHz, $CDCl_3$)



dihydrocodeinone (125)



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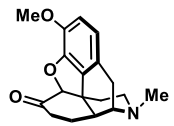
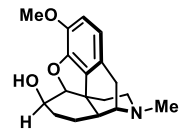
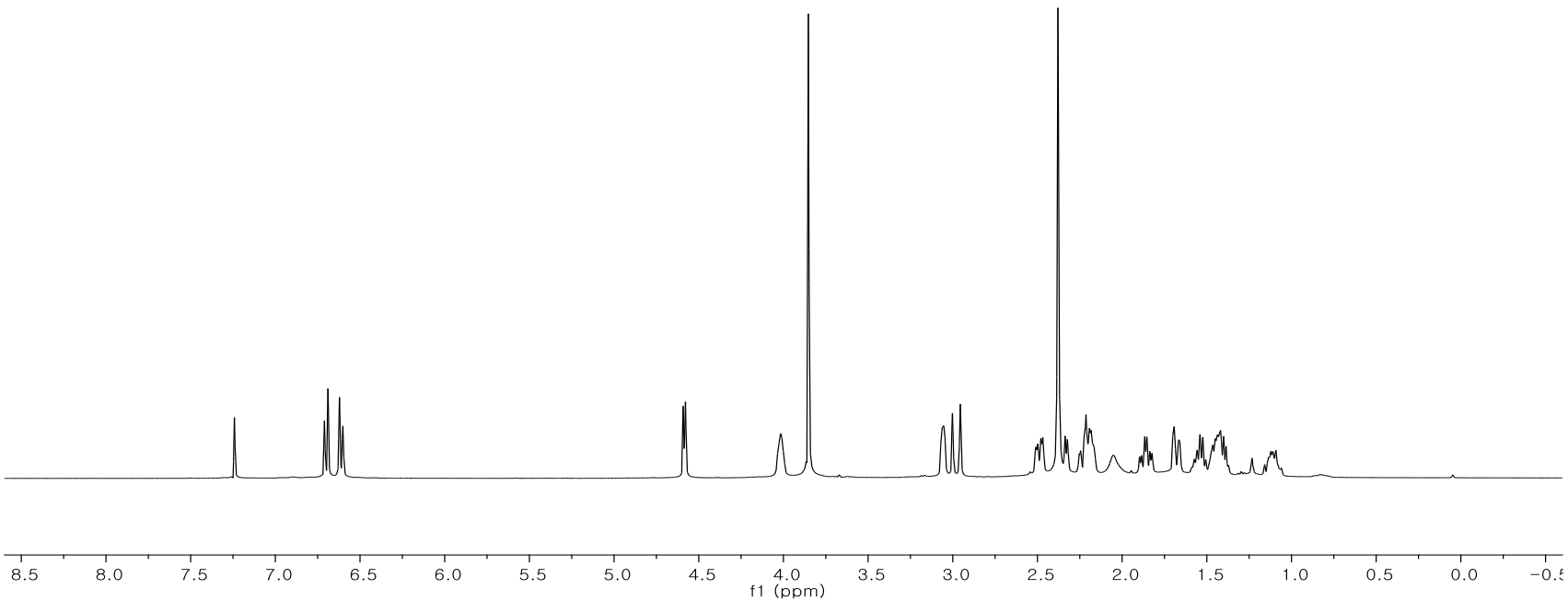


dihydrocodeinone (125)

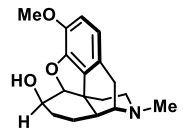
^{1}H NMR (400 MHz, $CDCl_3$)



dihydrocodeine (117)



^{13}C NMR (101 MHz, $CDCl_3$)



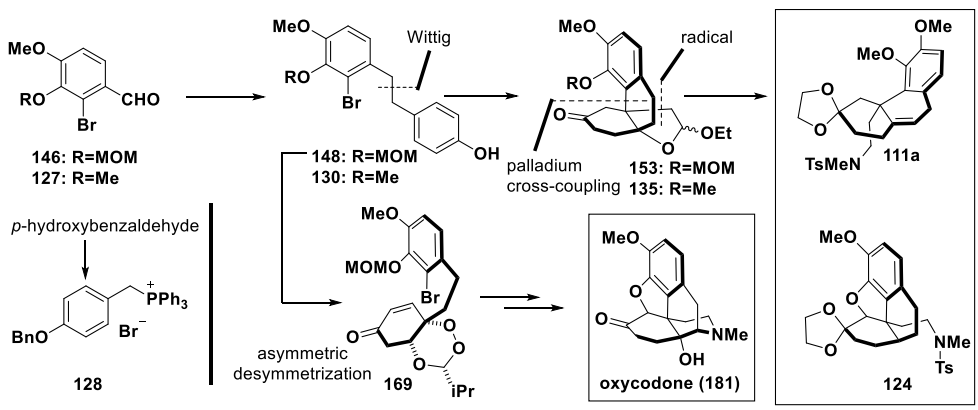
dihydrocodeine (117)

CHAPTER THREE

Second Generation Synthesis Key Intermediates En-Route to the Total Synthesis of dihydrocodeine and dihydrocodeinone And Asymmetric Total Synthesis of Oxycodone

ABSTRACT

In this Chapter, second generation syntheses of tricyclic intermediate **111a** and tetracyclic intermediate **124** have been realized through a revised synthetic strategy that involved a Wittig reaction, an intramolecular Heck reaction, and a Stork-Ueno radical cyclization. This newly developed synthetic sequence was further utilized in a desymmetrization-based asymmetric synthesis of the pharmacologically significant morphinan, oxycodone (**181**).

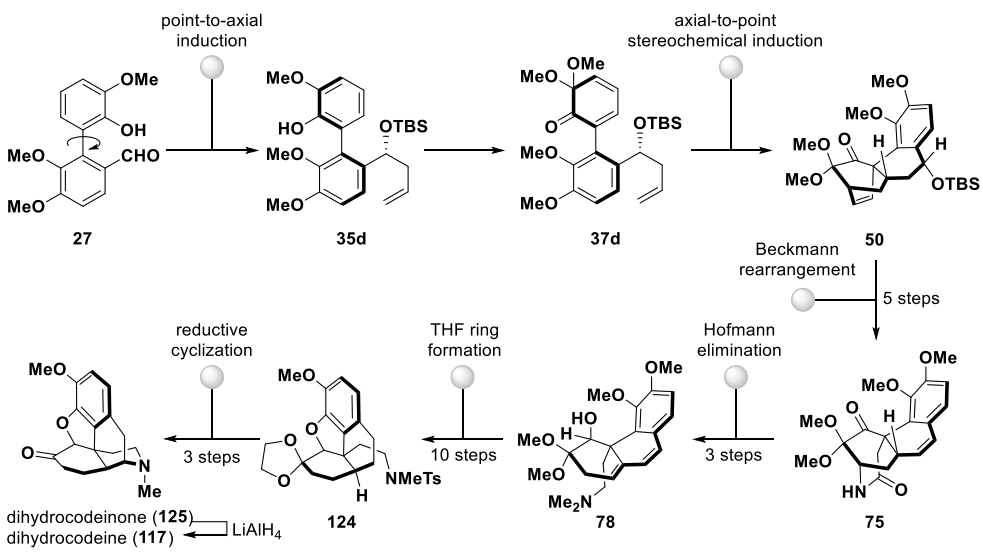


Keywords: chiral phosphoric acid catalysis, desymmetrization, Heck reaction, morphinan, oxycodone, Stork-Ueno radical cyclization, ,

Student Number: 2014-22396

Introduction

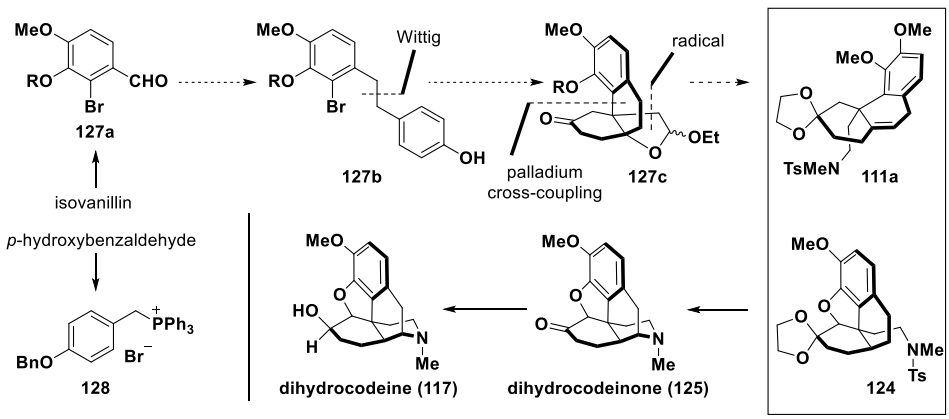
In Chapter One, a proof-of-concept demonstration of "serial stereochemical relay" in multi-step target-oriented synthesis was realized through a rationally designed biaryl system **35d**. In doing so, a highly functionalized tetracyclic system **50** containing a congested quaternary center was synthesized in a stereoselective manner (Scheme 1). In Chapter Two, recognizing the structural similarity between tetracycle **50** and the ring framework of the morphinan family of natural products, further synthetic elaborations of tetracycle **50** successfully led to the preparation of two signature morphinans dihydrocodeinone (**125**) and dihydrocodeine (**117**). This work featured a sequential Beckmann rearrangement[1] and Hofmann elimination[2] to rupture the [2.2.2]-bicyclic domain of tetracycle **50**, followed by a tetrahydrofuran construction and a late-stage reductive piperidine formation[3] to cast the caged core structure of the morphinans (Scheme 1).



Scheme 1: First Generation Synthesis of Dihydrocodeinone and Dihydrocodeine.

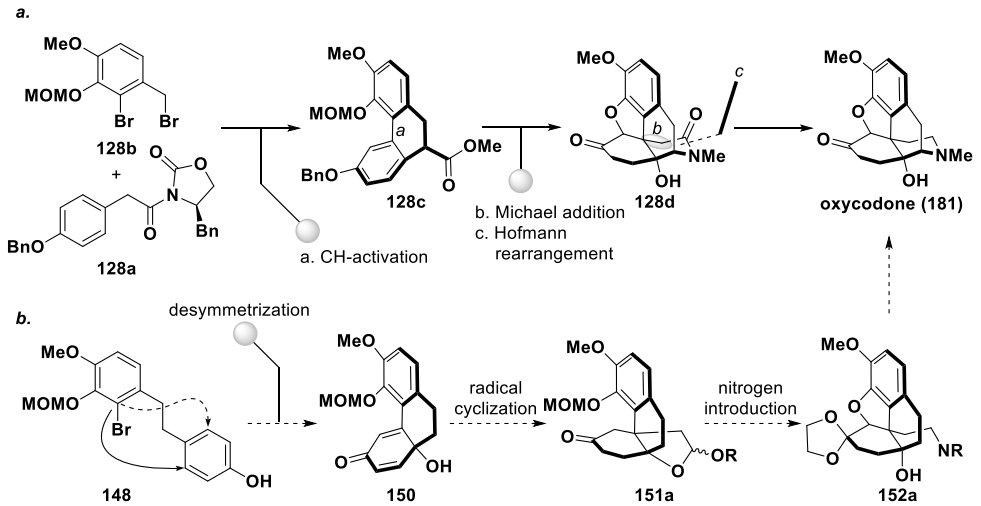
Although targeted morphinans were successfully synthesized, extensive functional group transformations and consequently a lengthy synthetic sequence was required. To address this shortcoming in the first-generation synthesis, a revised synthetic pathway was conceived as shown in Scheme 2. The unification of two aryl domains was envisioned

through a Wittig olefination,[4] followed by an intramolecular palladium-catalyzed cross-coupling reaction[5] and a radical cyclization[6] to construct the quaternary center containing phenanthrene system **127c**. In doing so, a more streamlined synthesis of tricyclic intermediate **111a** and tetracyclic intermediate **124** en-route to the first-generation synthesis of dihydrocodeine (**117**) and dihydrocodeinone (**125**) described in Chapter Two, is anticipated.



Scheme 2: Proposed Second-Generation Synthesis of Intermediates 111a and 124 en-route Toward Dihydrocodeinone (125) and Dihydrocodeine (117).

Furthermore, the tertiary oxygen containing intermediates in the proposed second-generation synthesis presented an additional opportunity to access a new morphinan target, oxycodone (**181**). The pharmacological property of the semi-synthetic morphinan oxycodone (**181**) has attracted much interest by the medical community and has been in clinical use since 1917.[7] Synthetically, the only total synthesis of oxycodone (**181**) to date reported by the Fukuyama laboratory featured numerous ingenious synthetic maneuvers, however, required 24 chemical transformations to complete the synthesis (Scheme 3).[8]



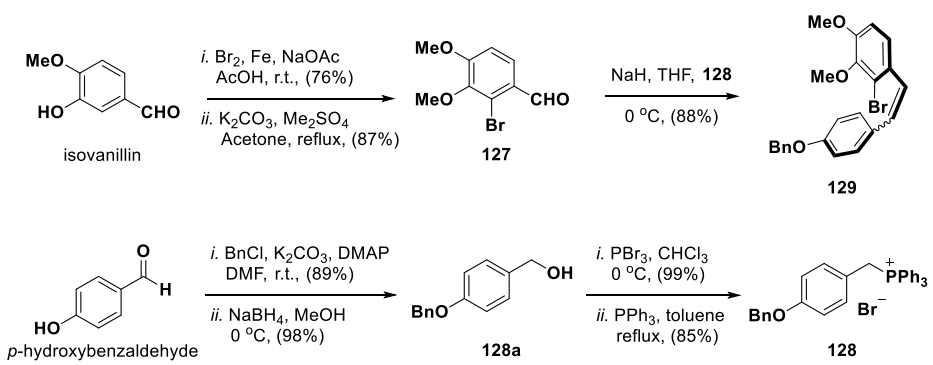
Scheme 3: *a.* Fukuyama Synthesis of Oxycodone (181); *b*. Proposed Synthetic Route Towards Oxycodone (181).

Finally, as part of an ongoing study to illustrate desymmetrization as a powerful synthetic concept in target-oriented synthesis,[9] enantioselective symmetry-breaking processes[10] will be identified and investigated on intermediates in the newly developed synthetic pathway, and in doing so render an asymmetric entry to the morphinan family of natural products.

RESULTS AND DISCUSSION

1.1 Second-Generation Synthesis of Tricyclic Intermediate 111a

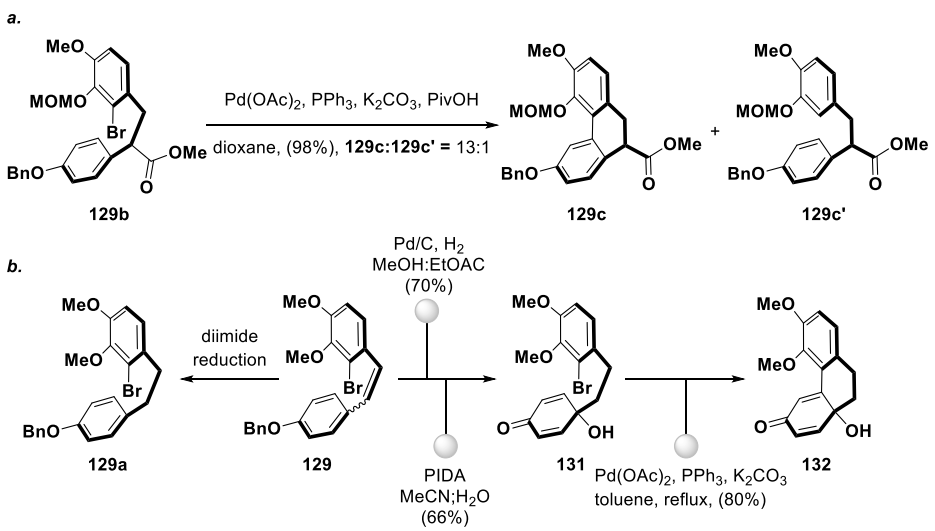
The synthetic investigations toward an improved synthesis of intermediate **111a** commenced with the preparation of the functionalized phenanthrene system **132.** In preparation for the opening Wittig olefination as shown in Scheme 4, benzyaldehyde **127**[11] was synthesized in two steps from isovanillin [(i) bromination (Br_2, Fe, NaOAc, AcOH, 76%); (ii) methylation (K_2CO_3, Me_2SO_4, acetone, 87%)] whereas phosphonium salt **128**[12] was easily prepared from *p*-hydroxybenzaldehyde **128** in a four-steps sequence [(i) benzylation (BnCl, K_2CO_3, DMAP, DMF, 89%); (ii) aldehyde reduction ($NaBH_4$, MeOH, 98%); (iii) bromination (PBr_3, $CHCl_3$, 99%); (iv) phosphonium salt formation (PPh_3, toluene, 85%)]. Gratifyingly, treatment of phosphonium salt **128** with NaH at low temperature followed by addition of benzyaldehyde **127** smoothly delivered stillbene **129** (88%) as an inconsequential mixture of geometric isomers (3:1).[12]



Scheme 4: Synthesis of Stilbene 129.

In preparation for the intramolecular carbon-carbon bond formation to cast the phenanthrene system, two complementary Pd-catalyzed processes were considered (Scheme 5). Inspired by the recent surge of CH-activation based cross-coupling reactions,[13] a closely

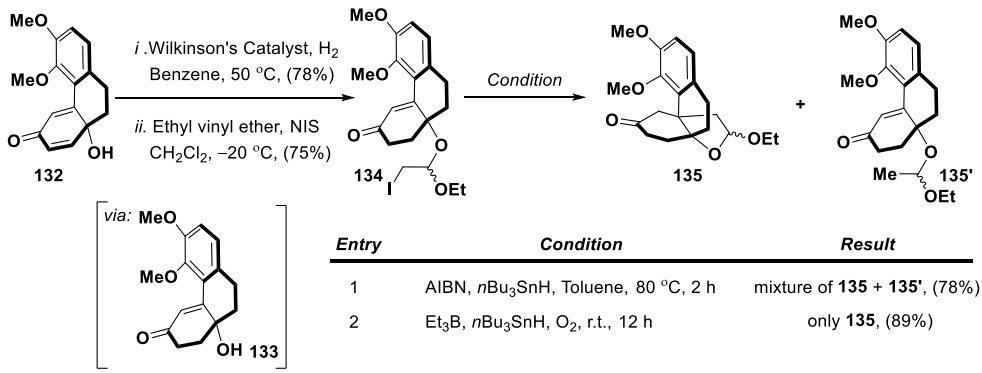
related substrate **129b** has been converted to tricycle **129c** by the Fukuyama laboratory[8] with remarkable efficiency (Scheme 5). Unfortunately, application of the reaction condition developed by the Fukuyama group on substrate **129a** only afforded recovered starting material. Undeterred by this initial set-back, attention was turned to an intramolecular Heck reaction[14] of the oxidative dearomatized dienone **131**. In this context, stilbene **129** was first converted to biaryl phenol **130** through a carefully controlled hydrogenation (Pd/C, H_2, MeOH:EtOAc, 70%) followed by a hypervalent-iodine mediated oxidative dearomatization[15] (PIDA, MeCN:H_2O, 66%) to afford hydroxy dienone **131**. Pleasingly, intramolecular Heck reaction of **131** under the standard conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3] proceeded smoothly to afford the targeted tricyclic dienone **132** (80%) (Scheme **5**).



Scheme 5: *a*. CH-Activation of Biaryl 129b Demonstrated by Fukuyama and Co-Workers; *b*. Attempted CH-Activation of Biaryl 129a and Successful C-C Bond Formation *via* Heck Reaction of Dienone 131.

With the phenanthrene system **132** in hand, formation of the all-carbon quaternary center through the proposed intramolecular Stork-Ueno radical cyclization[16] was investigated. Radical cyclization precursor iodoacetal **134** was prepared under the standard conditions [(i) $RhCl(PPh_3)_3$, benzene, 78%), (ii) NIS, ethyl vinyl ether, CH_2Cl_2, 75%] (Table 1) and the radical cyclization was examined under two conventional reaction conditions. While both thermally initiated AIBN[17] condition and Et_3B/O_2[17] (Et_3B, $n$$Bu_3SnH$, O_2, 89%)

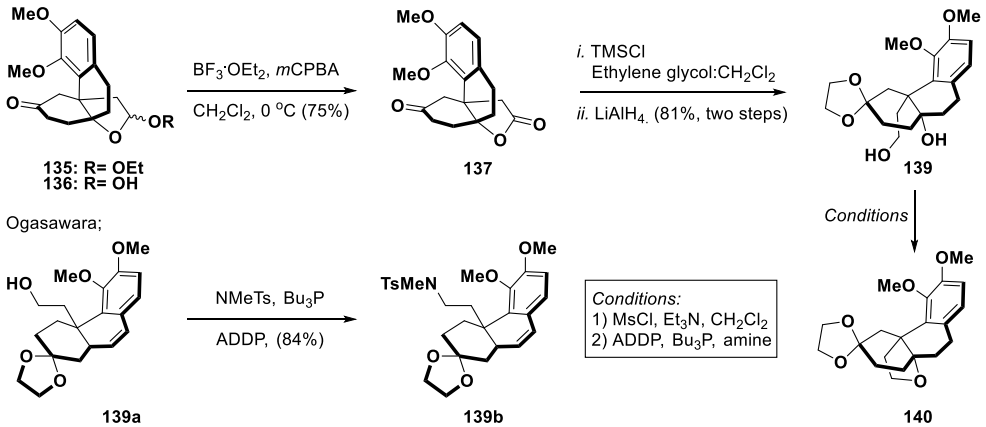
initiated condition in the presence of nBu$_3$SnH were effective, the thermal condition routinely afforded a notable amount of the reductive deiodonated side-product **135'** (Table 1).



Entry	Condition	Result
1	AIBN, nBu$_3$SnH, Toluene, 80 °C, 2 h	mixture of **135** + **135'**, (78%)
2	Et$_3$B, nBu$_3$SnH, O$_2$, r.t., 12 h	only **135**, (89%)

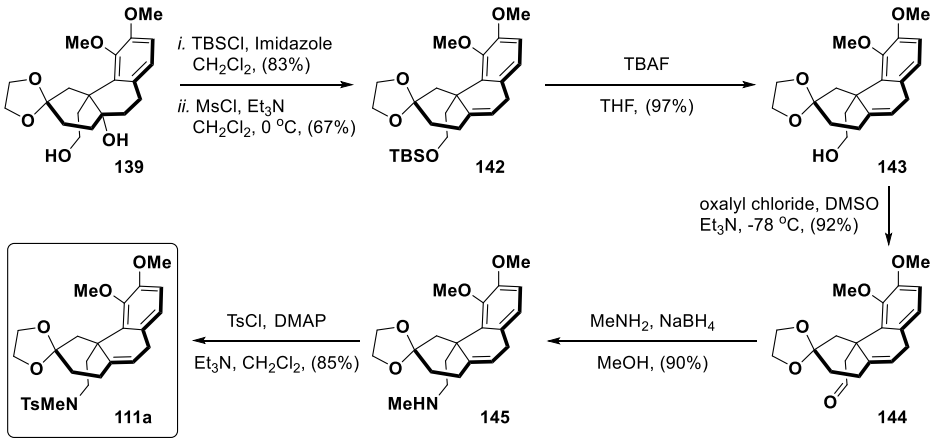
Table 1: Preparation of Radical Precursor 134 and Radical Cyclization of 134.

Further elaboration of tetracyclic intermediate **135** next called for the introduction of the nitrogen atom in the morphinan system. Reductive amination conditions (methylamine, NaCNBH$_3$, MeOH) was attempted on both acetal **135** and hemiacetal **136** without success, presumably due to the interfering tertiary alcohol and further complicated by the presence of the ketone functionality in **135** and **136** (Scheme 6). Undeterred by this initial setback, attention was turned to diol system **139** and the feasibility of this substrate to undergo nitrogen substitution selectively at its primary hydroxyl. Diol **139** was readily prepared through a three steps sequence involving lactol oxidation (mCPBA, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 75%),[18] ketone protection (ethyleneglycol, TMSCl, CH$_2$Cl$_2$)[19] and LiAlH$_4$ reduction (LiAlH$_4$, THF, 81% for two steps). At this point, recognizing the necessity to introduce the trisubstituted olefin in the targeted tricyclic intermediate **111a**, the possibility to simultaneously activate both primary and tertiary hydroxyl groups in **139** was enticing. Unfortunately, on treatment of diol **139** under MsCl/Et$_3$N conditions, tetrahyrofuran system **140** was obtained as the sole product. Application of the Mitsunobu protocol[20] that had been successfully demonstrated by Ogasawara and co-workers[21] in their morphinan synthesis also led to the same outcome (Scheme 6).



Scheme 6: Synthesis of Pentacycle 140.

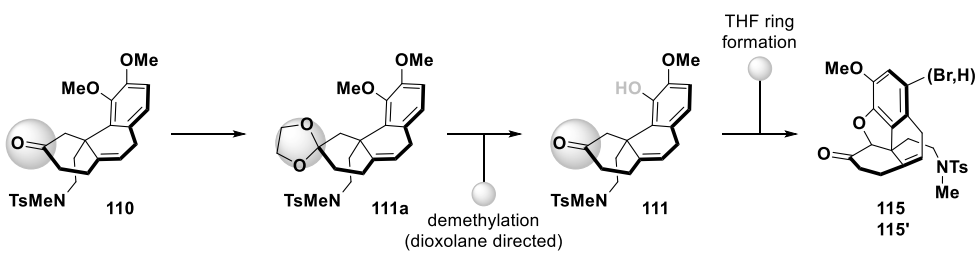
In view of the complication caused by the tertiary alcohol in the presence of an activated primary alcohol, elimination of the tertiary alcohol after selective silylation of primary alcohol **139** [(i) TBSCl, imidazole, CH_2Cl_2, 83%; (ii) MsCl, Et_3N, CH_2Cl_2, 67%] smoothly afforded tricyclic alkene **142** as a single regioisomer. With **142** in hand, its primary hydroxyl was unmasked and oxidized to the corresponding aldehyde **144** [(i) TBAF, THF, 97%; (ii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 92%] which further underwent reductive amination with methylamine followed by tosylation to complete the synthesis of sulfonamide **111a** [(i) $MeNH_2$, $NaBH_4$, MeOH, 90%; (ii) TsCl, DMAP, Et_3N, CH_2Cl_2, 85%] (Scheme **7**). Sulfonamide **111a** exhibited identical spectroscopic data compared to those obtained from the first generation synthesis described in Chapter One.



Scheme 7: Completion of Second Generation Synthesis of Intermediate 111a.

1.2 Second-Generation Synthesis of Tetracyclic Intermediate 124

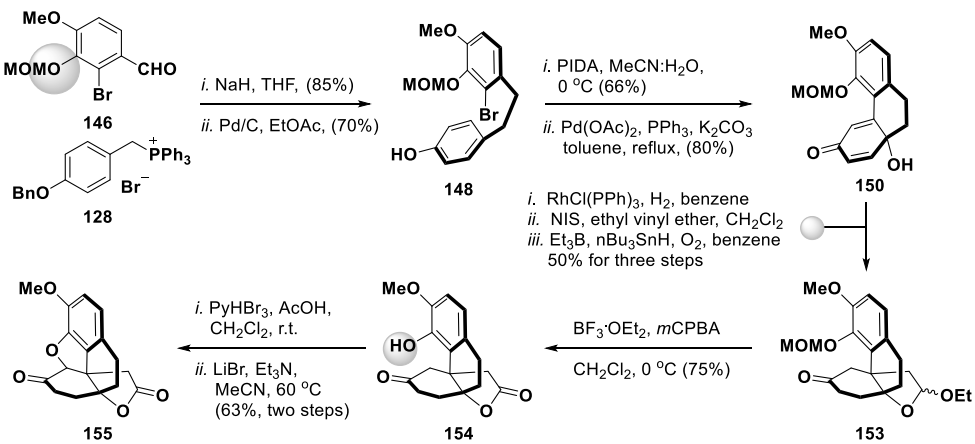
With an improved synthesis of tricyclic sulfonamide **111a** successfully realized, attention was turned to a more advanced intermediate in the first-generation synthesis. In this context, although the L-selectride mediated selective phenolic demethylation[22] was effective in the first-generation synthesis, the necessity to install a dioxolane directing group followed by its later removal in preparation for the formation of the tetrahydrofuran ring was synthetically unappealing (Scheme 8).



Scheme 8: First Generation Synthesis of Tetracycle 115/115'.

