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Ruthenium Catalyzed Diol-Diene Cycloaddition And Progress Toward Total Synthesis of Andrographolide

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Ruthenium Catalyzed Diol-Diene Cycloaddition And Progress Toward Total Synthesis of Andrographolide

by

Binit Sharma Poudel

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the Requirements

for the Degree of

Master of Arts

The University of Texas at Austin

August 2019

Dedication

I dedicate this to my family, my parents who always supported me in whatever I wanted to study or pursue in my life.

To my loving and caring brother who always keeps motivating me.

To my cousin Ganga for her continuous support and for always being on my side while I was pursuing my studies in the United States.

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Abstract

Ruthenium Catalyzed Diol-Diene Cycloaddition And Progress Toward Total Synthesis of Andrographolide

Binit Sharma Poudel, M. A.

The University of Texas at Austin, 2019

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In the first chapter, an example of highly *exo*-selective ruthenium(0) catalyzed transfer hydrogenative cycloaddition is described. These ruthenium catalyzed reactions are analogous to traditional Diels-Alder reactions of cyclohexadiene or norbornadiene but are performed with 1,2-diols instead of the π-unsaturated partners. Novel bridged bicyclic ring systems are accessed from diol, ketol or dione oxidation level with excellent diasteroselectivity. In the second chapter, the ongoing efforts toward the total synthesis of andrographolide, a diterpenoid lactone, is described. The effort supports a modular strategy to use diene intermediate obtained from transformations of *tert*-hydroxy prenylation product via reaction with π-allyliridium C, O-benzoate complex.

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Chapter 1: Ruthenium(0) Catalyzed Transfer Hydrogenative [4+2] Cycloaddition of 1,2-Diols with Cyclohexadiene or Norbornadiene *

1.1 INTRODUCTION

Bridged carbocycles is a common structural motif found in naturally occurring or unnatural bioactive compounds.[1-2] Diels-Alder and homo-Diels-Alder reaction has been a classic way to access bridged compounds but is limited in its scope.[3] Since the discovery, there has been development of different variations of these reactions. The most powerful method to construct these motifs is transition-metal catalyzed cycloadditions; however, most of the method only uses π-unsaturated reactants.[3-4] Transition metal catalyzed cycloadditions[5] consist of a broad class of C-C bond formations and are typically conducted in a redox-neutral mode.[6-7]

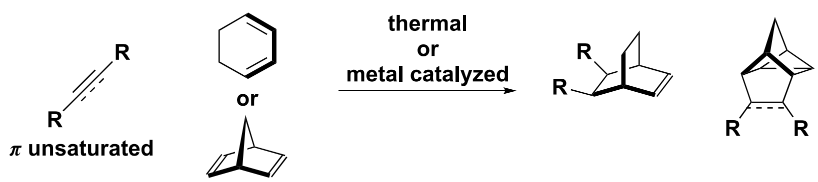


Figure 1.1 Classical Diels-Alder and homo-Diels-Alder reaction to access bridged carbocycles.

In connection with the development of ruthenium catalyzed hydrogen transfer reactions, Chatani and Murai reported the first oxidative coupling reactions using ruthenium(0).[8] A Pauson-Khand type conversion of alpha keto esters and ethylene in

*This chapter is partially based on the previous published work:
Sato, H.; Fukaya, K.; Poudel, B. S.; Krische, M. J. *Angew. Chem. Int. Ed.* **2017,** 56, 14667. B. S contributed to increase the substrate scope of the reactions (Table 1.3) and in optimization of the reaction in Schemes 1.1 and 1.2.

presence of carbon monoxide to obtain five membered lactones. Then, in 2011 Beller reported the borrowing-hydrogen, hydrogen autotransfer, process to convert alpha hydroxy amides to alpha amino amides (Figure 1.2). The domino sequence of insitu dehydrogenation followed by condensation and final hydrogenation yields the product and regenerates the catalyst.[9] Inspired by these outstanding body of work, these properties of Ru_3Co_{12} catalyst was used in the first transfer hydrogenative diene-carbonyl oxidative coupling by Krische group in 2012.[10]

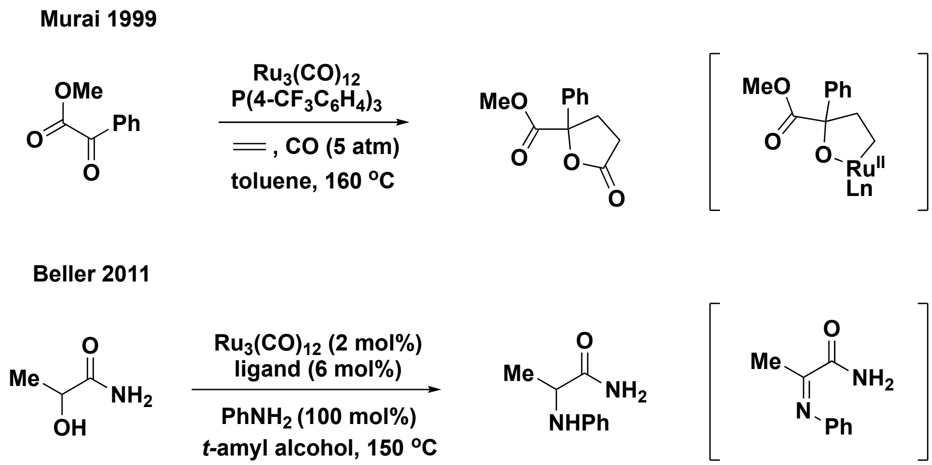


Figure 1.2 Seminal reports of oxidative coupling and hydrogen autotransfer process of Ru_3CO_{12} catalyst.

Following the report in 2012, investigations of ruthenium catalyzed transfer hydrogenative reactions were started. During further development of catalytic transfer hydrogenative coupling reactions that convert lower alcohols to higher alcohols,[11-12] it was recently discovered [4+2] cycloaddition of acyclic dienes with 1,2-diols (or α-ketols, 1,2-diones) to form substituted cyclohexene diols (Figure 1.3).[13-14] These unusual cycloadditions occur through a catalytic mechanism involving diol dehydrogenation to form a vicinal dicarbonyl species, which upon oxidative coupling forms a ruthenacyclic intermediate.[15] Then, intramolecular carbonyl allylruthenation followed by transfer hydrogenolysis provides the cycloadduct and return ruthenium to its zero-valent form.

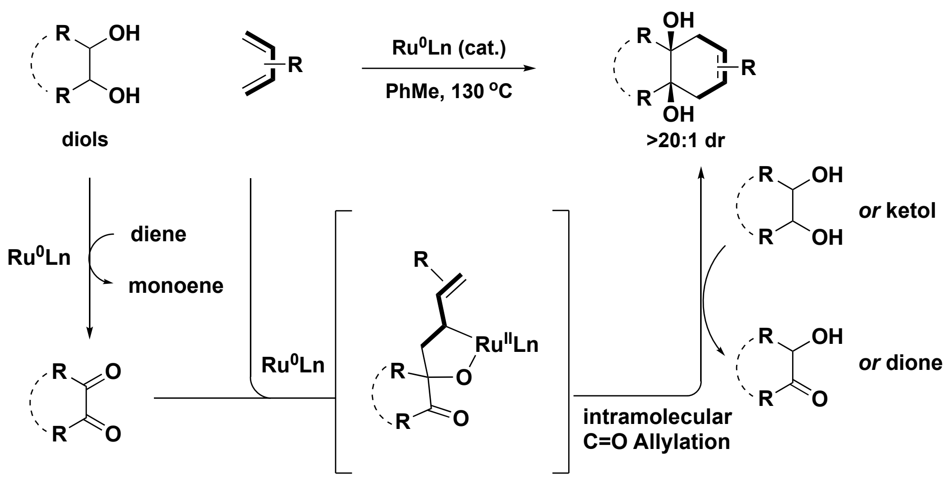


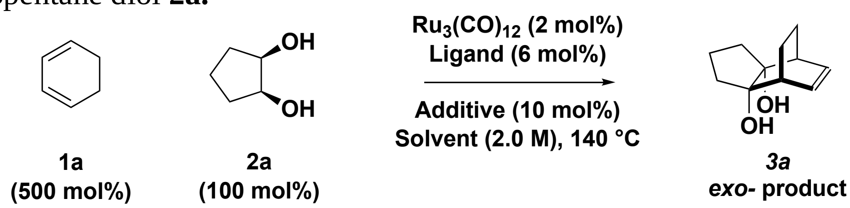
Figure 1.3 Proir work of ruthenium(0) catlayzed diene-diol cycloaddition using acyclic dienes.

The use of cyclic dienes, such as cyclohexadiene, and related compounds, such as norbornadiene, would represent a signficiant expansion in scope by providing access to bridged carbocycles from abudant chemical feedstocks. These can provide structures beyond those accessible via classical cycloaddition methodology. However, competing aromatization (CHD to benzene) and catalyst deactivation (Ru-NBD complexes) can impose significant challenges to overcome. Here, cyclohexadiene and norbornadiene can be used as efficient partners for diol-mediated cycloaddition, delivering bridged carbocycles with complete levels of *exo*-selectivity.

1.2 REACTION DEVELOPMENT AND SCOPE

In the initial investigation of cycloaddition, cyclohexadiene **1a** and cyclopentane diol **2a** was subjected to the ruthenium catalyst formed in situ from $Ru_3(CO)_{12}$ and different phosphine ligands. It was observed that the ruthenium(0) catalyst modified by bis(diphenylphosphino)ethane (dppe) gave the hydroxy-substituted bridged bicycle **3a** with 77% yield and complete *exo*-selectivity. In order to optimize the reaction, different solvents and neat conditions were tried (Table 1.1), where toluene gave the best result. According to the literature, carboxylic acids are known to co-catalyze the hydrogenolysis and transfer hydrogenolysis of metallacycles.[16] So, a series of carboxylic acids were investigated under the reaction condition. To our delight, presence of 3,5-dimethylbenzoic acid (10 mol%) gave 95% yield after isolation using silica gel chromatography. Reactions without ruthenium (entry 1) or ligand (entry 2) gave no product.

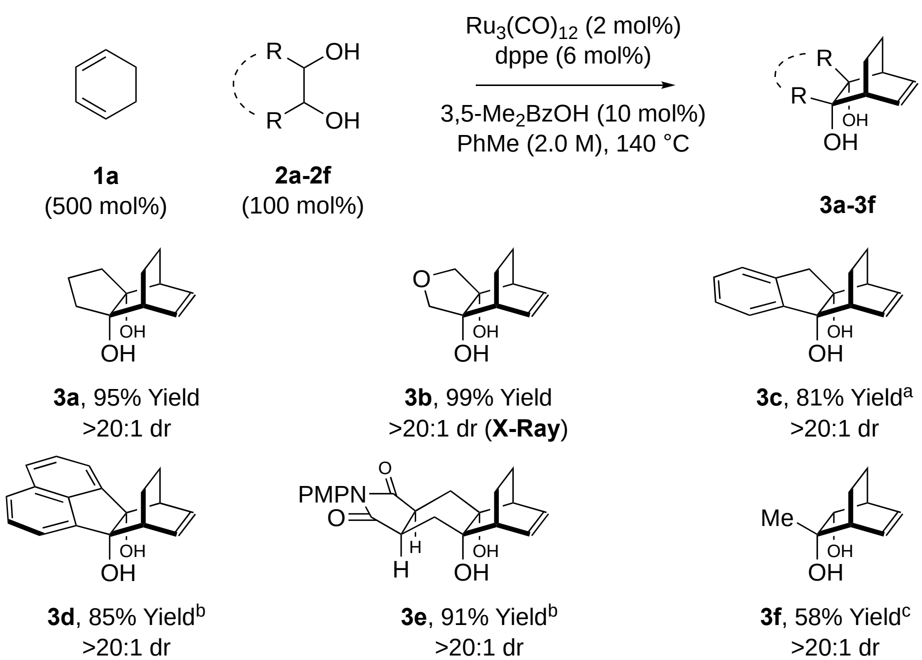
Table 1.1: Conditions for optimization of reaction using cyclohexadiene **1a** and cyclopentane diol **2a.**



Entry	Ligand	Solvent	Additive	Yield (%)
1[a]	-	PhMe	-	n.d.
2	-	PhMe	-	n.d.
3	dppm	PhMe	-	trace
4	**dppe**	**PhMe**	**-**	**77**
5	dCype	PhMe	-	59
6	dppp	PhMe	-	65
7	BINAP	PhMe	-	60
8	dppe	PhMe	-	77
9	dppe	*m*-Xylene	-	70
10	dppe	Dioxane	-	62
11	dppe	neat	-	67
12	dppe	PhMe	Ad-COOH	36
13	dppe	PhMe	H_2O (PhMe:H_2O = 1:1)	82
14	**dppe**	**PhMe**	**3,5-Me_2BzOH**	**95**

With the initial results in hand, we explored the scope of the diols for this cycloaddition reaction. As shown in Table 1.2**,** the condition allowed conversion of cyclic diols **2a-2e** and acyclic diol **2f** to the corresponding [4+2] cycloaddition products in good to excellent yields with complete *exo*-selectivity (Table 1.2). It was observed that the cycloaddition reaction was insensitive to the diol stereochemistry. Also, acyclic diol **2f** gave a reasonable yield 58% along with the ketol dehydro-**3f.**

Table 1.2: Ruthenium-catalyzed cycloaddition of cyclohexadiene **1a** with diols **2a-2f** to form bridged bicycles **3a-3f**.*

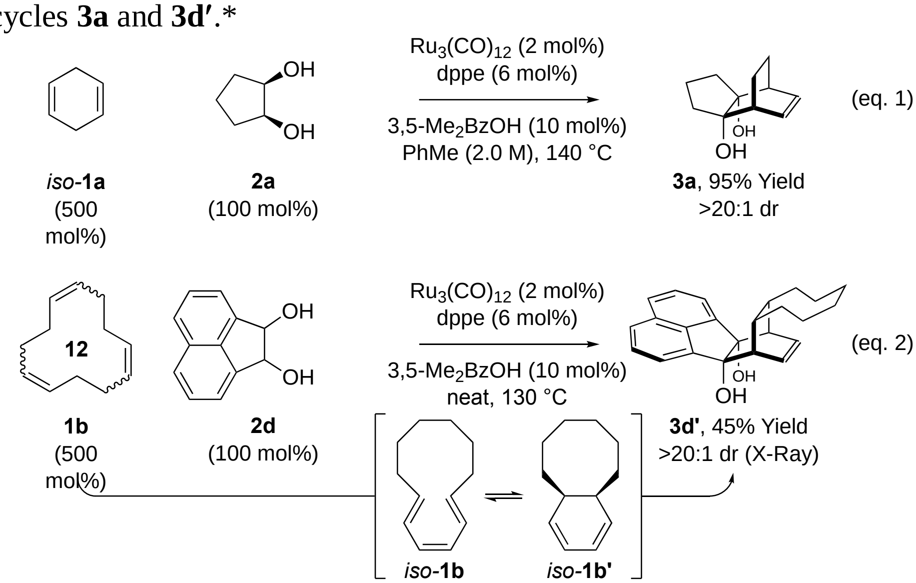


[a] rac-BINAP (6 mol%), [b] without 3,5-Me_2BzOH, 150 °C, [c] dCype (6 mol%)

*Yields are of material isolated by flash silica gel chromatography.

$Ru_3(CO)_{12}$ catalyzed olefin isomerization is known in the literature.[17] This gave an idea of engaging non-conjugated dienes in the [4+2] cycloaddition reaction. When 1,4 cyclohexadiene *iso*-**1a** was subjected to the standard condition with cyclopentane diol **2a**, the formation of bridged bicycle **3a** was observed in 95% yield (eq. 1, Scheme 1.1) A powerful application of tandem olefin isomerization–cycloaddition was found in the reaction of 1,5,9-cyclododecatriene **1b** with diol **2d** to form cycloadduct **3d′** (eq. 2, Scheme 1.1). Here, olefin isomerization generates a conjugated triene iso-**1b**, which exists in equilibrium with the corresponding [6.4.0] bicycle iso-**1b′** through electrocyclization.[18] Ruthenium(0) catalyzed cycloaddition onto the [6.4.0] bicycle provides cycloadduct **3d′** as a single diastereomer.

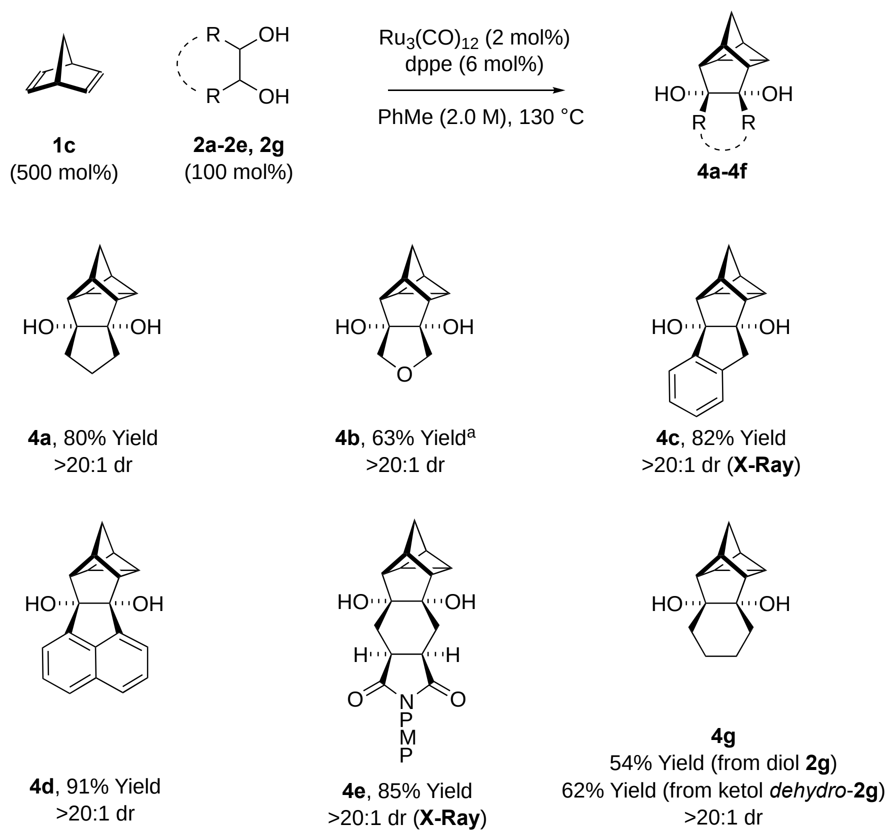
Scheme 1.1: Tandem olefin isomerization-cycloaddition reactions to formed bridged carbocycles **3a** and **3d′**.*



*Yields are of material isolated by flash silica gel chromatography.

Since 1958, norbornadiene **1c** has been known to undergo thermal homo-Diels-Alder reactions.[19] Subsequently, various reports of metal catalyzed dimerization of norbornadiene[20] and metal catalyzed cycloadditions[21] appeared in the literature. With the precedent of norbornadiene **1c** used in homo-Diels-Alder reactions, the ruthenium catalyzed cycloaddition was attempted using norbornadiene **1c** and cyclic diols **2a-2e** and **2g**. To our delight, only a minor adjustment of temperature gave the desired product in good yields with complete *exo*-selectivity. This reaction did not require any acid additive and cyclic diols **2a-2e** and **2g** gave their corresponding bridged products **4a-4g** (Table 1.3). Unlike cyclohexadiene, norbornadiene did not undergo cycloaddition with the acyclic diols.

Table 1.3: Ruthenium catalyzed cycloaddition of norbornadiene **1c** with diols **2a-2f** to form bridged bicycles **4a-4e**, **4g.***

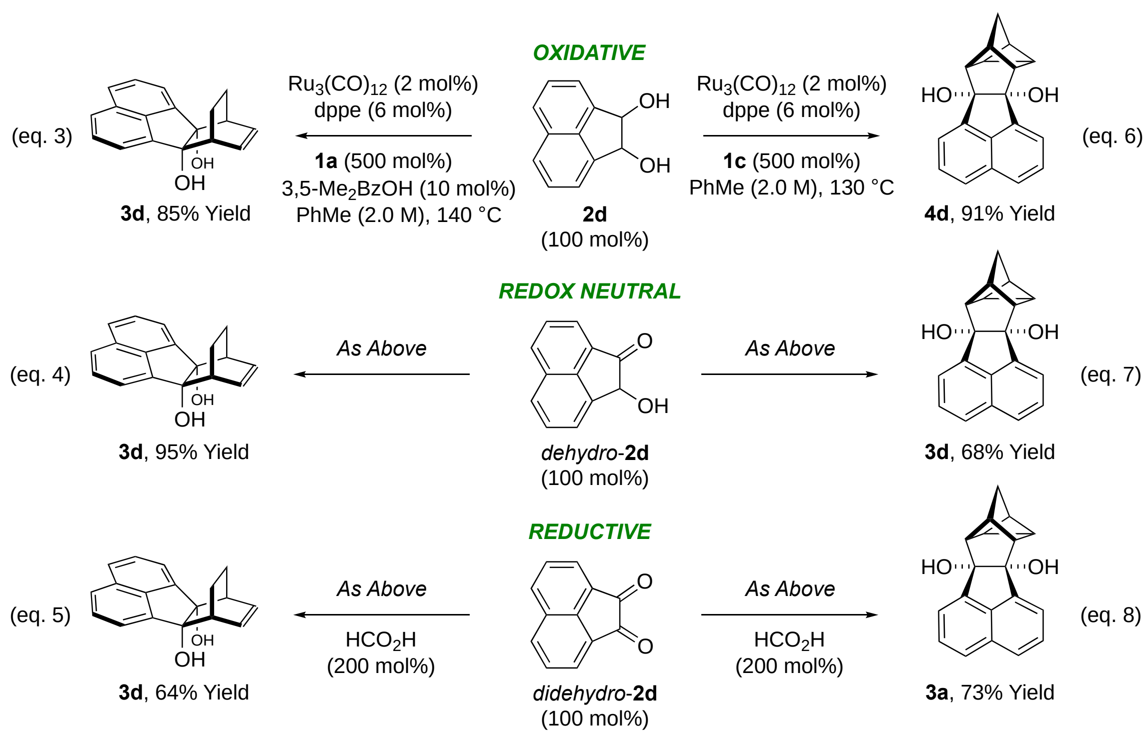


[a] dppb (6 mol%), 150 °C, dioxane (2.0 M)

*Yields are of material isolated by flash silica gel chromatography.

The above-mentioned cycloaddition reactions can be performed from diol, ketol or dione oxidation level. The reactions of dienes **1a** and **1c** with ketol dehydro-**2d** (Scheme 1.2, eq. (4) and (7)) or dione didehydro-**2d** (Scheme 1.2, eq. (5) and (8)), a redox-neutral and reductive cycloaddition is also possible. For these reactions, redox-neutral cycloadditions do not require a sacrificial oxidant or reductant, whereas oxidative processes use one equivalent of diene as a sacrificial hydrogen acceptor and reductive cycloadditions was mediated by formic acid (200 mol %) that generate carbon dioxide as the sole stoichiometric byproduct.

Scheme 1.2. Redox level independent cycloaddition of cyclohexadiene **1a** and norbornadiene **1c** with diol **2d**, ketol *dehydro*-**2d** and dione *didehydro*-**2d**.*

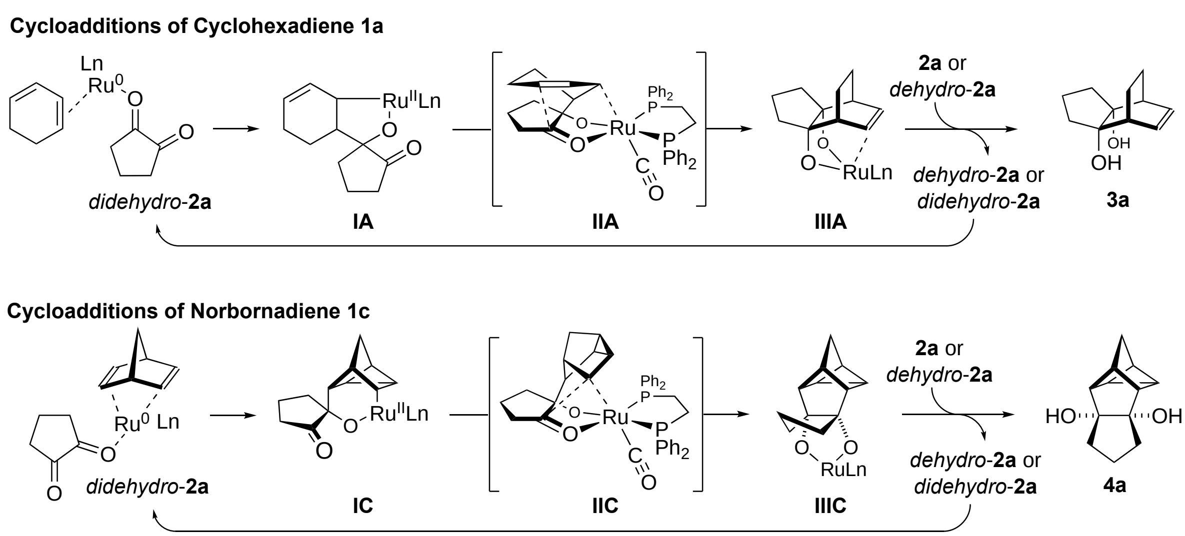


*Yields are of material isolated by flash silica gel chromatography.

1.3 MECHANISM AND DISCUSSION

A general catalytic mechanism is proposed along with a stereochemical model accounting for *exo*-selectivity, in couplings of cyclohexadiene **1a** and norbornadiene **1c** with diol **2a** (Scheme 1.3). The cycloaddition is started via dehydrogenation of diol **2a** to the dione didehydro-**2a**. Reversible ruthenium(0)-mediated oxidative coupling of dione didehydro-**2a** to cyclohexadiene **1a** and norbornadiene **1c** provides oxa-ruthenacycles **IA** and **IC**, respectively.[8] A second C-C bond is formed in a diastereoselective fashion by way of structures **IIA** and **IIC**. The resulting metallacycles **IIIA** and **IIIC** undergoes transfer hydrogenolytic cleavage mediated by diol or ketol releasing the cycloadducts **3a** and **4a**. The carboxylic acid co-catalyst is proposed to accelerate transfer hydrogenolysis of the sterically congested metallacycle **IIIA** via protonolytic cleavage of a ruthenium–oxygen bond to form a more accessible and labile ruthenium carboxylate.[22]

Scheme 1.3. General mechanism and stereochemical model accounting for exo-selectivity.



1.4 CONCLUSION

A highly *exo*-selective ruthenium(0) catalyzed transfer hydrogenative cycloaddition of cyclohexadiene or norbornadiene with 1,2-diols to access bridged bicycles is explained. A significant feature includes that these transformations are redox-independent in nature, and the cycloaddition can be conducted from the diol, ketol or dione oxidation levels. The reaction condition also allows in-situ isomerization of the olefin and the subsequent cycloaddition that further enhances the substrate scope. This work contributes to the ruthenium(0) catalyzed transfer hydrogenative cycloadditions, where lower alcohols are converted to higher alcohols in the absence of stoichiometric metals.

1.5 EXPERIMENTAL DETAILS

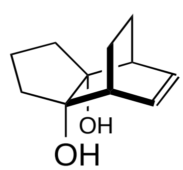
General Comments

All glassware was oven dried overnight and cooled in a desiccator. All ruthenium catalyzed reactions were carried in sealed pressure tubes (13 x 100 mm). THF was purified by distillation from sodium and benzophenone immediately before use. Ruthenium carbonyl [$Ru_3(CO)_{12}$], dppe, dCype, *rac*-BINAP, dppb, 3,5-dimethylbenzoic acid, dienes **1a**, *iso*-**1a**, triene **1b** and norbornadiene **1c** were purchased from commercial suppliers and used as received. Diols **2a**, **2f** and **2g** were purchased from commercially available sources and used without purification. **2b**,[1] **2c**,[2] **2d**[3] and **2e**[4] were prepared according to previous literature. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was accomplished with UV light followed by dipping in a cerium ammonium molybdate solution and heating. Purification of reaction products was carried out by flash column chromatography using 40-63 μm silica gel. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded with a Bruker AVANCE III (500 MHz supported by NSF grant 1 S10 OD021508-01) spectrometer in $CDCl_3$ solutions unless otherwise noted. ^{13}C NMR spectra were routinely run with broadband decoupling. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.26 ppm and triplet at 77.0 ppm, respectively). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), etc. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Mass spectra (MS) were obtained on Agilent Technologies 6530 Accurate-Mass Q-TOF and are reported as m/z. Masses are reported for the molecular ion (M-H, M, M+H or M+Na).

General Procedure and Spectral Data for Cycloaddition Reactions with Cyclohexadiene

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (3.8 mg, 0.006 mmol, 2 mol%), dppe (7.2 mg, 0.018 mmol, 6 mol%), 3,5-Me_2BzOH (4.5 mg, 0.03 mmol, 10 mol%), diol (0.3 mmol, 100 mol%) and 1,3 cyclohexadiene (1.5 mmol, 500 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.15 mL, 2.0 M) was added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 140 ˚C for 40 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the desired product **3a-3f**.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-2,3,4,7-tetrahydro-1*H*-4,7-ethanoindene-3a,7a-diol (3a)



The reaction was conducted with *cis*-cyclopentane-1,2-diol **2a** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 25:75) provided the title compound **3a** (51.2 mg, 0.29 mmol) in 95% yield as a white solid.

<u>TLC (SiO_2)</u>: R_f = 0.30 (AcOEt:hexanes = 3:7).

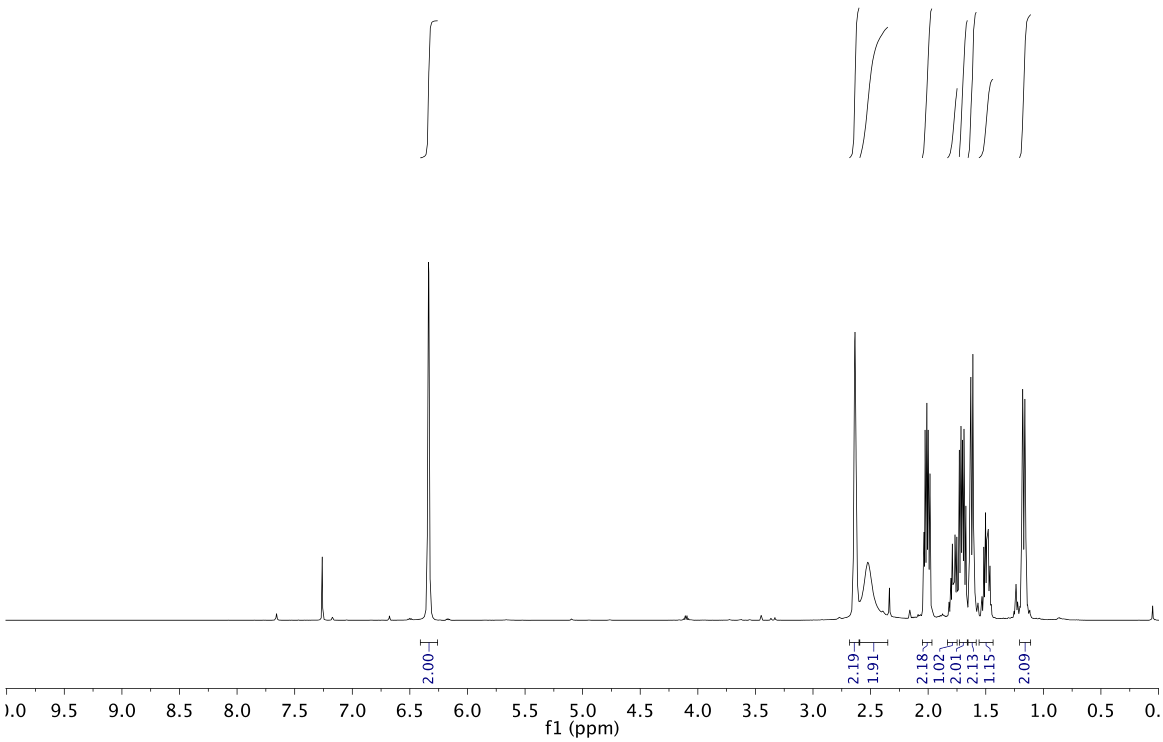
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 6.34 (dd, 4.5, 3.0 Hz, 2H), 2.64 (dt, *J* = 5.1, 2.7 Hz, 2H), 2.59 – 2.35 (m, 2H), 2.05 – 1.97 (m, 2H), 1.83 – 1.75 (m, 1H), 1.70 (dt, *J* = 14.6, 7.4 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.49 (m, 1H), 1.21 – 1.11 (m, 2H) ppm.

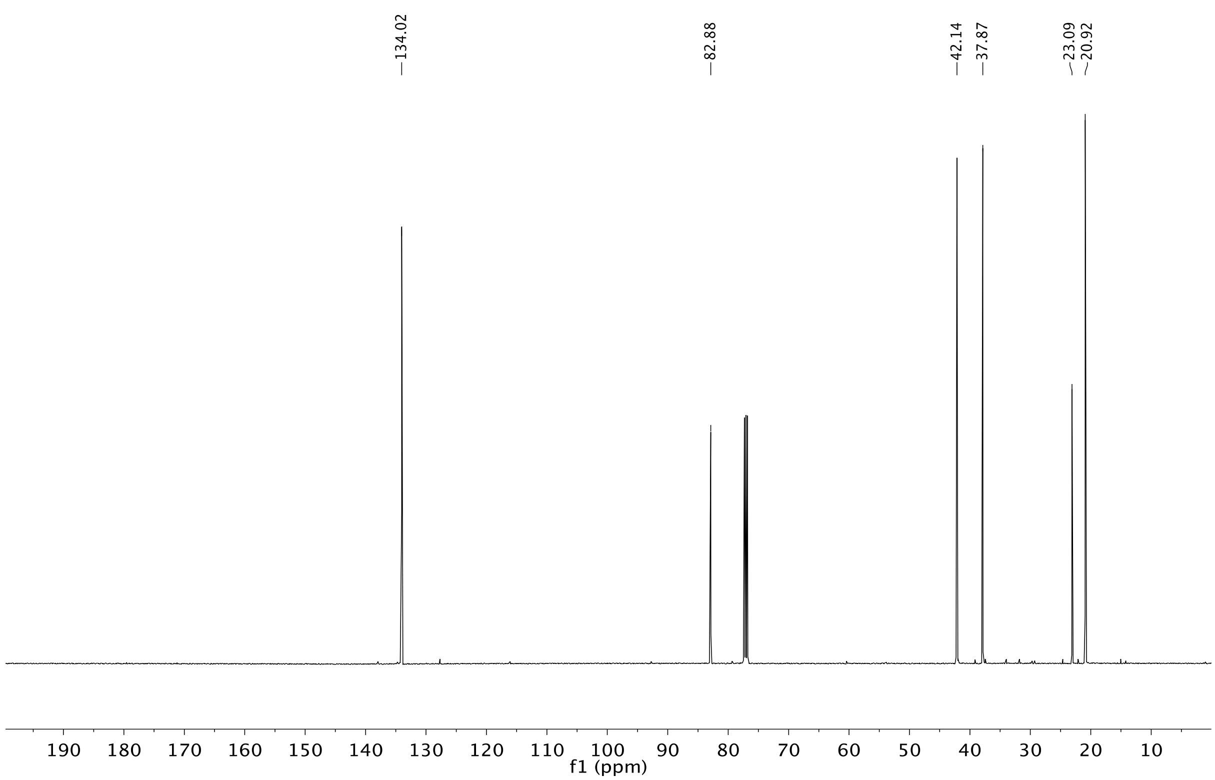
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 134.0, 82.9, 42.1, 37.9, 23.1, 20.9 ppm.

MP: 106.5-110.8 °C.

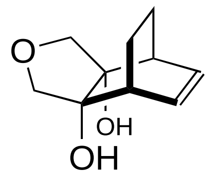
HRMS: (ESI) Calculated for $C_{11}H_{16}O_2Na$ [M+Na$^+$] = 203.1043, Found 203.1041.

FTIR: (neat): 2970, 2363, 2342, 1738 cm^{-1}.


2.00
2.19
1.91
2.18
1.02
2.01
2.13
1.15
2.09
f1 (ppm)


134.02
82.88
42.14
37.87
23.09
20.92
f1 (ppm)

(3a*RS*,4*RS*,7*SR*,7a*SR*)-4,7-dihydro-4,7-ethanoisobenzofuran-3a,7a(1*H*,3*H*)-diol (3b)



The reaction was conducted with *cis*-3,4-tetrahydrofuran diol **2b** in accordance with the general procedure. Flash column chromatography (AcOEt:hexanes = 80:20) provided the title compound **3b** (54.1 mg, 0.30 mmol) in 99% yield as a white solid.

TLC (SiO_2): R_f = 0.45 (AcOEt:hexanes = 8:2).

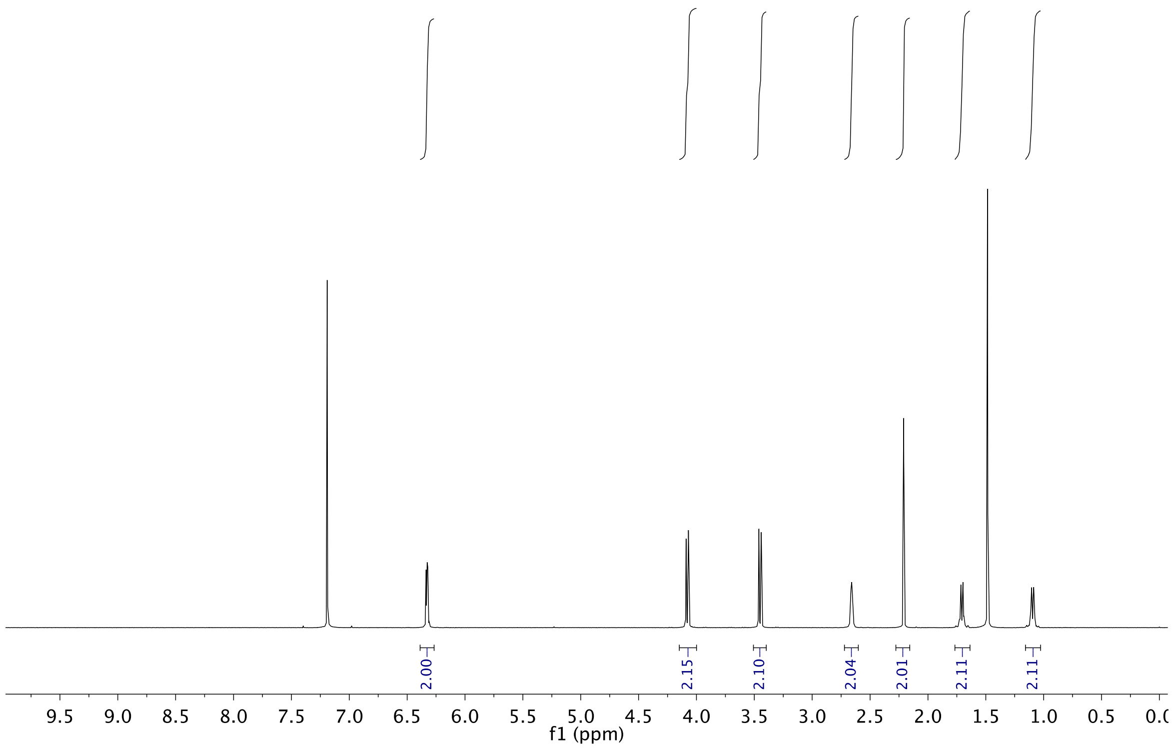
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 4.5, 3.0 Hz, 2H), 4.08 (d, *J* = 10.0 Hz, 2H), 3.45 (d, *J* = 10.0 Hz, 2H), 2.66 (dt, *J* = 4.6, 2.7 Hz, 2H), 2.21 (s, 2H), 1.77 – 1.64 (m, 2H), 1.16 – 1.03 (m, 2H) ppm.

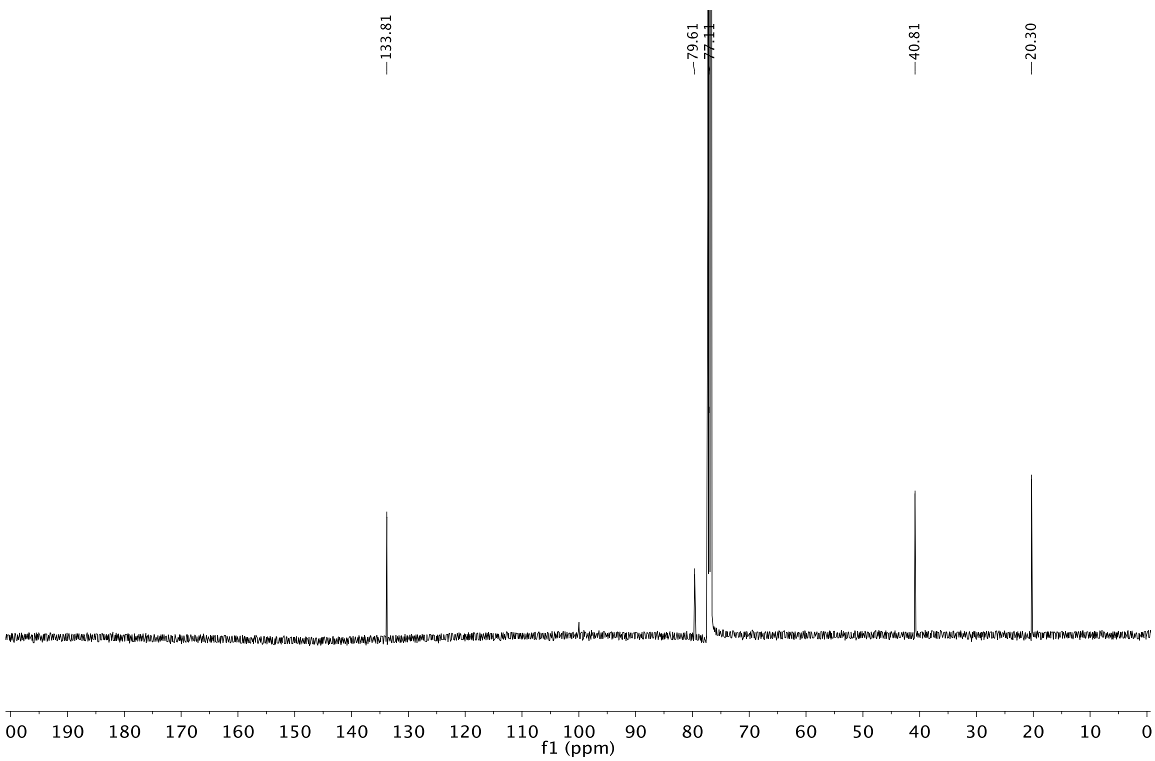
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 133.8, 79.6, 77.1, 40.8, 20.3 ppm.

MP: decomposed at 240 °C.

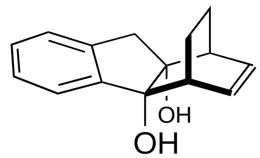
HRMS: (ESI) Calculated for $C_{10}H_{14}O_3Na$ [M+Na$^+$] = 205.0835, Found 2085.0836.

FTIR: (neat): 3400, 2869, 2364 cm^{-1}.


2.00
2.15
2.10
2.04
2.01
2.11
2.11
9.5 9.0 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
f1 (ppm)


133.81
79.61
77.11
40.81
20.30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(1*RS*,4*SR*,4a*SR*,9a*SR*)-1,4-dihydro-4a*H*-1,4-ethanofluorene-4a,9a(9*H*)-diol (3c)



The reaction was conducted with mixture of *trans*- and *cis*- 1,2-dihydroindenediol **2c** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 20:80) provided the title compound **3c** (55.5 mg, 0.24 mmol) in 81% yield as a white solid.