Therefore, in accordance to the preparation of tetracyclic acetal **135** described in the synthesis of sulfonamide **111a**, an analogous methoxylmethyl (MOM) derivative was prepared as outlined in Scheme 9 [(i) NaH, THF, 85%; (ii) Pd/C, EtOAc:MeOH, 70%; (iii)

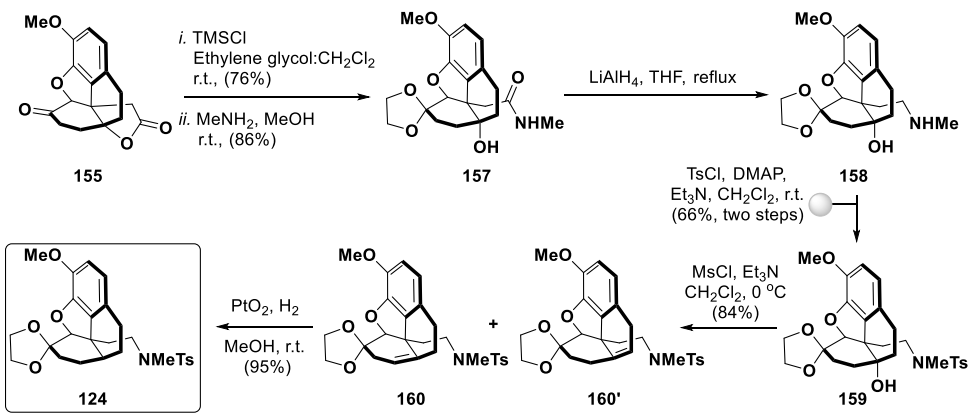
PIDA, MeCN:H_2O, 66%; (iv) $Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, 80%; (v) $RhCl(PPh)_3$, H_2, benzene; (vi) NIS, ethyl vinyl ether, CH_2Cl_2; (vii) Et_3B, *n*Bu_3SnH, O_2, benzene, 50% for three steps]. Oxidation of acetal **153** under *m*CPBA conditions in the presence of $BF_3{\cdot}OEt_2$[18] not only afforded the corresponding lactone, but also fortuitously removed the MOM ether to afford phenolic ketone **154** (75%). Taking advantage of this result, phenolic ketone **154** was poised to undergo tetrahydrofuran formation as demonstrated in the conversion of phenolic ketone **111** to tetracycle **115** in the first-generation synthesis described in Chapter Two. To this end, application of the previously established protocol [(i) $Py{\cdot}HBr_3$, AcOH, CH_2Cl_2; (ii) LiBr, Et_3N, MeCN, 63% for two steps][8] smoothly delivered pentacyclic lactone **155**, ready for further synthetic explorations (Scheme 9).



Scheme 9: Sythesis of Pentacycle 155.

At this juncture, instead of the earlier described reductive amination pathway to introduce the nitrogen atom through the intermediacy of TBS ether **142** (Scheme 7), a more streamlined sequence was investigated. To this end, upon protection of ketone **155** (ethyleneglycol, TMSCl, CH_2Cl_2, 76%) as its dioxolane derivative, it was found that lactone **156** could undergo a smooth amidation in the presence of methylamine to afford amide **157** (86%). Exhaustive reduction of amide **157** ($LiAlH_4$, THF) followed by tosylation (TsCl, DMAP, Et_3N, CH_2Cl_2) of the methylamine intermediate smoothly delivered sulfonamide **159**

(66% for two steps), with its tertiary alcohol being the only structural difference compared to the tetracyclic intermediate **124** described in the first-generation synthesis in Chapter Two. Therefore, elimination of the tertiary hydroxyl (MsCl, Et_3N, CH_2Cl_2, 84%) in **159** followed by a stereoselective hydrogenation (PtO_2, H_2, MeOH, 95%) of the trisubstituted olefin intermediate completed the second-generation synthesis of tetracyclic intermediate **124** (Scheme 10).

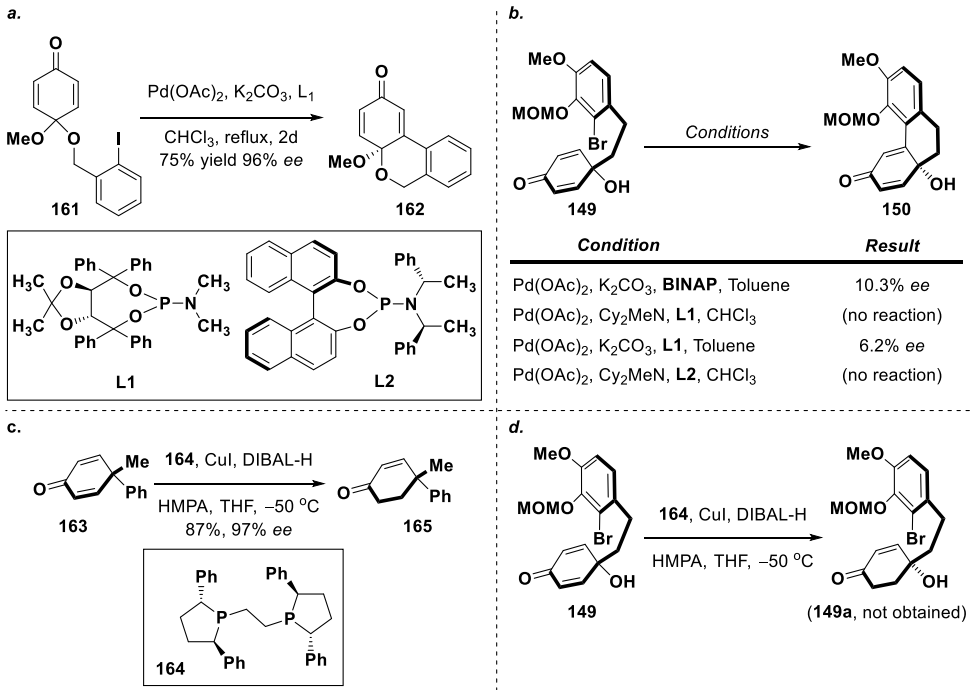


Scheme 10: Successful Second Generation Synthesis of Tetracycle 124.

1.3 Asymmetric Total Synthesis of Oxycodone

As alluded to in the introductory section, the tertiary oxygen containing intermediates **135** and **153** that led to the synthesis of tricycle **111a** and tetracycle **124** presented an enticing opportunity to access the semi-synthetic morphinan, oxycodone (**181**). In view of the asymmetric total synthesis of oxycodone (**181**) reported by Fukuyama and co-workers,[8] the immediate objective was to leverage on the aforementioned second-generation synthesis and explore an asymmetric variant. In this context and inspired by the work of Feringa,[23] an asymmetric variant of the Heck reaction previously demonstrated for hydroxy dienone **149** was first investigated. Unfortunately, after screening a few representative chiral ligands, all reaction conditions afforded near racemic product. Next, the asymmetric 1,4-reduction methodology recently developed by the Corey laboratory[24] for the

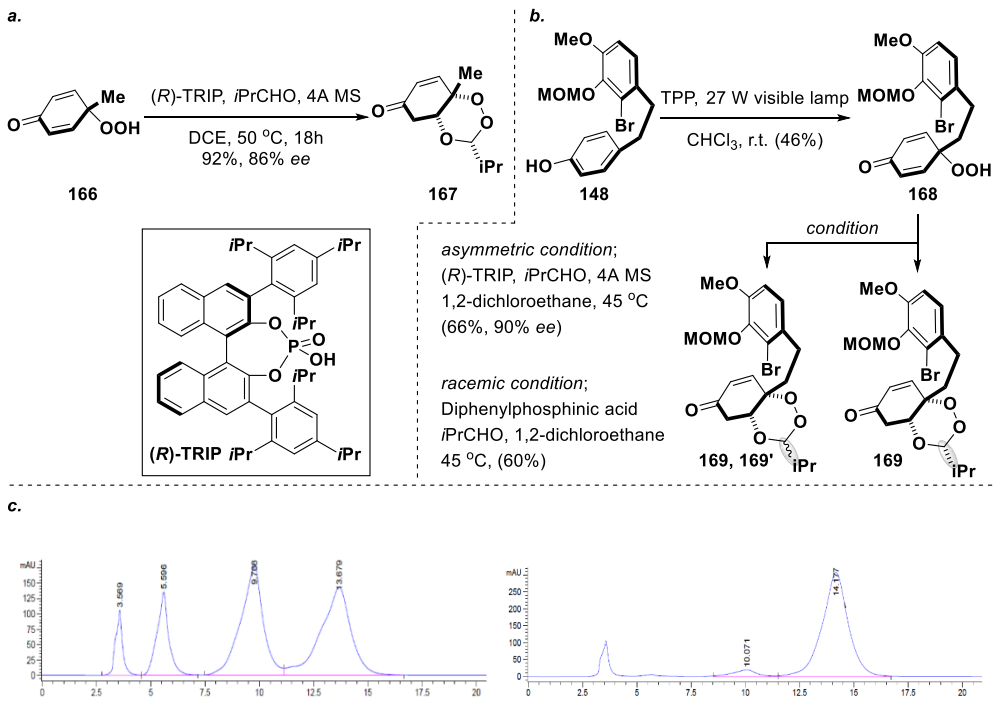
desymmetrization of 4,4-disubstituted cyclohexadienones was examined. Unfortunately, application of the reaction conditions developed by Corey and co-workers on substrate **149** only afforded recovered starting material (Scheme 11).



Scheme 11: *a.* Asymmetric Heck Reaction of Dienone 161 Demonstrated by Feringa; *b.* Attempted Asymmetric Heck Reaction of Dienone 149; *c.* Asymmetric Reduction of Dienone 163 Demonstrated by Corey; *d.* Attempted Asymmetric Reduction of Dienone 149.

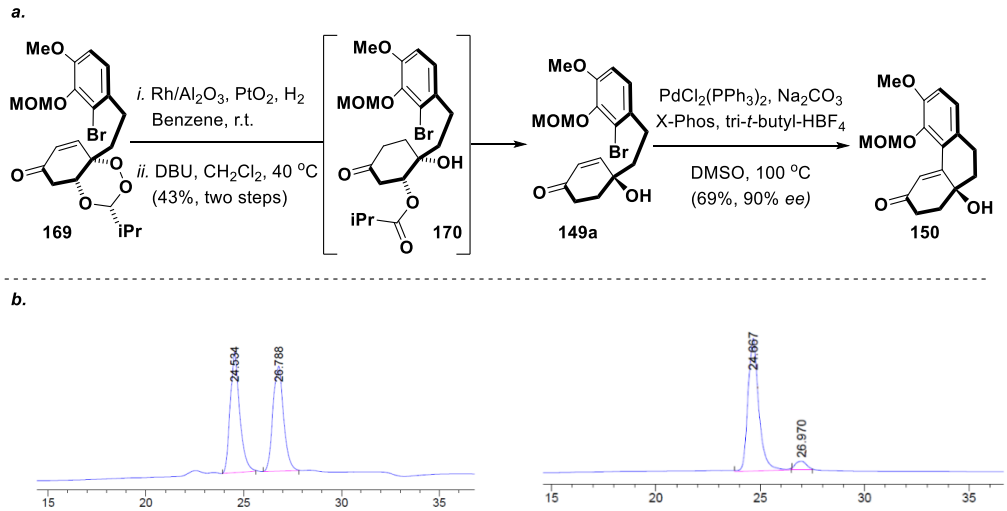
Undeterred by these early-stage setbacks, a newly developed asymmetric desymmetrization of peroxyquinol reported by Rovis and co-workers[25] presented an enticing opportunity, provided the optically active intermediate synthesized could be converted to an interception compound in the aforementioned second-generation synthesis. The prerequisite peroxyquinol **168** was readily prepared from biaryl phenol **148** under singlet oxygen conditions (TPP, 27W visible lamp, $CHCl_3$, 46%),[26] and on treatment with (*R*)-TRIP and isobutyraldehyde under the conditions described by Rovis (*R*-TRIP, *i*PrCHO, 4A MS, DCE, 60%) cleanly delivered peroxyacetal **169** as a single diastereoisomer in 95:5 er (HPLC analysis). Interestingly, treatment of peroxyquinol **168** under racemic conditions in the presence of diphenylphosphinic acid and isobutyraldehyde (diphenylphosphinic acid,

*i*PrCHO, DCE, 60%) afforded a mixture of diastereoisomers, suggesting the influence of the chiral Bronsted acid in both enantio- and diastereo-control (Scheme 12).



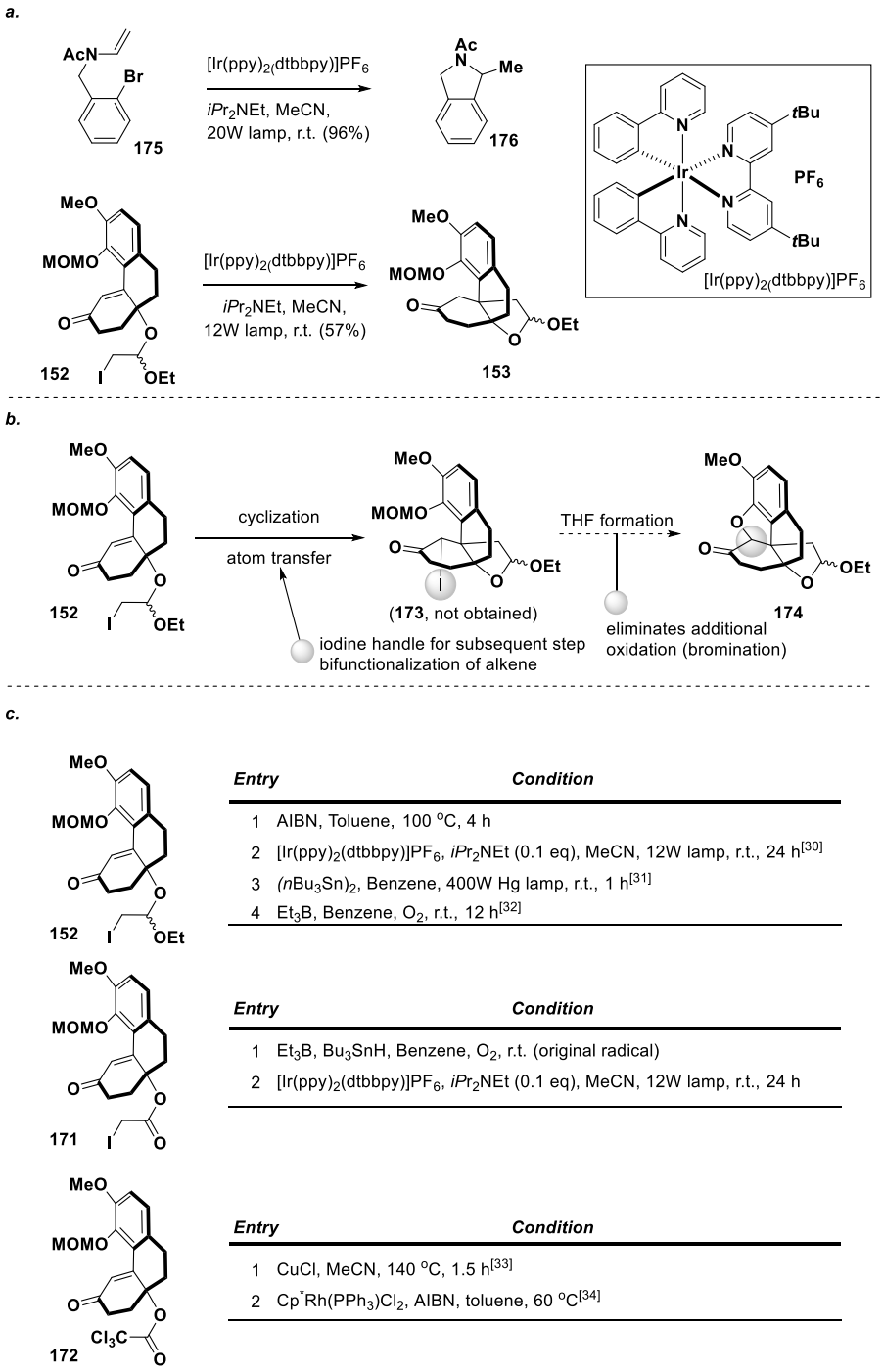
Scheme 12: *a.* Synthesis of Trioxane 167 *via* Asymmetric Desymmetrization of Peroxyquinol 166 demonstrated by Rovis; *b.* Synthesis of Racemic and Asymmetric Trioxanes 169, 169'; *c.* HPLC Trace of 169+169' and 169.

Peroxyacetal **169** was subsequently subjected to catalytic hydrogenation (Rh/Al_2O_3, PtO_2, H_2, benzene)[25] followed by a Kornblum-DeLaMare[27] type fragmentation/elimination (DBU, CH_2Cl_2, 43% for two steps) to afford hydroxy enone **149a** (Scheme 13a), in readiness for the conversion to the interception compound **150** through an intramolecular Heck reaction. Interestingly, the Heck condition previously developed for hydroxy dienone **149** was totally ineffective for hydroxy enone **149a**, hence a revised reagent blend was developed to realize the desired transformation [$PdCl_2(PPh_3)_2$, Na_2CO_3, X-Phos, tributylphosphine tetrafluoroborate, DMSO, 69%].[28] Chiral HPLC analysis of tricyclic hydroxy enone **150** (Scheme 13b) further confirmed the optical purity was completely preserved throughout the synthetic transformations from peroxyacetal **169** to enone **150**.



Scheme 13: *a*. Synthesis of Enantiopure Tricyclic Enone 150; *b*. HPLC traces of Racemic and Asymmetric Tricyclic Enone 150.

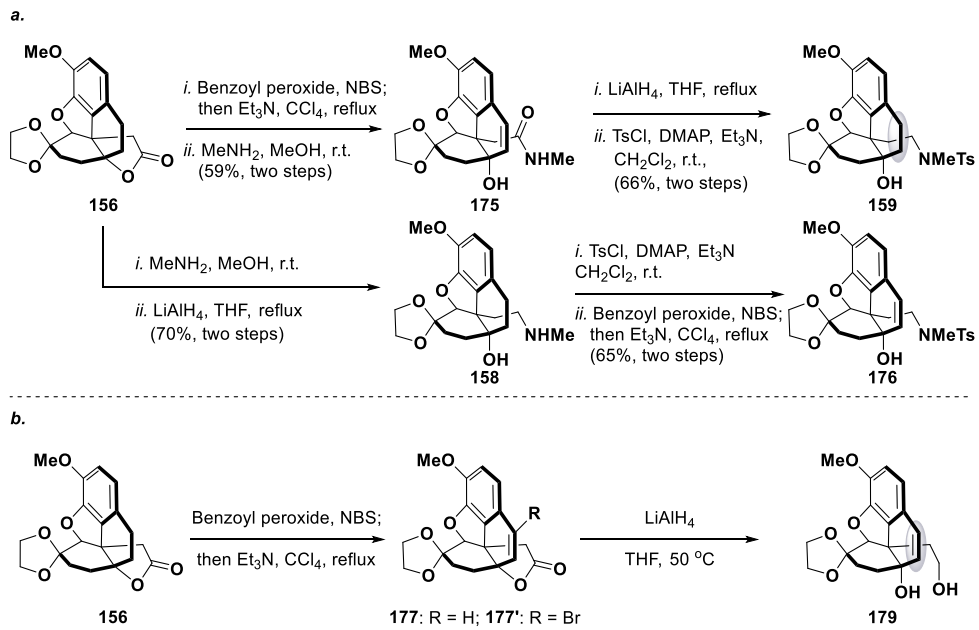
With optically active tricyclic hydroxy enone **150** in hand, although an identical synthetic sequence described for the synthesis of tetracyclic sulfonamide **124** could be repeated to reach pentacyclic ketolactone **155**, further improvements of the developed sequence were investigated. To this end, the previously described *n*Bu_3SnH-based radical cyclization for the formation of tetracyclic acetal **153** from iodoacetal **152** was replaced with a photoredox variant ([Ir(ppy)$_2$(dtbbpy)]PF_6, *i*Pr_2NEt, 12W lamp, MeCN, 57%) pioneered by Lee and co-worker[29] with more operational ease and safety (Scheme 14a). Tetrahydrofuran formation from phenolic ketone **154** was also reinvestigated to circumvent the previously developed bromination-cyclization sequence (**154** to **155**), through a proposed atom-transfer radical cyclization (ATRC) process (Scheme 14b). Unfortunately, several well-documented reaction ATRC conditions were examined on iodoacetal **152** without success,[30],[31],[32] and newly prepared radical cyclization precursors **171** and **172** also failed to undergo the desired transformation (Scheme 14c).[33],[34]



Scheme 14: *a*. Photoredox Cyclization of Aryl Bromide 175 Demonstrated by Lee and Photoredox Cyclization of Iodoacetal 152; *b*. Proposed Atom Transfer Radical Cyclization of Iodoacetal 152; *c*. Attempted Atom Transfer Radical Cyclization for Substrates 152, 171, 172.

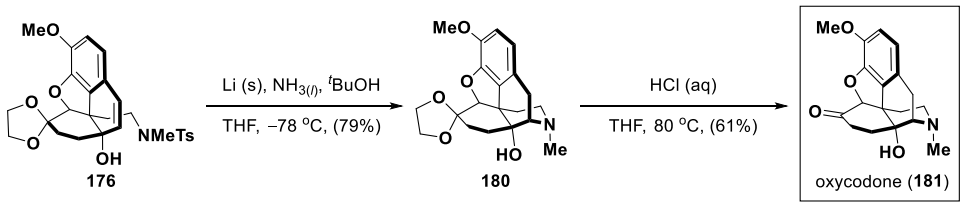
Advancing pentacyclic ketolactone **155** to the previously described tosylamide **159**

proceeded uneventfully, in readiness for the final drive towards oxycodone (**181**). In accordance to the synthetic sequence developed for preparation of dihydrocodeine (**117**) and dihydrocodeinone (**125**) from styrene **124a** described in Chapter Two, tosylamide **159** underwent benzylic bromination followed by HBr elimination (Benzoyl peroxide, NBS, Et_3N, CCl_4, 70%) to afford styrene **176**.[19] Interestingly, although the styrene introduction could be realized prior to the amide reduction (**156** to **175**), subsequent amide reduction unexpectedly saturated the styrene olefin. In stark contrast, reduction of lactone **177**/**177'** under similar conditions took place uneventfully without compromising the styrene olefin (Scheme 15).



Scheme 15: *a.* Synthesis of Tosyl Amide 159 and Tosyl Amide 176; *b.* Synthesis of Diol 179.

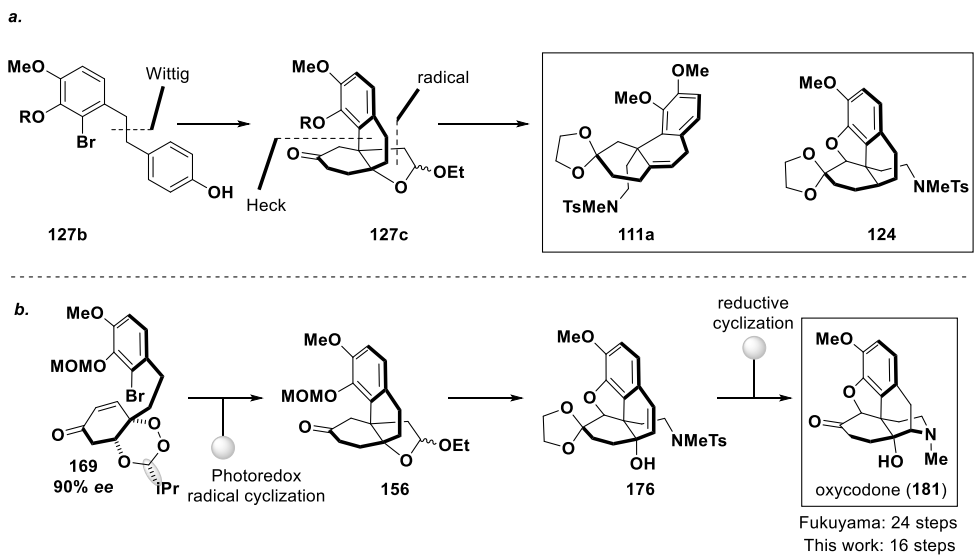
Reductive detosylation of tosylamide **176** under Birch-type conditions (Li, NH_3, *t*-BuOH, THF, 79%)[3] smoothly afforded dioxolane protected oxycodone **180**, and on further treatment under acidic conditions (HCl, THF, 61%) completed the total synthesis of oxycodone (**181**) with all spectroscopic data in full accordance with the literature report.[8]



Scheme 16: Successful Synthesis of Oxycodone (181).

Conclusion

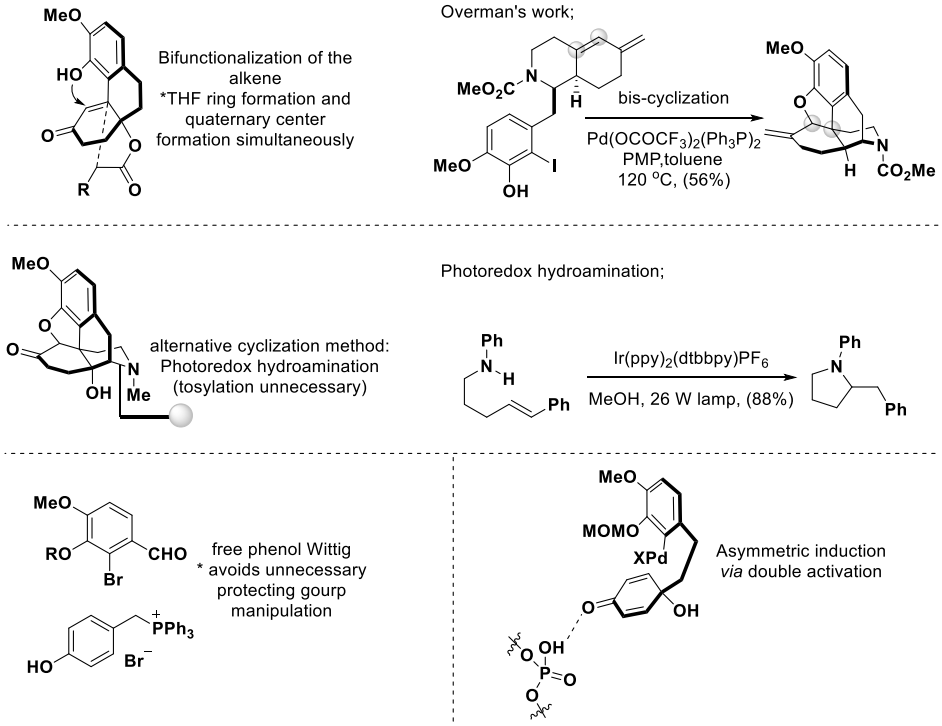
In this Chapter, improved second-generation syntheses of tricyclic intermediate **111a** and tetracyclic intermediate **124** have been realized, and in doing so rendered new and more streamlined syntheses of dihydrocodeine (**117**) and dihydrocodeinone (**125**). This revised synthetic pathway featured a Wittig reaction to unify two aryl subunits, an intramolecular Heck reaction to cast the phenanthrene backbone, a photoredox variant of Stork-Ueno radical cyclization to install the quaternary center, and a late-stage reductive cyclization to complete the core structure of the target molecules. Furthermore, an asymmetric version of the developed synthetic pathway was made possible through the first application of the Rovis asymmetric desymmetrization of peroxyquinol. The technologies described herein was also applied in the total synthesis of oxycodone (**181**), which represents a significant improvement in overall step-count compared to the first and only total synthesis reported by Fukuyama and co-workers.



Scheme 17: *a.* Second Generation Synthesis of Common Intermediates 111a and 124; *b.* Asymmetric Total Synthesis of Oxycodone (181).

Notwithstanding the accomplishments discussed herein, further inspection of the developed synthetic strategy towards the morphinans presented opportunities for further

improvements. Indeed, while the key bond-forming reactions proceeded smoothly (namely the Wittig reaction, Heck reaction, radical cyclization, tetrahydrofuran ring formation, and reductive piperdine formation), the preparatory steps that led to these key steps could be further streamlined to achieve a higher overall efficiency. For example, several reports of Wittig reactions based on unprotected phenols have been documented[35] which could be considered to avoid the benzyl protection early in the synthesis. The styrene olefin originated from the Wittig olefination and later facilitated the piperidine formation underwent several redundant reduction and oxidation processes. Similarly, the nitrogen-bearing carbon atom also underwent acetal-lactone-amine redox manipulations, so did the carbon atom involved in the tetrahydrofuran ring formation. Indeed, while the atom-transfer protocol was briefly examined to circumvent this latter deficiency, other related processes could potentially be implemented to install both the quaternary stereocenter and the tetrahydrofuran ring simultaneously as illustrated in Overman's approach to the morphinans.[36] While a dioxolane protection was necessary for the Birch-type reductive piperidine formation, recent advent in transition-metal and photoredox promoted hydroamination[37] may provide a protecting group free solution. The effectiveness of the Rovis desymmetrization chemistry also provided clues for related desymmetrization processes to be investigated. In this context, asymmetric induction through activation of the carbonyl group proved much more effective than addition of a chiral nucleophile, and recent reports of palladium-catalyzed cross-coupling reactions in conjunction with Bronsted acid catalysis could be explored to resurrect the asymmetric Heck process (Scheme 18).