TLC (SiO_2): R_f = 0.30 (AcOEt:hexanes = 3:7).

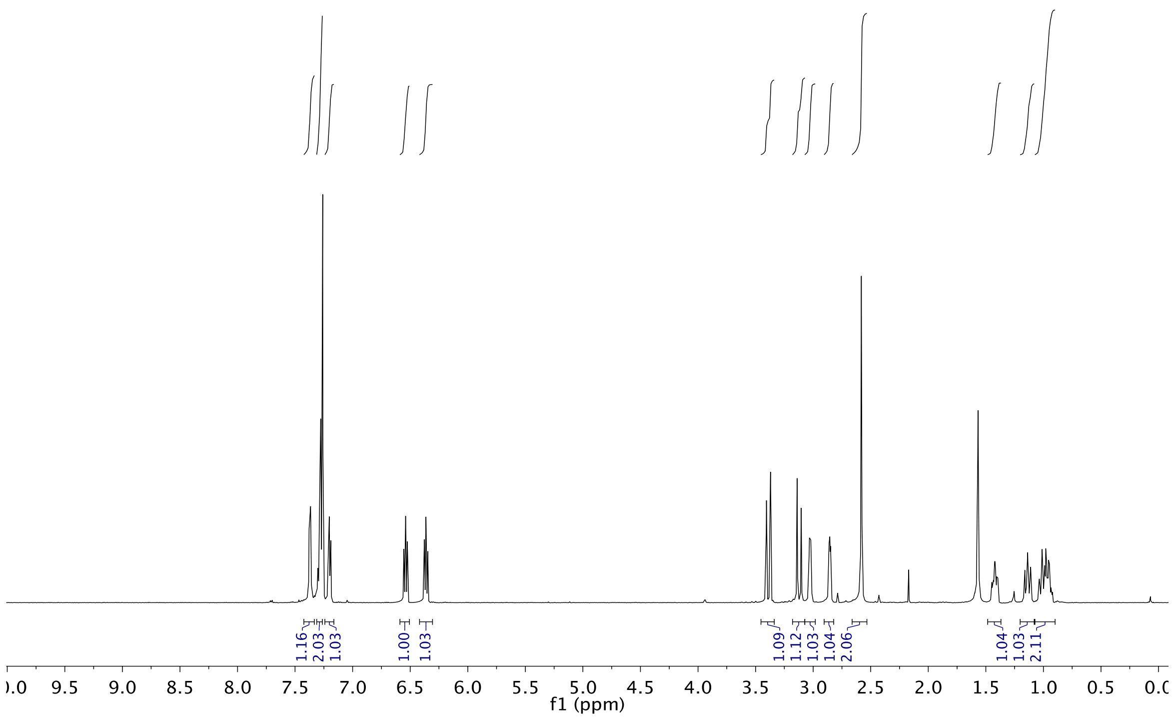
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.28 (td, *J* = 5.8, 5.1, 2.6 Hz, 2H), 7.20 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.54 (ddd, *J* = 7.7, 6.3, 1.1 Hz, 1H), 6.36 (dd, *J* = 7.9, 6.5 Hz, 1H), 3.39 (d, *J* = 17.8 Hz, 1H), 3.12 (d, J = 17.8 Hz, 1H), 3.03 (dt, *J* = 6.5, 2.9 Hz, 1H), 2.86 (dt, *J* = 5.1, 2.1 Hz, 1H), 2.58 (s, 2H), 1.42 (dddd, *J* = 13.7, 9.5, 4.7, 2.1 Hz, 1H), 1.14 (ddt, *J* = 13.4, 11.6, 4.1 Hz, 1H), 1.07 – 0.90 (m, 2H).

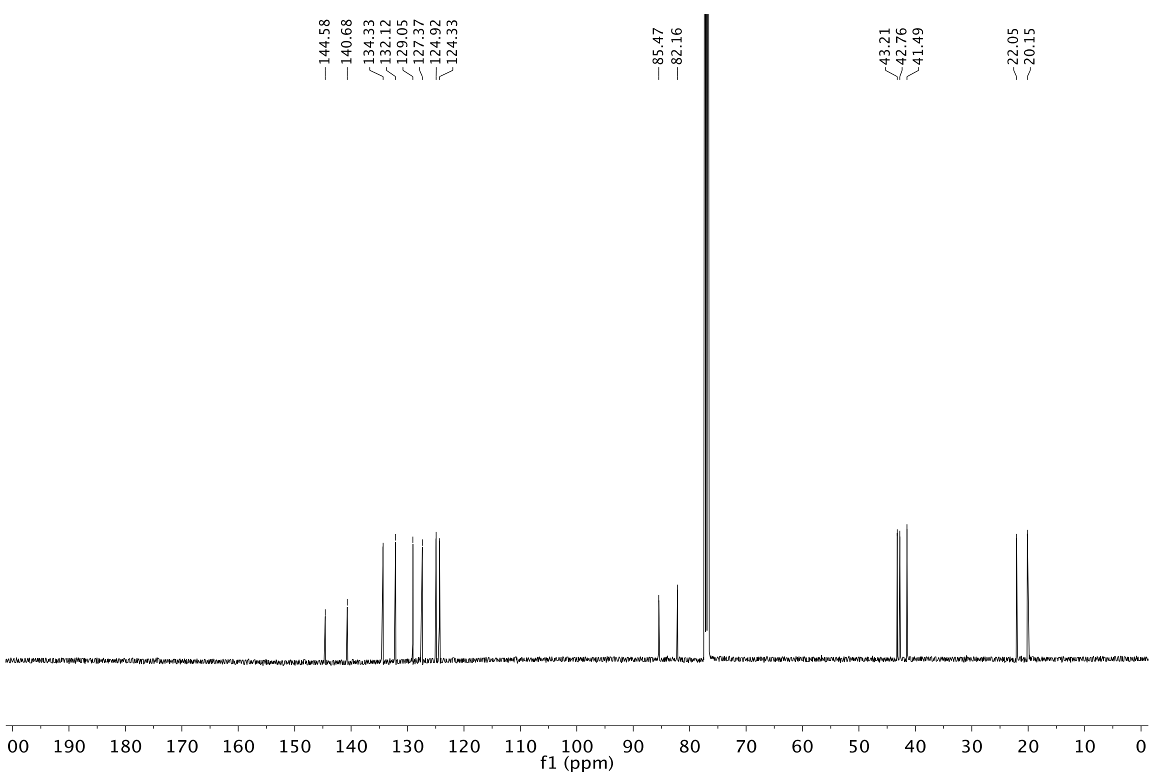
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 144.6, 140.7, 134.3, 132.1, 129.1, 127.4, 124.9, 124.3, 85.5, 82.2, 43.2, 42.8, 41.5, 22.1, 20.2 ppm.

MP: 114.2-116.8 °C.

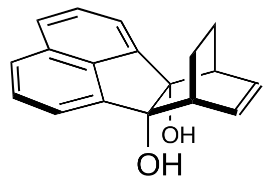
HRMS: (ESI) Calculated for $C_{15}H_{16}O_2Na$ [M+Na$^+$] = 251.1043, Found 251.1044.

FTIR: (neat): 3304, 2947, 2364, 1739 cm^{-1}.


1.16
2.03
1.03
1.00
1.03
1.09
1.12
1.03
1.04
2.06
1.04
1.03
2.11
f1 (ppm)


144.58
140.68
134.33
132.12
129.05
127.37
124.92
124.33
85.47
82.16
43.21
42.76
41.49
22.05
20.15
f1 (ppm)

(6b*RS*,7*RS*,10*SR*,10a*SR*)-7,10-dihydro-7,10-ethanofluoranthene-6b,10a-diol (3d)



The reaction was conducted with mixture of *trans*- and *cis*- acenaphthylene diol **2d** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 15:85) provided the title compound **3d** (67.5 mg, 0.26 mmol) in 85% yield as a white solid.

<u>TLC (SiO_2)</u>: R_f = 0.35 (AcOEt:hexanes = 3:7).

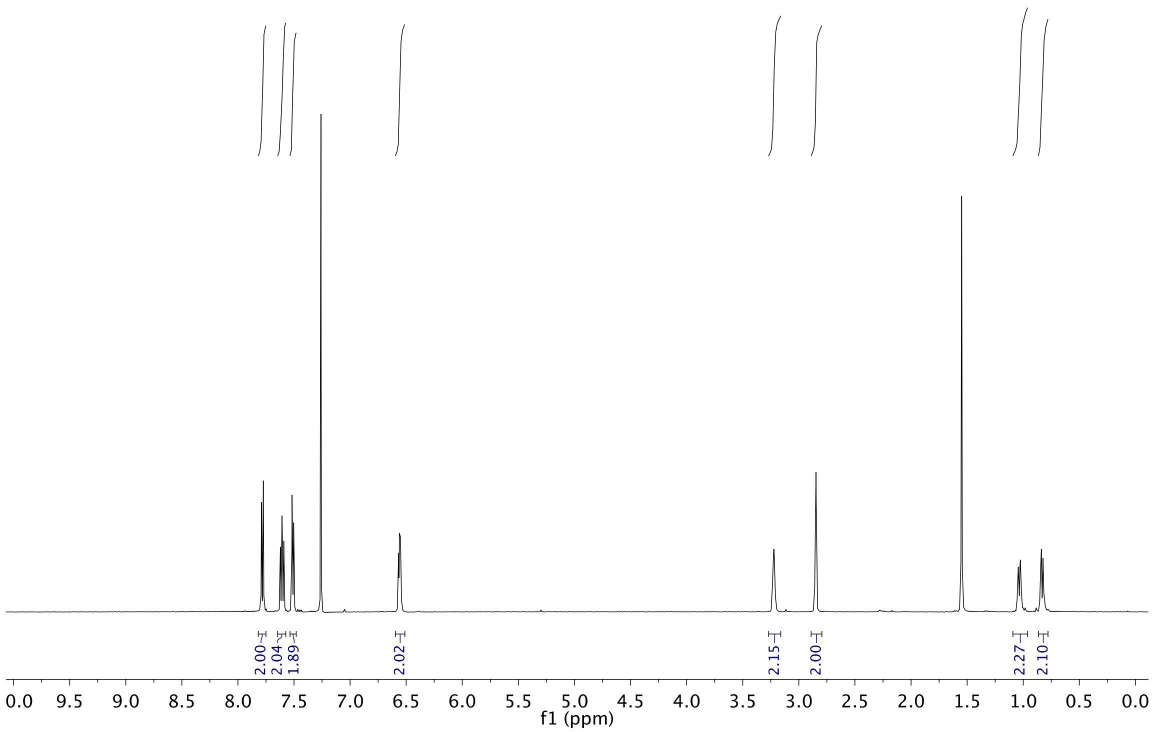
<u>^{1}H NMR</u>: (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.51 (d, *J* = 6.9 Hz, 2H), 6.56 (dt, *J* = 5.7, 2.9 Hz, 2H), 3.22 (dt, *J* = 5.3, 2.8 Hz, 2H), 2.85 (d, *J* = 1.3 Hz, 2H), 1.09 – 0.96 (m, 2H), 0.86 – 0.78 (m, 2H) ppm.

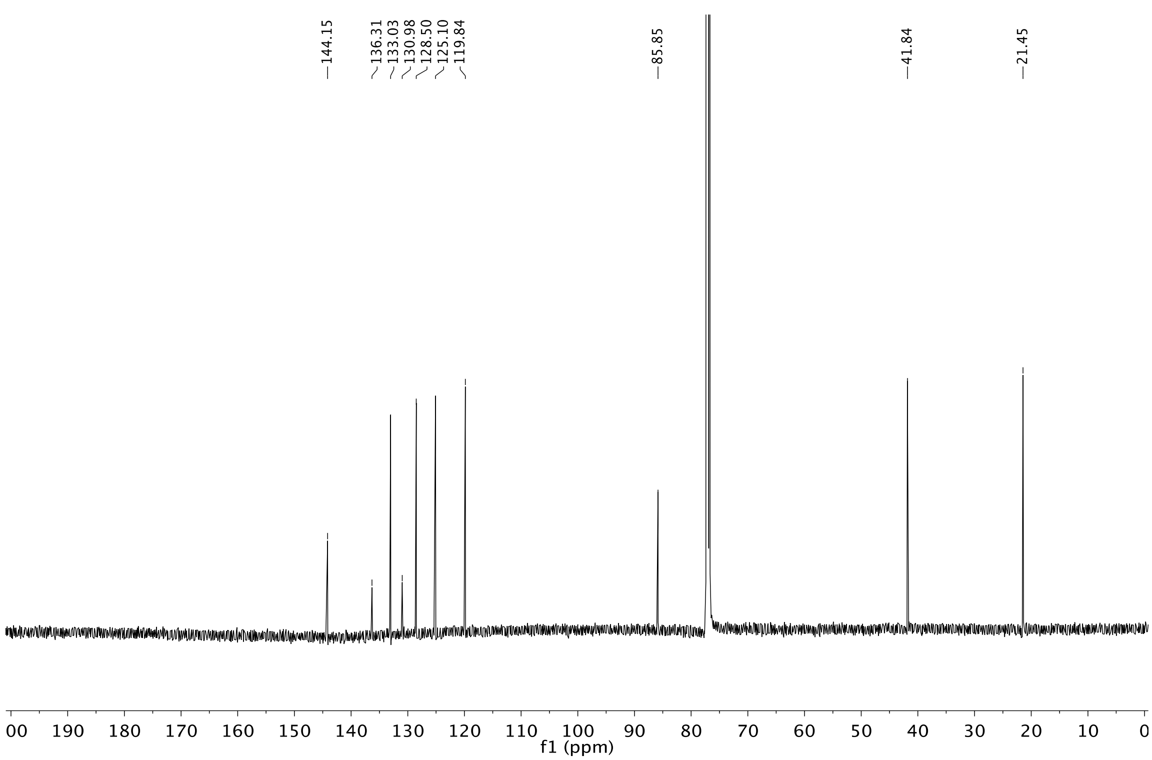
<u>^{13}C NMR:</u> (125 MHz, $CDCl_3$): δ = 144.2, 136.3, 133.0, 131.0, 128.5, 125.1, 119.8, 85.9, 41.8, 21.5 ppm.

<u>MP</u>: 195.5-197.0 °C.

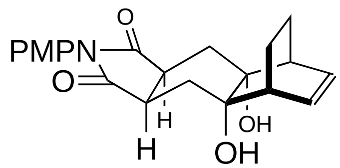
<u>HRMS</u>: (ESI) Calculated for $C_{18}H_{16}O_2Na$ [M+Na$^+$] = 287.1043, Found 287.1047.

<u>FTIR</u>: (neat): 3410, 2365, 1739 cm^{-1}.


2.00
2.04
1.89
2.02
2.15
2.00
2.27
2.10
f1 (ppm)


144.15
136.31
133.03
130.98
128.50
125.10
119.84
85.85
41.84
21.45
f1 (ppm)

(3a*RS*,4a*SR*,5*RS*,8*SR*,8a*RS*,9a*SR*)-4a,8a-dihydroxy-2-(4-methoxyphenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-1*H*-5,8-ethanobenzo[*f*]isoindole-1,3(2*H*)-dione (3e)



The reaction was conducted with (3a*RS*,5*RS*,6*SR*,7a*SR*)-5,6-phthalimide diol **2e** without 3,5-Me_2BzOH at 150 ˚C. Flash column chromatography (SiO_2, AcOEt:hexanes = 70:30) provided the title compound **3e** (99.6 mg, 0.27 mmol) in 91% yield as a white solid.

TLC (SiO_2): R_f = 0.35 (AcOEt:hexanes = 8:2).

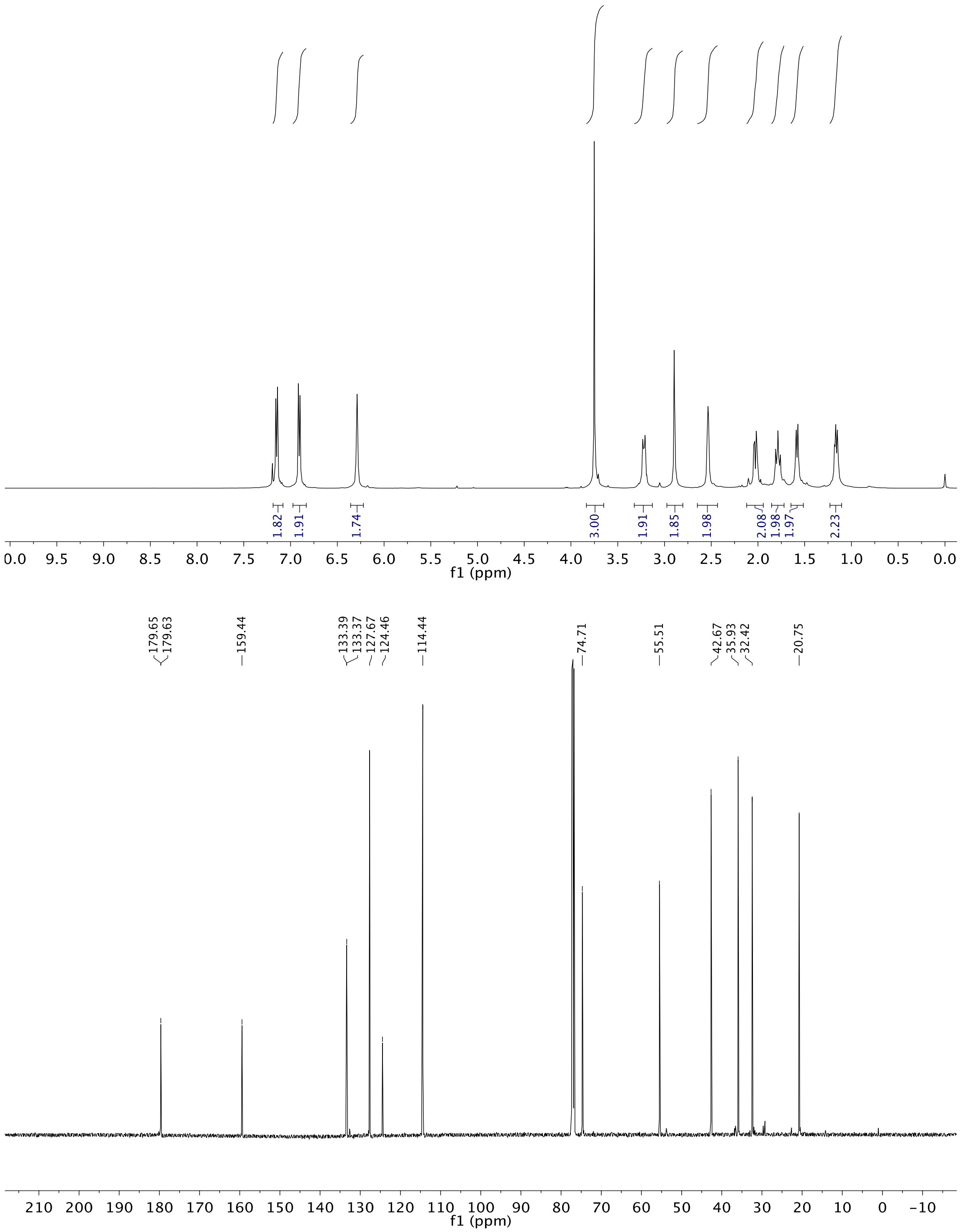
^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.29 (t, *J* = 3.8 Hz, 2H), 3.75 (s, 3H), 3.23 (m, 2H), 2.90 (s, 2H), 2.53 (d, *J* = 4.2 Hz, 2H), 2.12 – 1.94 (m, 2H), 1.79 (t, *J* = 12.8 Hz, 2H), 1.58 (t, *J* = 7.7 Hz, 2H), 1.23 – 1.11 (m, 2H) ppm.

^{13}C NMR: (125 MHz, $CDCl_3$): δ = 179.7, 179.6, 159.4, 133.4, 133.4, 127.7, 124.5, 114.4, 74.7, 55.5, 42.7, 35.9, 32.4, 20.8 ppm.

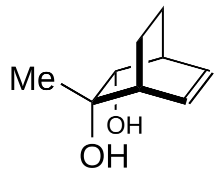
MP: 230.6-240.2 °C.

HRMS: (ESI) Calculated for $C_{21}H_{32}O_5Na$ [M+Na$^+$] =392.1468, Found 392.1468.

FTIR: (neat): 3487, 2946, 2364, 1693, 1514 cm^{-1}.


1.82
1.91
1.74
3.00
1.91
1.85
1.98
2.08
1.98
1.97
2.23
f1 (ppm)
179.65
179.63
159.44
133.39
133.37
127.67
124.46
114.44
74.71
55.51
42.67
35.93
32.42
20.75
f1 (ppm)

(1*RS*,2*SR*,3*RS*,4*SR*)-2-methylbicyclo[2.2.2]oct-5-ene-2,3-diol (3f)



The reaction was conducted with 1,2-propanediol **1f** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 30:70) provided **S1** (5.5 mg, 0.04 mmol) in 13% as yellow liquid, and (AcOEt:hexanes = 60:40) the title compound **3f** (26.8 mg, 0.17 mmol) in 58% yield as slightly yellow liquid.