Scheme 18: Proposed Improvement of Synthesis of Oxycodone (181) .

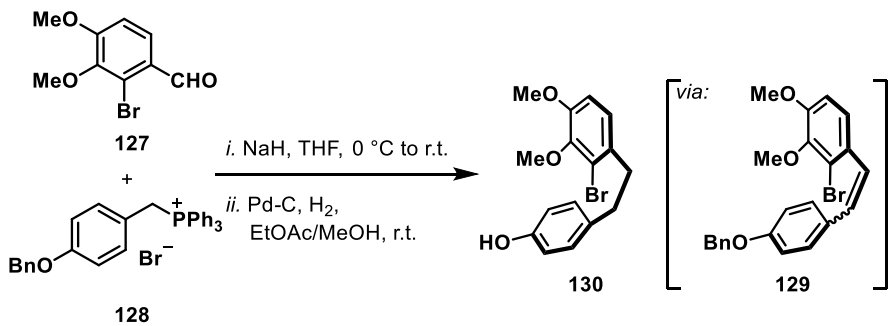
EXPERIMENTAL

General Procedures

Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2) and toluene were dried and distilled according to the standard protocols. Benzene and acetonitrile (CH_3CN) were purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc), Et_2O, CH_2Cl_2, hexanes and water were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F–254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde or potassium permanganate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer and IRTracer-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

Section 1.1

Biaryl Phenol 130

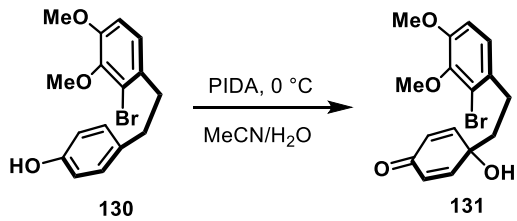


(i) To a stirred solution of phosphonium salt **128** (dried over P_2O_5 overnight, 19.8 g, 36.7 mmol) in THF (350 mL) at 0 ℃ was added NaH (3.06 g, 128 mmol). The resulting mixture was stirred for 2 h before a solution of benzaldehyde **127** (8.77 g, 31.9 mmol) in THF (50 mL) was added. The resulting mixture was warmed to room temperature and stirred for 4 h before it was cooled to 0 ℃ and quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded a geometric mixture of stilbene **129** (12.3 g, 85%) as an amorphous yellow solid. **129**: R_f = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).

(ii) To a stirred solution of stilbene **129** (14.5 g, 31.8 mmol) in EtOAc/MeOH (4:1, 320 mL) at room temperature was added Pd/C (10% wt/wt, 1.70 g, 1.60 mmol). The resulting mixtu re was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H_2 (balloon) for 1 h. The resulting mixture was filtered through Celite® and eluted with EtOAc (3 × 80 mL), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl phenol **130** (8.19 g, 70%) as an amorphous white solid. **130**: R_f = 0.27 (silica gel, hexanes:EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): 7.05 (d,

J = 7.2 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 7.3 Hz, 2H), 4.75 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.97–2.90 (m, 2H), 2.82–2.76 ppm (m, 2H).

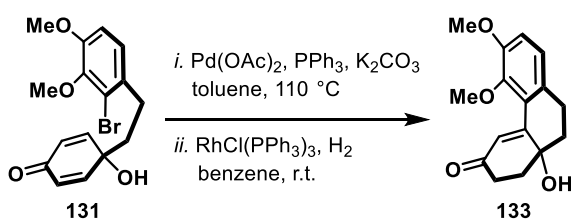
Dienone 131



130 **131**

To a stirred solution of phenol **130** (6.30 g, 17.2 mmol) in MeCN/H_2O (1:1, 170 mL) at 0 ℃ was added PIDA (6.63 g, 20.6 mmol). The resulting mixture was stirred for 2 h before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (50 mL, sat. aq.) and water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL), the combined organic layer was washed with $NaHCO_3$ (100 mL, sat. aq.), bri ne (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded dienone **131** (4.34 g, 66%) as an orange amorphous solid. **131**: R_f = 0.30 (silica gel, hexanes:EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (d, *J* = 10.4 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.23 (d, *J* = 10.3 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.69–2.63 (m, 2H), 2.04–1.98 ppm (m, 2H).

Tricyclic Enone 133



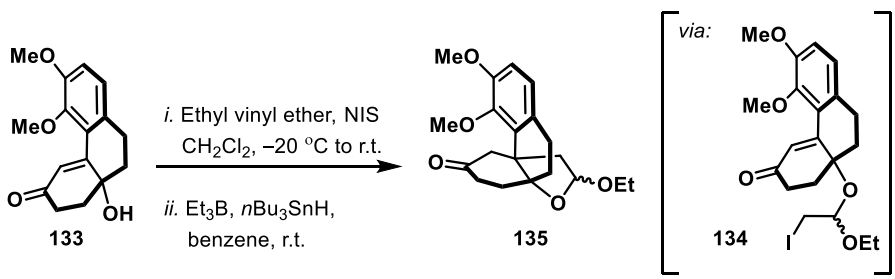
131 **133**

(i) To a stirred solution of dienone **131** (2.80 g, 7.30 mmol) in toluene (80.0 mL) at room temperature was added K_2CO_3 (43.0 g, 21.9 mmol), $Pd(OAc)_2$ (0.26 g, 1.11 mmol) and PPh_3

(0.58 g, 2.19 mmol). The resulting mixture was warmed to 110 °C and stirred for 24 h before it was cooled to room temperature and diluted with water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic dienone **132** (1.77 g, 80%) as an amorphous yellow solid.

(ii) To a stirred solution of tricyclic dienone **132** in benzene (1.77 g, 5.85 mmol) at room temperature was added $RhCl(PPh_3)_3$ (0.27 g, 0.29 mmol). The resulting mixture was evacuated and filled with argon (3 ×) followed by hydrogen (3 ×), and stirred under an atmosphere of H_2 (balloon) for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic enone **133** (1.39 g, 78%) as an amorphous brown solid. **133**: R_f = 0.31 (silica gel, hexane:EtOAc 1:1); ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.87 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 3.09–3.01 (m, 1H), 2.89–2.80 (m, 1H), 2.68 (dt, *J* = 16.8, 3.8 Hz, 1H), 2.48 (s, 1H), 2.38 (dt, *J* = 16.8, 3.8 Hz, 1H), 2.17–2.05 (m, 2H), 1.99–1.85 ppm (m, 2H).

Tetracycle 135

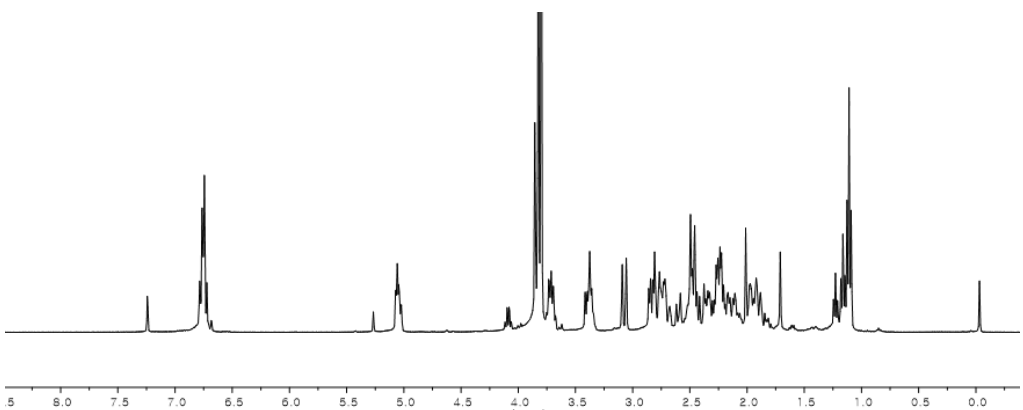


(i) To a stirred solution of tertiary alcohol **133** (1.5 g, 4.93 mmol) in CH_2Cl_2 (50 mL) at –20 °C was added ethyl vinyl ether (1.89 mL, 19.8 mmol) followed by NIS (3.32 g, 14.8 mmol). The resulting mixture was stirred for 1 h before additional ethyl vinyl ether (1.89 mL, 19.8 mmol) and NIS (3.32 g, 14.8 mmol) were added. The resulting mixture was warmed to

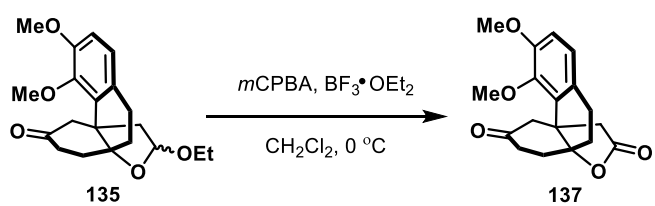
room temperature and stirred for 12 h before it was quenched with $Na_2S_2O_3$ (80 mL, sat. aq.) and water (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2→CH_2Cl_2:Et_2O 1:0→8:1) afforded iodide **134** (mixture of diastereoisomers, as an amorphous yellow solid. **134**: R_f = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).

(ii) To a stirred solution of iodide **134** in benzene (300 mL) at room temperature was added *n*Bu_3SnH (1.77 mL, 6.58 mmol), Et_3B (1.0 M in hexane, 6.58 mL, 6.58 mmol) and small amount of air. The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 5:1) afforded tetracycle **135** (mixture of diastereoisomers, 1.15 g, 62% over two steps) as an amorphous yellow solid. **135**: R_f = 0.39, 0.43 (silica gel, hexanes:EtOAc 3:1).

^{1}H NMR (400 MHz, $CDCl_3$), Semi-Pure

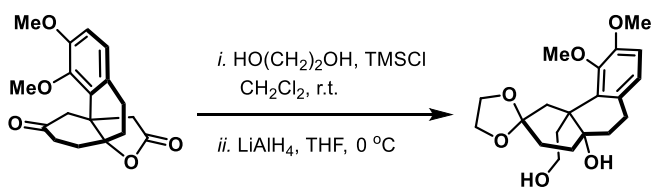


Lactone 137



(i) To a stirred solution of acetal **135** (1.15 g, 3.05 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *m*CPBA (2.64 g, 10.7 mmol) and boron trifluoride diethyl etherate complex (0.8 mL, 6.48 mmol). The resulting mixture was stirred for 15 min before it was quenched with $Na_2S_2O_3$ (30 mL, sat. aq.) and water (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded lactone **137** (591 mg, 64% over two steps) as an amorphous yellow solid. **137**: R_f = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3095, 2831, 1776, 1719, 767 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.00 (s, 1H), 3.87 (s, 3H), 3.32 (d, *J* = 15.0 Hz, 1H), 3.11 (d, *J* = 19.7 Hz, 1H), 3.06 (d, *J* = 19.7 Hz, 1H), 2.95–2.88 (m, 1H), 2.86–2.80 (m, 1H), 2.78 (d, *J* = 15.8 Hz, 1H), 2.55–2.46 (m, 1H), 2.45–2.23 (m, 4H), 2.11–2.04 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.8, 174.9, 145.3, 143.6, 127.5, 125.5, 119.5, 109.8, 85.4, 56.2, 46.5, 45.3, 42.1, 35.4, 32.7, 32.1, 25.6 ppm; HRMS calcd. For $C_{17}H_{18}O_5Na^+$ [M + Na]$^+$ 325.1046, found 325.1047.

Diol 139

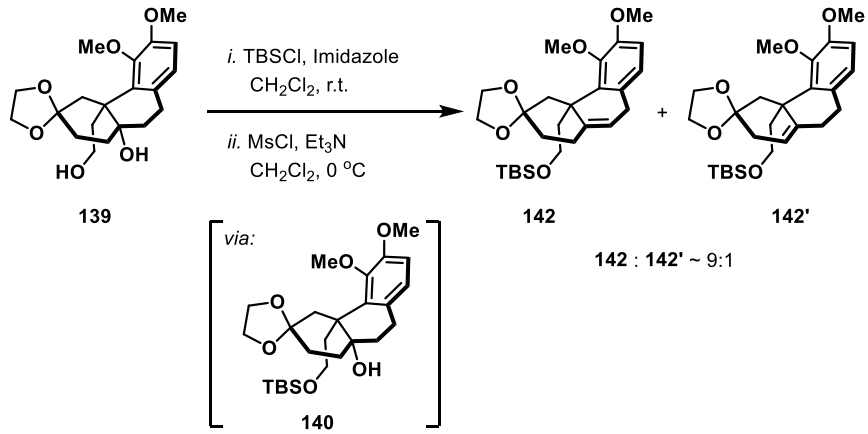


(i) To a stirred solution of ketone **137** (222 mg, 0.70 mmol) in CH_2Cl_2 (10.0 mL) at room temperature was added ethylene glycol (10 mL, 21.9 mmol) and TMSCl (0.41 mL, 3.23 mmol). The resulting mixture was stirred for 7 h before it was quenched with $NaHCO_3$ (30 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded dioxolane **138** (230 mg, 91%) as an amorphous yellow solid.

138: R_f = 0.41 (silica gel, hexanes:EtOAc 1:1).

(ii) To a stirred solution of lactone **138** (obtained above, 230 mg, 0.64 mmol) in THF (10.0 mL) at 0 °C was added $LiAlH_4$ (120 mg, 3.17 mmol). The resulting mixture was stirred for 1 h before it was warmed to room temperature and quenched with sodium potassium tartrate (5 mL, sat. aq.) and diluted with EtOAc (5 mL), and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded diol **139** (210 mg, 90%) as an amorphous yellow solid. **139:** R_f = 0.15 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3757, 3692, 3053, 2985, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.76 (s, 2H), 4.10 (br, 1H), 3.98–3.94 (m, 2H), 3.88–3.81 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.67 (br t, *J* = 9.4 Hz, 1H), 3.37 (br t, *J* = 9.4 Hz, 1H), 3.15–3.02 (m, 1H), 2.71–2.61 (m, 1H), 2.56–2.46 (m, 1H), 2.39–2.31 (m, 1H), 2.30 (d, *J* = 14.6 Hz, 1H), 2.19–1.96 (m, 3H), 1.84–1.72 (m, 2H), 1.71–1.61 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.5, 148.3, 135.0, 129.0, 124.2, 111.3, 108.8, 71.5, 64.2, 63.9, 60.2, 60.1, 55.9, 47.6, 42.9, 37.9, 34.9, 31.5, 31.2, 26.2 ppm; HRMS calcd. For $C_{20}H_{28}O_6Na^+$ $[M + Na]^+$ 387.1778, found 387.1779.

Alkene 142

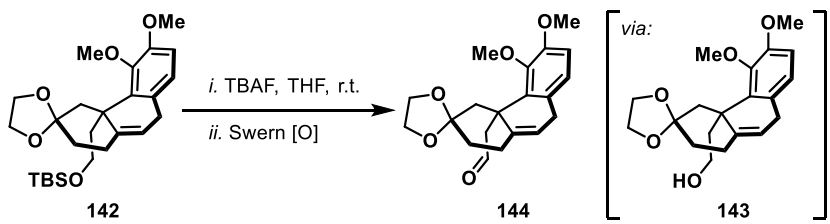


(i) To a stirred solution of diol **139** (900 mg, 2.47 mmol) in CH_2Cl_2 (30.0 mL) at room temperature was added TBSCl (558 mg, 3.70 mmol) and imidazole (252 mg, 3.70 mmol). The resulting mixture was stirred for 1 h before it was quenched with NH_4Cl (40 mL, sat. aq.) and water (40 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layer was washed with water (80 mL), brine (80 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded TBS ether **140** (981 mg, 83%) as an amorphous clear solid. **140:** R_f = 0.37 (silica gel, hexanes:EtOAc 3:1).

(ii) To a stirred solution of tertiary alcohol **140** (obtained above, 800 mg, 1.67 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added triethylamine (1.40 mL, 10.0 mmol) followed by methanesulfonyl chloride (0.39 mL, 5.02 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h before it was quenched with $NaHCO_3$ (45 mL, sat. aq.) and water (45 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 8:1) afforded an inseparable mixture of alkenes **141** and **141'** (**141**:**141'** ~9:1 based on ^{1}H NMR analysis, 513 mg, 67% combined yield) and recovered tertiary alcohol **141** (130 mg, 16%) as amorphous yellow solids. **141:** R_f = 0.67 (silica gel, hexanes:EtOAc 3:1); IR (film) ν_{max} 3053, 2985, 1601, 1422, 708 cm^{-1}; ^{1}H NMR (499 MHz,

$CDCl_3$, major isomer **141**): δ 6.79 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 5.67 (br s, 1H), 4.13–4.08 (m, 1H), 4.05–4.00 (m, 1H), 3.95–3.91 (m, 1H), 3.89–3.87 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.37–3.32 (m, 1H), 3.30 (br s, 2H), 3.11–3.04 (m, 2H), 2.73–2.62 (m, 2H), 2.36–2.30 (m, 1H), 2.20–2.16 (m, 1H), 1.89–1.84 (m, 1H), 1.64–1.58 (m, 2H), 0.77 (s, 9H), –0.11 ppm (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, major isomer **141**): 151.4, 148.0, 138.2, 134.4, 126.8, 123.0, 118.9, 111.5, 109.2, 64.5, 63.7, 61.2, 60.2, 56.0, 45.1, 42.2, 37.9, 36.5, 30.4, 30.1, 25.9, 18.2, –5.4 ppm; HRMS calcd. For $C_{26}H_{40}O_5SiNa^+$ [M + Na]$^+$ 483.2537, found 483.2538.

Aldehyde 144

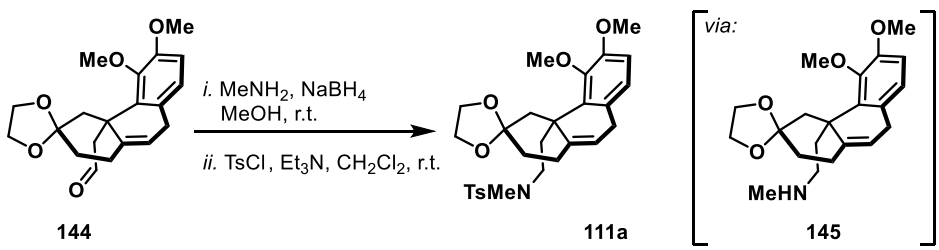


(i) To a stirred solution of TBS ether **142** (515 mg, 1.18 mmol) in THF (20.0 mL) at room temperature was added TBAF (1.0 M in THF, 2.24 mL, 2.24 mmol). The resulting mixture was stirred for 12 h before it was quenched with NH_4Cl (30 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alcohol **143** (374 mg, 97%) as an amorphous solid. **143:** R_f = 0.15 (silica gel, hexanes:EtOAc 2:1)

(ii) To a stirred solution of oxalyl chloride (0.92 mL, 10.7 mmol) in CH_2Cl_2 (15.0 mL) at –78 ℃ was added DMSO (1.52 mL, 21.4 mmol). The resulting mixture was stirred for 15 min before a solution of alcohol **143** (370 mg, 1.07 mmol) in CH_2Cl_2 (8.0 mL) was added. The resulting mixture was stirred for 2 h before Et_3N (4.47 mL, 32.1 mmol) was added, and the resulting mixture was warmed to room temperature and stirred for 2h before it was quenched

with NH_4Cl (20 mL, sat. aq.) and water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded aldehyde **144** (340 mg, 92%) as an amorphous yellow solid. **144:** R_f = 0.65 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3053, 2986, 1715, 1601, 1422, 744 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 9.24 (t, *J* = 3.0 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.77 (s, 1H), 4.09–4.04 (m, 1H), 4.02–3.99 (m, 1H), 3.95–3.88 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.42–3.35 (m, 3H), 3.16 (d, *J* = 16.9 Hz, 1H), 2.98 (d, *J* = 14.0 Hz, 1H), 2.63 (t, *J* = 14.0 Hz, 1H), 2.27–2.23 (m, 1H), 1.90–1.86 (m, 1H), 1.65 (d, *J* = 13.9 Hz, 1H), 1.62 ppm (td, *J* = 13.5, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): 204.1, 151.4, 147.5, 137.1, 132.6, 126.1, 123.4, 120.2, 112.0, 108.7, 64.5, 63.8, 60.2, 55.8, 49.0, 44.9, 40.7, 36.2, 30.0, 29.8 ppm; HRMS calcd. For $C_{20}H_{24}O_5Na^+$ $[M + Na]^+$ 367.1516, found 367.1516.

Tosyl amide 111a



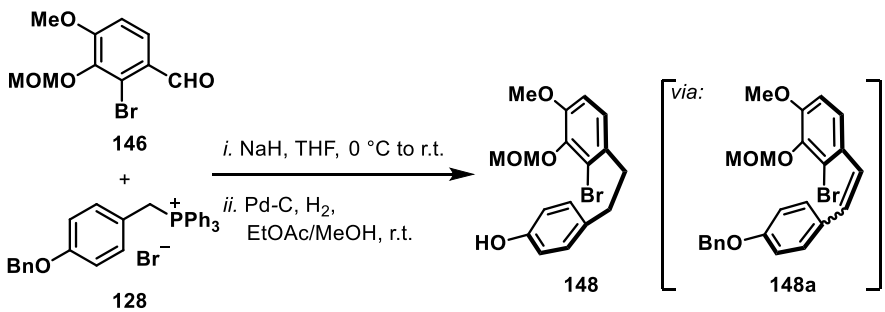
(i) To a stirred solution of aldehyde **144** (80.0 mg, 0.23 mmol) in methanol (10.0 mL) at room temperature was added methylamine (40 wt % in H_2O 0.40 mL, 4.80 mmol). The resulting mixture was stirred for 1 h before it was cooled to 0 °C and sodium borohydride (87.8 mg, 2.32 mmol) was added. The resulting mixture was stirred for 1 h before it was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure afforded amine **145** as an

amorphous yellow solid, which was used directly in the subsequent step without further purification.

(ii) To a stirred solution of crude amine **145** (obtained above) in CH_2Cl_2 (2.5 mL) at room temperature was added TsCl (35.7 mg, 0.19 mmol) and Et_3N (50 μL, 0.36 mmol). The resulting mixture was stirred for 4 h before it was quenched with H_2O (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded tosyl amide **111a** (47 mg, 66% over two steps) as an amorphous yellow solid. **111a**: R_f = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3500, 2950, 1530, 1340, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 1H), 4.16–4.12 (m, 1H), 3.97 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.88 (dd, *J* = 13.0, 6.4 Hz, 1H), 3.85–3.74 (m, 1H), 3.83 (s, 3H), 3.32 (td, *J* = 13.0, 4.7 Hz, 1H), 2.90 (dd, *J* = 17.8, 8.2 Hz, 1H), 2.80 (td, *J* = 12.8, 4.6 Hz, 1H), 2.70–2.58 (m, 1H), 2.66 (s, 3H), 2.39 (s, 3H), 2.30–2.10 (m, 2H), 1.93 (td, *J* = 13.1, 4.2 Hz, 1H), 1.81 (td, *J* = 12.7, 4.6 Hz, 1H), 1.77–1.68 (m, 1H), 1.68–1.58 (m, 1H), 1.54–1.47 (m, 1H), 1.47–1.36 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.7, 143.1, 141.9, 134.8, 130.3, 129.6, 127.3, 124.7, 120.2, 114.2, 108.0, 92.2, 72.8, 66.1, 65.0, 56.6, 50.7, 47.3, 35.5, 35.3, 33.6, 31.8, 27.4, 24.5, 21.5 ppm; HRMS calcd. For $C_{27}H_{33}NO_7SNa^+$ $[M + Na]^+$ 538.1870, found 538.1872.

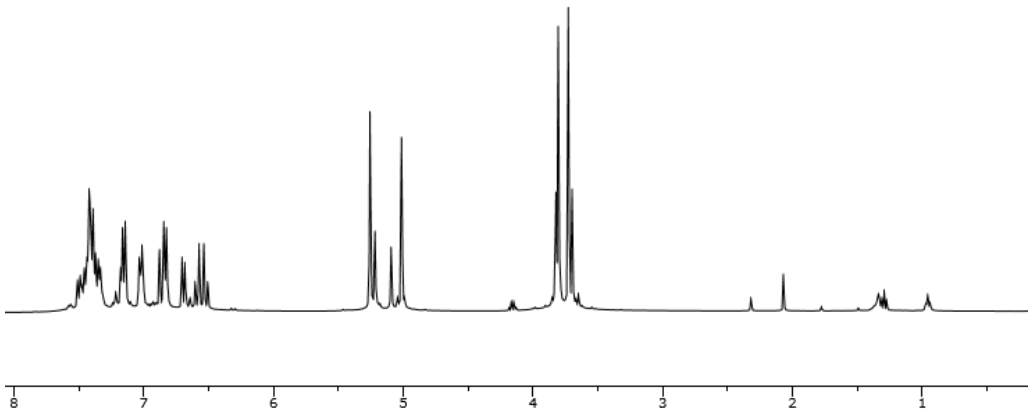
Section 1.2

Biaryl Phenol 148



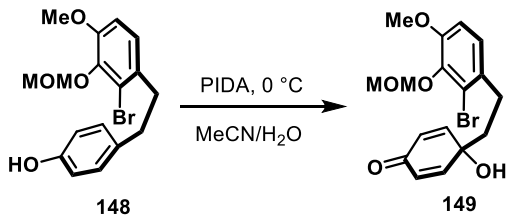
(i) To a stirred solution of phosphonium salt **128** (dried over P_2O_5 under vacuum overnight, 19.8 g, 36.7 mmol) in THF (350 mL) at 0 ℃ was added NaH (3.06 g, 128 mmol). The resulting mixture was stirred for 2 h before a solution of benzaldehyde **146** (8.77 g, 31.9 mmol) in THF (50 mL) was added. The resulting mixture was warmed to room temperature and stirred for 4 h before it was cooled to 0 ℃ and quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded an inconsequential geometric mixture of stilbene **148a** (12.3 g, 85%) as an amorphous yellow solid. **148a**: R_f = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).

148a: ^{1}H NMR (400 MHz, $CDCl_3$)



(ii) To a stirred solution of stilbene **148a** (14.5 g, 31.8 mmol) in EtOAc/MeOH (4:1, 320 mL) at room temperature was added Pd/C (10% wt/wt, 1.70 g, 1.60 mmol). The resulting mixtu re was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H_2 (balloon) for 1 h. The resulting mixture was filtered through Celite® and eluted with EtOAc (3 × 80 mL), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl phenol **148** (8.19 g, 70%) as an amorphous white solid. **148**: R_f = 0.27 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3690, 3054, 2987, 1421, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.04 (d, *J* = 7.2 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 7.3 Hz, 2H), 5.17 (s, 2H), 4.73 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 2.95–2.91 (m, 2H), 2.81–2.77 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7, 151.4, 143.3, 134.2, 133.8, 129.6, 125.2, 120.1, 115.1, 111.2, 98.6, 58.0, 56.1, 38.4, 35.4 ppm; HRMS calcd. For $C_{17}H_{19}BrO_4$ Na^+ $[M + Na]^+$ 389.0359, found 389.0361.

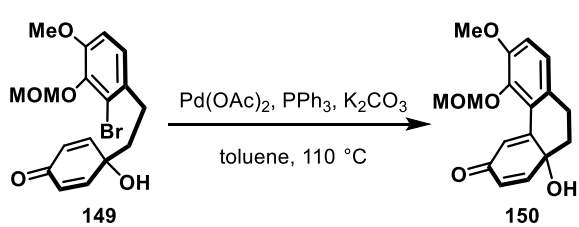
Dienone 149



148 149

To a stirred solution of phenol **148** (6.30 g, 17.2 mmol) in MeCN/H_2O (1:1, 170 mL) at 0 ℃ was added PIDA (6.63 g, 20.6 mmol). The resulting mixture was stirred for 2 h before it was warmed to room temperature and quenched with $Na_2S_2O_3$ (50 mL, sat. aq.) and water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL), the combined organic layer was washed with $NaHCO_3$ (100 mL, sat. aq.), bri ne (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded dienone **149** (4.34 g, 66%) as an orange amorphous solid. **149**: R_f = 0.30 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3583, 3153, 2985, 1671, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, *J* = 10.4 Hz, 3H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.24 (d, *J* = 10.3 Hz, 2H), 5.13 (s, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 2.69–2.65 (m, 2H), 2.08 (br s, 1H), 2.04–1.99 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 185.4, 151.7, 150.5, 143.5, 133.2, 128.7, 124.9, 120.1, 111.4, 98.6, 69.8, 58.1, 56.1, 56.1, 40.0, 30.4 ppm; HRMS calcd. For $C_{17}H_{19}BrO_5$ Na^+ $[M + Na]^+$ 405.0308, found 405.0312.