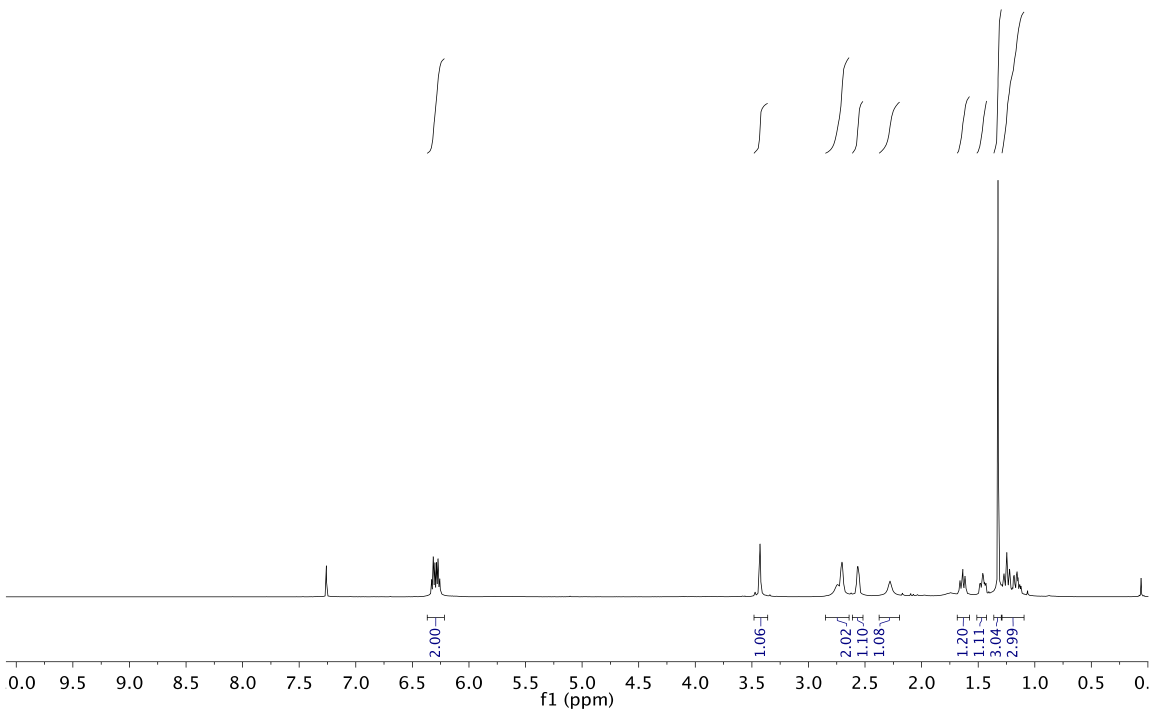
TLC (SiO_2): R_f = 0.45 (AcOEt:hexanes = 8:2).

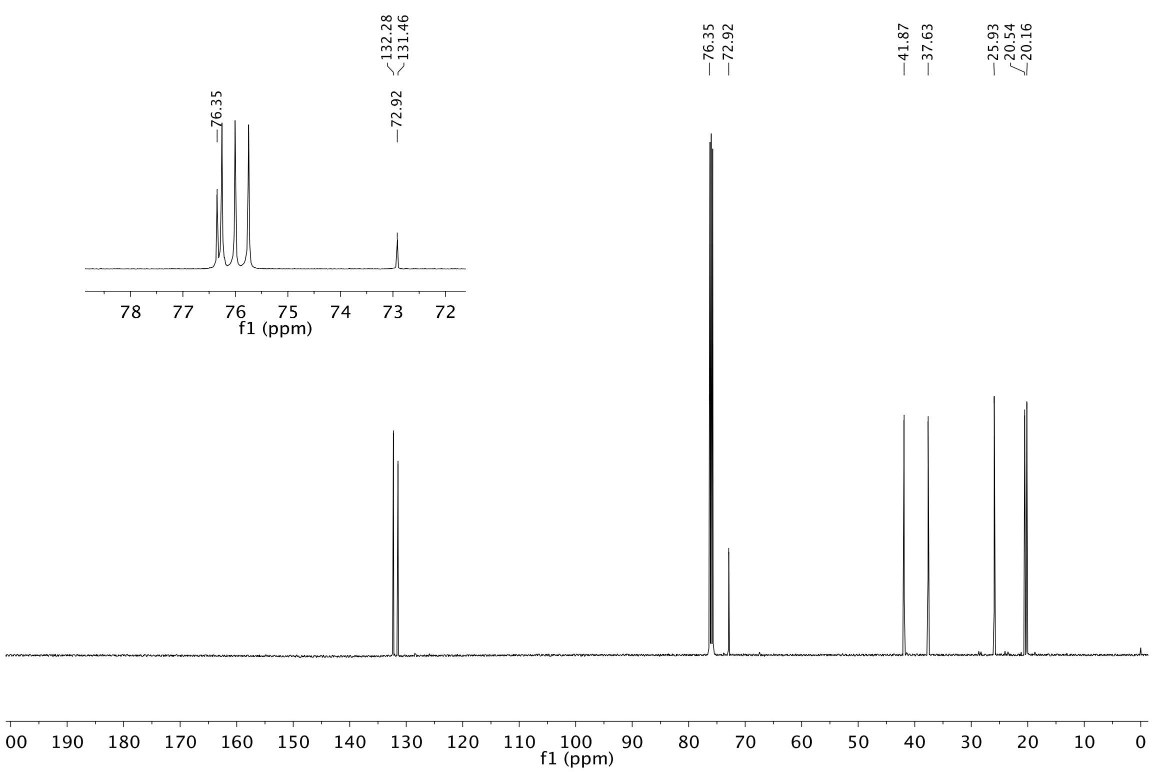
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 6.37 – 6.22 (m, 2H), 3.43 (d, *J* = 2.7 Hz, 1H), 2.85 – 2.64 (m, 2H), 2.61 – 2.52 (m, 1H), 2.28 (s, 1H), 1.64 (ddt, *J* = 13.0, 9.9, 3.1 Hz, 1H), 1.46 (dddd, *J* = 11.7, 9.3, 4.8, 2.1 Hz, 1H), 1.32 (s, 3H), 1.29 – 1.09 (m, 3H) ppm

^{13}C NMR: (125 MHz, $CDCl_3$): δ = 132.3, 131.5, 76.4, 72.9, 41.9, 37.6, 25.9, 20.5, 20.2 ppm.

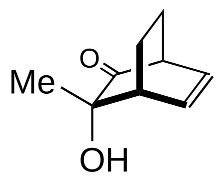
HRMS: (ESI) Calculated for $C_9H_{14}O_2Na$ [$M+Na^+$] =177.0886, Found177.0888.

FTIR: (neat): 3360, 2949 cm^{-1}.


2.00
1.06
2.02
1.10
1.08
1.20
1.11
3.04
2.99
f1 (ppm)


132.28
131.46
76.35
72.92
41.87
37.63
25.93
20.54
20.16
f1 (ppm)

(1*SR*,3*SR*,4*RS*)-3-hydroxy-3-methylbicyclo[2.2.2]oct-5-en-2-one (S1)



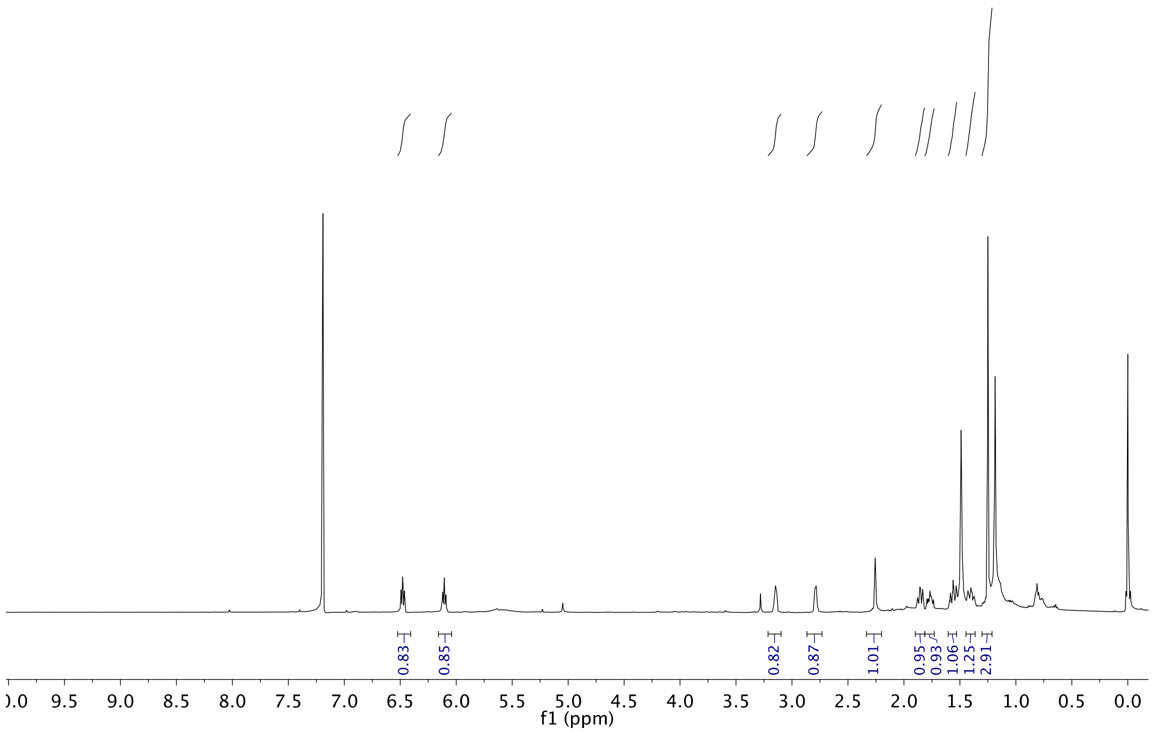
TLC (SiO_2): R_f = 0.25 (AcOEt:hexanes = 3:7).

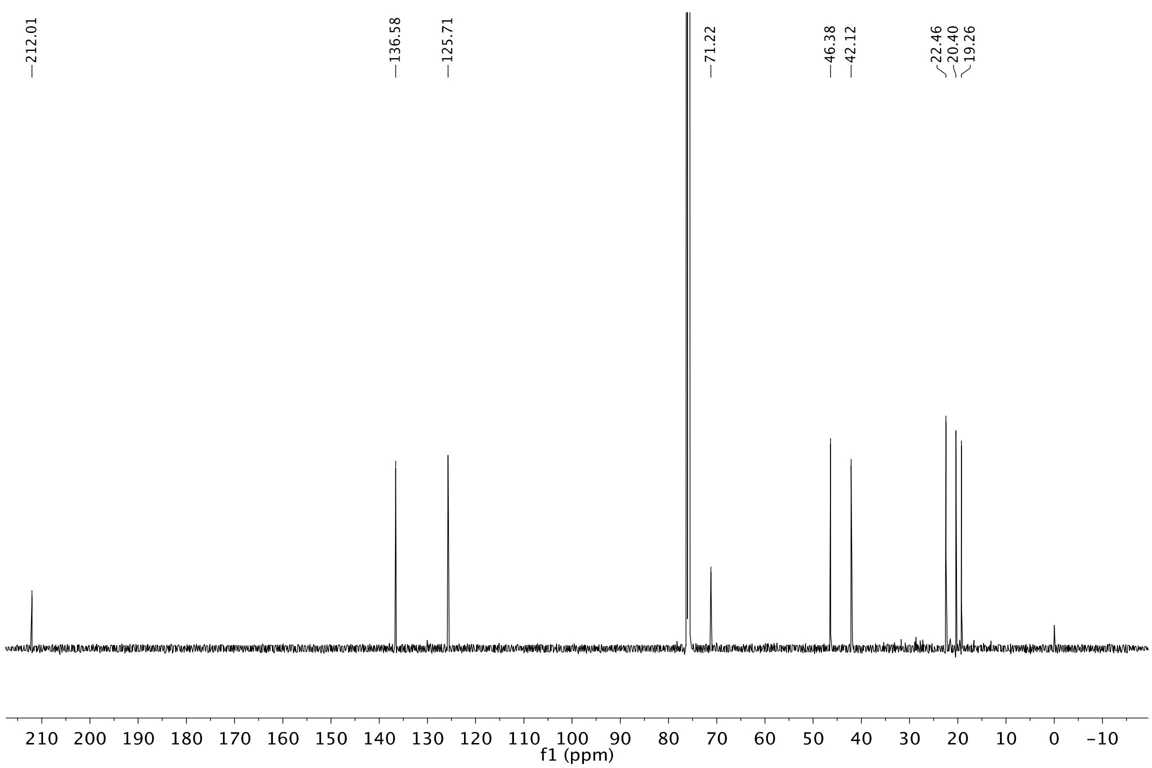
^{1}H NMR: (500 MHz, $CDCl_3$): δ 6.59 – 6.48 (m, 1H), 6.18 (ddd, *J* = 8.1, 6.5, 1.7 Hz, 1H), 3.22 (ddt, *J* = 6.7, 3.3, 1.5 Hz, 1H), 2.94 – 2.80 (m, 1H), 2.33 (s, 1H), 1.92 (ddt, *J* = 12.8, 9.7, 3.1 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.63 (ddd, *J* = 13.1, 10.9, 3.3 Hz, 1H), 1.47 (tdd, *J* = 12.3, 5.5, 2.7 Hz, 1H), 1.32 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$): δ = 212.0, 136.6, 125.7, 71.2, 46.4, 42.1, 22.5, 20.4, 19.3 ppm.

HRMS: (ESI) Calculated for $C_9H_{12}O_2Na$ [M+Na$^+$] = 175.0730, Found 175.0728.

FTIR: (neat): 2929, 2363, 2341, 1738, 1365 cm^{-1}.

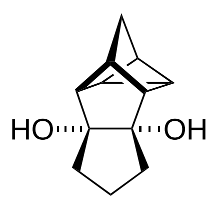

0.83
0.85
0.82
0.87
1.01
0.95
0.93
1.06
1.25
2.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


212.01
136.58
125.71
71.22
46.38
42.12
22.46
20.40
19.26
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

General Procedure and Spectral Data for Cycloaddition Reactions with Norbornadiene

A resealable pressure tube (ca. 13 x 100 mm) was charged with $[Ru_3(CO)_{12}]$ (3.8 mg, 0.006 mmol, 2 mol%), dppe (7.2 mg, 0.018 mmol, 6 mol%), diol (0.30 mmol, 100 mol%) and norbornadiene (0.15 mL, 1.5 mmol, 500 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.15 mL, 2.0 M) was added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 130 ˚C for 40 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the desired product **4a-4e** and **4g**.

(3b*RS*,6a*SR*)-octahydro-3b*H*-2,3,7-(epimethanetriyl)cyclopenta[*a*]pentalene-3b,6a(4*H*)-diol (4a)



The reaction was conducted with *cis*-cyclopentane-1,2-diol **1a** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 25:75) provided the title compound **4a** (46.2 mg, 0.24 mmol) in 80% yield as a white solid.

<u>TLC (SiO_2)</u>: R_f = 0.25 (AcOEt:hexanes = 3:7).

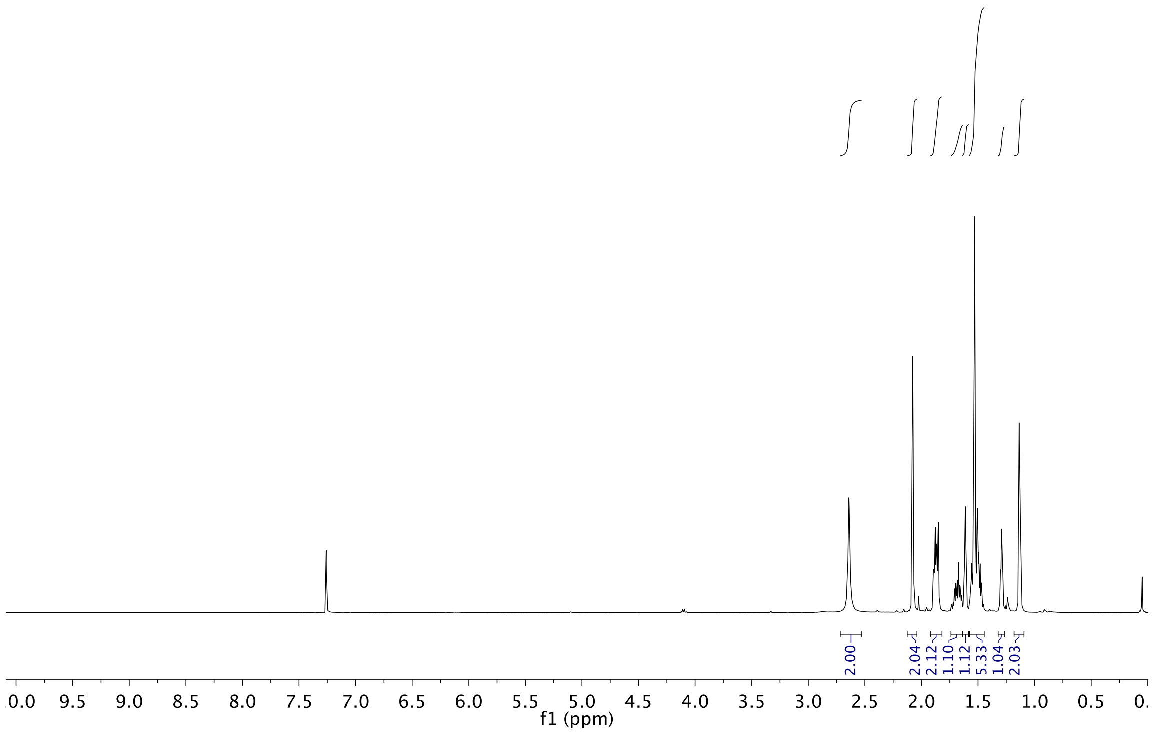
[1]H NMR: (500 MHz, $CDCl_3$): δ = 2.59 (s, 2H), 2.03 (d, *J* = 2.1 Hz, 2H), 1.87 – 1.77 (m, 2H), 1.69 – 1.59 (m, 1H), 1.56 (s, 1H), 1.53 – 1.40 (m, 5H), 1.24 (t, *J* = 5.1 Hz, 1H), 1.08 (d, *J* = 4.8 Hz, 2H) ppm.

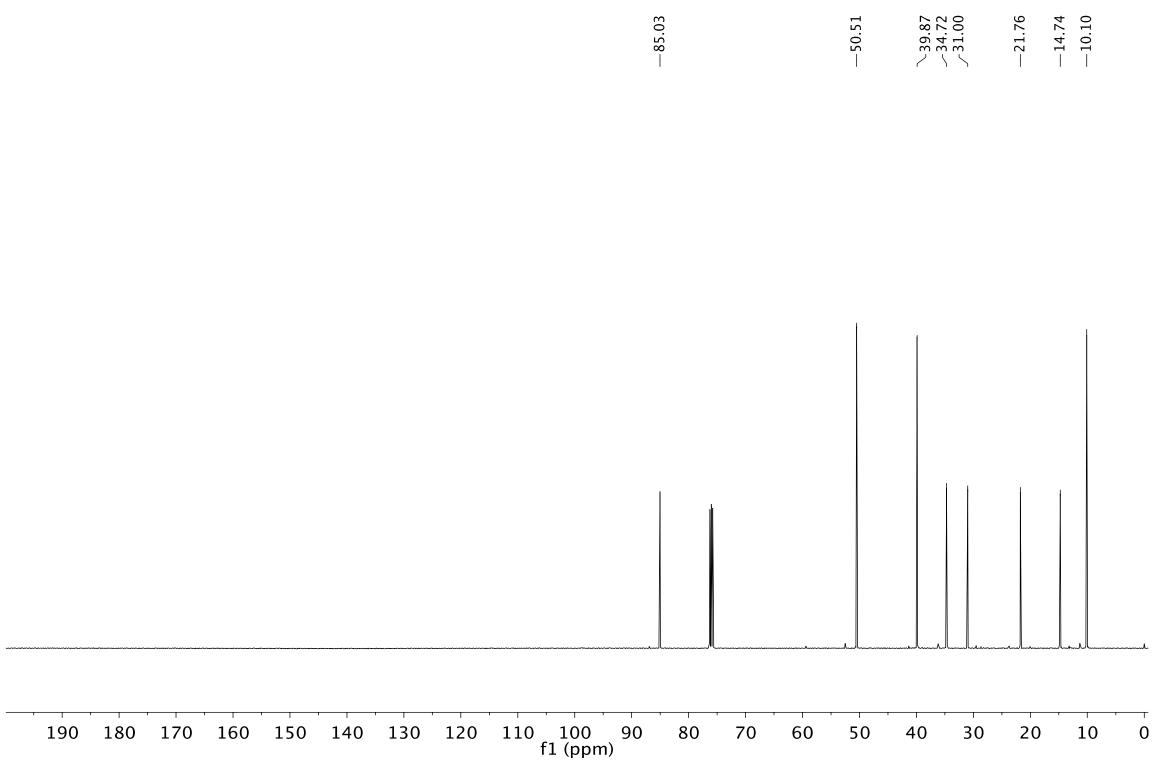
[13]C NMR: (125 MHz, $CDCl_3$): δ = 85.0, 50.5, 39.9, 34.7, 31.0, 21.8, 14.7, 10.1 ppm.

MP: 59.5-62.0 °C.

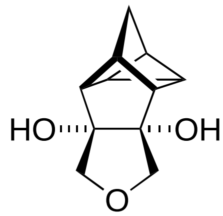
HRMS: (ESI) Calculated for $C_{12}H_{16}O_2Na$ [M+Na$^+$] =215.1046, Found 215.1043.

FTIR: (neat): 3214, 2922, 2364, 1739 cm^{-1}.


2.00
2.04
2.12
1.10
1.12
5.33
1.04
2.03
0.0 9.5 9.0 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.
f1 (ppm)


85.03
50.51
39.87
34.72
31.00
21.76
14.74
10.10
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(3a*RS*,7a*SR*)-hexahydro-4,5,7-(epimethanetriyl)pentaleno[1,2-*c*]furan-3a,7a(1*H*,3*H*)-diol (4b)



The reaction was conducted with cis-3,4-tetrahydrofuran-diol **2b** in accordance with the general procedure using dppb (1,4-bis(diphenylphosphino)butane) at 150 ˚C for 72 h. Flash column chromatography (SiO_2, AcOEt:hexanes = 60:40) provided the title compound **4b** (36.7 mg, 0.19 mmol) in 63% yield as a slightly yellow solid.

TLC (SiO_2): R_f = 0.44 (AcOEt : hexanes = 2:1).