Tricyclic Dienone 150

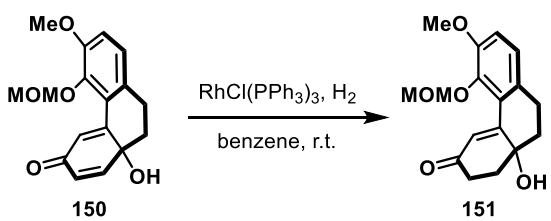


149 150

To a stirred solution of dienone **149** (2.80 g, 7.30 mmol) in toluene (80.0 mL) at room temperature was added K_2CO_3 (3.03 g, 21.9 mmol), $Pd(OAc)_2$ (0.26 g, 1.16 mmol) and PPh_3

(0.61 g, 2.32 mmol). The resulting mixture was warmed to 110 °C and stirred for 24 h before it was cooled to room temperature and diluted with water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic dienone **150** (1.77 g, 80%) as an amorphous yellow solid. **150**: R_f = 0.32 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3585, 3154, 2940, 1660, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.90 (s, 1H), 6.87 (d, *J* = 11.0 Hz, 1H), 6.24 (d, *J* = 10.0 Hz, 1H), 4.96 (s, 2H), 3.84 (s, 3H), 3.38 (s, 3H), 3.21–3.12 (m, 1H), 2.90 (dd, *J* = 17.1, 7.6 Hz, 1H), 2.49 (s, 1H), 2.28 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.83–1.79 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.3, 153.0, 151.1, 150.8, 145.2, 130.3, 127.6, 127.4, 126.7, 124.3, 113.9, 99.6, 66.9, 57.9, 56.1, 34.3, 24.2 ppm; HRMS calcd. For $C_{17}H_{18}O_5Na^+$ $[M + Na]^+$ 325.1046, found 325.1047.

Tricyclic Enone 151

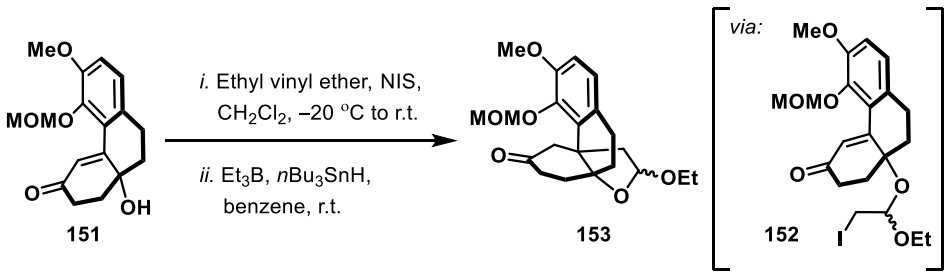


150 151

To a stirred solution of tricyclic dienone **150** in benzene (1.77 g, 5.85 mmol) at room temperature was added $RhCl(PPh_3)_3$ (0.27 g, 0.29 mmol). The resulting mixture was evacuated and filled with argon (3 ×) followed by hydrogen (3 ×), and stirred under an atmosphere of H_2 (balloon) for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic enone **151** (1.39 g, 78%) as an amorphous brown solid. **151**: R_f = 0.31 (silica gel, hexane:EtOAc 1:1); IR (film) ν_{max} 3586, 3054, 2830, 1713, 1662, 714 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 6.94 (d, *J* = 8.0

Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.70 (s, 1H), 4.98 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.43 (s, 3H), 2.90–2.84 (m, 2H), 2.62–2.58 (m, 1H), 2.48–2.44 (m, 1H), 2.44 (s, 1H), 2.23–2.15 (m, 2H), 2.15–2.10 (m, 1H), 1.94–1.90 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.1, 152.5, 151.1, 145.6, 132.7, 128.2, 127.8, 123.5, 113.8, 99.5, 68.8, 58.0, 56.1, 38.0, 35.8, 33.6, 26.1 ppm; HRMS calcd. For $C_{17}H_{20}O_5Na^+$ $[M + Na]^+$ 327.1203, found 327.1204.

Tetracycle 153

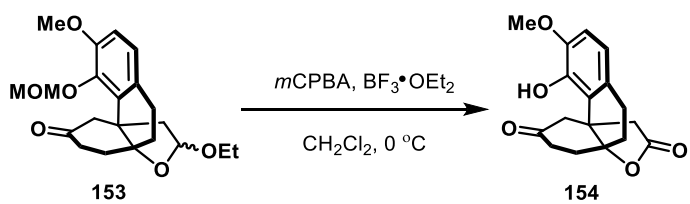


(i) To a stirred solution of hydroxy enone **151** (1.5 g, 4.93 mmol) in CH_2Cl_2 (50 mL) at –20 °C was added ethyl vinyl ether (1.89 mL, 19.7 mmol) followed by NIS (3.32 g, 14.8 mmol). The resulting mixture was stirred for 1 h before additional ethyl vinyl ether (1.89 mL, 19.7 mmol) and NIS (3.32 g, 14.8 mmol) were added. The resulting mixture was warmed to room temperature and stirred for 12 h before it was quenched with $Na_2S_2O_3$ (80 mL, sat. aq.) and water (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2→CH_2Cl_2:Et_2O 1:0→8:1) afforded iodide **152** (mixture of diastereoisomers, as an amorphous yellow solid. **152**: R_f = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).

(ii) To a stirred solution of iodide **152** in benzene (300 mL) at room temperature was added *n*Bu_3SnH (1.77 mL, 6.58 mmol), Et_3B (1.0 M in hexane, 6.58 mL, 6.58 mmol) and small amount of air (*via* an empty syringe filled with air). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica

gel, hexanes:EtOAc 5:1) afforded tetracycle **153** (mixture of diastereoisomers, 1.15 g, 62% over two steps) as an amorphous yellow solid. **153**: R_f = 0.39, 0.43 (silica gel, hexanes:EtOAc 3:1); IR (film) ν_{max} 3050, 2987, 1714, 1550, 715 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$, mixture of isomers): δ 6.81–6.74 (m, 2H), 5.23 (d, *J* = 4.5 Hz, 1H), 5.13 (d, *J* = 5.0 Hz, 0.4H), 5.10 (d, *J* = 4.5 Hz, 0.3H), 5.09 (d, *J* = 4.5 Hz, 0.3H), 5.03 (d, *J* = 4.8 Hz, 1H), 3.80 (s, 3H), 3.77–3.71 (m, 1H), 3.63 (s, 2.2H), 3.63 (s, 0.8H), 3.54 (d, *J* = 16.1 Hz, 0.4H), 3.44–3.36 (m, 1H), 3.19 (d, *J* = 13.8 Hz, 0.6H), 2.93 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.83 (td, *J* = 14.7, 4.4 Hz, 1H), 2.76 (td, *J* = 14.5, 4.7 Hz, 1H), 2.70–2.61 (m, 1H), 2.57 (d, *J* = 13.8 Hz, 1H), 2.54–2.46 (m, 0.4H), 2.47 (d, *J* = 16.3 Hz, 0.6H), 2.39–2.30 (m, 1H), 2.30–2.22 (m, 1H), 2.22–2.12 (m, 1H), 2.05–1.96 (m, 1H), 1.96–1.87 (m, 1H), 1.18 (t, *J* = 7.0 Hz, 1.2H), 1.13 ppm (t, *J* = 7.0 Hz, 1.8H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of isomers): δ 213.2, 211.4, 150.6, 145.0, 144.8, 136.5, 136.0, 128.2, 127.9, 123.8, 123.6, 111.2, 111.1, 103.2, 102.7, 99.0, 99.0, 83.4, 63.3, 63.1, 57.8, 57.7, 55.9, 50.5, 50.3, 49.4, 48.6, 47.7, 46.3, 35.3, 35.0, 34.0, 33.5, 32.2, 30.1, 27.7, 26.7, 15.2, 15.0 ppm; HRMS calcd. For $C_{21}H_{28}O_6Na^+$ $[M + Na]^+$ 399.1778, found 399.1778.

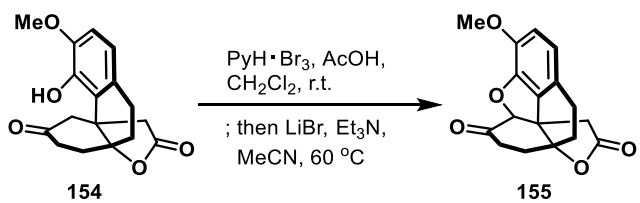
Phenolic Lactone 154



To a stirred solution of tetracyclic acetal **153** (2.50 g, 6.64 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added *m*CPBA (70%~75%, 2.98 g, 12.1 mmol) and boron trifluoride diethyl etherate complex (1.64 mL, 13.3 mmol). The resulting mixture was stirred for 15 min before it was quenched with $Na_2S_2O_3$ (30 mL, sat. aq.) and water (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was washed with $NaHCO_3$ (100 mL, sat. aq.), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1)

afforded phenolic lactone **154** (1.51 mg, 75%) as an amorphous yellow solid. **154**: R_f = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3095, 2831, 1776, 1719, 767 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.99 (s, 1H), 3.87 (s, 3H), 3.32 (d, *J* = 15.0 Hz, 1H), 3.11 (d, *J* = 19.7 Hz, 1H), 3.06 (d, *J* = 19.7 Hz, 1H), 2.95–2.88 (m, 1H), 2.86–2.80 (m, 1H), 2.78 (d, *J* = 15.8 Hz, 1H), 2.55–2.46 (m, 1H), 2.45–2.23 (m, 4H), 2.11–2.04 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.8, 175.0, 145.4, 143.6, 127.5, 125.5, 119.6, 109.8, 85.4, 56.2, 46.5, 45.3, 42.1, 35.4, 32.7, 32.1, 25.6 ppm; HRMS calcd. For $C_{17}H_{18}O_5Na^+$ $[M + Na]^+$ 325.1046, found 325.1047.

Pentacycle 155

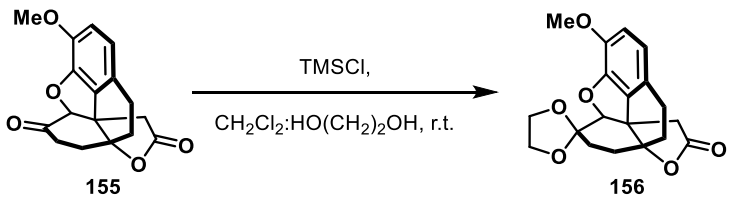


To a stirred solution of phenolic ketone **154** (95.0 mg, 0.31 mmol) in CH_2Cl_2 (3.0 mL) at room temperature was added a solution of pyridinium tribromide (111 mg, 0.35 mmol) in acetic acid (10.2 mL) dropwise. The resulting mixture was stirred for 30 min before it was diluted with toluene and concentrated under reduced pressure. The resulting residue was redissolved in CH_2Cl_2 (5.0 mL) and water (5.0 mL), extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude residue, which was used directly in the subsequent step without further purification.

To a stirred solution of crude residue (obtained above) in MeCN (5.0 mL) at room temperature was added LiBr (164 mg, 1.89 mmol) and Et_3N (70 μL, 0.50 mmol). The resulting mixture was warmed to 60 °C and stirred for 10 min before it was cooled to room temperature and quenched with NH_4Cl (5 mL, sat. aq.) and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under

reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded pentacycle **155** (60 mg, 64% over two steps) as an amorphous yellow solid. **155**: R_f = 0.30 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3111, 2985, 1790, 1604, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.93 (s, 1H), 3.90 (s, 3H), 3.18 (d, *J* = 18.8 Hz, 1H), 2.95 (dt, *J* = 16.8, 5.6 Hz, 1H), 2.89 (d, *J* = 19.0 Hz, 1H), 2.80 (td, *J* = 13.4, 4.5 Hz, 1H), 2.69–2.57 (m, 1H), 2.51 (dt, *J* = 14.8, 4.2 Hz, 1H), 2.30 (dt, *J* = 14.5, 4.1 Hz, 1H), 2.25–2.15 (m, 1H), 2.10–2.02 (m, 1H), 1.98 ppm (td, *J* = 13.5, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4, 174.0, 146.5, 143.2, 125.5, 124.5, 121.3, 115.5, 91.8, 84.9, 56.7, 54.3, 43.6, 33.8, 33.3, 31.5, 24.3 ppm; HRMS calcd. For $C_{17}H_{16}O_5Na^+$ [M + Na]$^+$ 323.0890, found 323.0893.

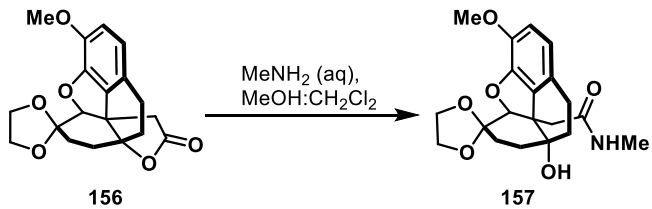
Dioxolane 156



To a stirred solution of pentacyclic ketone **155** (60.0 mg, 0.20 mmol) in CH_2Cl_2/ethylene glycol (1:1, 2.0 mL) at room temperature was added TMSCl (0.12 mL, 0.95 mmol). The resulting mixture was stirred for 7 h before it was quenched with $NaHCO_3$ (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded dioxolane **156** (52.0 mg, 76%) as an amorphous yellow solid. **156**: R_f = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 2950, 1770, 1500, 1450, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 4.61 (s, 1H), 4.21–4.19 (m, 1H), 3.87–3.82 (m, 2H), 3.87 (s, 3H), 3.80–3.73 (m, 1H), 2.96 (d, *J* = 18.6 Hz, 1H), 2.94–2.85 (m, 1H), 2.76 (d, *J* = 18.6 Hz, 1H), 2.73–2.62 (m, 1H), 2.25–1.99 (m, 3H), 1.94–1.74 (m, 2H), 1.62–1.46 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6,

147.5, 142.5, 127.6, 124.7, 120.2, 114.7, 106.8, 94.6, 85.7, 66.7, 65.2, 56.7, 50.6, 44.8, 34.4, 28.5, 27.9, 24.7 ppm; HRMS calcd. For $C_{19}H_{20}O_6Na^+$ $[M + Na]^+$ 367.1152, found 367.1154.

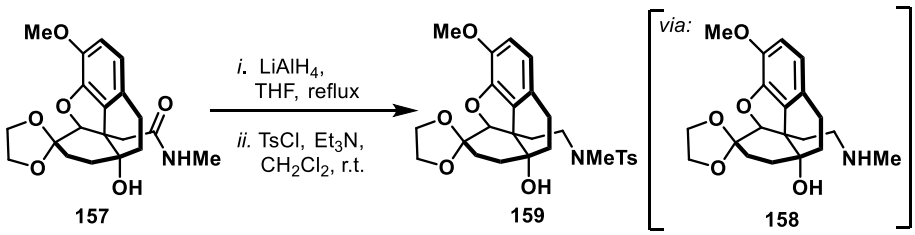
Amide 157



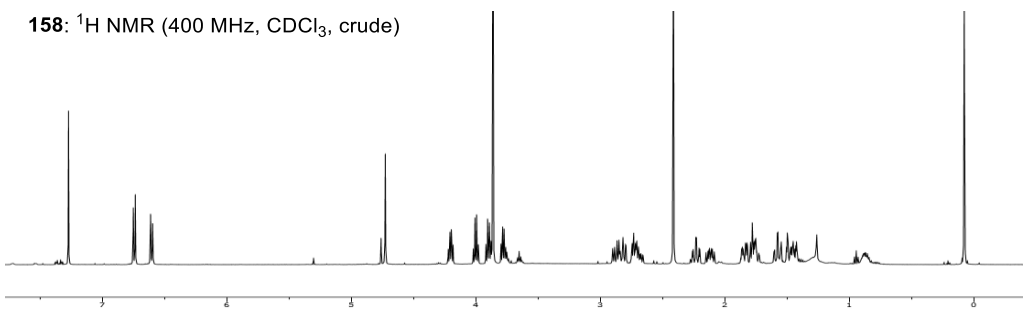
156 **157**

To a stirred solution of lactone **156** (80.0 mg, 0.23 mmol) in $MeOH/CH_2Cl_2$ (6:1, 3.5 mL) at room temperature was added $MeNH_2$ (40% aq., 0.23 mL, 2.7 mmol). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 1:1) afforded amide **157** (75.0 mg, 86%) as a white amorphous solid. **157**: R_f = 0.13 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3250, 2930, 1640, 1510, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 5.68 (br s, 1H), 4.75 (s, 1H), 4.15–4.12 (m, 1H), 3.90–3.81 (m, 2H), 3.86 (s, 3H), 3.75–3.72 (m, 1H), 2.97 (d, *J* = 15.7 Hz, 1H), 2.89–2.78 (m, 4H), 2.64–2.62 (m, 1H), 2.30 (d, *J* = 15.6 Hz, 1H), 2.13–2.06 (m, 2H), 1.87 (dd, *J* = 14.5, 7.1 Hz, 1H), 1.56–1.53 (m, 2H), 1.43 ppm (dt, *J* = 17.4, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 146.1, 142.3, 132.2, 124.7, 119.9, 113.6, 108.5, 93.0, 71.1, 66.3, 64.8, 56.3, 51.1, 44.2, 33.8, 30.6, 28.2, 26.7, 24.9 ppm; HRMS calcd. For $C_{20}H_{25}NO_6Na^+$ $[M + Na]^+$ 398.1574, found 398.1577.

Tosyl Amide 159



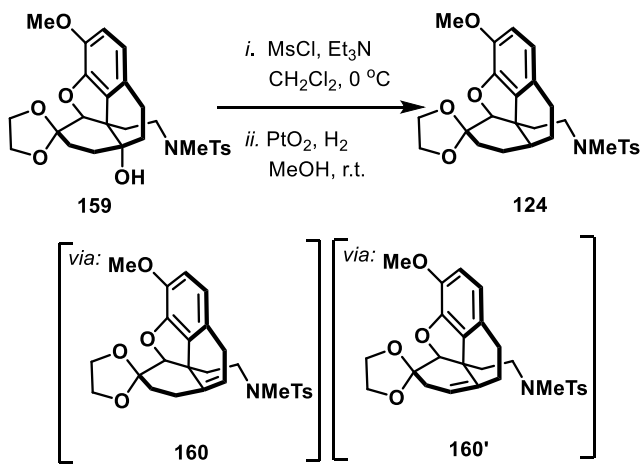
(i) To a stirred solution of amide **157** (52.0 mg, 0.14 mmol) in THF (1.5 mL) at 0 °C was added $LiAlH_4$ (52.6 mg, 1.39 mmol). The resulting mixture was warmed to reflux and stirred for 12 h before it was cooled to 0 °C and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure afforded crude amine **158**, which was used directly in the subsequent step without further purification.



(ii) To a stirred solution of crude amine **158** (obtained above) in CH_2Cl_2 (2.5 mL) at room temperature was added TsCl (35.7 mg, 0.19 mmol) and Et_3N (50 μL, 0.36 mmol). The resulting mixture was stirred for 4 h before it was quenched with H_2O (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded tosyl amide **159** (47 mg, 66% over two steps) as an amorphous yellow solid. **159**: R_f = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3500, 2950, 1530, 1340, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.7

Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 1H), 4.16–4.12 (m, 1H), 3.97 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.88 (dd, *J* = 13.0, 6.4 Hz, 1H), 3.85–3.74 (m, 1H), 3.83 (s, 3H), 3.32 (td, *J* = 13.0, 4.7 Hz, 1H), 2.90 (dd, *J* = 17.8, 8.2 Hz, 1H), 2.80 (td, *J* = 12.8, 4.6 Hz, 1H), 2.70–2.58 (m, 1H), 2.66 (s, 3H), 2.39 (s, 3H), 2.30–2.10 (m, 2H), 1.93 (td, *J* = 13.1, 4.2 Hz, 1H), 1.81 (td, *J* = 12.7, 4.6 Hz, 1H), 1.77–1.68 (m, 1H), 1.68–1.58 (m, 1H), 1.54–1.47 (m, 1H), 1.47–1.36 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.7, 143.1, 141.9, 134.8, 130.3, 129.6, 127.3, 124.7, 120.2, 114.2, 108.0, 92.2, 72.8, 66.1, 65.0, 56.6, 50.7, 47.3, 35.5, 35.3, 33.6, 31.8, 27.4, 24.5, 21.5 ppm; HRMS calcd. For $C_{27}H_{33}NO_7SNa^+$ $[M + Na]^+$ 538.1870, found 538.1872.

Tosyl Amide 124



(i) To a stirred solution of tertiary alcohol **159** (80 mg, 0.16 mmol) in CH_2Cl_2 (5.0 mL) at 0 ℃ was added triethylamine (0.21 mL, 1.6 mmol) followed by methanesulfonyl chloride (0.12 mL, 1.6 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h before it was quenched with $NaHCO_3$ (5 mL, sat. aq.) and water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel,

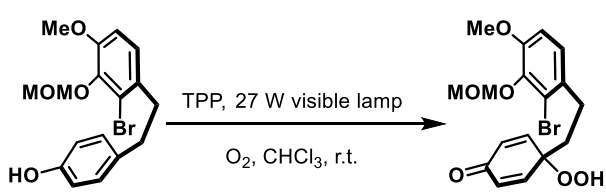
hexanes:EtOAc 8:1) afforded an inseparable mixture of alkenes **160** and **160'** (**160**:**160'** ~5:1 based on ^{1}H NMR analysis, 64.7 mg, 84% combined yield).

(ii) To a stirred solution of alkenes **160**/**160'** (61.7 mg, 0.12 mmol) in MeOH (5.0 mL) at room temperature was added PtO_2 (15.0 mg, 66 μmol). The resulting mixture was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H_2 (balloon) for 24 h. The resulting mixture was filtered through Celite® and eluted with EtOAc (3 × 10 mL), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded intermediate **124** (58.9 mg, 95%) as an amorphous white solid.

124: R_f = 0.27 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3690, 3054, 2987, 1421, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.04 (d, *J* = 7.2 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 7.3 Hz, 2H), 5.16 (s, 2H), 4.73 (s, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.95–2.90 (m, 2H), 2.80–2.76 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7, 151.4, 143.3, 134.2, 133.8, 129.6, 125.2, 120.2, 115.1, 111.2, 98.7, 58.1, 56.1, 38.4, 35.5 ppm; HRMS calcd. For $C_{17}H_{19}BrO_4$ Na^+ $[M + Na]^+$ 389.0359, found 389.0361.

Section 1.3

Peroxyquinol 168

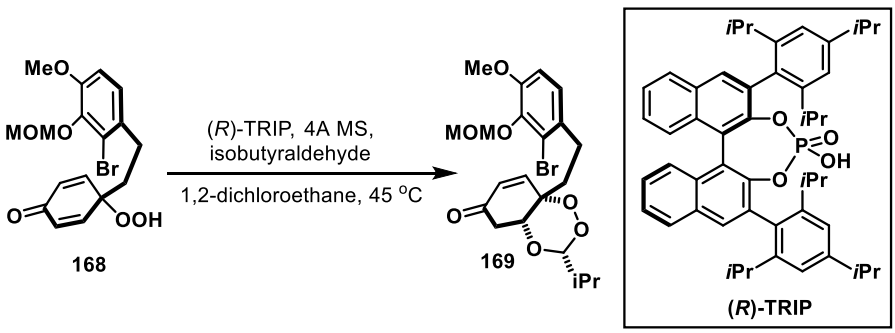


148 **168**

To a stirred solution of biaryl phenol **148** (565 mg, 1.54 mmol) in $CHCl_3$ (30.0 mL) at room temperature was added TPP (47.6 mg, 77 μmol). The resulting mixture was exposed to 27W household lamp and stirred for 5 d under an atmosphere of oxygen (balloon) before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded peroxyquinol **168** (284 mg, 46%) as an yellow amorphous solid.

168: R_f = 0.25 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 2950, 1680, 1490, 1270, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 6.94 (d, *J* = 10.2 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 10.2 Hz, 2H), 5.13 (s, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 2.67–2.63 (m, 2H), 1.98–1.93 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.3, 151.8, 148.1, 143.5, 132.8, 131.6, 125.0, 120.0, 111.4, 98.6, 81.3, 58.1, 56.1, 36.1, 30.2 ppm; HRMS calcd. For $C_{17}H_{19}BrO_6$ Na^+ $[M + Na]^+$ 421.0257, found 421.0260.

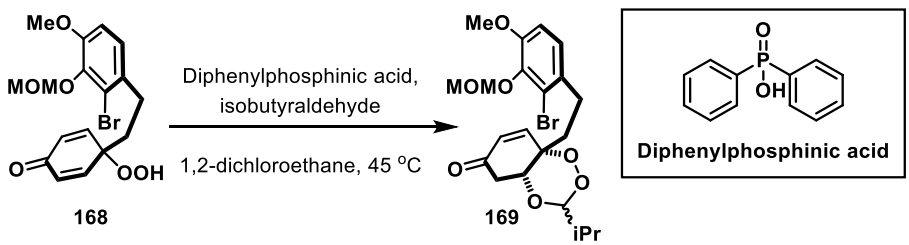
1,2,4-Trioxane 169 (absolute stereochemistry arbitrarily shown)



To a stirred solution of peroxyquinol **168** (90 mg, 0.23 mmol) in 1,2-dichloroethane (1.1 mL) at room temperature was added (*R*)-TRIP (8.5 mg, 11 μmol), isobutyraldehyde (26 μL, 0.28 mmol) and 4Å MS (30.0 mg). The resulting mixture was warmed to 45 °C and stirred for 21 h before it was cooled to room temperature and diluted with water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layer was washed with water (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded 1,2,4-trioxane **169** (70 mg, 66%) as an amorphous yellow solid. **169**: R_f = 0.67 (silica gel, hexanes:EtOAc 2:1); $[\alpha]_D^{25}$ = –116 (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2980, 1685, 1485, 1265, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.12 (d, *J* = 10.5 Hz, 1H), 5.13 (s, 2H), 5.03 (d, *J* = 5.2 Hz, 1H), 4.26 (s, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.91 (td, *J* = 12.8, 4.9 Hz, 1H), 2.76 (td, *J* = 12.8, 4.9 Hz, 1H), 2.75–2.70 (m, 2H), 2.00 (td, *J* = 12.8, 4.9 Hz, 1H), 1.89 (td, *J* = 12.8, 4.9 Hz,

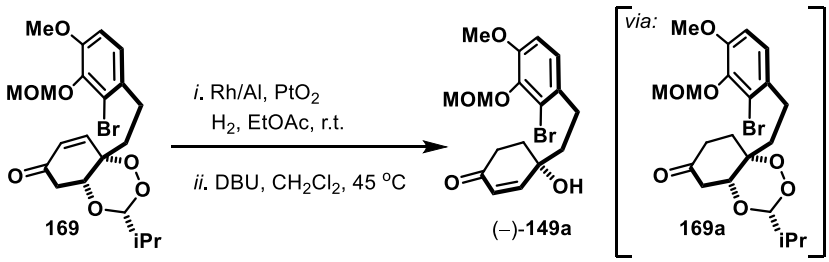
1H), 1.83–1.75 (m, 1H), 0.89 ppm (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.2, 151.8, 150.2, 143.6, 133.1, 130.0, 125.0, 119.9, 111.5, 107.1, 98.6, 79.6, 75.0, 58.1, 56.1, 40.8, 36.0, 30.9, 29.4, 16.7, 16.7 ppm; HRMS calcd. For $C_{21}H_{27}BrO_7Na^+$ $[M + Na]^+$ 493.0832, found 493.0835.

1,2,4-Trioxane 169 (Racemic)



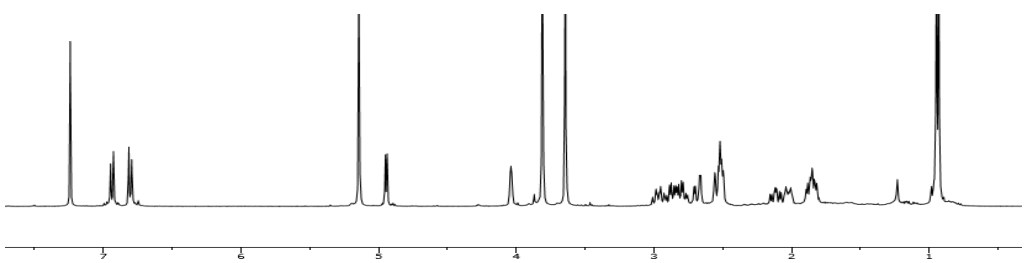
To a stirred solution of peroxyquinol **168** (24 mg, 60 μmol) in 1,2-dichloroethane (1.0 mL) at room temperature was added diphenylphosphinic acid (3.9 mg, 18 μmol) and isobutyraldehyde (11 μL, 0.12 mmol). The resulting mixture was warmed to 45 °C and stirred for 21 h before it was cooled to room temperature and diluted with water (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded 1,2,4-trioxane **169** as an amorphous yellow solid.

Enone 149a (absolute stereochemistry arbitrarily shown)



(i) To a stirred solution of 1,2,4-trioxane **169** (37.0 mg, 78 μmol) in EtOAc (3.0 mL) at room temperature was added Rh/Al (5.0 mg) and PtO_2 (5.0 mg, 22 μmol). The resulting mixture was evacuated and filled with argon (3 ×) followed by hydrogen (3 ×), and stirred under an atmosphere of H_2 (balloon) for 3 h before it was filtered through Celite® and eluted with EtOAc (3 × 5 mL). The resulting filtrate was concentrated under reduced pressure to afford ketone **169a** as an amorphous yellow solid, which was used directly in the subsequent step without further purification.

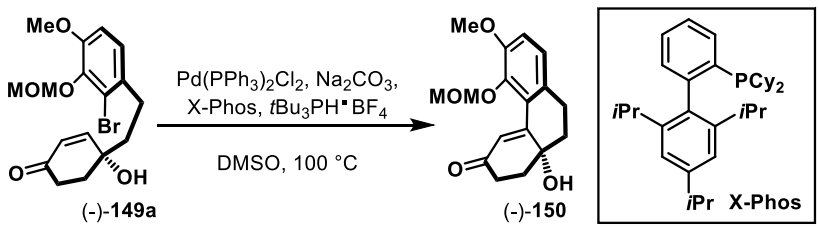
169a: ^{1}H NMR (400 MHz, $CDCl_3$, crude)



(ii) To a stirred solution of crude residue (obtained above) in CH_2Cl_2 (3.0 mL) at room temperature was added DBU (30 μL, 0.20 mmol). The resulting mixture was warmed to 45 °C and stirred for 4 h before it was cooled to room temperature and diluted with water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded enone **(-)-149a** (13.0 mg, 43% over two steps) as an amorphous

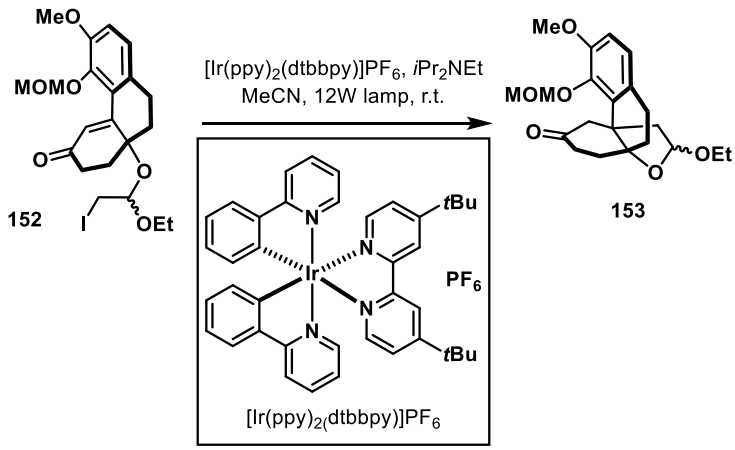
yellow solid. **149a**: R_f = 0.35 (silica gel, hexanes:EtOAc 1:1); $[\alpha]_D^{24}$ = –39 (*c* = 0.1, $CHCl_3$); IR (film) ν_{max} 2850, 1680, 1490, 1270, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (d, *J* = 8.3 Hz, 1H), 6.81 (t, *J* = 8.3 Hz, 2H), 5.93 (d, *J* = 10.1 Hz, 1H), 5.14 (s, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 2.93–2.79 (m, 2H), 2.68–2.61 (m, 1H), 2.51–2.43 (m, 1H), 2.29–2.24 (m, 1H), 2.15–2.08 (m, 1H), 1.96–1.87 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 153.5, 151.6, 143.5, 133.8, 128.7, 124.9, 120.0, 111.5, 98.6, 70.3, 58.1, 56.1, 40.2, 34.9, 34.5, 30.2 ppm; HRMS calcd. For $C_{17}H_{21}BrO_5Na^+$ $[M + Na]^+$ 407.0465, found 407.0469.

Hydroxy Enone 150



To a stirred solution of hydroxy enone **(-)-149a** (12.0 mg, 31 μmol) in DMSO (0.8 mL) at room temperature was added Na_2CO_3 (9.9 mg, 93 μmol) and X-Phos (5.9 mg, 12 μmol). The resulting mixture was stirred for 15 min before the addition of *t*$Bu_3PH•BF_4$ (7.2 mg, 25 μmol) and $Pd(PPh_3)_2Cl_2$ (4.4 mg, 6.3 μmol). The resulting mixture was warmed to 100 °C and stirred for 40 h before it was cooled to room temperature and diluted with water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 3 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic enone **(-)-150** (6.5 mg, 69%) as an amorphous yellow solid. All physical characteristics of hydroxy enone **(-)-150** are identical to those obtained from $RhCl(PPh_3)_3$ catalyzed hydrogenation of hydroxy dienone **150**. $[\alpha]_D^{25}$ = –109 (*c* = 0.1, $CHCl_3$).

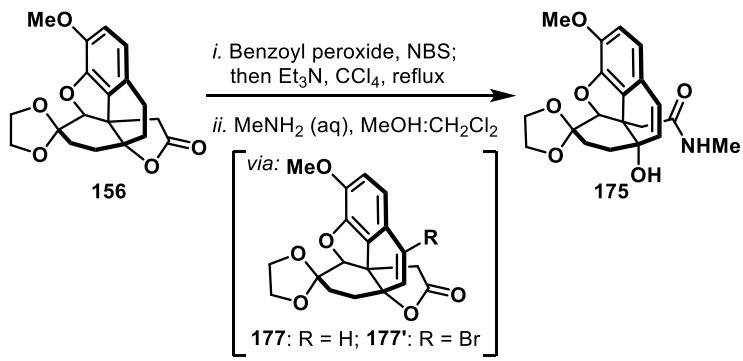
Tetracycle 153



Photoredox Condition:

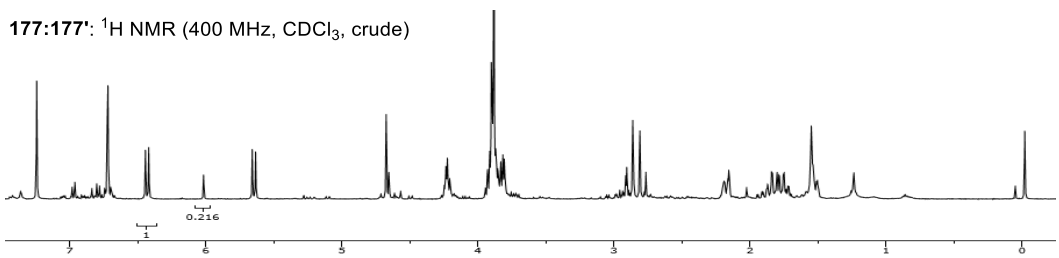
To a stirred solution of iodide **152** (40 mg, 80 μmol) in acetonitrile (4.0 mL) at room temperature was added $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 μmol) and *i*Pr_2NEt (0.14 mL, 0.8 mmol). The resulting mixture was exposed to 12W household lamp and stirred for 36 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 5:1) afforded tetracycle **153** (mixture of diastereoisomers, 17.1 mg, 57%) as an amorphous yellow solid. All physical data of tetracycle **153** are identical to those obtained from the *n*Bu_3SnH/Et_3B mediated cyclization of iodide **153**.

Styrene Amide 175



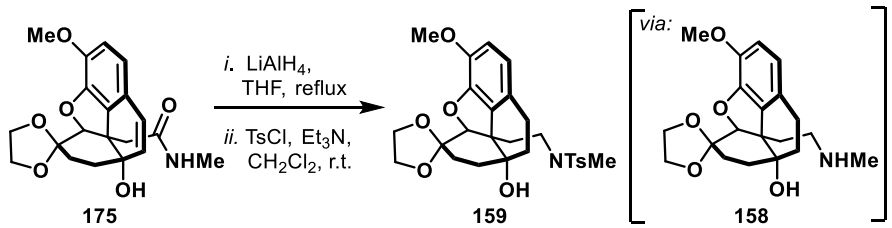
(i) To a stirred solution of dioxolane **156** (220 mg, 0.64 mmol) in carbon tetrachloride (freshly distilled, 91 mL) at room temperature was added benzoyl peroxide (freshly recrystallized, 15

mg, 62 μmol) and *N*-bromosuccinimide (123 mg, 0.69 mmol). The resulting mixture was warmed to reflux and stirred for 45 min before it was cooled to room temperature and added Et_3N (0.5 mL, 3.58 mmol). The resulting mixture was warmed to reflux and stirred for 10 min before it was cooled to room temperature. The resulting mixture was washed with $NaHCO_3$ (50 mL, sat. aq.), $Na_2S_2O_3$ (50 mL, sat. aq.), brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded mixture of styrene **177** and vinyl bromide **177'** (**177**:**177'** ca. 5:1, 140 mg, 64%) as an amorphous solid.



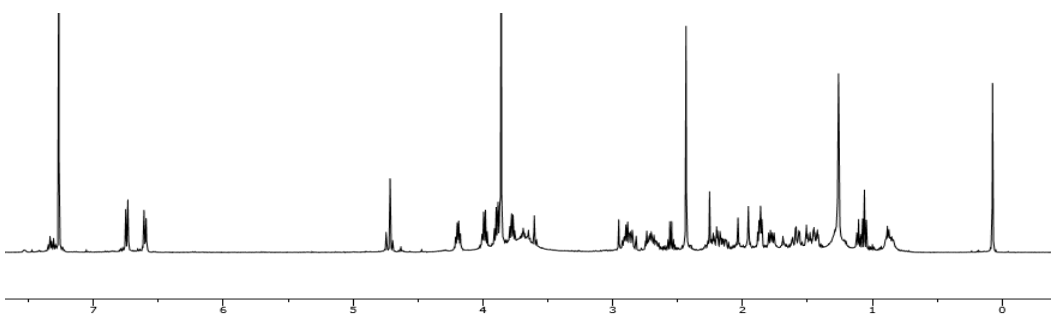
(ii) To a stirred solution of mixture of styrene **177** and **177'** (18 mg, 40 μmol) in MeOH/CH_2Cl_2 (6:1, 0.7 mL) at room temperature was added $MeNH_2$ (40% aq., 0.1 mL, 1.16 mmol). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 1:1) afforded styrene amide **175** (18 mg, 92%) as an amorphous solid. **175**: R_f = 0.14 (silica gel, hexanes:EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.16 (d, *J* = 9.6 Hz, 1H), 6.04 (s, 1H), 5.61 (d, *J* = 9.6 Hz, 1H), 5.23 (br s, 1H), 4.65 (s, 1H), 4.19–4.16 (m, 1H), 3.99–3.91 (m, 1H), 3.90–3.82 (m, 1H), 3.84 (s, 3H), 3.82–3.79 (m, 1H), 2.69 (d, *J* = 4.8 Hz, 3H), 2.56 (s, 2H), 1.97 (t, *J* = 13.7 Hz, 1H), 1.83 (d, *J* = 14.1 Hz, 1H), 1.58 (t, *J* = 13.7 Hz, 1H), 1.45 ppm (d, *J* = 13.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 145.7, 144.1, 138.6, 129.0, 123.1, 121.4, 117.3, 113.1, 108.2, 95.3, 74.2, 66.5, 64.9, 56.2, 52.5, 43.4, 32.7, 27.0, 26.8 ppm.

Tosyl Amide 159



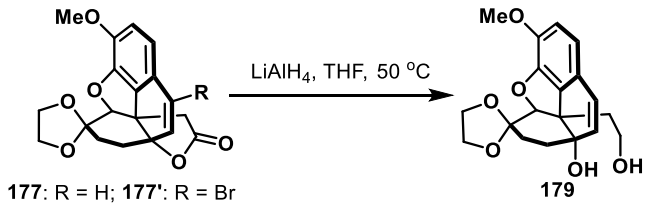
(i) To a stirred solution of styrene amide **175** (18.0 mg, 48 μmol) in THF (1.0 mL) at 0 ℃ was added $LiAlH_4$ (15.1 mg, 0.40 mmol). The resulting mixture was warmed to reflux and stirred for 12 h before it was cooled to 0 ℃ and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure afforded crude amine **158** (11.0 mg, 63%), which was used directly in the subsequent step.

158: ^{1}H NMR (499 MHz, $CDCl_3$, crude)



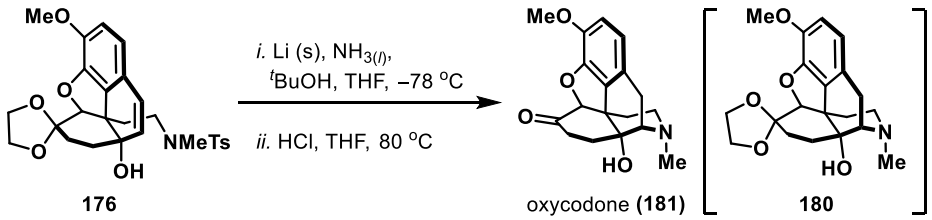
(ii) To a stirred solution of crude amine **158** (obtained above) in CH_2Cl_2 (1.0 mL) at room temperature was added TsCl (8.80 mg, 46 μmol) and Et_3N (60 μL, 0.43 mmol). The resulting mixture was stirred for 3 h before it was quenched with H_2O (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layer was washed with water (8 mL), brine (8 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded tosyl amide **159** (12 mg, 76%) as an amorphous yellow solid. All physical properties of tosyl amide **159** are identical to those obtained from amide **157**.

Diol 179



To a stirred solution of lactones **177** and **177'** (12.0 mg, 35 μmol) in THF (3.0 mL) at 0 °C was added $LiAlH_4$ (11 mg, 0.29 mmol). The resulting mixture was warmed to 50 °C and stirred for 5 h before it was cooled to 0 °C and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded diol **179** (6.2 mg, 51%) as an amorphous solid. **179:** R_f = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3756, 3692, 3056, 2990, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 5.66 (d, *J* = 9.6 Hz, 1H), 4.60 (s, 1H), 4.31 (br s, 1H), 4.21–4.17 (m, 1H), 4.05–3.97 (m, 1H), 3.93–3.83 (m, 1H), 3.86 (s, 3H), 3.84–3.78 (m, 1H), 3.69–3.50 (m, 2H), 2.25–2.16 (m, 1H), 2.07 (br s, 1H), 1.91 (td, *J* = 13.6, 2.6 Hz, 1H), 1.84–1.77 (m, 2H), 1.64 (td, *J* = 14.1, 2.2 Hz, 1H), 1.43 ppm (dt, *J* = 13.3, 2.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.2, 144.2, 137.9, 129.3, 123.5, 122.9, 117.5, 112.9, 108.3, 96.4, 73.8, 66.5, 65.0, 58.5, 56.3, 51.3, 38.8, 33.1, 27.0 ppm; HRMS calcd. For $C_{19}H_{22}O_6Na^+$ $[M + Na]^+$ 369.1309, found 369.1310.

Oxycodone 181



(i) To a stirred solution liquid ammonia (10 mL), THF (1.0 mL) and ^{t}BuOH (0.1 mL) at –78 °C was added lithium metal (finely-cut, 30 mg) in small portions. The resulting solution was stirred for 15 min before a solution of alkene **176** (37.0 mg, 72 μmol) in THF (3.0 mL) was added *via* a cannula. The resulting mixture was stirred for 10 min before it was quenched with $NaHCO_3$ (10 mL, sat. aq.) and MeOH (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH 94:2:1) afforded oxycodone ethylene ketal (**180**, 18.0 mg, 70%) as an amorphous clear solid. **180**: R_f = 0.39 (silica gel, EtOAc:MeOH 1:2); IR (film) ν_{max} 2940, 1735, 1505, 1380, 1250 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.57 (s, 1H), 4.20 (dd, *J* = 12.6, 6.9 Hz, 1H), 4.03 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.91 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.88 (s, 3H), 3.79 (dd, *J* = 12.3, 6.5 Hz, 1H), 3.13 (d, *J* = 18.3 Hz, 1H), 2.81 (d, *J* = 5.0 Hz, 1H), 2.57 (dd, *J* = 16.9, 6.0 Hz, 1H), 2.49–2.38 (m, 1H), 2.39 (s, 3H), 2.32–2.12 (m, 3H), 1.62–1.49 (m, 3H), 1.45 ppm (dd, *J* = 12.4, 2.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.3, 142.3, 130.8, 124.9, 118.1, 114.0, 108.9, 93.8, 70.0, 66.4, 64.9, 56.6, 47.4, 45.6, 42.6, 31.0, 29.1, 28.8, 22.0 ppm; HRMS calcd. For $C_{20}H_{26}NO_5^+$ [M + H]$^+$ 360.1805, found 360.1807.

(ii) To a stirred solution of oxycodone ethylene ketal (**180**, 6.7 mg, 18 μmol) in THF (1.0 mL) at room temperature was added HCl (2.0 N aq., 0.1 mL). The resulting mixture was warmed to 80 °C stirred for 12 h before it was cooled to 0 °C quenched with $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL), the combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash

column chromatography (silica gel, CH_2Cl_2:MeOH:NH_4OH 94:2:1) afforded oxycodone (**181**, 3.6 mg, 61%) as a clear amorphous solid. **181**: R_f = 0.39 (silica gel, EtOAc:MeOH 1:2); IR (film) ν_{max} 2910, 1740, 1460, 1275, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.68 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.64 (s, 1H), 3.88 (s, 3H), 3.14 (d, *J* = 18.6 Hz, 1H), 3.00 (td, *J* = 14.4, 5.0 Hz, 1H), 2.86 (d, *J* = 5.7 Hz, 1H), 2.54 (dd, *J* = 18.5, 5.9 Hz, 1H), 2.50–2.32 (m, 2H), 2.37 (s, 3H), 2.28 (dt, *J* = 14.2, 2.8 Hz, 1H), 2.19–2.11 (m, 1H), 1.90–1.79 (m, 1H), 1.59 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.5, 145.0, 142.9, 129.3, 124.8, 119.4, 114.8, 90.4, 70.3, 64.6, 56.8, 50.2, 45.2, 42.7, 36.1, 31.4, 30.5, 21.9 ppm; HRMS calcd. For $C_{18}H_{22}NO_4^+$ $[M + H]^+$ 316.1543, found 316.1546.

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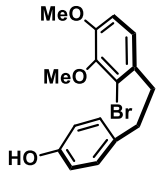
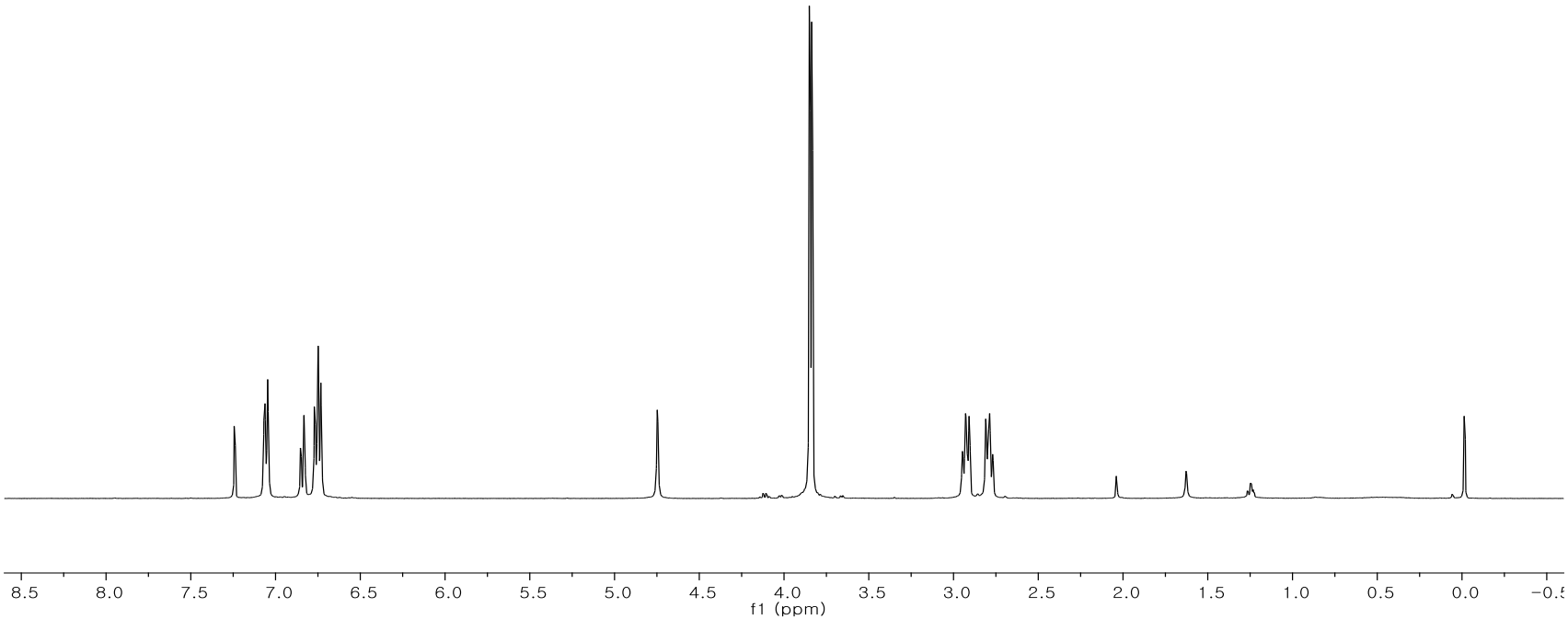
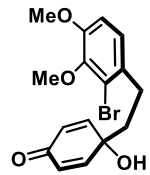
^{1}H NMR (400 MHz, $CDCl_3$)



130

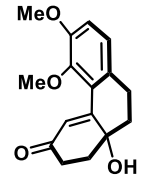


^{1}H NMR (400 MHz, $CDCl_3$)



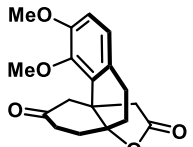
131

^{1}H NMR (400 MHz, $CDCl_3$)

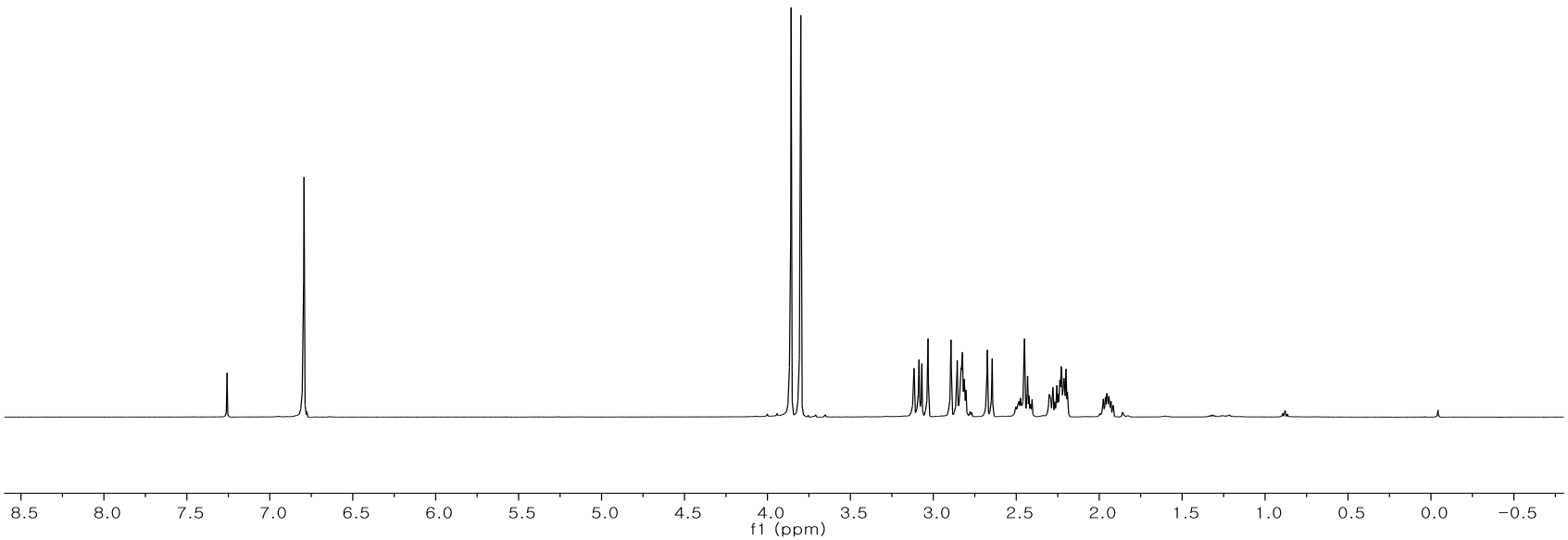


133

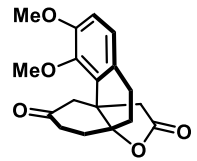
^{1}H NMR (499 MHz, $CDCl_3$)



137



^{13}C NMR (101 MHz, $CDCl_3$)



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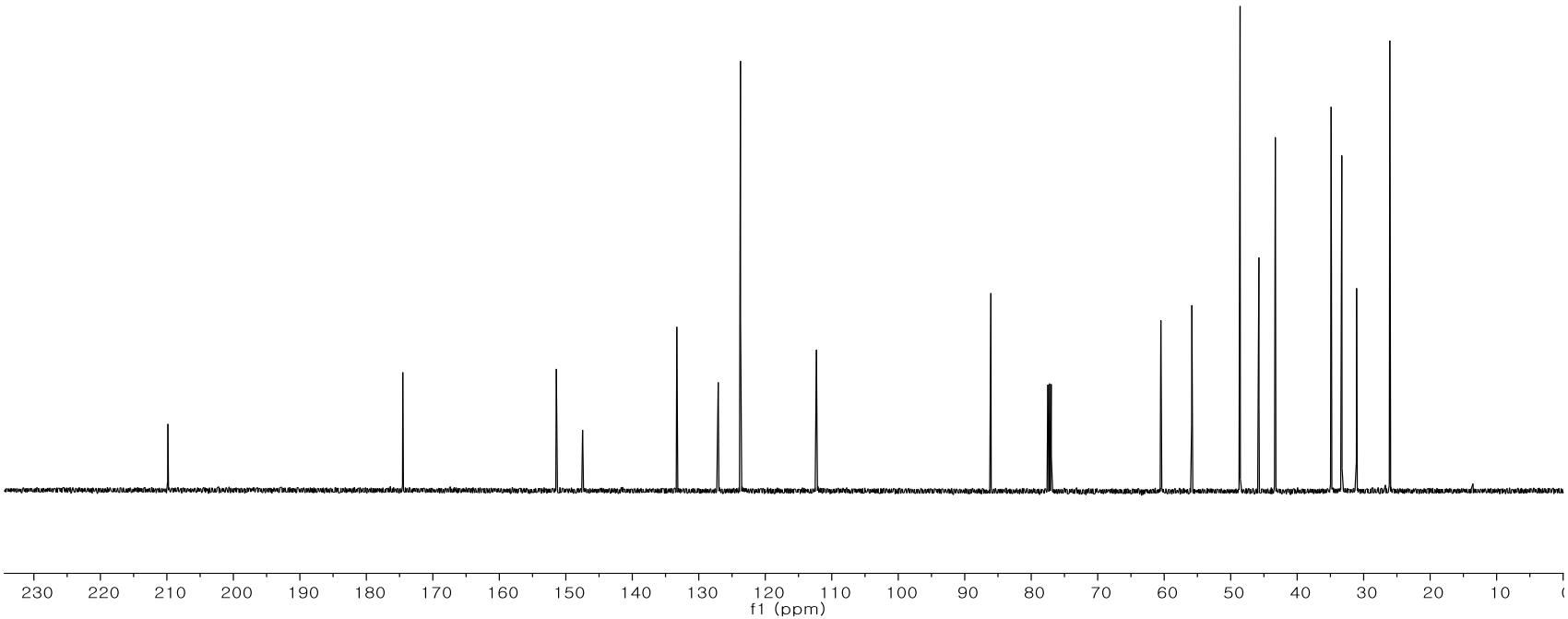
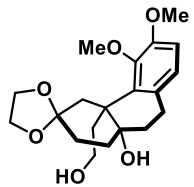


^{1}H NMR (400 MHz, $CDCl_3$)