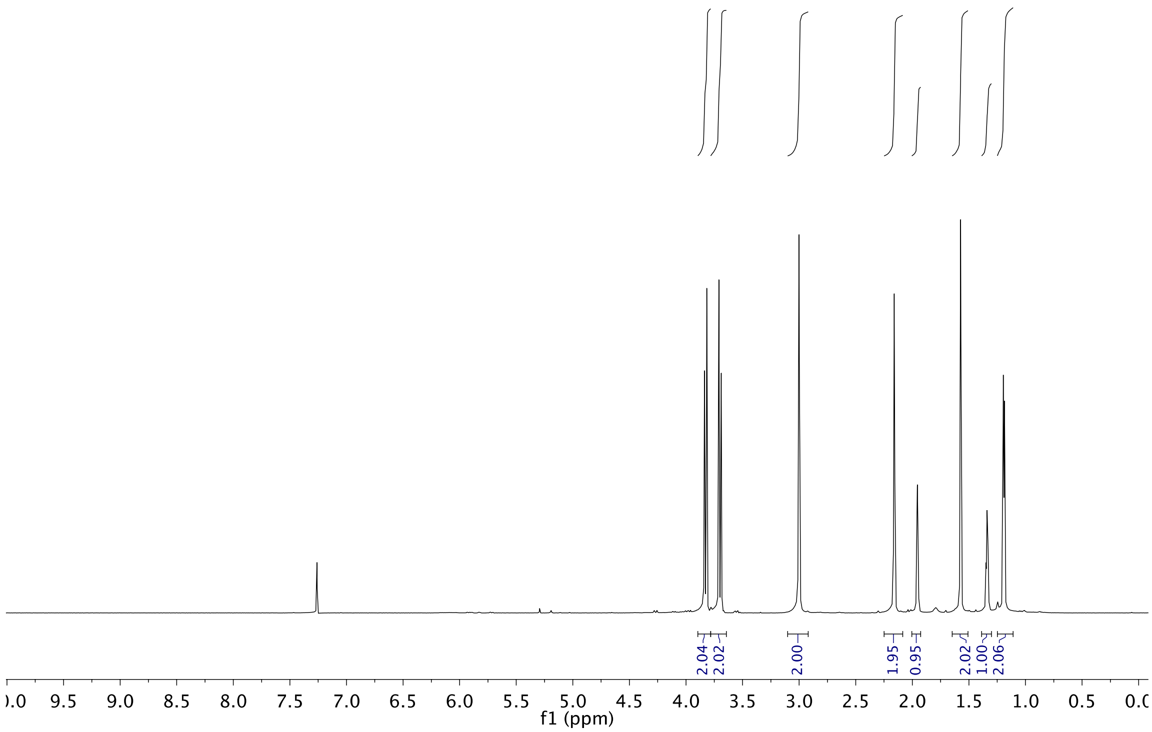
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 10.1 Hz, 2H), 3.70 (d, *J* = 10.2 Hz, 2H), 3.00 (s, 2H), 2.25 – 2.08 (m, 2H), 1.95 (s, 1H), 1.57 (t, *J* = 1.5 Hz, 2H), 1.34 (dt, *J* = 4.9, 2.6 Hz, 1H), 1.19 (d, *J* = 4.9 Hz, 2H) ppm.

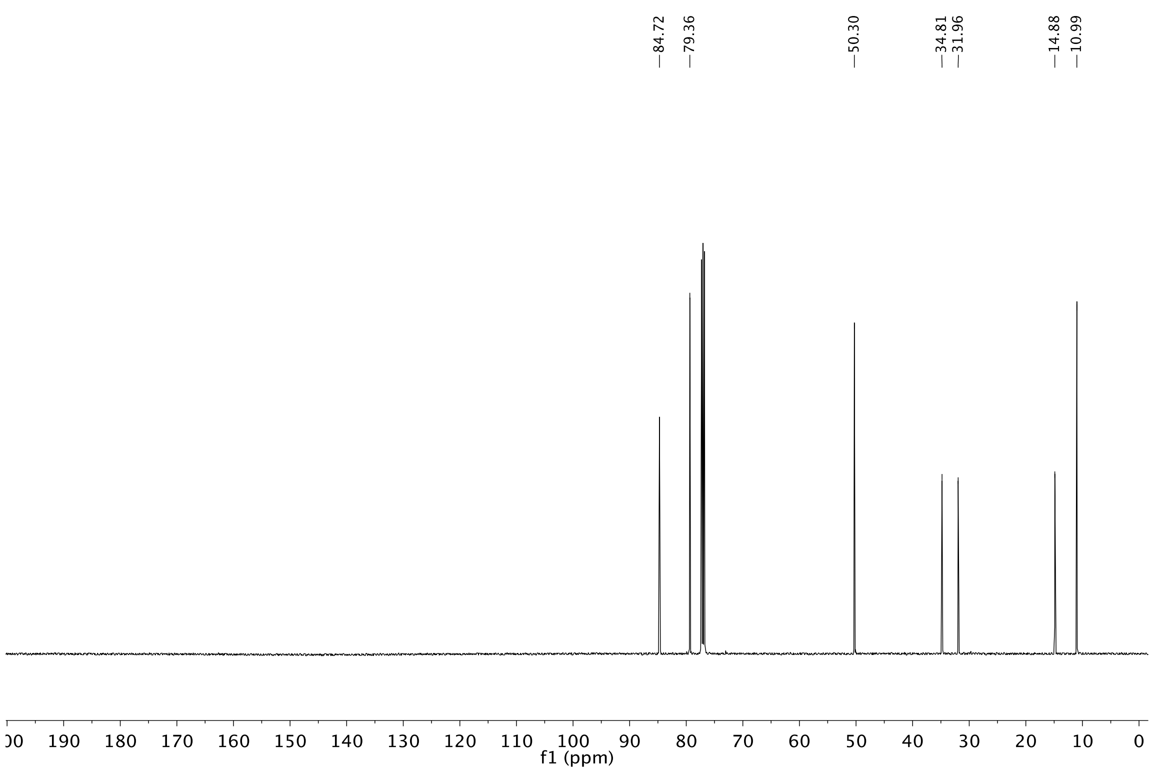
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 84.7, 79.4, 50.3, 34.8, 32.0, 14.9, 11.0 ppm.

MP: 148.6 – 149.5 °C.

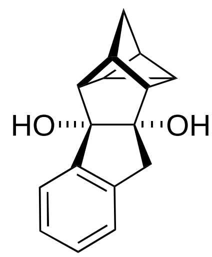
HRMS: (ESI) Calculated for $C_{11}H_{14}O_3$ Na [M+Na$^+$] = 217.0835, Found 217.0838.

FTIR: (neat): 3383, 2935, 2872 cm^{-1}.


2.04
2.02
2.00
1.95
0.95
2.02
1.00
2.06
10.0 9.5 9.0 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)


84.72
79.36
50.30
34.81
31.96
14.88
10.99
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(3b*SR*,8a*SR*)-1,2,3,3a,9,9a-hexahydro-3b*H*-2,3,9-(epimethanetriyl)pentaleno[1,2-*a*]indene-3b,8a(8*H*)-diol (4c)



The reaction was conducted with mixture of 1,2- *trans*- and *cis*- dihydroindene diol **2c** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 20:80) provided the title compound **4c** (59.1 mg, 0.25 mmol) in 82% yield as a white solid.

TLC (SiO_2): R_f = 0.30 (AcOEt:hexanes = 3:7).

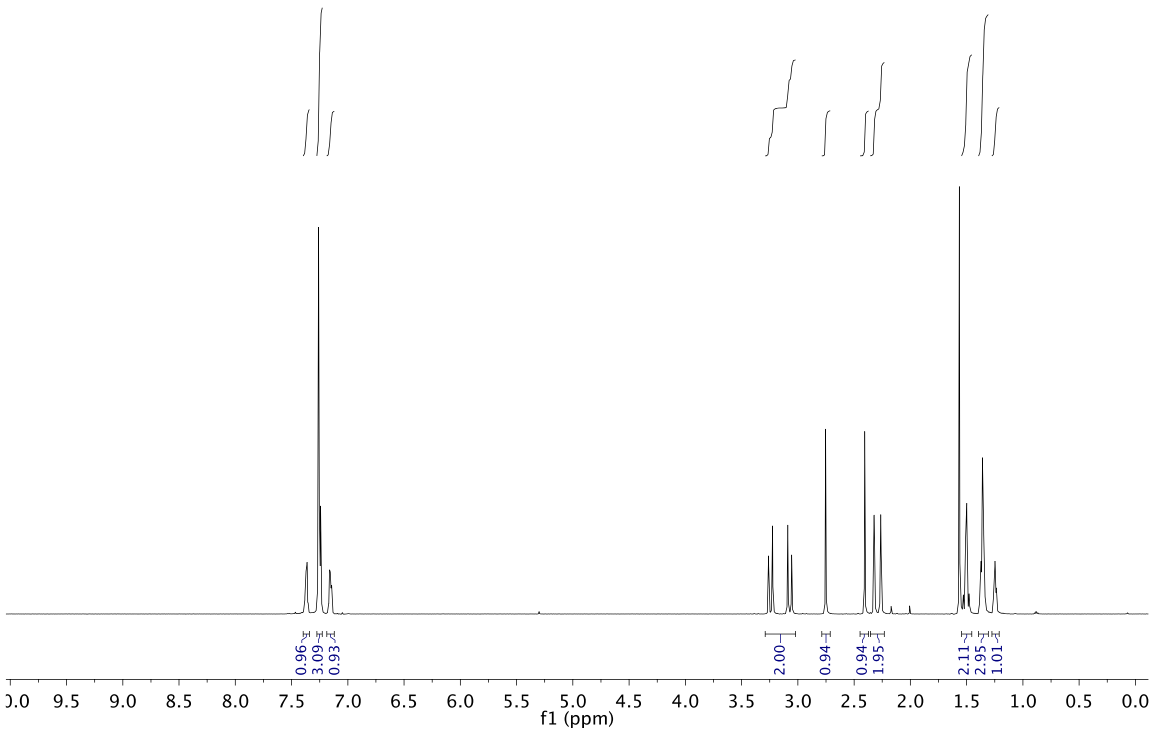
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 5.4, 3.4 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.19 – 7.12 (m, 1H), 3.29 – 3.02 (m, 2H), 2.75 (s, 1H), 2.41 (s, 1H), 2.29 (dt, *J* = 28.9, 2.0 Hz, 2H), 1.54 – 1.45 (m, 2H), 1.39 – 1.31 (m, 3H), 1.25 (td, *J* = 5.7, 1.7 Hz, 1H) ppm.

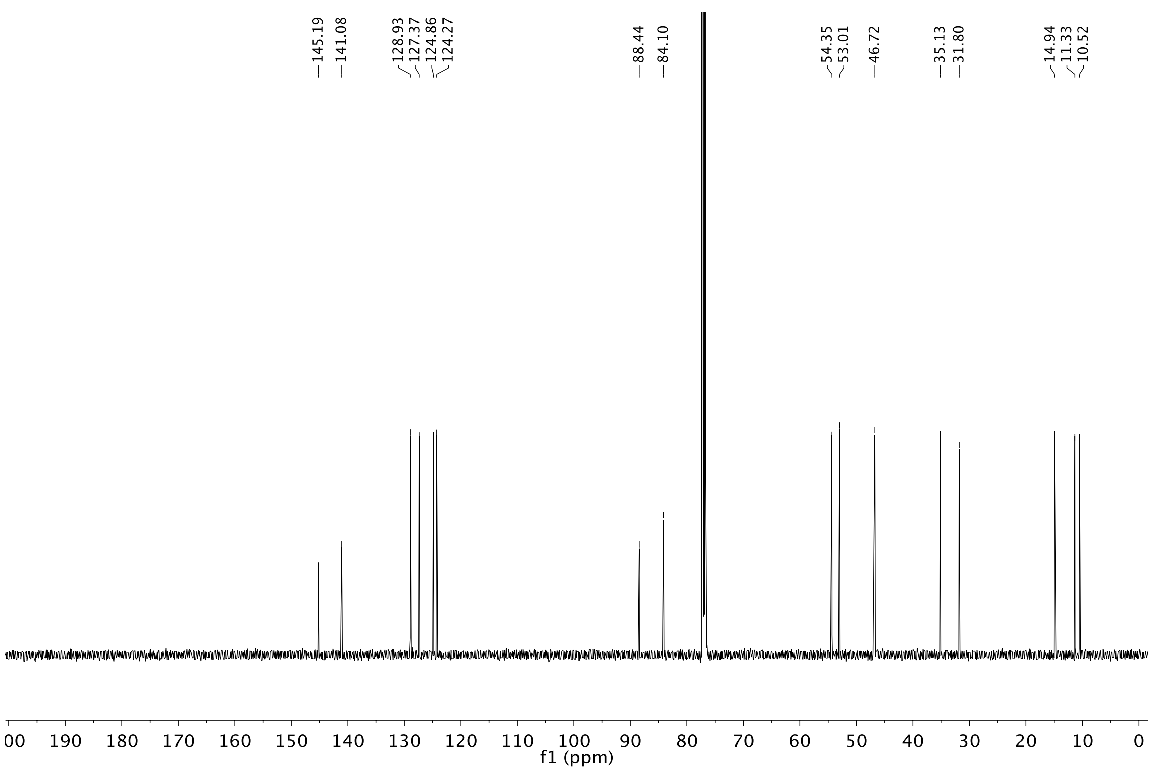
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 145.2, 141.1, 128.9, 127.4, 124.9, 124.3, 88.4, 84.1, 54.4, 53.0, 46.7, 35.1, 31.8, 14.9, 11.3, 10.5 ppm.

MP: 115.8-119.4 °C.

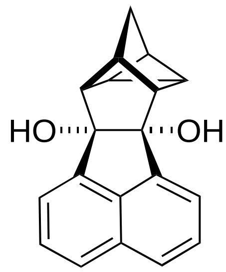
HRMS: (ESI) Calculated for $C_{16}H_{16}O_2Na$ [M+Na$^+$] = 263.1043, Found 263.1043.

FTIR: (neat): 3399, 2940, 2365, 1743 cm^{-1}.


0.96
3.09
0.93
2.00
0.94
0.94
1.95
2.11
2.95
1.01
f1 (ppm)


145.19
141.08
128.93
127.37
124.86
124.27
88.44
84.10
54.35
53.01
46.72
35.13
31.80
14.94
11.33
10.52
f1 (ppm)

(6b*RS*,10a*SR*)-6c,7,8,9,9a,10-hexahydro-7,8,10-(epimethanetriyl)pentaleno[1,2-*a*]acenaphthylene-6b,10a-diol (4d)



The reaction was conducted with mixture of *trans*- and *cis*- acenaphthylene diol **2d** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 15:85) provided the title compound **4d** (75.4 mg, 0.27 mmol) in 91% yield as a white solid.

TLC (SiO_2): R_f = 0.30 (AcOEt:hexanes = 3:7).

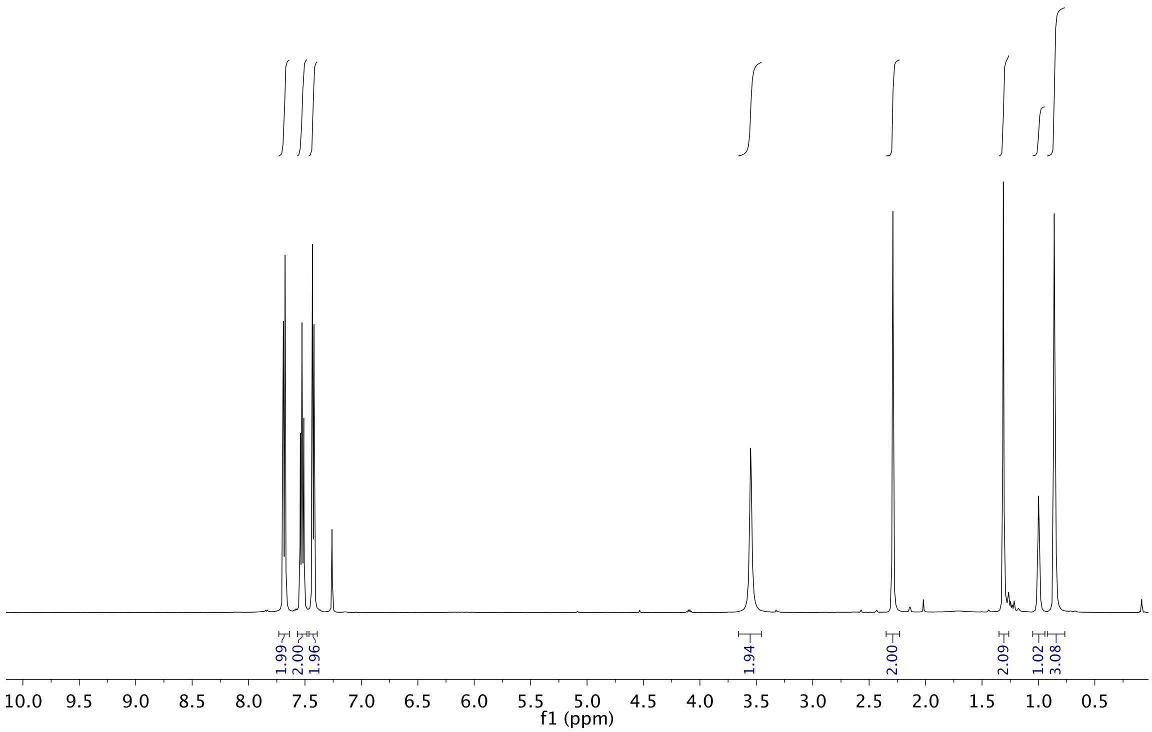
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.1 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 6.9 Hz, 2H), 3.55 (s, 2H), 2.29 (s, 2H), 1.31 (s, 2H), 0.99 (d, *J* = 5.0 Hz, 1H), 0.85 (d, *J* = 5.3 Hz, 3H). ppm.

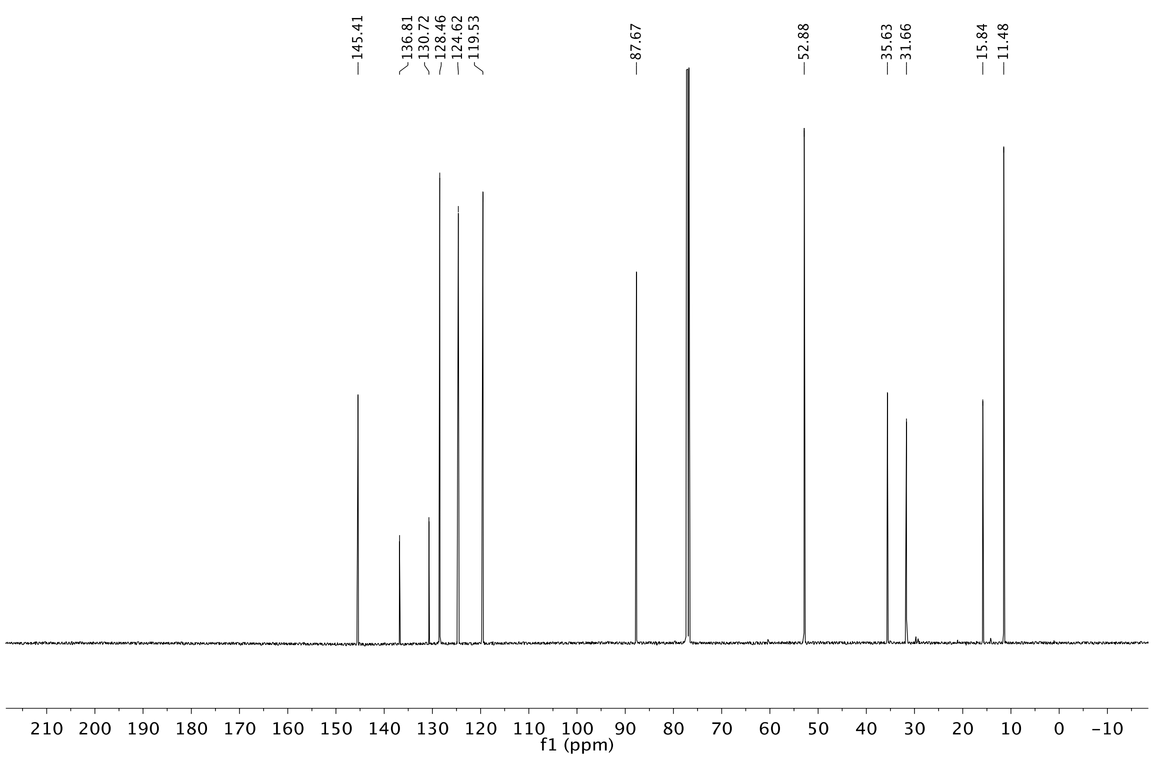
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 145.4, 136.8, 130.7, 128.5, 124.6, 119.5, 87.7, 52.9, 35.6, 31.7, 15.8, 11.5 ppm.

MP: 188.2-190.5°C.

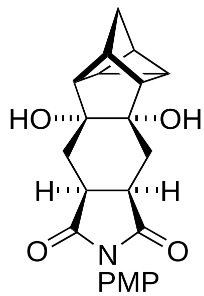
HRMS: (ESI) Calculated for $C_{19}H_{16}O_2Na$ [M+Na$^+$] =299.1043, Found 299.1042.

FTIR: (neat): 3437, 2942, 2364, 1739 cm^{-1}.


1.99
2.00
1.96
1.94
2.00
2.09
1.02
3.08
10.0 9.5 9.0 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
f1 (ppm)


145.41
136.81
130.72
128.46
124.62
119.53
87.67
52.88
35.63
31.66
15.84
11.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

(3a*RS*,4a*SR*,8a*RS*,9a*SR*)-4a,8a-dihydroxy-2-(4-methoxyphenyl)dodecahydro-1*H*-5,6,8-(epimethanetriyl)pentaleno[1,2-*f*]isoindole-1,3(2*H*)-dione (4e)



The reaction was conducted with (3a*RS*,5*RS*,6*SR*,7a*SR*)-5,6-phthalimide diol **2e** in accordance with the general procedure. Flash column chromatography (SiO_2, EtOAc:hexane = 75:25) provided the title compound **4e** (65.0 mg, 0.26 mmol) in 85% yield as a white solid.