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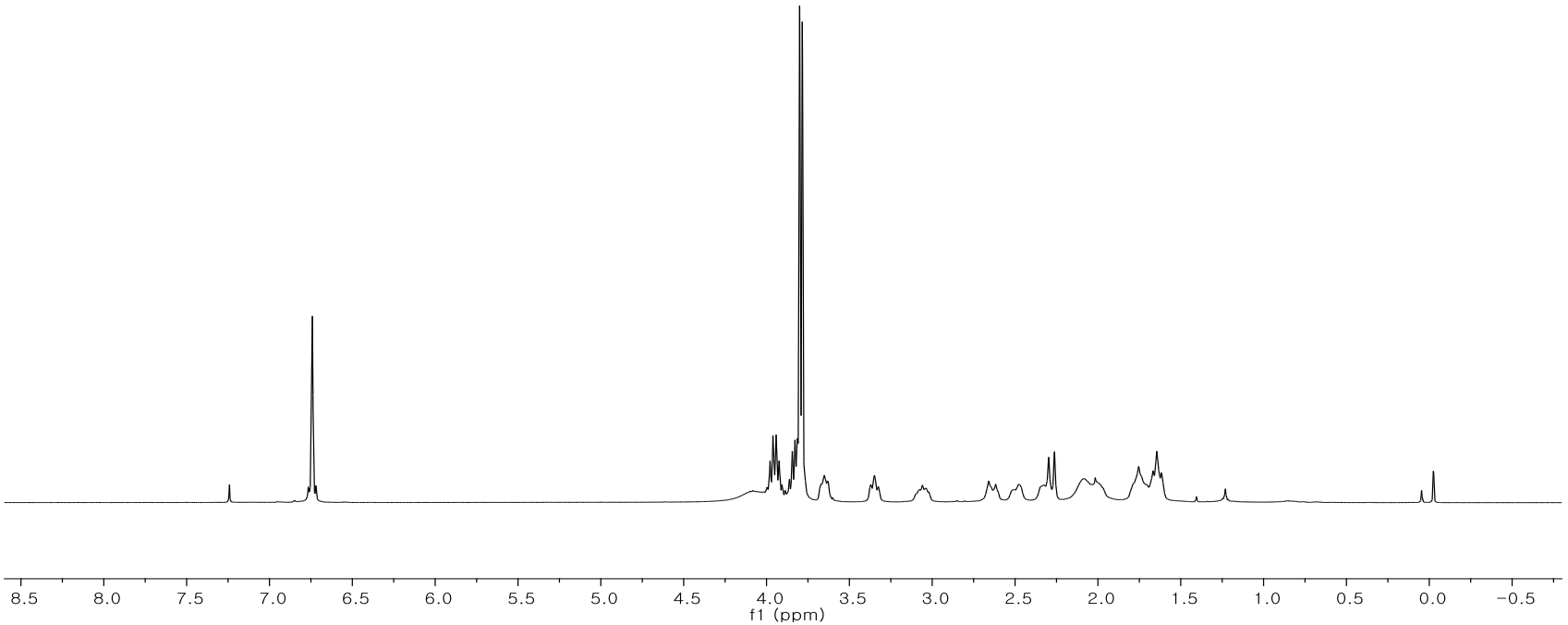
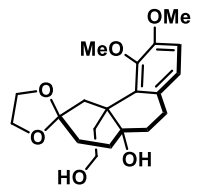


^{13}C NMR (101 MHz, $CDCl_3$)



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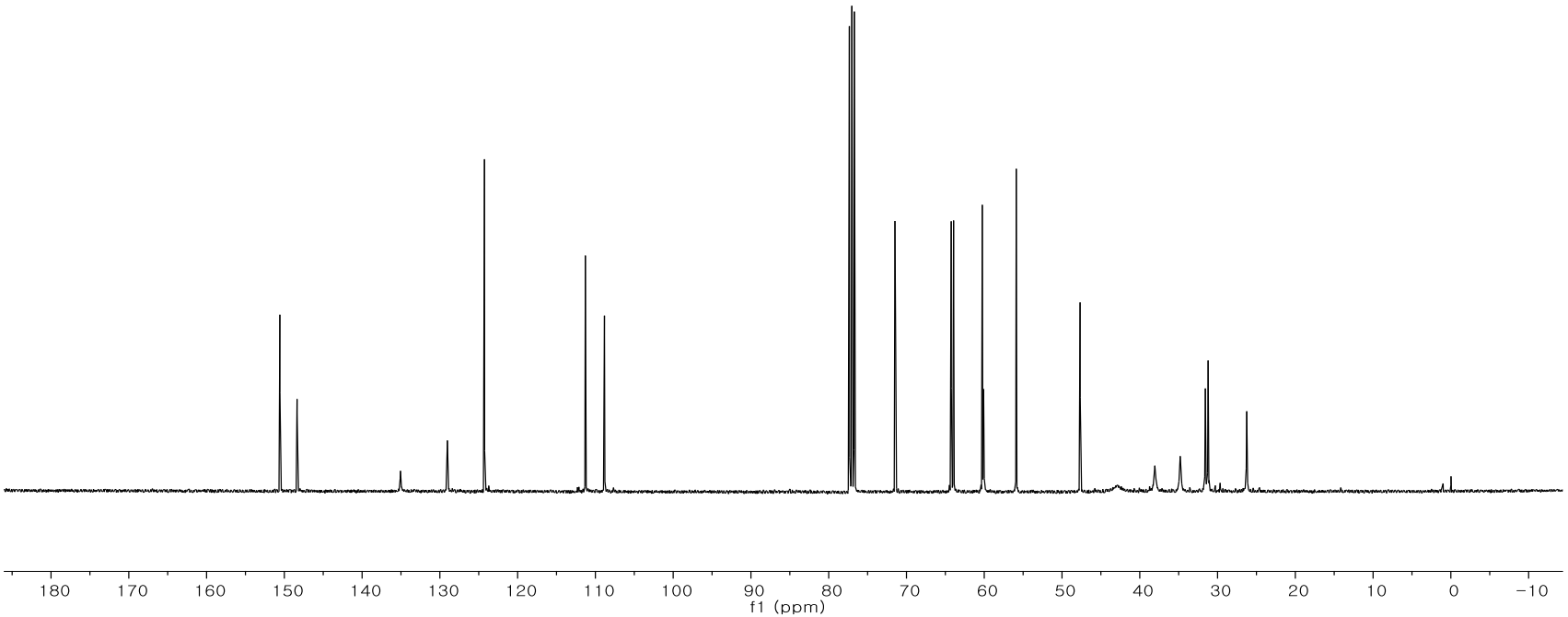
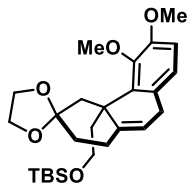
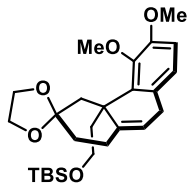


^{1}H NMR (499 MHz, $CDCl_3$)



142

^{13}C NMR (126 MHz, $CDCl_3$)



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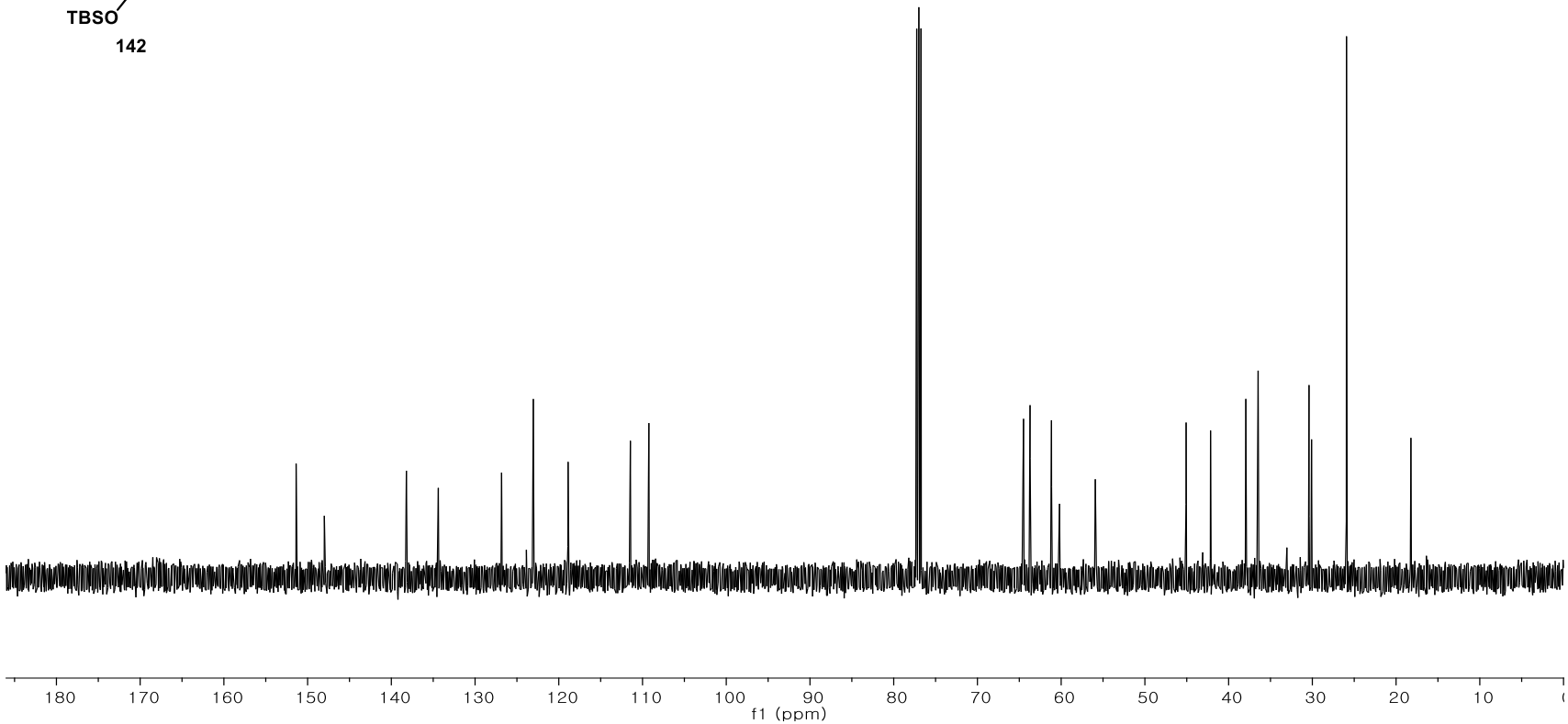
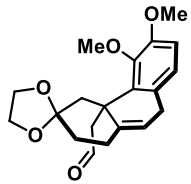


^{1}H NMR (499 MHz, $CDCl_3$)



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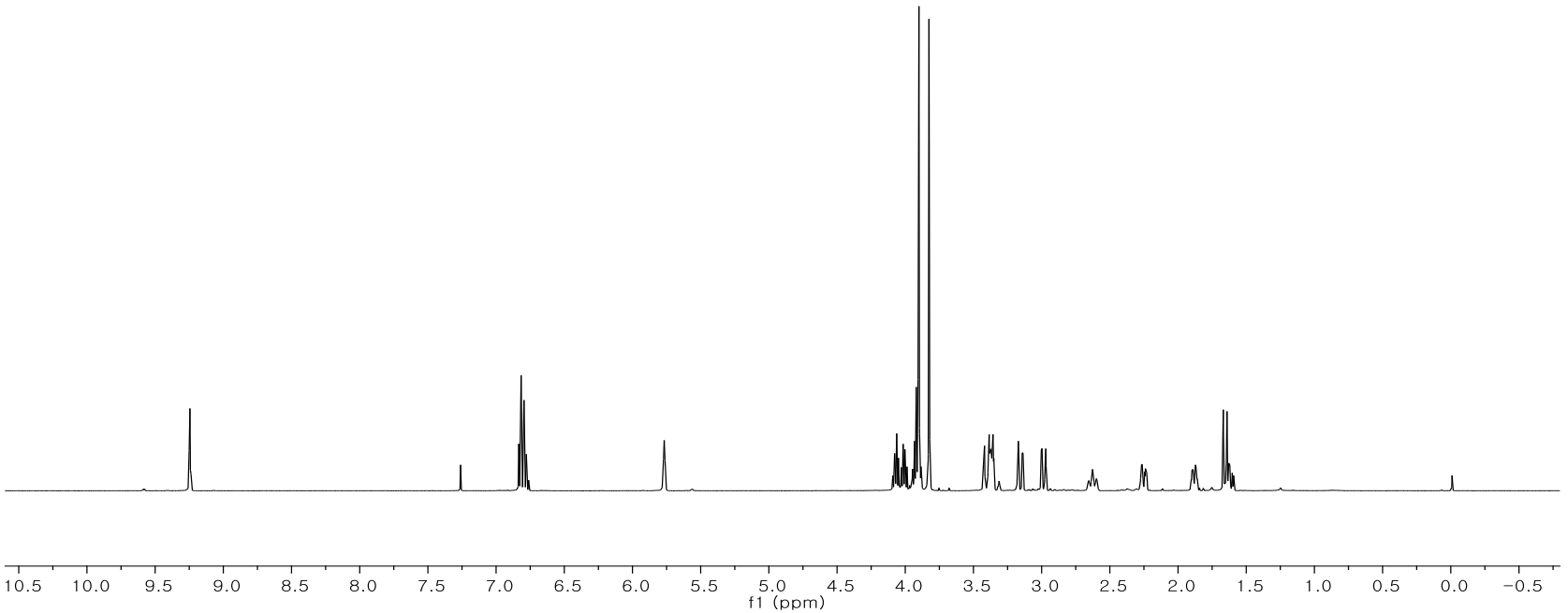
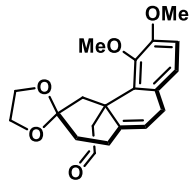


^{13}C NMR (126 MHz, $CDCl_3$)



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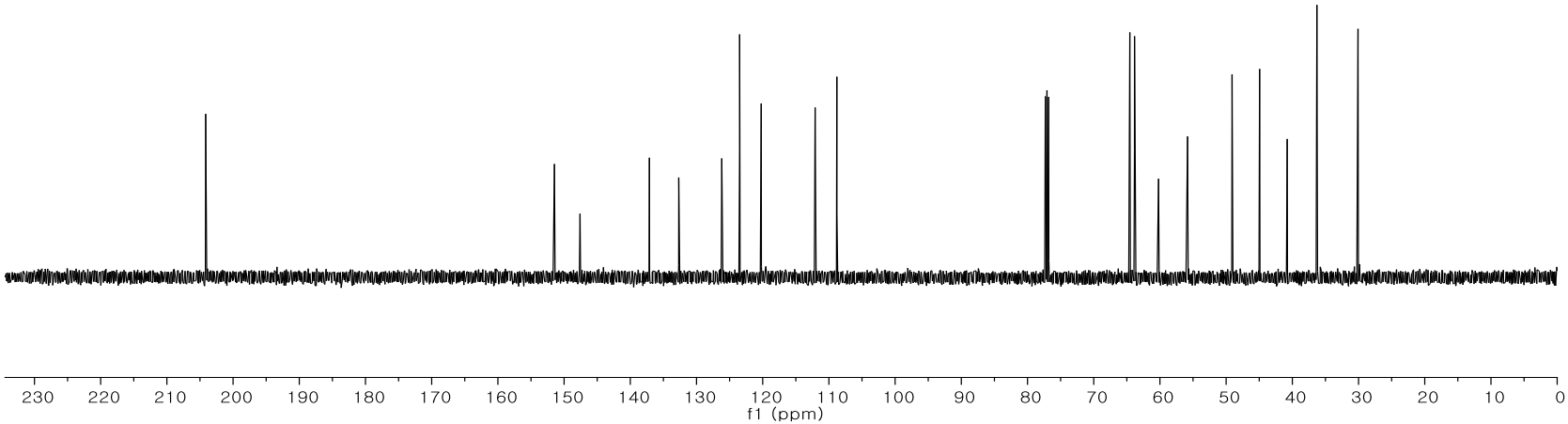
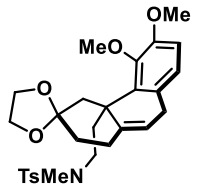


^{1}H NMR (499 MHz, $CDCl_3$)



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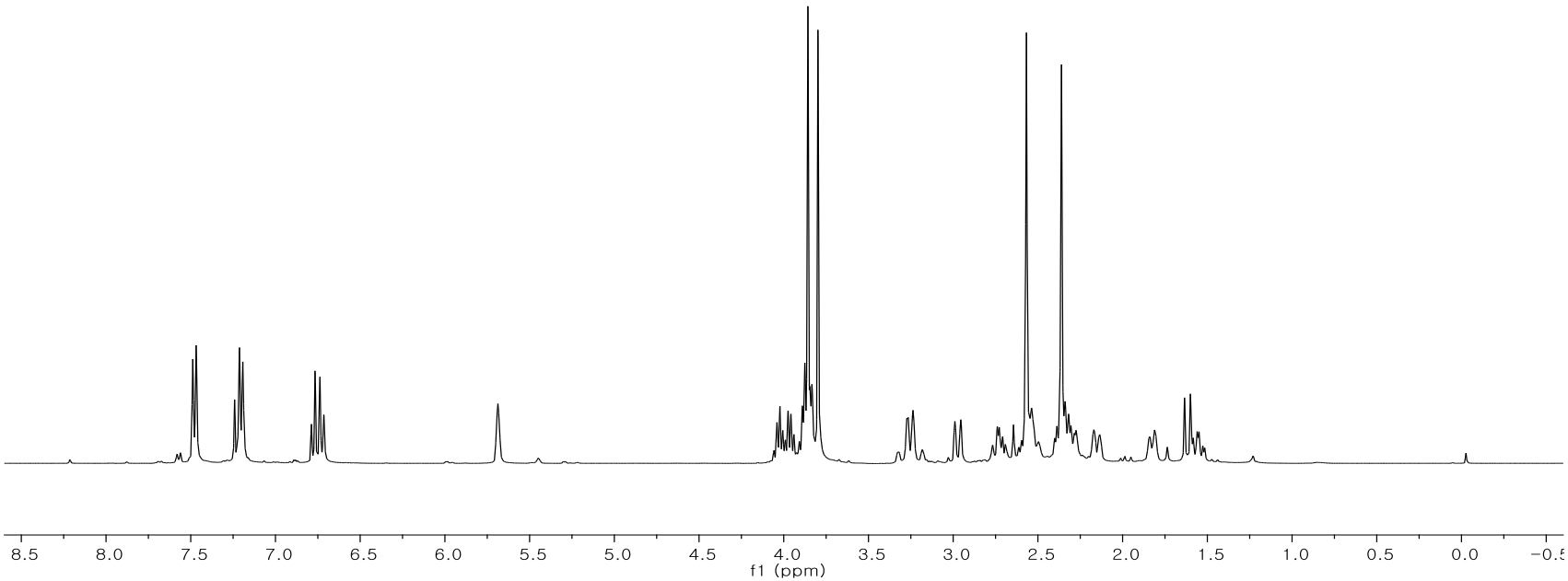
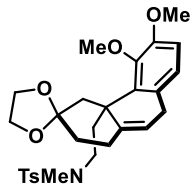
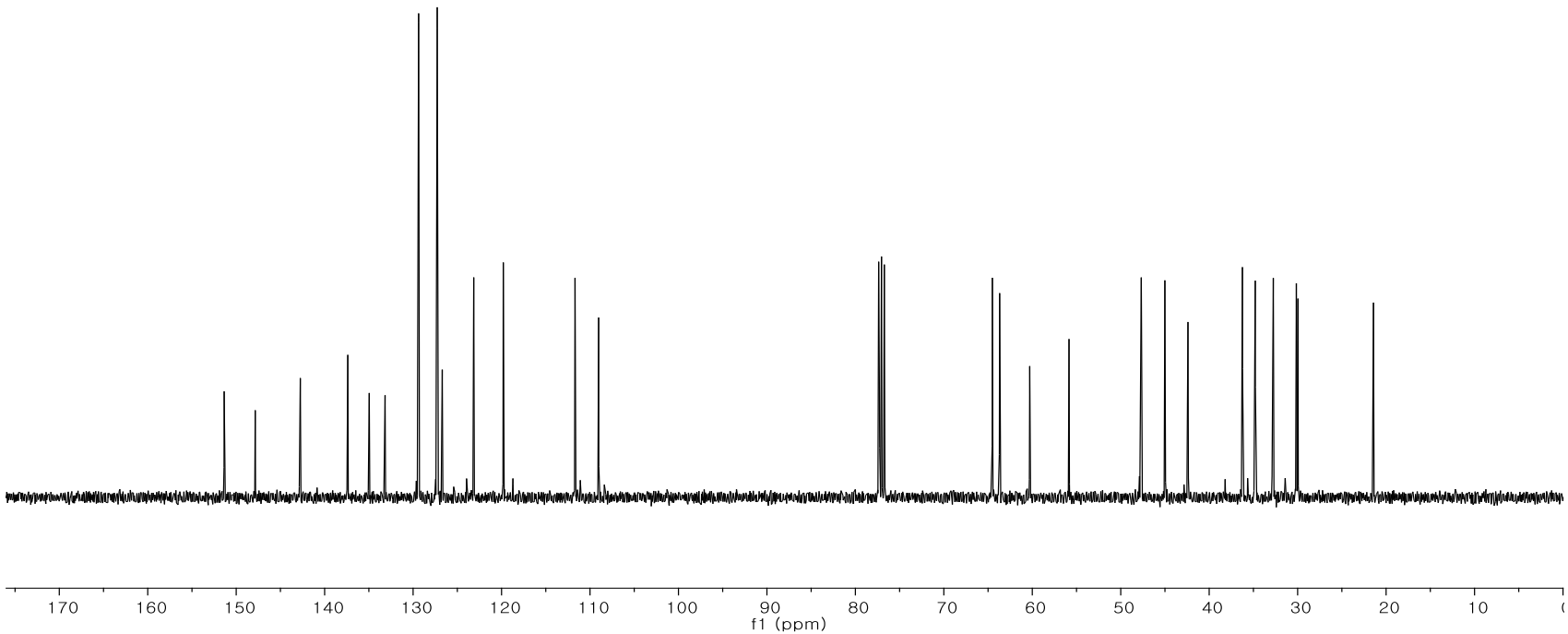


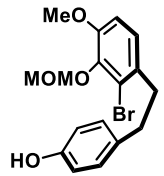
^{13}C NMR (101 MHz, $CDCl_3$)



111a



^{1}H NMR (400 MHz, $CDCl_3$)



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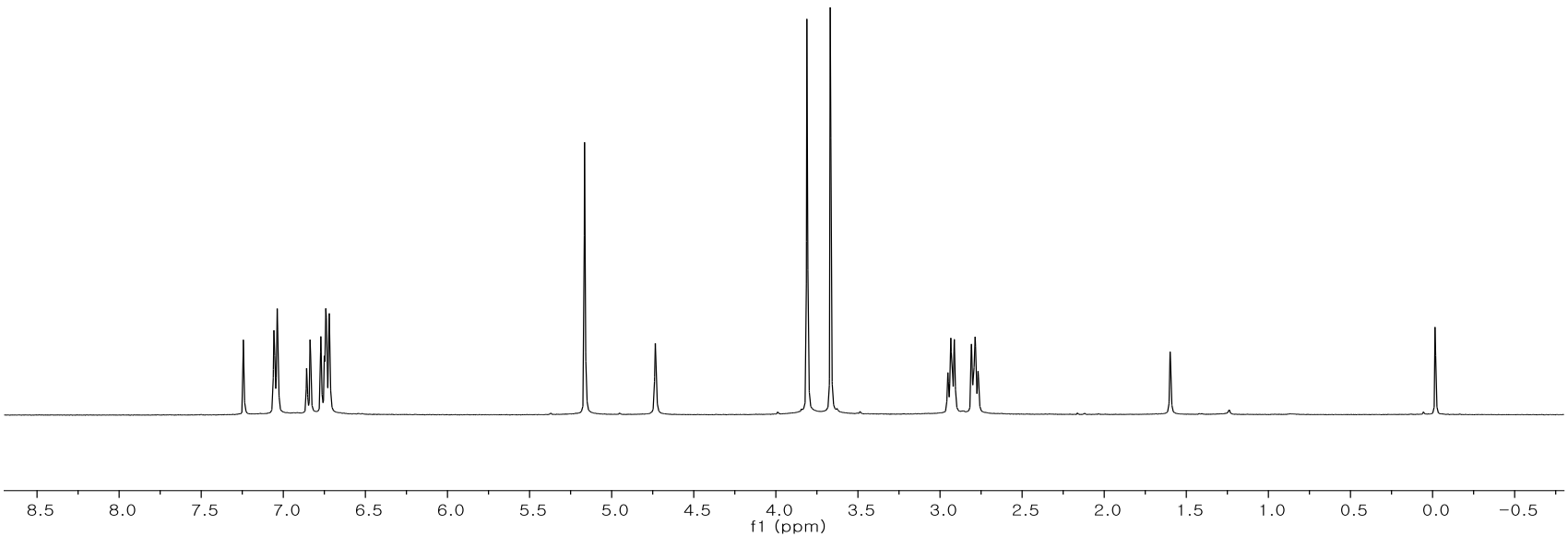
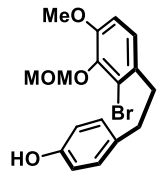


^{13}C NMR (101 MHz, $CDCl_3$)



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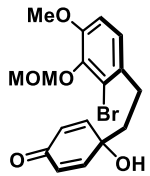
^{1}H NMR (400 MHz, $CDCl_3$)



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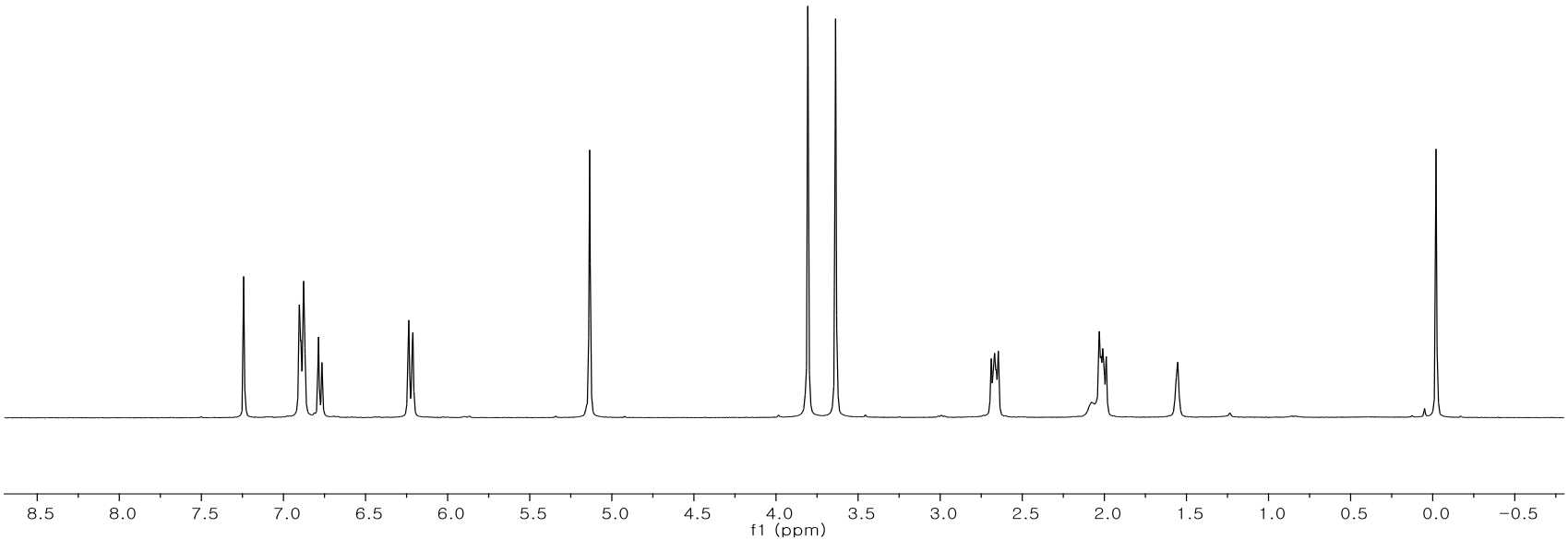
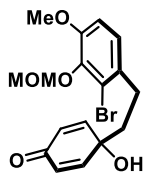


^{13}C NMR (126 MHz, $CDCl_3$)



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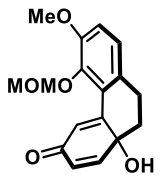
^{1}H NMR (400 MHz, $CDCl_3$)



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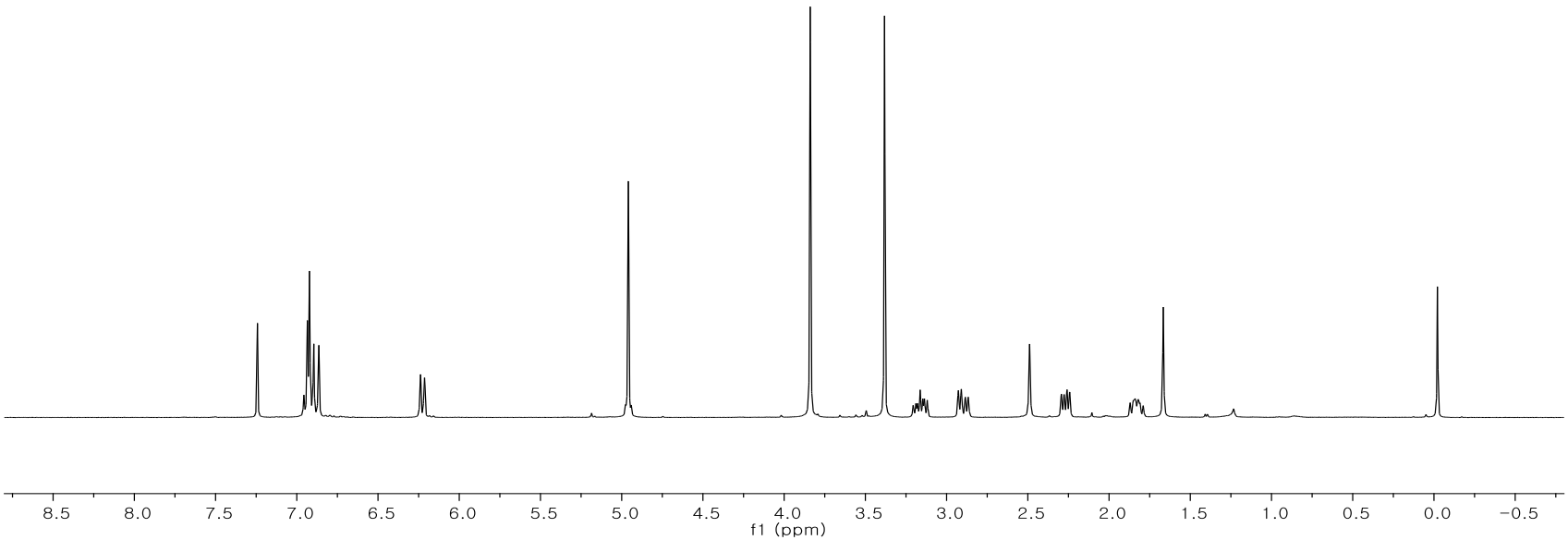
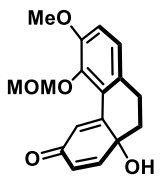


^{13}C NMR (101 MHz, $CDCl_3$)



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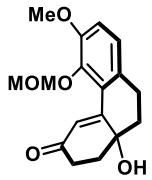
^{1}H NMR (400 MHz, $CDCl_3$)



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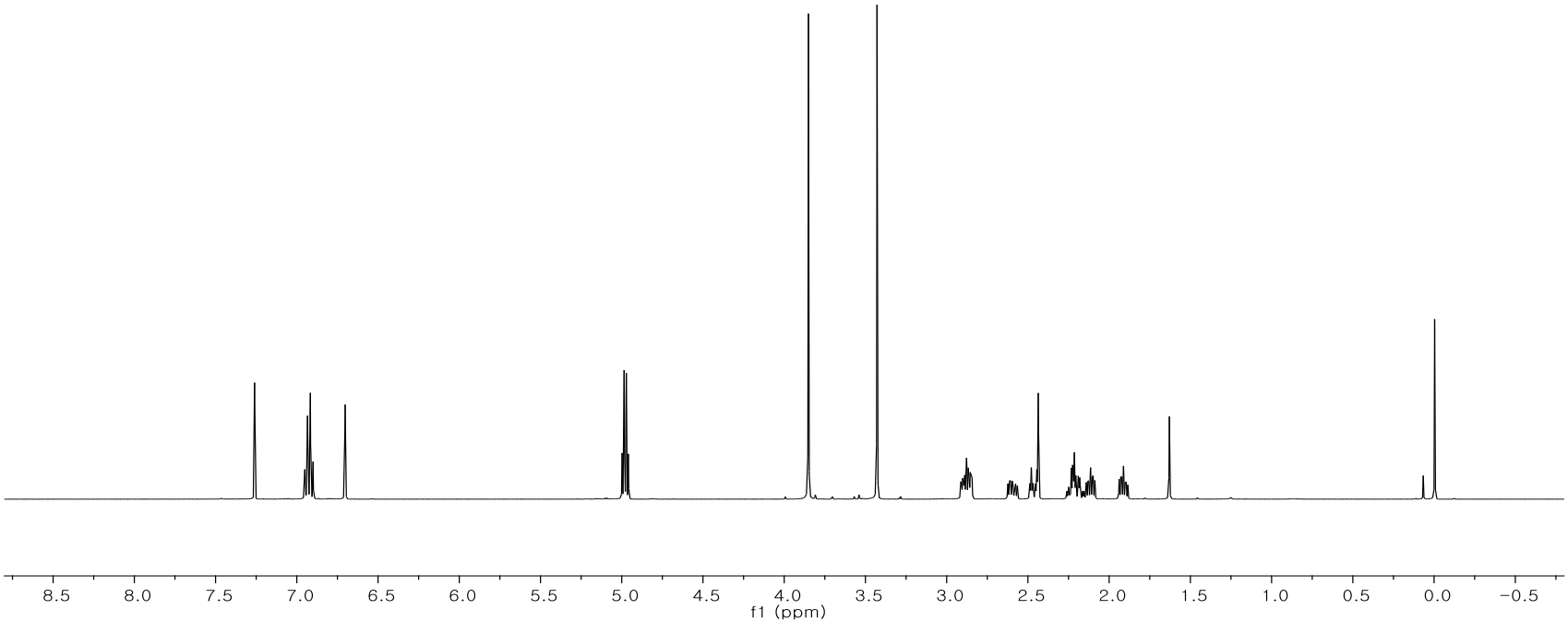
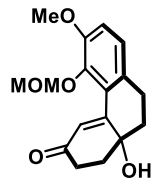
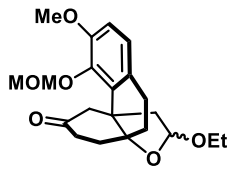


^{13}C NMR (101 MHz, $CDCl_3$)



151

^{1}H NMR (499 MHz, $CDCl_3$)



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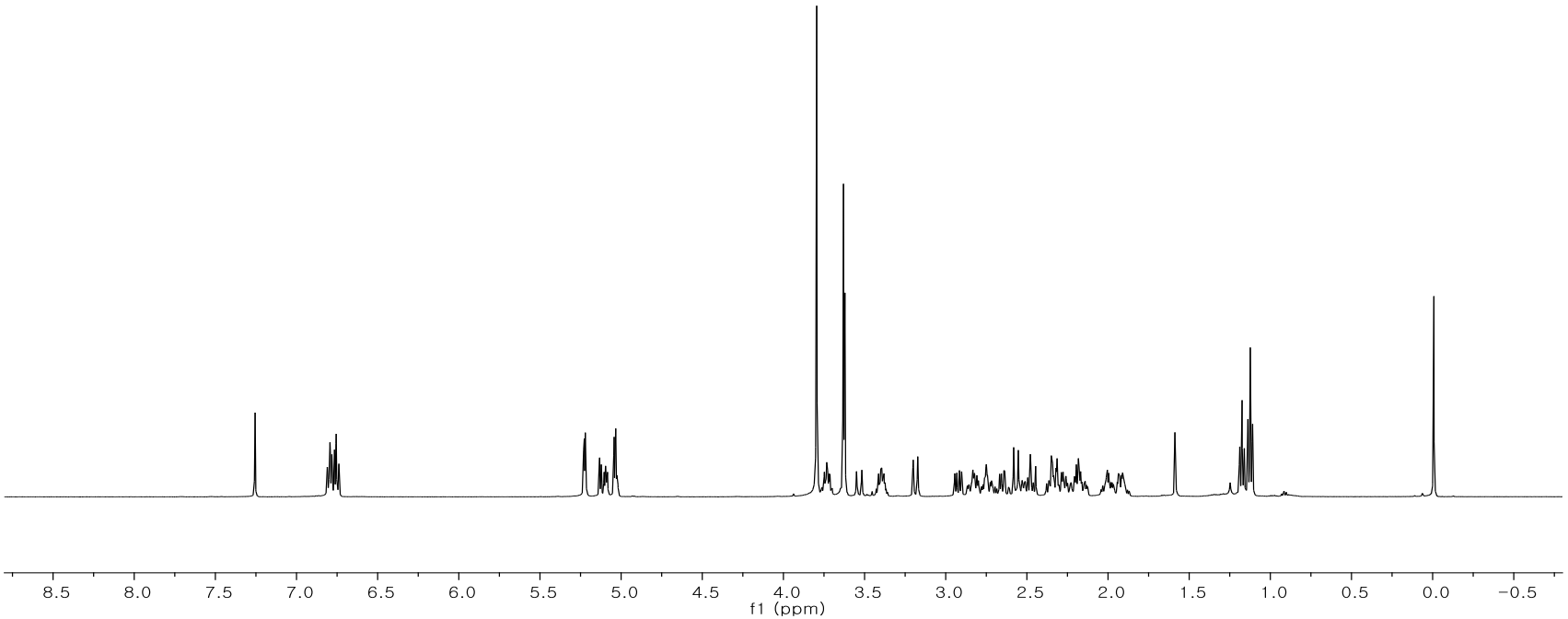
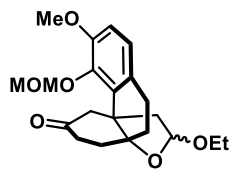
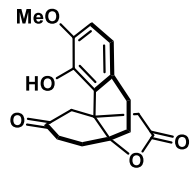


^{13}C NMR (101 MHz, $CDCl_3$)



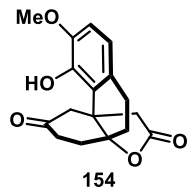
153

^{1}H NMR (499 MHz, $CDCl_3$)



154

^{13}C NMR (101 MHz, $CDCl_3$)



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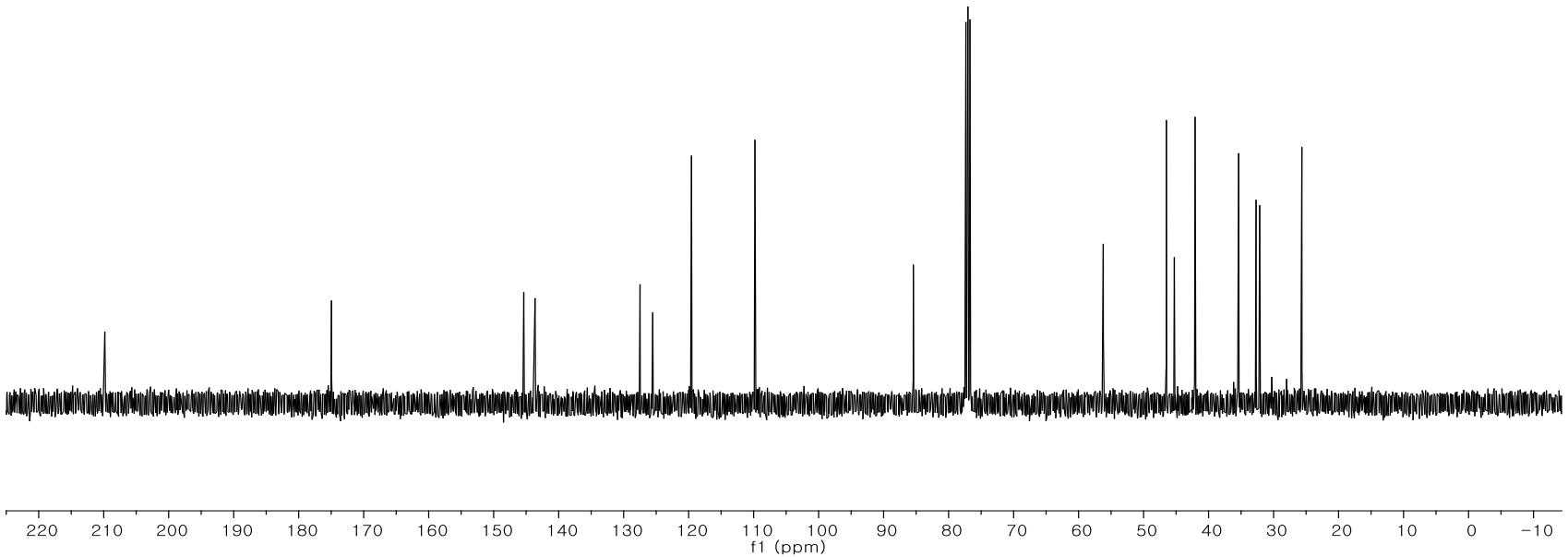
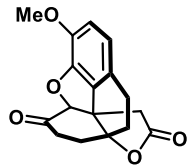


^{1}H NMR (400 MHz, $CDCl_3$)



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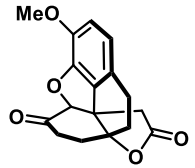
^{13}C NMR (101 MHz, $CDCl_3$)



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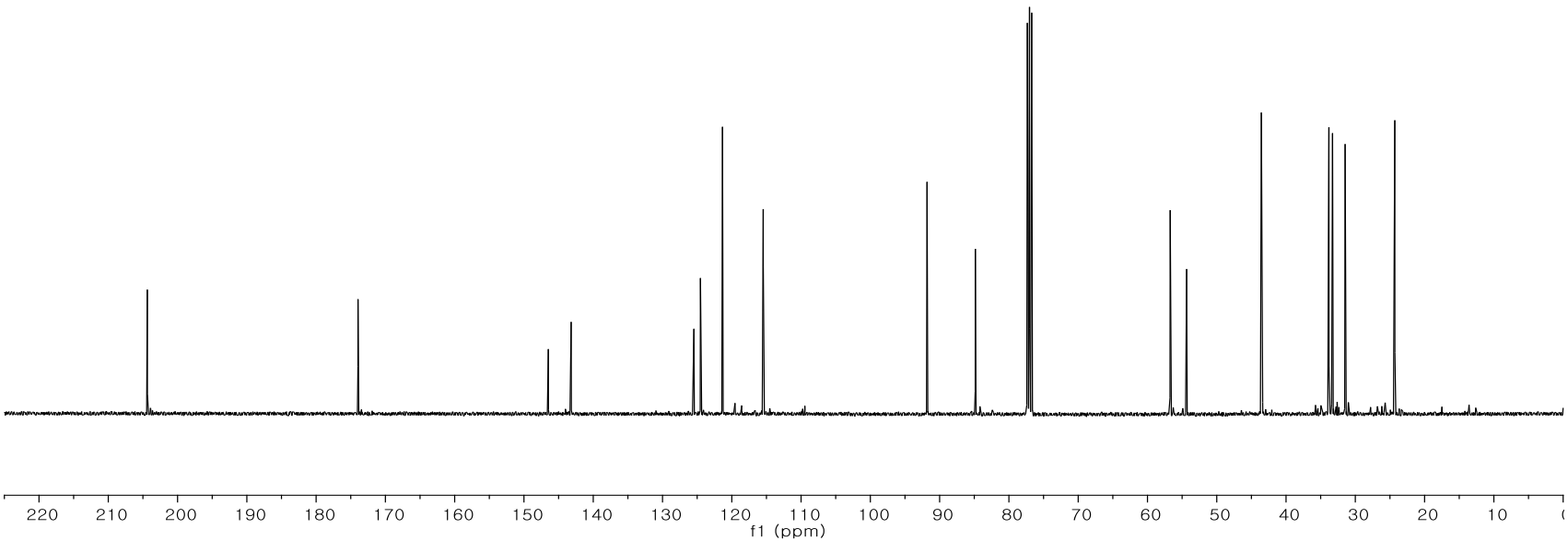
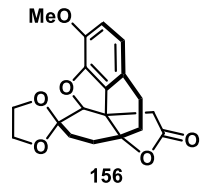


^{1}H NMR (400 MHz, $CDCl_3$)



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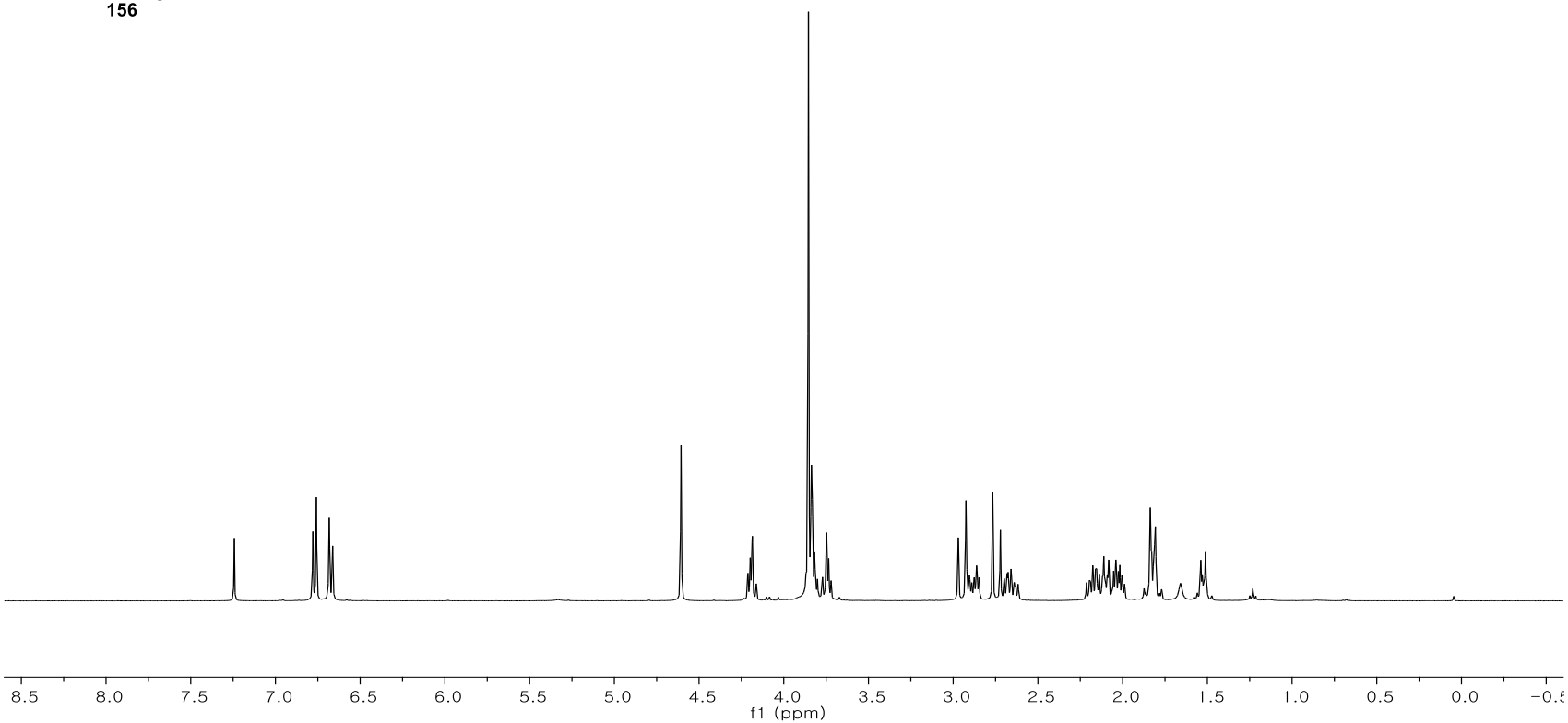
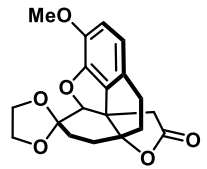


^{13}C NMR (101 MHz, $CDCl_3$)



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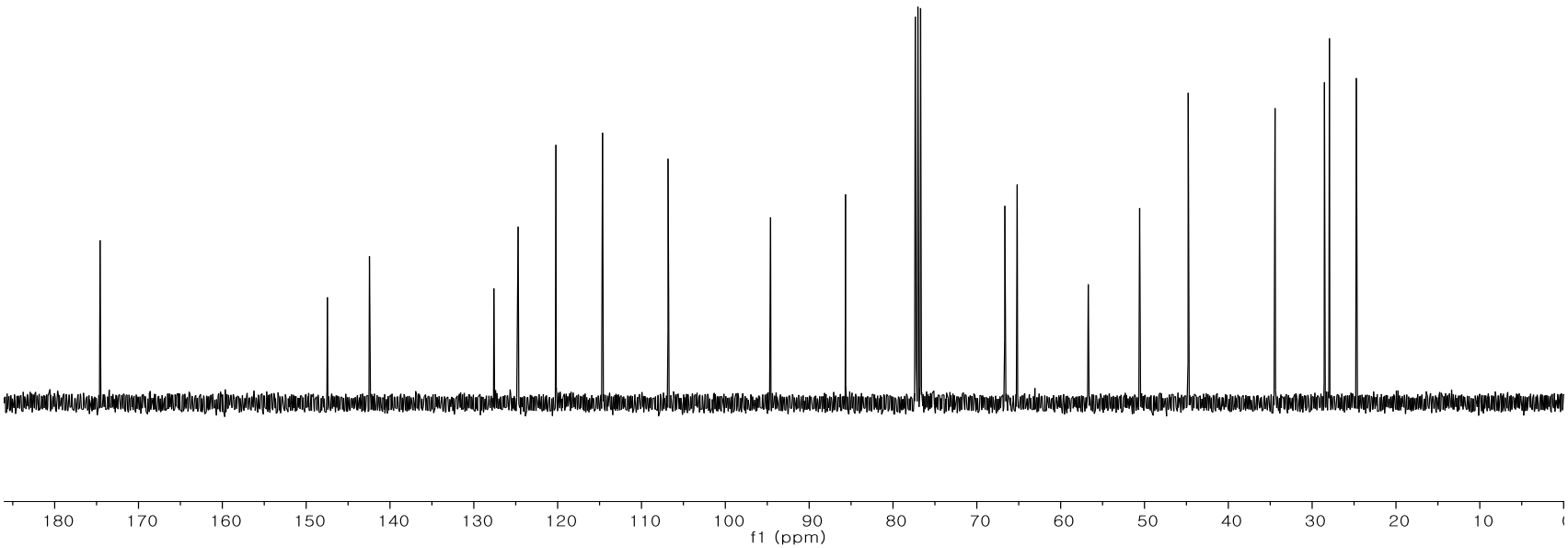
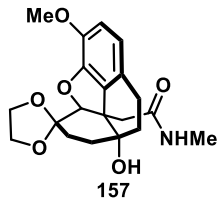


^{1}H NMR (400 MHz, $CDCl_3$)



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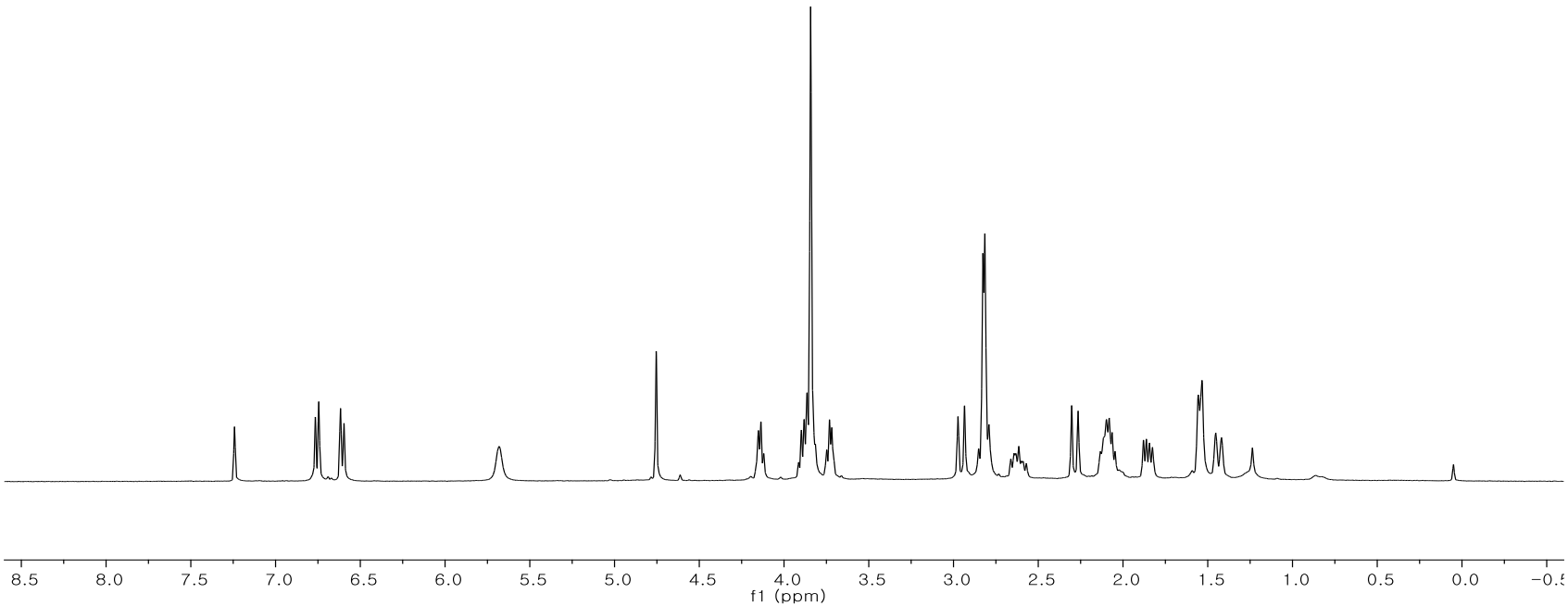
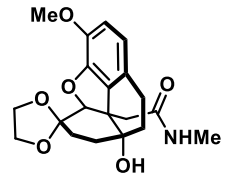


^{13}C NMR (101 MHz, $CDCl_3$)



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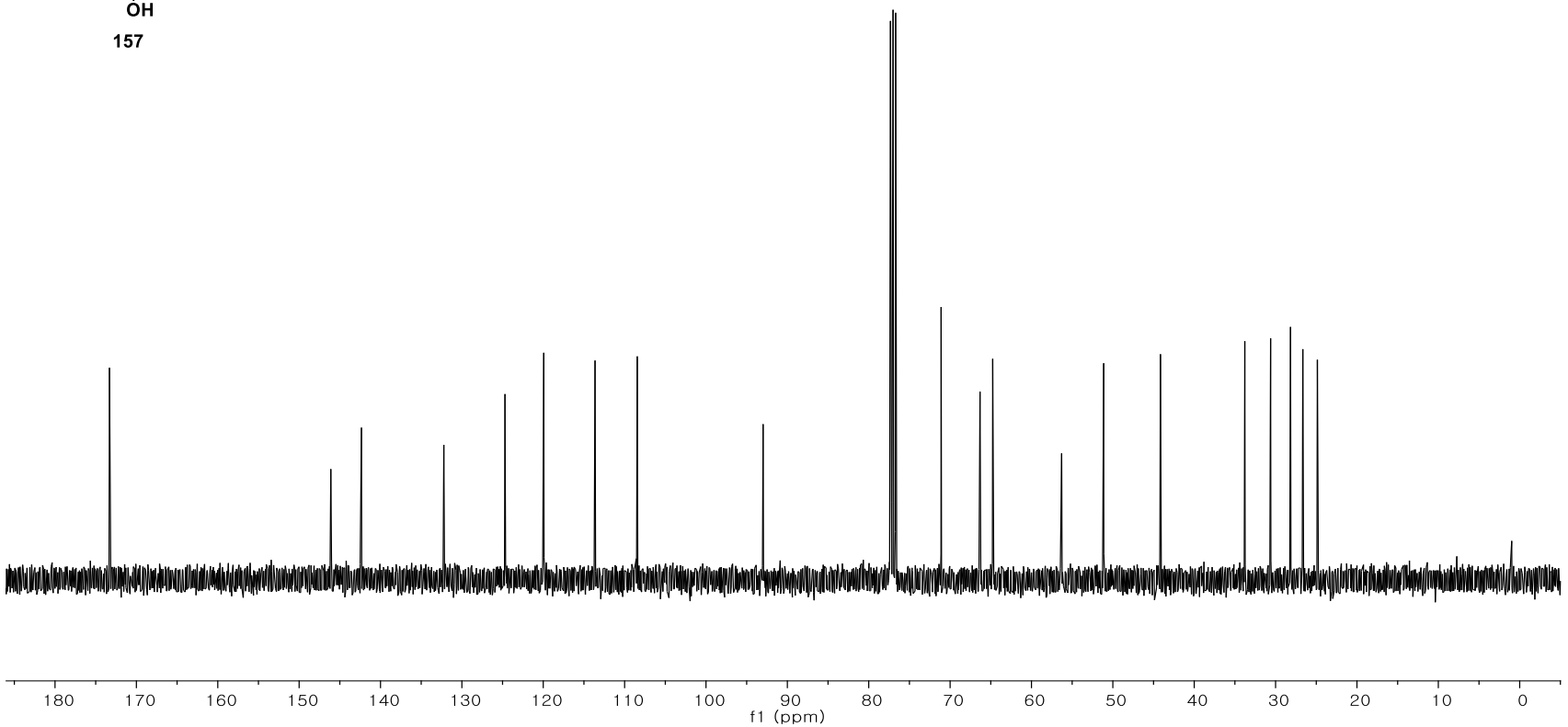
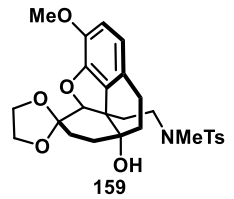