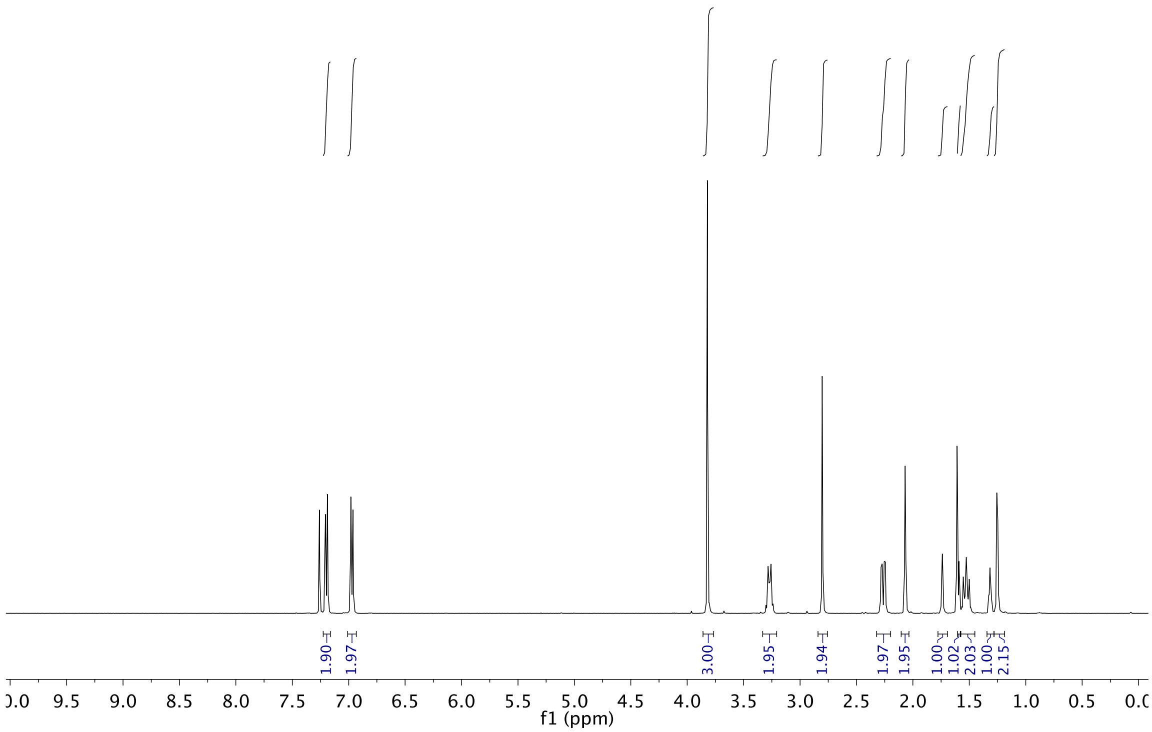
<u>TLC (SiO_2)</u>: R_f = 0.52 (AcOEt:hexanes = 4:1).

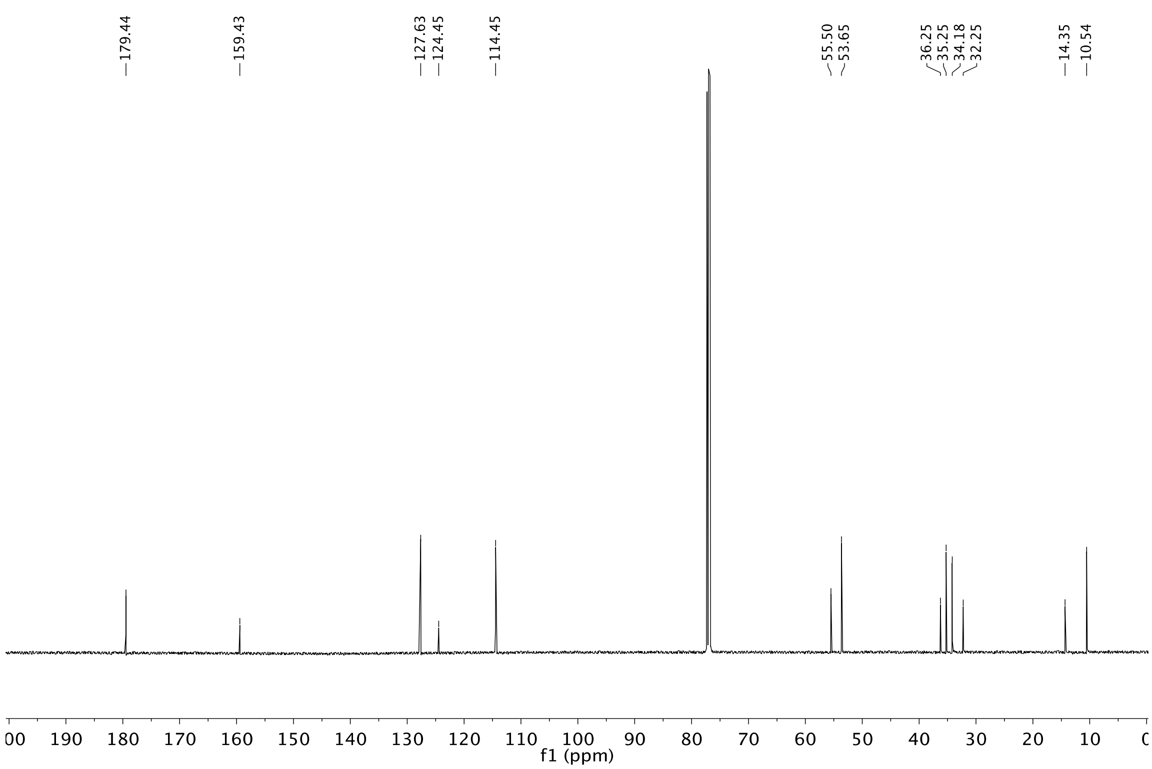
<u>^{1}H NMR</u>: (500 MHz, $CDCl_3$): δ = 7.23 – 7.16 (m, 2H), 7.01 – 6.93 (m, 2H), 3.82 (s, 3H), 3.33 – 3.21 (m, 2H), 2.80 (s, 2H), 2.26 (dd, *J* = 14.4, 4.9 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.74 (s, 1H), 1.60 (d, *J* = 8.7 Hz, 2H), 1.58 – 1.45 (m, 2H), 1.32 (t, *J* = 5.0 Hz, 1H), 1.25 (d, *J* = 4.8 Hz, 2H) ppm.

<u>^{13}C NMR:</u> (125 MHz, $CDCl_3$): δ = 179.4, 159.4, 127.6, 124.5, 114.5, 55.5, 53.7, 36.3, 35.3, 34.2, 32.3, 14.4, 10.5 ppm.

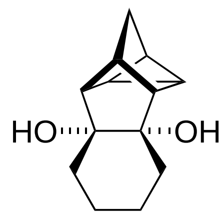
<u>MP</u>: 228.3 – 230.4 °C.

<u>HRMS</u>: (ESI) Calculated for $C_{22}H_{24}NO_5$ [M+H$^+$] = 382.1649, Found 382.1652.
<u>FTIR</u>: (neat): 3387, 2921, 1687 cm^{-1}.


1.90
1.97
3.00
1.95
1.94
1.97
1.95
1.00
1.02
2.03
1.00
2.15
f1 (ppm)


179.44
159.43
127.63
124.45
114.45
55.50
53.65
36.25
35.25
34.18
32.25
14.35
10.54
f1 (ppm)

(3b*SR*,8a*SR*)-1,2,3,3a,9,9a-hexahydro-3b*H*-2,3,9-(epimethanetriyl)pentaleno[1,2-*a*]indene-3b,8a(8*H*)-diol (4g)



The reaction was conducted with *trans*-1,2-hexane diol **2g** in accordance with the general procedure. Flash column chromatography (SiO_2, AcOEt:hexanes = 25:75) provided the title compound **4g** (33.4 mg, 0.16 mmol) in 54% yield as a white solid.

TLC (SiO_2): R_f = 0.35 (AcOEt:hexanes = 3:7).

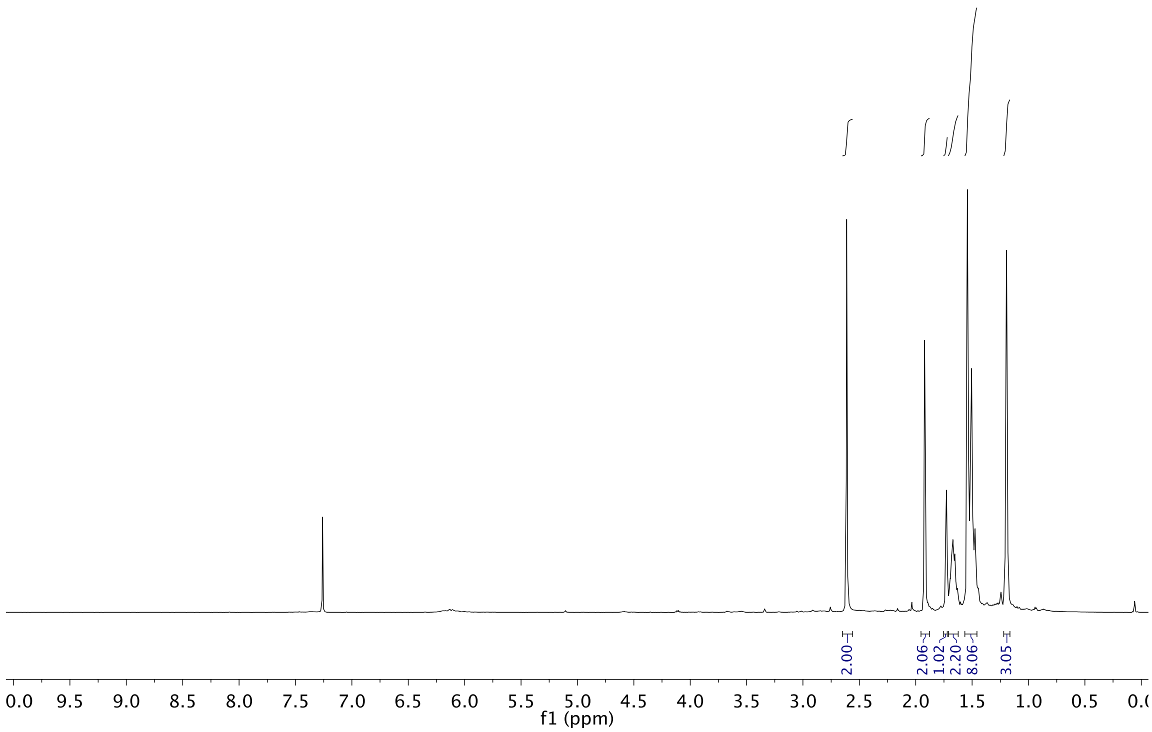
^{1}H NMR: (500 MHz, $CDCl_3$): δ = 2.61 (s, 2H), 1.92 (d, *J* = 2.1 Hz, 2H), 1.73 (s, 1H), 1.66 (tdd, *J* = 12.4, 6.3, 2.1 Hz, 2H), 1.56 – 1.46 (m, 8H), 1.20 (s, 3H) ppm.

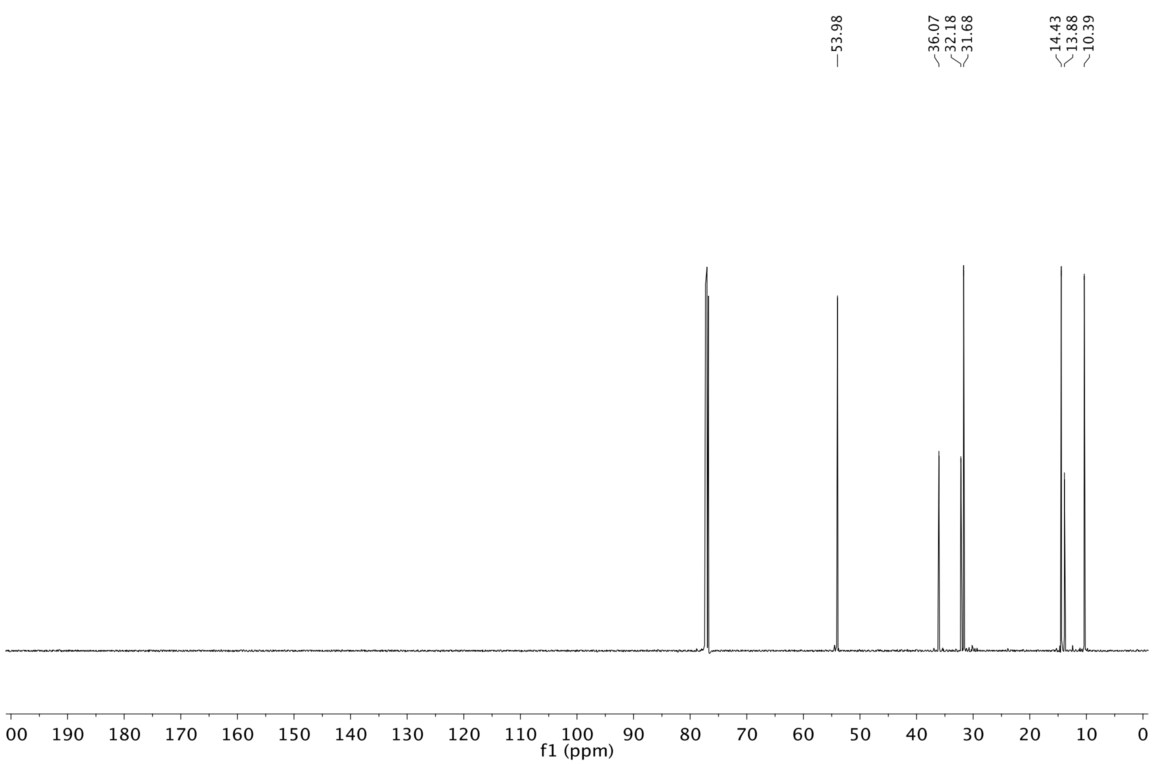
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 54.0, 36.1, 32.2, 31.7, 14.4, 13.9, 10.4 ppm.

MP: 114.2-116.5 °C.

HRMS: (ESI) Calculated for $C_{13}H_{18}O_6Na$ [M+Na$^+$] =229.1199, Found 229.1197.

FTIR: (neat): 3279, 2927, 2364, 1205 cm^{-1}.


2.00
2.06
1.02
2.20
8.06
3.05
0.0
9.5
9.0
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
f1 (ppm)


53.98
36.07
32.18
31.68
14.43
13.88
10.39
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

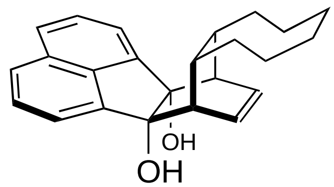
Procedure for Cycloaddition Reactions with Non-Conjugated Alkenes

<u>Reaction with 1,4-Cycohexadiene</u>

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (3.8 mg, 0.006 mmol, 2 mol%), dppe (7.2 mg, 0.018 mmol, 6 mol%), 3,5-Me_2BzOH (4.5 mg, 0.03 mmol, 10 mol%), *cis*-1,2 cyclopentane diol **2a** (30.6 mg, 0.3 mmol, 100 mol%) and 1,4-cyclohexadiene (0.14 mL, 1.5 mmol, 500 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.15 mL, 2.0 M) was added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 140 ˚C for 40 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, AcOEt:hexanes = 25:75), which provided the title compound **3a** (51.2 mg, 0.29 mmol) in 95% yield as a white solid. The characterization data of the furnished compound matched with that provided from 1,3-cyclohexadiene in all respects.

<u>Reaction with 1,5,9-Cyclododecatriene</u>

(6bRS,7RS,7aRS,13aSR,14SR,14aRS)-7,7a,8,9,10,11,12,13,13a,14-decahydro-7,14-ethenocycloocta[k]fluoranthene-6b,14a-diol (3d')



A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (3.8 mg, 0.006 mmol, 2 mol%), dppe (7.2 mg, 0.018 mmol, 6 mol%), mixture of *trans*- and *cis*-acenaphthylene diol **2d** (55.9 mg, 0.3 mmol, 100 mol%) and 1,5,9-cyclododecatriene (0.27 mL, 1.5 mmol, 500 mol%). The reaction vessel was placed under an atmosphere of argon. The reaction vessel was sealed and the reaction mixture was allowed to stir at 130 ˚C for 40 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, AcOEt:hexanes = 13:87), which provided the title compound **3d'** (44.6 mg, 0.13 mmol) in 43% yield as a white solid.

<u>TLC (SiO_2)</u>: R_f = 0.32 (AcOEt:hexanes = 3:7).

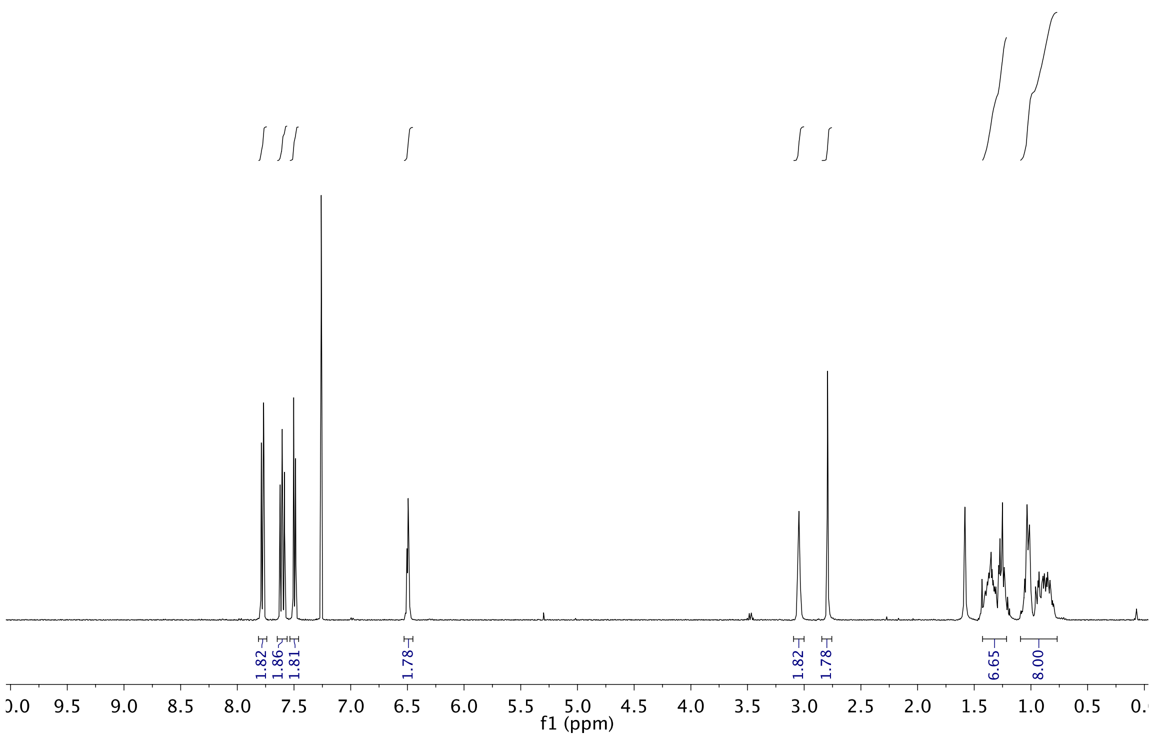
<u>^{1}H NMR</u>: (500 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 8.3, 0.7 Hz, 2H), 7.60 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.50 (dd, *J* = 7.0, 0.8 Hz, 2H), 6.53 – 6.45 (m, 2H), 3.09 – 3.00 (m, 2H), 2.79 (d, *J* = 1.0 Hz, 2H), 1.43 – 1.22 (m, 6H), 1.03 (td, *J* = 8.3, 5.9 Hz, 4H), 0.98 – 0.77 (m, 4H) ppm.

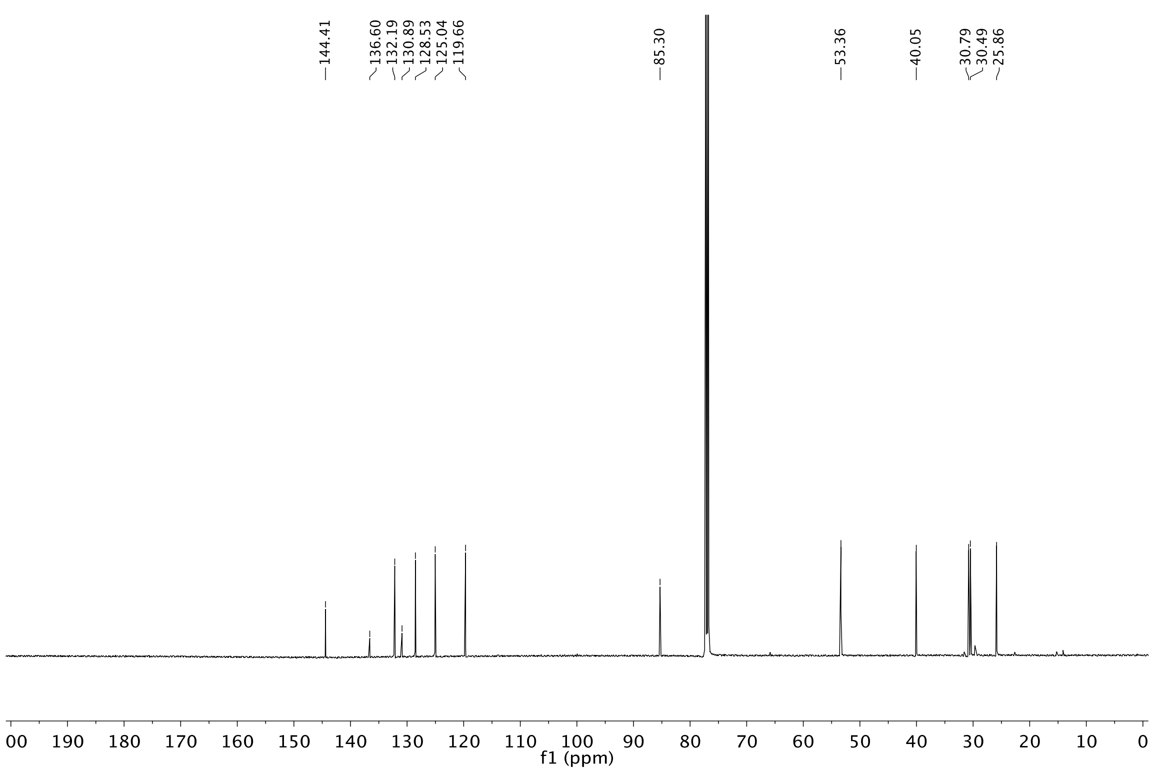
^{13}C NMR: (125 MHz, $CDCl_3$): δ = 144.4, 136.2, 132.2, 130.9, 128.5, 125.1, 119.7, 85.3, 53.4, 40.1, 30.8, 30.5, 25.9 ppm.