^{1}H NMR (400 MHz, $CDCl_3$)



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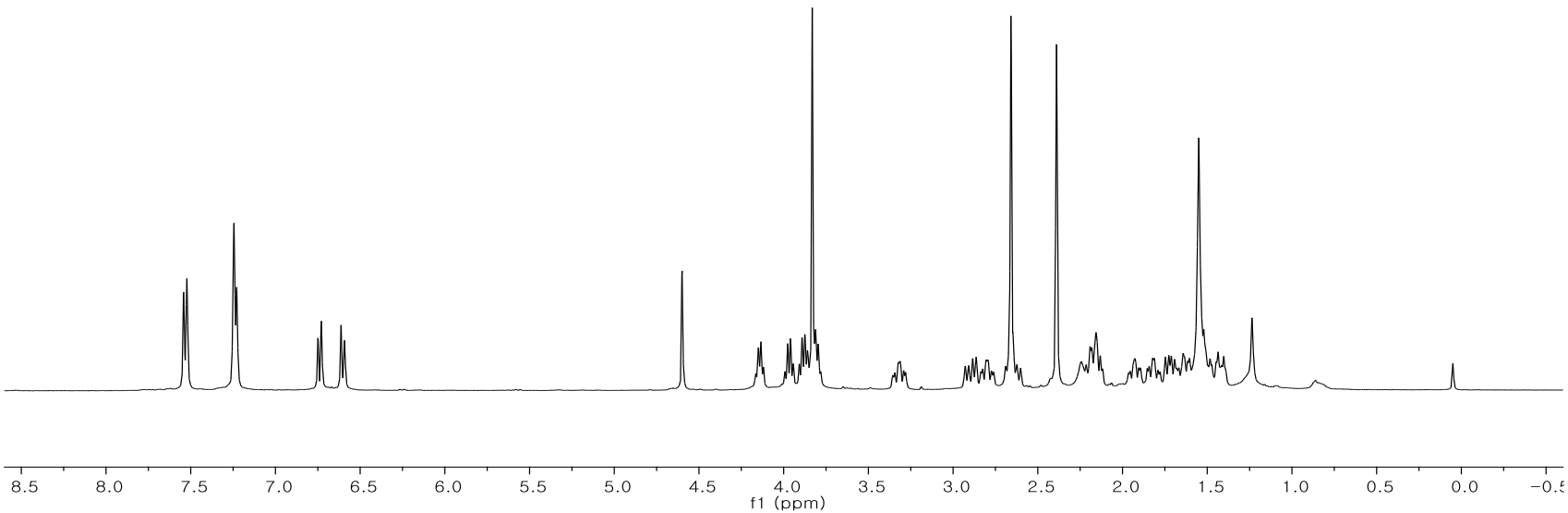

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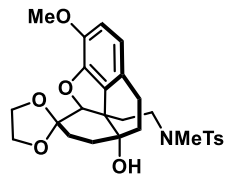

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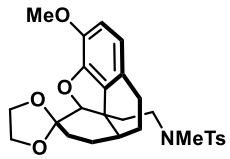

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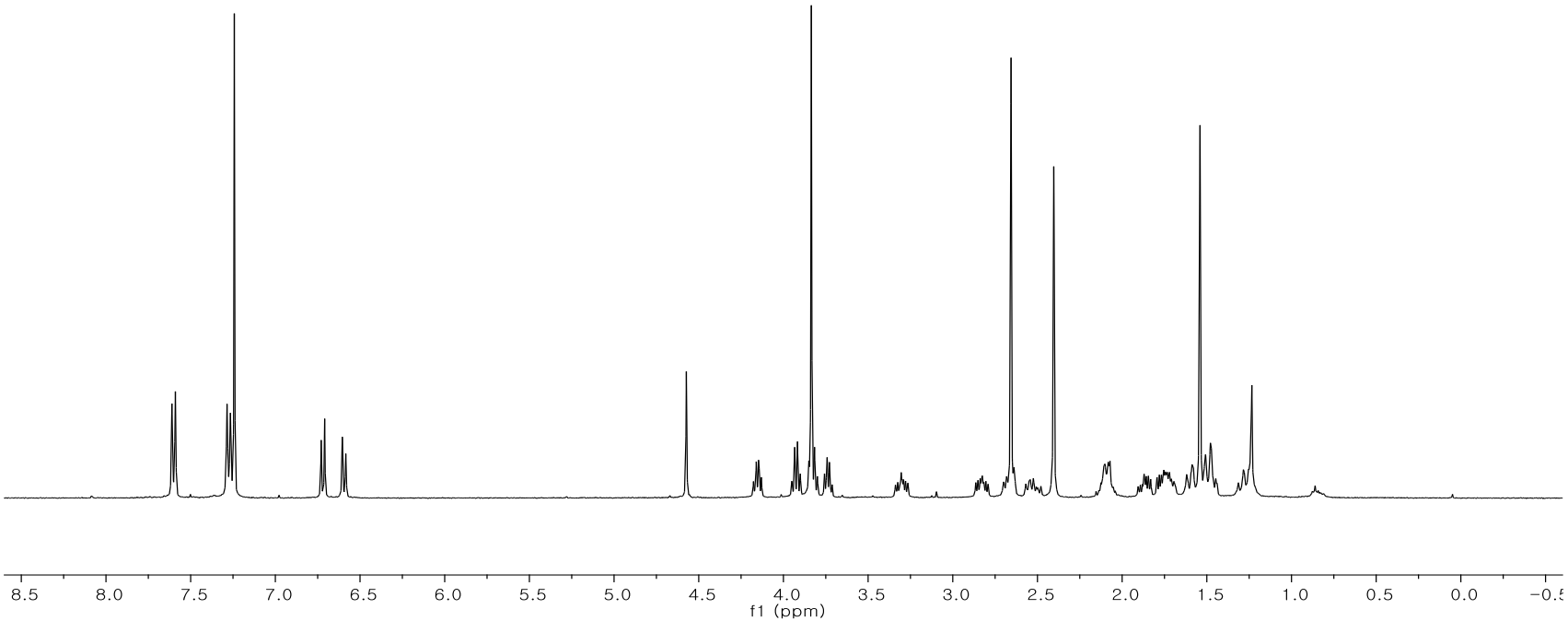

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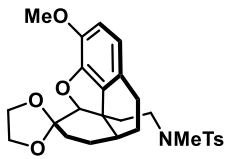

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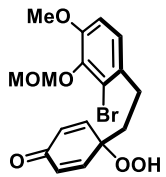

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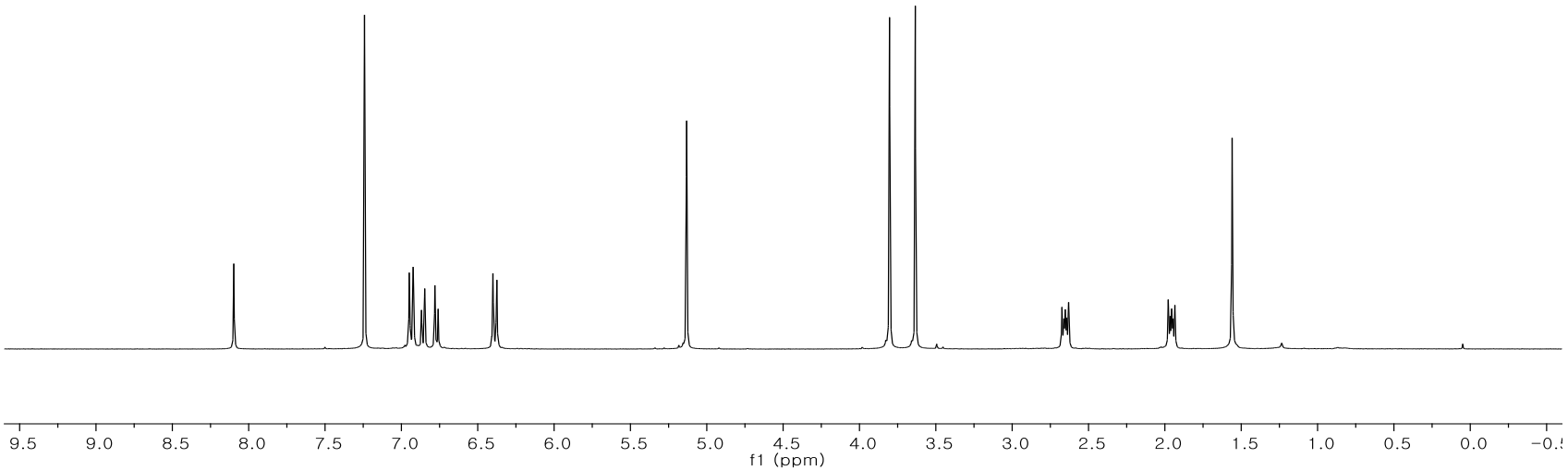

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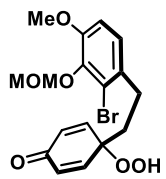

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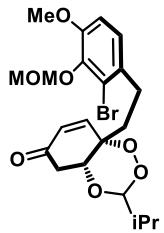

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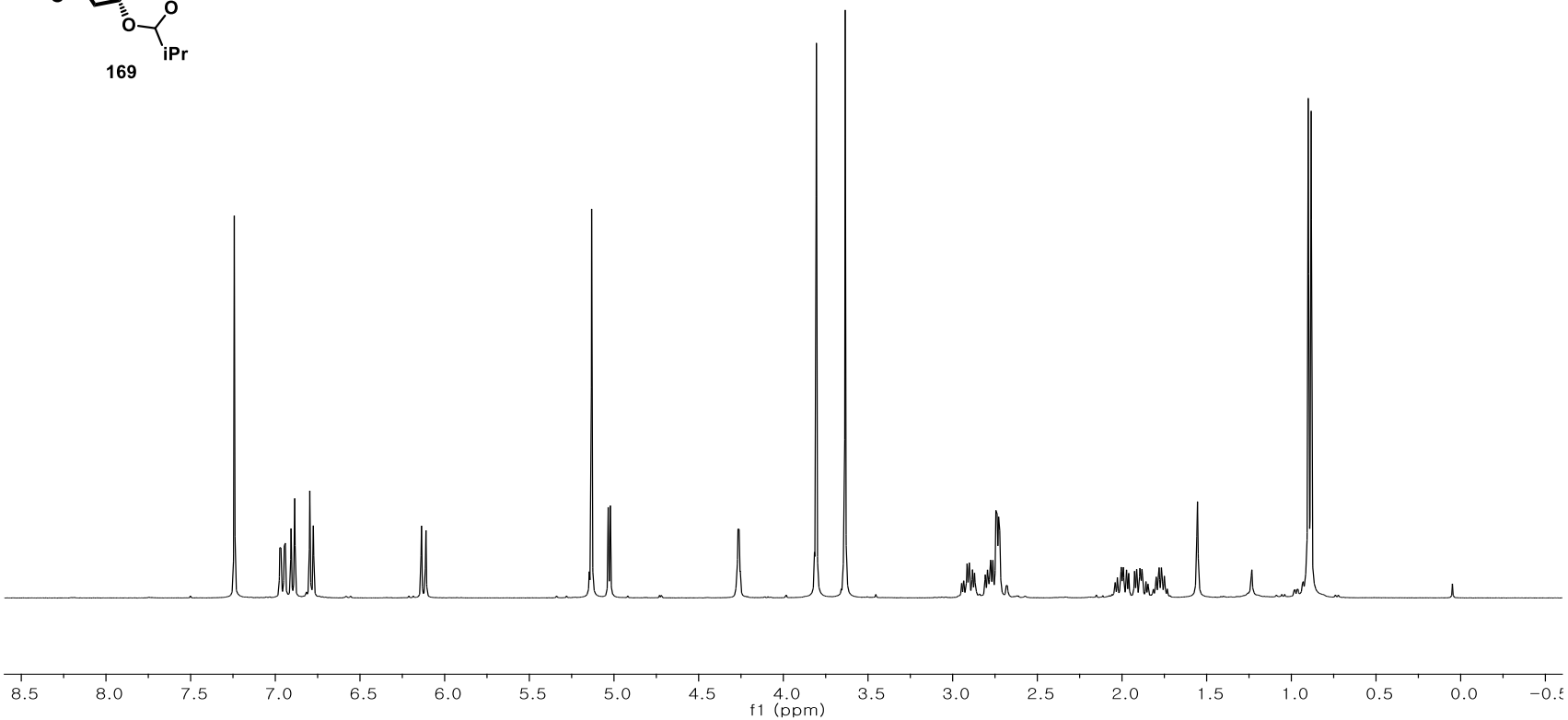

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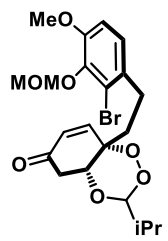

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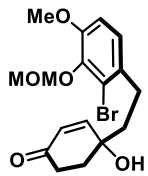

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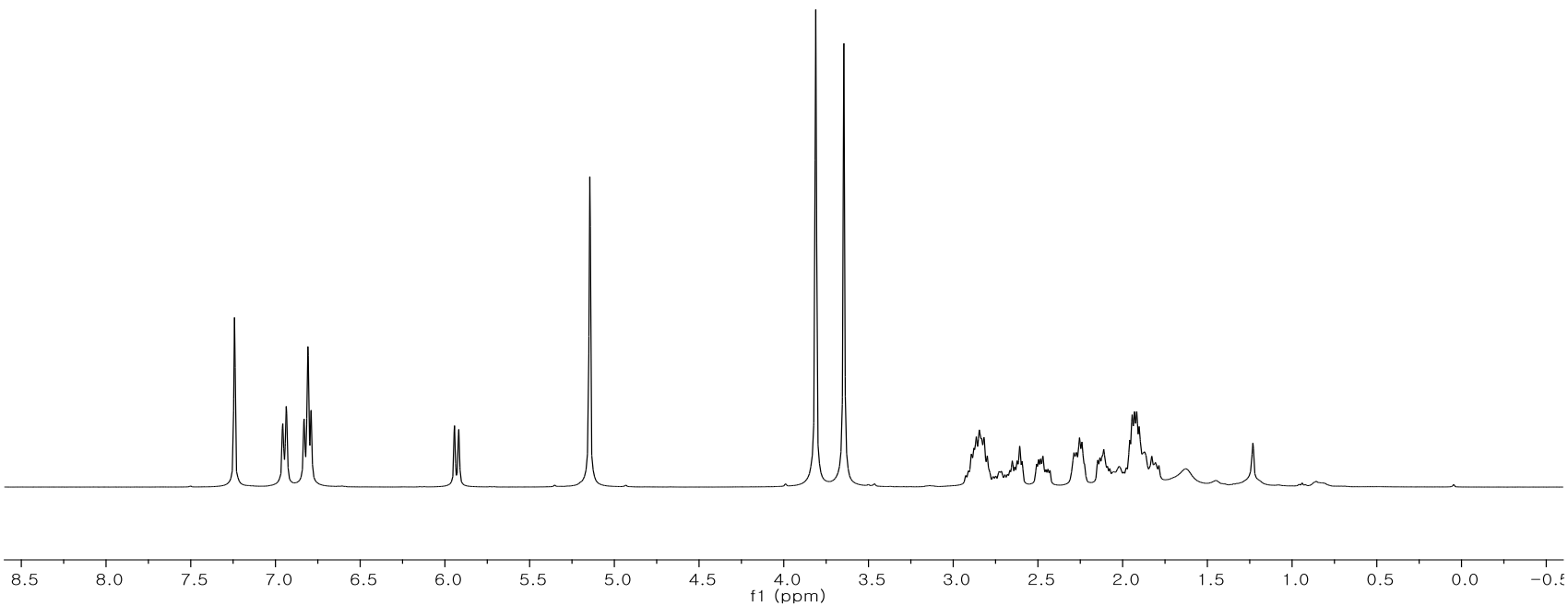

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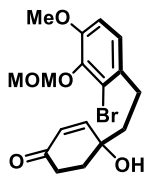

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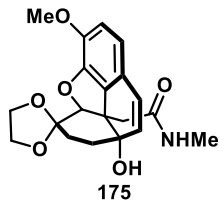

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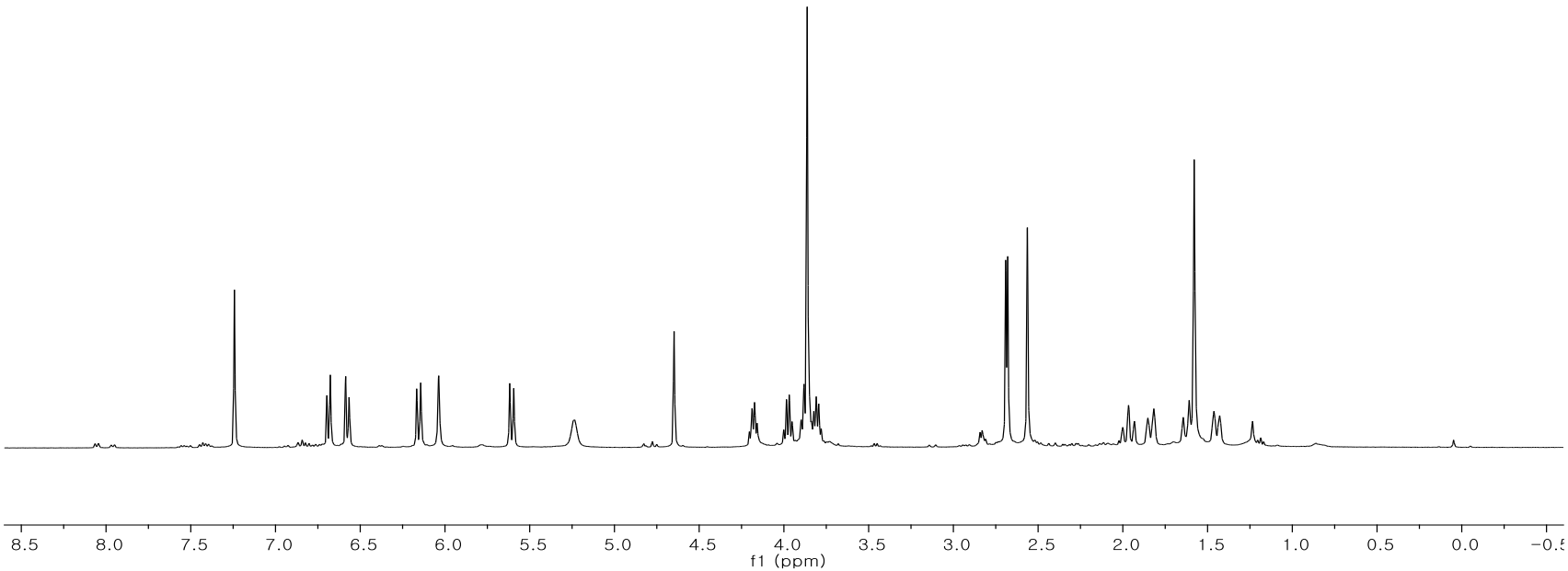

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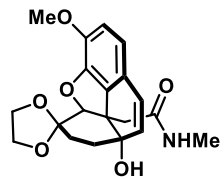

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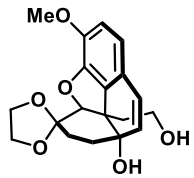

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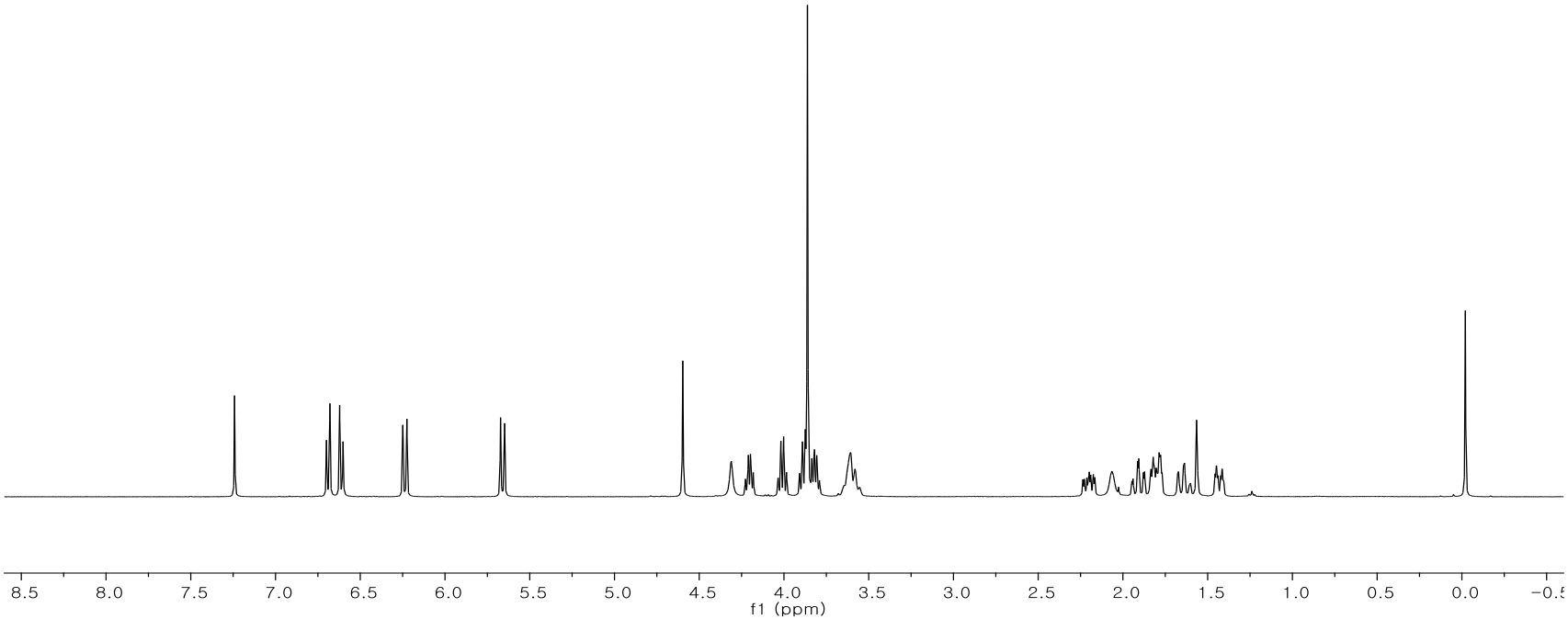

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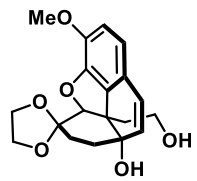

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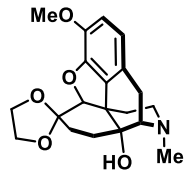

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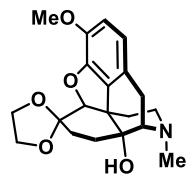

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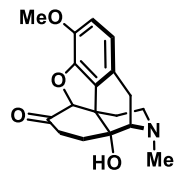

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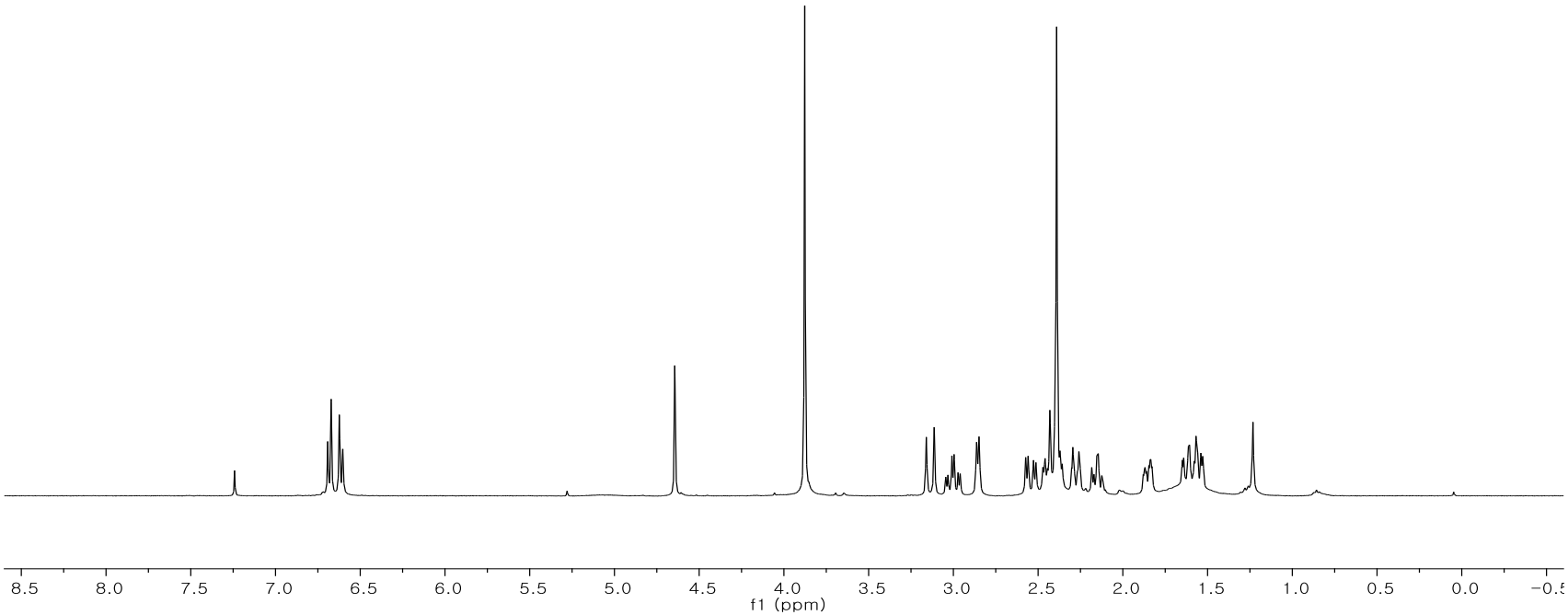

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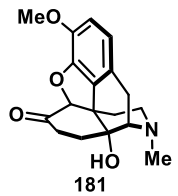

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LIST OF ABBREVIATIONS

Ac	acetate
ADDP	1,1’-(azodicarbonyl)dipiperidine
AIBN	azobisisobutyronitrile
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
Bu	butyl
CSA	camphorsulfonic acid
$Cy_3P{\cdot}HBF_4$	tricyclohexylphosphine tetrafluoroborate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
Et	ethyl
IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide
*m*CPBA	*meta*-chloroperoxy benzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
PCC	pyridinium chlorochromate
PIDA	(diacetoxyiodo)benzene

PIFA	[bis(trifluoroacetoxy)iodo]benzene
PTSA	*p*-toluenesulfonic acid
$Py{\cdot}HBr_3$	pyridinium tribromide
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	tert-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TPP	5,10,15,20-tetraphenyl-21*H*,23*H*-porphine
(*R*)-TRIP	(*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate
Ts	*p*-toluenesulfonyl
x-phox	2-dicyclohexylphosphino-2′,4′,6′ triisopropylbiphenyl

국문초록

모르핀은 식물로부터 유래된 알칼로이드 천연물로서 복잡한 구조로 인해 유기합성 화학자들로부터 많은 주목을 받아왔다. 첫 장에서는 중간체 50 의 합성을 위해 분자의 비대칭화 과정과 분자 내의 스테레오 센터 이전을 적용하였다. 이를 위해 oxidatative dearomatization, 디엘즈-알더 반응이 이루어 졌으며, 모르핀의 key quaternary center 와 phenanthrene의 핵심구조를 형성하게 된다. 두 번째 장에서는 (중간체 50)를 사용해 모르핀의 유도체인 디하이드로코디논과 디하이드로코딘을 합성 하였다. 이 과정에서 Beckmann 재배열 반응과 호프만 제거반응을 사용하여 알칼로이드 분자의 특징 중의 하나인 질소 원자를 효과적으로 삽입할 수 있었고, 알파 키토 옥시데이션 S_N2 반응을 통한 테트라히드로푸란링 합성, 그리고 reductive birch-type detosylation을 이용한 피페리딘링 합성이 진행되었다. 세 번째 장은, 앞서 서술 되었던 합성과 비교하여 더 높은 효율성을 가진 방식이 도입되었다. 이 과정에서 새로운 모르핀 유도체 옥시코돈을 합성 할 수 있었다. 광반응을 사용한 5각형 고리의 합성과 Rovis가 발표했던 asymmetric 비대칭성을 방식을 적용하여 광학활성이 있는 트리옥세인 169 을 합성 할 수 있었다.

주요어: 모르핀, 스테레오 센터 이전, 옥시코돈, Beckmann 재배열 반응, Hofmann 제거반응, 비대칭성, 광반응

학번: 2014-22396

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Finally, I would like to take the opportunity to especially thank my family for their moral support during my studies. Without their collective love and enduring support during

these very difficult time, this thesis completion would not have been possible. I want thank my family one more time and tell them I love them very much.