MP: 136 – 138 °C.

HRMS: (ESI) Calculated for $C_{24}H_{26}O_2Na$ [$M+Na^+$] =369.1825, Found 369.1832.

FTIR: (neat): 3363, 3047, 2921, 2851, 1494, 1363 cm^{-1}.


1.82
1.86
1.81
1.78
1.82
1.78
6.65
8.00
f1 (ppm)


144.41
136.60
132.19
130.89
128.53
125.04
119.66
85.30
53.36
40.05
30.79
30.49
25.86
f1 (ppm)

Procedure for Redox Level Independent Cycloaddition Reactions

Reaction of *Dehydro-2g with* Norbornadiene

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (3.8 mg, 0.006 mmol, 2 mol%), dppe (7.2 mg, 0.018 mmol, 6 mol%), ketol dimer (34.2 mg, 0.15 mmol, 100 mol%) and norbornadiene (0.15 mL, 1.5 mmol, 500 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.15 mL, 2.0 M) was added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 130 ˚C for 40 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, AcOEt:hexanes = 20:80), which provided the title compound **4g** (38.4 mg, 0.186 mmol) in 62% yield as a white solid. The characterization data of the furnished compound matched with that provided from **2g** in all respects.

Reaction *with* 1,3-Cyclohexadiene

From *dehydro*-**2d**:

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (2.6 mg, 0.004 mmol, 2 mol%), dppe (4.8 mg, 0.012 mmol, 6 mol%), 3,5-Me_2BzOH (3.0 mg, 0.02 mmol, 10 mol%), *dehydro*-**2d**(36.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.1 mL, 2.0 M) and **1a** (99 µL, 1.0 mmol, 500 mol%) were added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 140 ˚C for 40 hours. After cooling to room temperature, the mixture was purified by flash column chromatography (SiO_2: AcOEt:hexanes= 25:75) to give **3d** (50.8 mg, 0.19 mmol) in 95% yield as a slightly yellow solid.

From *didehydro*-**2d**:

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (2.6 mg, 0.004 mmol, 2 mol%), dppe (4.8 mg, 0.012 mmol, 6 mol%), 3,5-Me_2BzOH (3.0 mg, 0.02 mmol, 10 mol%), *didehydro*-**2d** (36.4 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.1 mL, 2.0 M), **1a** (99 μL, 1.0 mmol, 500 mol%) and formic acid (17 μL, 88% in H_2O, 0.4 mmol, 200 mol%) were added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 140 ˚C for 40 hours. After cooling to room temperature, the mixture was purified by flash column chromatography (SiO_2: AcOEt:hexanes = 25:75) to give **3d** (34.4 mg, 0.13 mmol) in 64% yield as a slightly yellow solid.

Reaction *with* Norbornadiene

From *dehydro*-**2d**:

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (2.6 mg, 0.004 mmol, 2 mol%), dppe (4.8 mg, 0.012 mmol, 6 mol%) and *dehydro*-**2d** (36.8 mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.1 mL, 2.0 M) and **1c** (102 μL, 1.0 mmol, 500 mol%) were added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 130 ˚C for 40 hours. After cooling to room temperature, the mixture was purified by flash column chromatography (SiO_2: AcOEt:hexanes = 25:75) to give **4d** (37.4 mg, 0.14 mmol) in 68% yield as a slightly yellow solid.

From *didehydro*-**2d**:

A resealable pressure tube (ca. 13 x 100 mm) was charged with [$Ru_3(CO)_{12}$] (2.6 mg, 0.004 mmol, 2 mol%), dppe (4.8 mg, 0.012 mmol, 6 mol%) and *didehydro*-**2d** (36.4

mg, 0.2 mmol, 100 mol%). The reaction vessel was placed under an atmosphere of argon, and PhMe (0.1 mL, 2.0 M), **1c** (102 μL, 1.0 mmol, 500 mol%) and formic acid (17 μL, 88% in H_2O, 0.4 mmol, 200 mol%) were added. The reaction vessel was sealed and the reaction mixture was allowed to stir at 130 ˚C for 40 hours. After cooling to room temperature, the mixture was purified by flash column chromatography (SiO_2: AcOEt:hexanes = 75:25) to give **4d** (40.5 mg, 0.15 mmol) in 73% yield as a slightly yellow solid.

Single Crystal Diffraction Data

X-ray Experimental for complex **3b**–CH_2Cl_2

X-ray Experimental for complex $C_{10}H_{14}O_3$: Crystals grew as thin, colorless needles by slow evaporation fromCH_2Cl_2/pentane. The data crystal was cut from a larger crystal and had approximate dimensions; 0.25 x 0.06 x 0.03 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 1058 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 12 seconds per frame with a detector offset of +/- 41.6° and 32 seconds per frame with a detector offset of +/- 109.0°. The data were collected at 100 K using an Oxford 700 Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data collection, unit cell refinement and data reduction were performed using Agilent Technologies CrysAlisPro V 1.171.38.43f.[5] The structure was solved by direct methods using SHELXT[6] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2016/6.[3] Structure analysis was aided by use of the programs PLATON[7] and WinGX.[8] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

The function, $\Sigma w(|Fo|2 - |Fc|2)^2$, was minimized, where $w = 1/[(\sigma(Fo))^2 + (0.1*P)^2]$ and $P = (|Fo|^2 + 2|Fc|^2)/3$. $Rw(F^2)$ refined to 0.151, with R(F) equal to 0.0445 and a goodness of fit, S, = 1.07. Definitions used for calculating R(F), Rw(F2) and the goodness of fit, S, are given below.[9] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[10] All figures were generated using SHELXTL/PC.[11] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1.4 Crystal data and structure refinement for **3b**.

Empirical formula	C10 H14 O3	
Formula weight	182.21	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 20.1033(9) Å	α= 90°.
	b = 6.2090(3) Å	β= 110.335(5)°.
	c = 14.4437(8) Å	γ= 90°.
Volume	1690.52(15) Å^3	
Z	8	
Density (calculated)	1.432 Mg/m^3	
Absorption coefficient	0.861 mm^{-1}	
F(000)	784	
Crystal size	0.260 x 0.060 x 0.020 mm^3	
Theta range for data collection	3.263 to 75.732°.	
Index ranges	-24<=h<=21, -7<=k<=7, -18<=l<=17	
Reflections collected	10619	

Table 1.4 (Cont'd)

Independent reflections	3446 [R(int) = 0.0314]
Completeness to theta = 67.684°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.899
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3446 / 0 / 240
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0713, wR2 = 0.1852
R indices (all data)	R1 = 0.0773, wR2 = 0.1924
Extinction coefficient	n/a
Largest diff. peak and hole	0.951 and -0.327 e.Å^{-3}

Table 1.5 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **3d**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	2867(1)	4512(1)	1313(1)	14(1)
C2	2939(1)	2928(1)	1149(1)	15(1)
C3	1692(2)	2329(1)	756(1)	19(1)
C4	2182(2)	766(1)	709(1)	22(1)
C5	3851(2)	-154(1)	1030(1)	21(1)
C6	5171(2)	451(1)	1419(1)	17(1)
C7	6985(2)	-304(1)	1730(1)	20(1)

Table 1.5 (Cont'd)

C8	8132(2)	481(1)	2041(1)	20(1)
C9	7568(1)	2037(1)	2093(1)	17(1)
C10	5814(1)	2777(1)	1825(1)	14(1)
C11	4799(1)	4397(1)	1803(1)	14(1)
C12	4653(1)	1994(1)	1474(1)	14(1)
C13	1384(1)	4959(1)	2040(1)	16(1)
C14	1676(2)	6419(1)	2266(1)	19(1)
C15	3273(2)	6281(1)	2699(1)	19(1)
C16	4484(1)	4699(1)	2859(1)	15(1)
C17	3506(1)	3473(1)	3544(1)	13(1)
C18	3589(1)	3536(1)	4655(1)	17(1)
C19	3768(2)	1948(1)	5424(1)	20(1)
C20	2339(2)	1035(1)	5318(1)	19(1)
C21	393(2)	1851(1)	5441(1)	19(1)
C22	-700(1)	2667(1)	4450(1)	19(1)
C23	-87(1)	4042(1)	3707(1)	16(1)
C24	1576(1)	3666(1)	3065(1)	14(1)
O1	2601(1)	5654(1)	345(1)	19(1)
O2	5685(1)	5577(1)	1225(1)	18(1)

Table 1.6 Bond lengths [Å] and angles [°] for **3d**.

C1-O1	1.4404(12)	C14-C15	1.3291(17)
C1-C2	1.5157(14)	C14-H14	0.95
C1-C13	1.5443(14)	C15-C16	1.5116(14)
C1-C11	1.5978(14)	C15-H15	0.95
C2-C3	1.3710(15)	C16-C17	1.5567(13)
C2-C12	1.4089(14)	C16-H16	1.00
C3-C4	1.4224(16)	C17-C18	1.5410(14)
C3-H3	0.95	C17-C24	1.5742(14)
C4-C5	1.3766(17)	C17-H17	1.00
C4-H4	0.95	C18-C19	1.5305(15)
C5-C6	1.4160(16)	C18-H18A	0.99
C5-H5	0.95	C18-H18B	0.99
C6-C12	1.4089(14)	C19-C20	1.5274(15)
C6-C7	1.4241(16)	C19-H19A	0.99
C7-C8	1.3746(16)	C19-H19B	0.99
C7-H7	0.95	C20-C21	1.5360(15)
C8-C9	1.4223(15)	C20-H20A	0.99
C8-H8	0.95	C20-H20B	0.99
C9-C10	1.3719(14)	C21-C22	1.5324(15)
C9-H9	0.95	C21-H21A	0.99
C10-C12	1.4082(14)	C21-H21B	0.99
C10-C11	1.5185(14)	C22-C23	1.5358(14)
C11-O2	1.4311(12)	C22-H22A	0.99
C11-C16	1.5461(14)	C22-H22B	0.99
C13-C14	1.5091(15)	C23-C24	1.5486(14)
C13-C24	1.5623(14)	C23-H23A	0.99
C13-H13	1.00	C23-H23B	0.99

Table 1.6 (Cont'd)

O1-C1-C2	108.86(8)	C10-C9-H9	120.7
O1-C1-C13	109.75(8)	C8-C9-H9	120.7
C2-C1-C13	113.83(8)	C9-C10-C12	119.10(9)
O1-C1-C11	110.58(8)	C9-C10-C11	131.67(10)
C2-C1-C11	104.73(8)	C12-C10-C11	109.21(9)
C13-C1-C11	108.99(8)	O2-C11-C10	112.64(8)
C3-C2-C12	119.34(10)	O2-C11-C16	106.47(8)
C3-C2-C1	131.81(10)	C10-C11-C16	114.64(8)
C12-C2-C1	108.85(9)	O2-C11-C1	111.55(8)
C2-C3-C4	118.06(10)	C10-C11-C1	103.97(8)
C2-C3-H3	121.0	C16-C11-C1	107.54(8)
C4-C3-H3	121.0	C10-C12-C2	113.11(9)
C5-C4-C3	122.82(10)	C10-C12-C6	123.44(10)
C5-C4-H4	118.6	C2-C12-C6	123.41(10)
C3-C4-H4	118.6	C14-C13-C1	107.70(8)
C4-C5-C6	120.04(10)	C14-C13-C24	107.61(8)
C4-C5-H5	120.0	C1-C13-C24	110.13(8)
C6-C5-H5	120.0	C14-C13-H13	110.4
C12-C6-C5	116.31(10)	C1-C13-H13	110.4
C12-C6-C7	116.22(10)	C24-C13-H13	110.4
C5-C6-C7	127.43(10)	C15-C14-C13	114.21(9)
C8-C7-C6	120.16(10)	C15-C14-H14	122.9
C8-C7-H7	119.9	C13-C14-H14	122.9
C6-C7-H7	119.9	C14-C15-C16	114.19(9)
C7-C8-C9	122.39(10)	C14-C15-H15	122.9
C7-C8-H8	118.8	C16-C15-H15	122.9
C9-C8-H8	118.8	C15-C16-C11	107.18(8)
C10-C9-C8	118.62(10)	C15-C16-C17	108.61(8)

Table 1.6 (Cont'd)

C11-C16-C17	110.21(8)	H20A-C20-H20B	107.6
C15-C16-H16	110.3	C22-C21-C20	115.42(9)
C11-C16-H16	110.3	C22-C21-H21A	108.4
C17-C16-H16	110.3	C20-C21-H21A	108.4
C18-C17-C16	109.93(8)	C22-C21-H21B	108.4
C18-C17-C24	116.84(8)	C20-C21-H21B	108.4
C16-C17-C24	108.87(8)	H21A-C21-H21B	107.5
C18-C17-H17	106.9	C21-C22-C23	118.90(9)
C16-C17-H17	106.9	C21-C22-H22A	107.6
C24-C17-H17	106.9	C23-C22-H22A	107.6
C19-C18-C17	113.40(8)	C21-C22-H22B	107.6
C19-C18-H18A	108.9	C23-C22-H22B	107.6
C17-C18-H18A	108.9	H22A-C22-H22B	107.0
C19-C18-H18B	108.9	C22-C23-C24	117.13(9)
C17-C18-H18B	108.9	C22-C23-H23A	108.0
H18A-C18-H18B	107.7	C24-C23-H23A	108.0
C20-C19-C18	115.36(9)	C22-C23-H23B	108.0
C20-C19-H19A	108.4	C24-C23-H23B	108.0
C18-C19-H19A	108.4	H23A-C23-H23B	107.3
C20-C19-H19B	108.4	C23-C24-C13	108.36(8)
C18-C19-H19B	108.4	C23-C24-C17	117.92(8)
H19A-C19-H19B	107.5	C13-C24-C17	108.22(8)
C19-C20-C21	114.26(9)	C23-C24-H24	107.3
C19-C20-H20A	108.7	C13-C24-H24	107.3
C21-C20-H20A	108.7	C17-C24-H24	107.3
C19-C20-H20B	108.7	C1-O1-H1O	104.0(12)
C21-C20-H20B	108.7	C11-O2-H2O	108.2(13

Table 1.7 Anisotropic displacement parameters ($Å^2$x 10^3) for **3d**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(1)	14(1)	13(1)	-1(1)	2(1)	-2(1)
C2	15(1)	17(1)	12(1)	-3(1)	4(1)	-4(1)
C3	16(1)	28(1)	16(1)	-7(1)	3(1)	-7(1)
C4	25(1)	30(1)	19(1)	-12(1)	7(1)	-16(1)
C5	29(1)	19(1)	18(1)	-7(1)	9(1)	-10(1)
C6	23(1)	15(1)	13(1)	-3(1)	6(1)	-4(1)
C7	26(1)	14(1)	16(1)	-3(1)	6(1)	1(1)
C8	18(1)	22(1)	15(1)	-2(1)	2(1)	4(1)
C9	15(1)	21(1)	13(1)	-4(1)	2(1)	-4(1)
C10	15(1)	14(1)	11(1)	-2(1)	4(1)	-3(1)
C11	14(1)	13(1)	15(1)	-2(1)	4(1)	-4(1)
C12	16(1)	15(1)	11(1)	-3(1)	4(1)	-4(1)
C13	13(1)	15(1)	16(1)	-2(1)	2(1)	0(1)
C14	21(1)	12(1)	21(1)	-2(1)	7(1)	0(1)
C15	24(1)	13(1)	21(1)	-6(1)	8(1)	-6(1)
C16	15(1)	14(1)	16(1)	-5(1)	3(1)	-5(1)
C17	14(1)	13(1)	14(1)	-4(1)	3(1)	-3(1)
C18	17(1)	20(1)	16(1)	-7(1)	3(1)	-7(1)
C19	20(1)	24(1)	15(1)	-3(1)	0(1)	-5(1)
C20	22(1)	16(1)	16(1)	-2(1)	3(1)	-4(1)
C21	22(1)	18(1)	16(1)	-4(1)	5(1)	-7(1)
C22	16(1)	20(1)	19(1)	-4(1)	5(1)	-6(1)
C23	14(1)	16(1)	18(1)	-4(1)	4(1)	-2(1)
C24	14(1)	13(1)	15(1)	-3(1)	3(1)	-3(1)

Table 1.7 (Cont'd)

O1	20(1)	17(1)	15(1)	2(1)	1(1)	-2(1)
O2	21(1)	16(1)	19(1)	-4(1)	8(1)	-8(1)

Table 1.8 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **3d.**

	x	y	z	U(eq)
H3	534	2941	522	23
H4	1320	338	445	27
H5	4117	-1195	989	25
H7	7402	-1352	1722	24
H8	9345	-36	2228	24
H9	8389	2553	2310	20
H13	159	5132	1721	19
H14	793	7355	2112	23
H15	3624	7106	2891	23
H16	5661	4672	3186	18
H17	4205	2433	3519	16
H18A	4630	3989	4752	20
H18B	2479	4229	4792	20
H19A	4974	1319	5358	24
H19B	3717	2096	6115	24
H20A	2603	21	5833	22
H20B	2432	834	4641	22
H21A	-253	1074	5859	22

Table 1.8 (Cont'd)

H21B	432	2626	5819	22
H22A	-1957	3035	4631	22
H22B	-732	1880	4081	22
H23A	182	4738	4101	20
H23B	-1114	4628	3236	20
H24	1527	2674	2902	16
H1O	3260(20)	6330(20)	400(13)	44(5)
H2O	6280(30)	5230(20)	728(15)	56(5)

Table 1.9 Torsion angles [°] for **3d**.

O1-C1-C2-C3	-61.80(14)	C8-C9-C10-C11	179.48(10)
C13-C1-C2-C3	60.96(14)	C9-C10-C11-O2	53.93(14)
C11-C1-C2-C3	179.91(10)	C12-C10-C11-O2	-124.49(9)
O1-C1-C2-C12	117.56(9)	C9-C10-C11-C16	-68.02(14)
C13-C1-C2-C12	-119.68(9)	C12-C10-C11-C16	113.55(9)
C11-C1-C2-C12	-0.73(10)	C9-C10-C11-C1	174.86(10)
C12-C2-C3-C4	1.01(15)	C12-C10-C11-C1	-3.57(10)
C1-C2-C3-C4	-179.68(10)	O1-C1-C11-O2	7.09(11)
C2-C3-C4-C5	-0.72(16)	C2-C1-C11-O2	124.20(8)
C3-C4-C5-C6	-0.50(16)	C13-C1-C11-O2	-113.64(9)
C4-C5-C6-C12	1.35(15)	O1-C1-C11-C10	-114.56(8)
C4-C5-C6-C7	-176.27(10)	C2-C1-C11-C10	2.55(9)
C12-C6-C7-C8	-1.24(14)	C13-C1-C11-C10	124.71(8)
C5-C6-C7-C8	176.38(10)	O1-C1-C11-C16	123.48(8)
C6-C7-C8-C9	1.68(16)	C2-C1-C11-C16	-119.41(8)
C7-C8-C9-C10	0.11(15)	C13-C1-C11-C16	2.76(10)
C8-C9-C10-C12	-2.22(14)	C9-C10-C12-C2	-175.25(9)

Table 1.9 (Cont'd)

C11-C10-C12-C2	3.40(11)	C1-C11-C16-C15	-58.18(10)
C9-C10-C12-C6	2.71(15)	O2-C11-C16-C17	179.53(8)
C11-C10-C12-C6	-178.64(9)	C10-C11-C16-C17	-55.22(11)
C3-C2-C12-C10	177.84(9)	C1-C11-C16-C17	59.85(10)
C1-C2-C12-C10	-1.62(11)	C15-C16-C17-C18	-75.97(10)
C3-C2-C12-C6	-0.13(15)	C11-C16-C17-C18	166.89(8)
C1-C2-C12-C6	-179.58(9)	C15-C16-C17-C24	53.19(10)
C5-C6-C12-C10	-178.82(9)	C11-C16-C17-C24	-63.95(10)
C7-C6-C12-C10	-0.93(14)	C16-C17-C18-C19	-144.88(9)
C5-C6-C12-C2	-1.07(15)	C24-C17-C18-C19	90.44(11)
C7-C6-C12-C2	176.82(9)	C17-C18-C19-C20	-53.88(12)
O1-C1-C13-C14	-67.07(11)	C18-C19-C20-C21	-60.20(12)
C2-C1-C13-C14	170.65(8)	C19-C20-C21-C22	100.45(11)
C11-C1-C13-C14	54.16(10)	C20-C21-C22-C23	-64.10(13)
O1-C1-C13-C24	175.84(8)	C21-C22-C23-C24	75.68(13)
C2-C1-C13-C24	53.57(11)	C22-C23-C24-C13	150.73(9)
C11-C1-C13-C24	-62.92(10)	C22-C23-C24-C17	-85.99(11)
C1-C13-C14-C15	-59.80(12)	C14-C13-C24-C23	70.97(10)
C24-C13-C14-C15	58.91(11)	C1-C13-C24-C23	-171.89(8)
C13-C14-C15-C16	1.03(13)	C14-C13-C24-C17	-57.97(10)
C14-C15-C16-C11	59.93(11)	C1-C13-C24-C17	59.16(10)
C14-C15-C16-C17	-59.13(12)	C18-C17-C24-C23	5.11(13)
O2-C11-C16-C15	61.51(10)	C16-C17-C24-C23	-120.11(9)
C10-C11-C16-C15	-173.24(8)	C18-C17-C24-C13	128.46(9)
		C16-C17-C24-C13	3.24(1

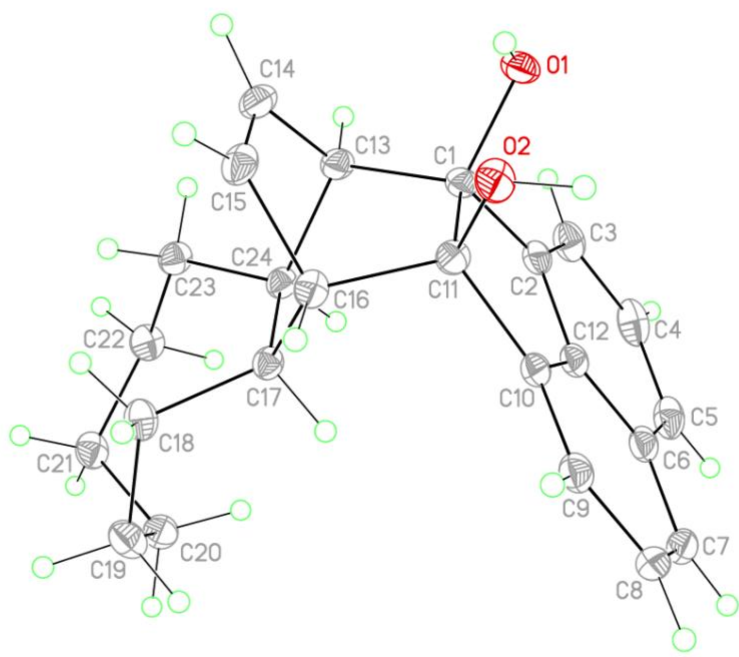
Table 1.10 Hydrogen bonds for **3d′** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O1-H1O...O2	0.885(18)	2.076(18)	2.6350(12)	120.2(15)
O2-H2O...O1#1	0.90(2)	1.96(2)	2.8494(11)	174.3(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z

Figure 1.4 View of **3d′** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for complex **4c**–CH_2Cl_2

X-ray Experimental for $C_{16}H_{16}O_2$ – 1/8 C_5H_{12} - 1/8 CH_2Cl_2: Crystals grew as clusters of colorless prisms by vapor diffusion of pentane into a dichloromethane solution. The data crystal was cut from a larger crystal and had approximate dimensions; 0.40 x 0.30 x 0.25 mm. The data were collected on a Rigaku SCX-Mini diffractometer with a Mercury 2 CCD using a graphite monochromator with MoKα radiation (λ = 0.71075Å). A total of 469 frames of data were collected using ω-scans with a scan range of 1˚and a counting time of 60 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 21. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[13] The structure was solved by direct methods using SIR2004[17] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2014/7.[15] Structure analysis was aided by use of the programs PLATON98[16] and WinGX.[9] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on the hydroxyl oxygen atoms were observed in a ΔF map and refined with isotropic displacement parameters.

Both a molecule of dichloromethane and a molecule of n-pentane were disordered around a crystallographic inversion center. The dichloromethane was disordered around an inversion center at 1/2, 0, 1/2, while the n-pentane molecule was disordered around an inversion center at 0, 1, 0. In each case, the site occupancy factors were set to 1/2. For pentane, the C-C bond and the C-C-C bond angles were restrained to be equivalent. For DCM, the C-Cl bond lengths were restrained to be equivalent and the Cl...Cl distance was restrained to be approximately 2.95Å in order to maintain a Cl-C-Cl bond angle close to 109 degrees. The DCM molecule was located near an inversion center in such a manner that the carbon atom resided very near where a Cl atom of the symmetry related molecule resided. As a result, the displacement parameter for the carbon atom was highly correlated to that of the Cl atom. In the final refinement model, the isotropic displacement parameter for the carbon atom, C1b, was tied to be 1.2 times the Ueq for Cl2.

The function, $\sum w(|Fo|^2 - |Fc|^2)^2$, was minimized, where $w = 1/[(\sigma(Fo))^2 + (0.0705*P)^2 + (2.1979*P)]$ and $P = (|Fo|^2 + 2|Fc|2)/3$. Rw(F2) refined to 0.148, with R(F) equal to 0.0543 and a goodness of fit, S, = 1.03. Definitions used for calculating R(F), Rw(F2) and the goodness of fit, S, are given below.[10] The data were checked for secondary extinction but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[11] All figures were generated using SHELXTL/PC.[12] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1.11 Crystal data and structure refinement for **4c**.

Empirical formula	C16.75 H17.75 Cl0.25 O2	
Formula weight	259.92	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.728(4) Å	α= 79.921(7)°.
	b = 11.923(4) Å	β= 79.758(7)°.
	c = 19.838(7) Å	γ= 77.926(8)°.
Volume	2642.1(16) $Å^3$	
Z	8	
Density (calculated)	1.307 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	
F(000)	1108	
Crystal size	0.400 x 0.300 x 0.250 mm	
Theta range for data collection	3.163 to 27.447°.	
Index ranges	-15<=h<=15, -15<=k<=15, -25<=l<=25	
Reflections collected	24332	
Independent reflections	11921 [R(int) = 0.0267]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.874	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11921 / 36 / 749	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0543, wR2 = 0.1393	
R indices (all data)	R1 = 0.0644, wR2 = 0.1481	

Table 1.12 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **4c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	6663(1)	5901(1)	3237(1)	21(1)
O2	8454(1)	6018(1)	2136(1)	20(1)
C1	6778(2)	7061(1)	2937(1)	17(1)
C2	5591(2)	7679(2)	2689(1)	21(1)
C3	5882(2)	8041(1)	1918(1)	20(1)
C4	5107(2)	8600(2)	1450(1)	26(1)
C5	5548(2)	8795(2)	750(1)	32(1)
C6	6746(2)	8458(2)	515(1)	32(1)
C7	7526(2)	7917(2)	981(1)	25(1)
C8	7082(2)	7712(1)	1683(1)	19(1)
C9	7770(2)	7122(1)	2269(1)	17(1)
C10	8568(2)	7865(2)	2453(1)	21(1)
C11	9268(2)	7170(2)	3019(1)	24(1)
C12	8343(2)	7078(2)	3661(1)	24(1)
C13	7187(2)	7726(2)	3420(1)	20(1)
C14	7706(2)	8712(2)	2914(1)	21(1)
C15	8504(2)	9118(2)	3323(1)	27(1)
C16	9174(2)	7932(2)	3576(1)	27(1)
O3	7427(1)	4687(1)	1456(1)	17(1)
O4	6544(1)	3828(1)	2782(1)	18(1)
C17	6297(1)	4373(1)	1509(1)	15(1)
C18	5420(1)	5483(1)	1271(1)	18(1)
C19	4434(1)	5630(1)	1875(1)	18(1)

Table 1.12 (Cont'd)

C20	3413(2)	6481(2)	1918(1)	23(1)
C21	2599(2)	6443(2)	2521(1)	27(1)
C22	2796(2)	5575(2)	3081(1)	27(1)
C23	3820(2)	4730(2)	3045(1)	22(1)
C24	4631(1)	4765(1)	2436(1)	17(1)
C25	5773(1)	3910(1)	2285(1)	15(1)
C26	5567(2)	2699(1)	2232(1)	18(1)
C27	6744(2)	1868(1)	2088(1)	19(1)
C28	7240(2)	2304(1)	1345(1)	19(1)
C29	6317(1)	3354(1)	1120(1)	17(1)
C30	5210(2)	2849(1)	1498(1)	19(1)
C31	5419(2)	1612(2)	1320(1)	24(1)
C32	6666(2)	1232(2)	1500(1)	22(1)
O5	8304(1)	2164(1)	3339(1)	20(1)
O6	8548(1)	4231(1)	3682(1)	25(1)
C33	8533(2)	2074(2)	4032(1)	20(1)
C34	9688(2)	1174(2)	4110(1)	21(1)
C35	10534(2)	1822(2)	4311(1)	23(1)
C36	11704(2)	1420(2)	4417(1)	32(1)
C37	12357(2)	2206(2)	4539(1)	40(1)
C38	11852(2)	3369(2)	4556(1)	38(1)
C39	10683(2)	3770(2)	4459(1)	30(1)
C40	10025(2)	2987(2)	4343(1)	24(1)
C41	8758(2)	3262(2)	4211(1)	22(1)
C42	7857(2)	3465(2)	4865(1)	30(1)
C43	6605(2)	3798(2)	4677(1)	35(1)
C44	6363(2)	2681(2)	4492(1)	28(1)
C45	7496(2)	1796(2)	4592(1)	22(1)

Table 1.12 (Cont'd)

C46	7760(2)	2218(2)	5240(1)	28(1)
C47	6576(2)	2368(2)	5723(1)	36(1)
C48	5827(2)	3069(2)	5193(1)	37(1)
O7	10408(1)	4441(1)	2624(1)	18(1)
O8	9280(1)	3196(1)	2001(1)	18(1)
C49	11206(1)	3693(1)	2186(1)	15(1)
C50	12020(2)	2801(2)	2637(1)	18(1)
C51	11896(2)	1626(2)	2499(1)	19(1)
C52	12479(2)	531(2)	2764(1)	24(1)
C53	12202(2)	-456(2)	2594(1)	28(1)
C54	11359(2)	-360(2)	2159(1)	29(1)
C55	10786(2)	730(2)	1884(1)	23(1)
C56	11065(1)	1720(1)	2058(1)	17(1)
C57	10538(1)	2975(1)	1824(1)	15(1)
C58	10884(1)	3380(2)	1048(1)	17(1)
C59	10366(2)	4666(2)	851(1)	18(1)
C60	11055(2)	5314(2)	1193(1)	18(1)
C61	11896(1)	4355(1)	1567(1)	16(1)
C62	12189(1)	3529(2)	1004(1)	18(1)
C63	12441(2)	4317(2)	318(1)	22(1)
C64	11351(2)	5252(2)	423(1)	21(1)
C1A	1254(7)	8451(6)	442(4)	59(2)
C2A	959(5)	9721(5)	98(3)	52(2)
C3A	-355(4)	10015(5)	46(3)	48(2)
C4A	-681(6)	11253(5)	-356(3)	49(2)
C5A	-2042(7)	11488(6)	-371(3)	61(2)
Cl1	5041(1)	556(1)	3857(1)	43(1)
Cl2	4820(1)	260(2)	5383(1)	38(1)

Table 1.13 Bond lengths [Å] and angles [°] for **4c**.

O1-C1	1.431(2)	C11-H11	1.00
O1-H1O	0.86(3)	C12-C16	1.520(3)
O2-C9	1.432(2)	C12-C13	1.525(3)
O2-H2O	0.84(3)	C12-H12	1.00
C1-C13	1.539(2)	C13-C14	1.559(2)
C1-C2	1.552(3)	C13-H13	1.00
C1-C9	1.603(2)	C14-C15	1.539(3)
C2-C3	1.513(2)	C14-H14	1.00
C2-H2A	0.99	C15-C16	1.515(3)
C2-H2B	0.99	C15-H15A	0.99
C3-C8	1.397(3)	C15-H15B	0.99
C3-C4	1.401(3)	C16-H16	1.00
C4-C5	1.390(3)	O3-C17	1.4320(19)
C4-H4	0.95	O3-H3O	0.81(3)
C5-C6	1.396(3)	O4-C25	1.430(2)
C5-H5	0.95	O4-H4O	0.79(2)
C6-C7	1.398(3)	C17-C29	1.543(2)
C6-H6	0.95	C17-C18	1.555(2)
C7-C8	1.395(2)	C17-C25	1.600(2)
C7-H7	0.95	C18-C19	1.517(2)
C8-C9	1.518(2)	C18-H18A	0.99
C9-C10	1.542(2)	C18-H18B	0.99
C10-C11	1.529(3)	C19-C24	1.396(2)
C10-C14	1.563(2)	C19-C20	1.398(2)
C10-H10	1.00	C20-C21	1.392(3)
C11-C12	1.524(3)	C20-H20	0.95
C11-C16	1.525(2)	C21-C22	1.397(3)

Table 1.13 (Cont'd)

C21-H21	0.95	C33-C45	1.544(2)
C22-C23	1.397(3)	C33-C34	1.555(2)
C22-H22	0.95	C33-C41	1.604(2)
C23-C24	1.398(2)	C34-C35	1.519(2)
C23-H23	0.95	C34-H34A	0.99
C24-C25	1.522(2)	C34-H34B	0.99
C25-C26	1.537(2)	C35-C36	1.397(3)
C26-C27	1.534(2)	C35-C40	1.399(3)
C26-C30	1.557(2)	C36-C37	1.404(3)
C26-H26	1.00	C36-H36	0.95
C27-C32	1.524(2)	C37-C38	1.393(3)
C27-C28	1.528(2)	C37-H37	0.95
C27-H27	1.00	C38-C39	1.390(3)
C28-C32	1.527(2)	C38-H38	0.95
C28-C29	1.532(2)	C39-C40	1.401(3)
C28-H28	1.00	C39-H39	0.95
C29-C30	1.560(2)	C40-C41	1.513(3)
C29-H29	1.00	C41-C42	1.540(2)
C30-C31	1.536(2)	C42-C43	1.533(3)
C30-H30	1.00	C42-C46	1.560(3)
C31-C32	1.523(3)	C42-H42	1.00
C31-H31A	0.99	C43-C48	1.524(3)
C31-H31B	0.99	C43-C44	1.535(3)
C32-H32	1.00	C43-H43	1.00
O5-C33	1.428(2)	C44-C48	1.527(3)
O5-H5O	0.88(3)	C44-C45	1.534(3)
O6-C41	1.430(2)	C44-H44	1.00
O6-H6O	0.83(3)	C45-C46	1.561(3)

Table 1.13 (Cont'd)

C45-H45	1.00	C57-C58	1.539(2)
C46-C47	1.536(3)	C58-C59	1.535(2)
C46-H46	1.00	C58-C62	1.563(2)
C47-C48	1.513(3)	C58-H58	1.00
C47-H47A	0.99	C59-C64	1.526(2)
C47-H47B	0.99	C59-C60	1.532(2)
C48-H48	1.00	C59-H59	1.00
O7-C49	1.4342(19)	C60-C64	1.517(2)
O7-H7O	0.79(3)	C60-C61	1.525(2)
O8-C57	1.4332(19)	C60-H60	1.00
O8-H8O	0.82(3)	C61-C62	1.563(2)
C49-C61	1.536(2)	C61-H61	1.00
C49-C50	1.545(2)	C62-C63	1.532(2)
C49-C57	1.601(2)	C62-H62	1.00
C50-C51	1.513(2)	C63-C64	1.520(3)
C50-H50A	0.99	C63-H63A	0.99
C50-H50B	0.99	C63-H63B	0.99
C51-C56	1.398(2)	C64-H64	1.00
C51-C52	1.402(3)	C1A-C2A	1.544(6)
C52-C53	1.393(3)	C1A-H1A1	0.98
C52-H52	0.95	C1A-H1A2	0.98
C53-C54	1.400(3)	C1A-H1A3	0.98
C53-H53	0.95	C2A-C3A	1.526(6)
C54-C55	1.398(3)	C2A-H2A1	0.99
C54-H54	0.95	C2A-H2A2	0.99
C55-C56	1.401(2)	C3A-C4A	1.556(6)
C55-H55	0.95	C3A-H3A1	0.99
C56-C57	1.519(2)	C3A-H3A2	0.99

Table 1.13 (Cont'd)

C4A-C5A	1.566(6)	C5A-H5A3	0.98
C4A-H4A1	0.99	Cl1-C1B	1.780(7)
C4A-H4A2	0.99	Cl2-C1B	1.779(7)
C5A-H5A1	0.98	C1B-H1BA	0.99
C5A-H5A2	0.98	C1B-H1BB	0.99

C1-O1-H1O	107(2)	C6-C5-H5	119.6
C9-O2-H2O	107.7(18)	C5-C6-C7	120.50(18)
O1-C1-C13	113.35(14)	C5-C6-H6	119.8
O1-C1-C2	107.90(13)	C7-C6-H6	119.8
C13-C1-C2	113.04(14)	C8-C7-C6	118.72(18)
O1-C1-C9	113.22(13)	C8-C7-H7	120.6
C13-C1-C9	102.63(13)	C6-C7-H7	120.6
C2-C1-C9	106.54(13)	C7-C8-C3	120.83(17)
C3-C2-C1	105.71(14)	C7-C8-C9	127.06(17)
C3-C2-H2A	110.6	C3-C8-C9	112.10(15)
C1-C2-H2A	110.6	O2-C9-C8	112.19(13)
C3-C2-H2B	110.6	O2-C9-C10	109.54(14)
C1-C2-H2B	110.6	C8-C9-C10	113.90(14)
H2A-C2-H2B	108.7	O2-C9-C1	114.05(13)
C8-C3-C4	120.24(17)	C8-C9-C1	103.85(13)
C8-C3-C2	111.71(16)	C10-C9-C1	102.96(13)
C4-C3-C2	128.01(17)	C11-C10-C9	109.72(14)
C5-C4-C3	118.86(19)	C11-C10-C14	97.09(14)
C5-C4-H4	120.6	C9-C10-C14	104.05(14)
C3-C4-H4	120.6	C11-C10-H10	114.7
C4-C5-C6	120.83(19)	C9-C10-H10	114.7
C4-C5-H5	119.6	C14-C10-H10	114.7

Table 1.13 (Cont'd)

C12-C11-C16	59.83(12)	C14-C15-H15B	112.3
C12-C11-C10	103.97(15)	H15A-C15-H15B	109.9
C16-C11-C10	108.24(15)	C15-C16-C12	107.30(16)
C12-C11-H11	122.7	C15-C16-C11	107.25(16)
C16-C11-H11	122.7	C12-C16-C11	60.07(12)
C10-C11-H11	122.7	C15-C16-H16	122.1
C16-C12-C11	60.11(12)	C12-C16-H16	122.1
C16-C12-C13	108.48(15)	C11-C16-H16	122.1
C11-C12-C13	104.94(15)	C17-O3-H3O	109.6(17)
C16-C12-H12	122.3	C25-O4-H4O	107.6(17)
C11-C12-H12	122.3	O3-C17-C29	113.71(13)
C13-C12-H12	122.3	O3-C17-C18	107.73(13)
C12-C13-C1	111.30(14)	C29-C17-C18	113.05(13)
C12-C13-C14	96.90(14)	O3-C17-C25	113.08(13)
C1-C13-C14	103.41(13)	C29-C17-C25	102.64(12)
C12-C13-H13	114.5	C18-C17-C25	106.45(12)
C1-C13-H13	114.5	C19-C18-C17	105.72(13)
C14-C13-H13	114.5	C19-C18-H18A	110.6
C15-C14-C13	104.90(15)	C17-C18-H18A	110.6
C15-C14-C10	104.63(15)	C19-C18-H18B	110.6
C13-C14-C10	94.16(13)	C17-C18-H18B	110.6
C15-C14-H14	116.7	H18A-C18-H18B	108.7
C13-C14-H14	116.7	C24-C19-C20	119.84(16)
C10-C14-H14	116.7	C24-C19-C18	111.67(14)
C16-C15-C14	97.36(14)	C20-C19-C18	128.48(16)
C16-C15-H15A	112.3	C21-C20-C19	119.30(17)
C14-C15-H15A	112.3	C21-C20-H20	120.3
C16-C15-H15B	112.3	C19-C20-H20	120.3

Table 1.13 (Cont'd)

C20-C21-C22	120.78(17)	C28-C27-H27	122.7
C20-C21-H21	119.6	C26-C27-H27	122.7
C22-C21-H21	119.6	C32-C28-C27	59.86(11)
C21-C22-C23	120.25(17)	C32-C28-C29	108.24(14)
C21-C22-H22	119.9	C27-C28-C29	104.53(13)
C23-C22-H22	119.9	C32-C28-H28	122.5
C22-C23-C24	118.80(17)	C27-C28-H28	122.5
C22-C23-H23	120.6	C29-C28-H28	122.5
C24-C23-H23	120.6	C28-C29-C17	111.00(13)
C19-C24-C23	121.01(16)	C28-C29-C30	96.85(13)
C19-C24-C25	112.06(14)	C17-C29-C30	103.30(13)
C23-C24-C25	126.91(16)	C28-C29-H29	114.6
O4-C25-C24	111.86(13)	C17-C29-H29	114.6
O4-C25-C26	110.10(13)	C30-C29-H29	114.6
C24-C25-C26	112.90(13)	C31-C30-C26	104.83(14)
O4-C25-C17	114.33(12)	C31-C30-C29	105.29(14)
C24-C25-C17	104.08(13)	C26-C30-C29	94.52(12)
C26-C25-C17	103.21(12)	C31-C30-H30	116.5
C27-C26-C25	110.83(13)	C26-C30-H30	116.5
C27-C26-C30	97.09(13)	C29-C30-H30	116.5
C25-C26-C30	103.29(13)	C32-C31-C30	97.08(13)
C27-C26-H26	114.6	C32-C31-H31A	112.3
C25-C26-H26	114.6	C30-C31-H31A	112.3
C30-C26-H26	114.6	C32-C31-H31B	112.3
C32-C27-C28	60.03(11)	C30-C31-H31B	112.3
C32-C27-C26	107.85(14)	H31A-C31-H31B	109.9
C28-C27-C26	104.22(14)	C31-C32-C27	107.36(14)
C32-C27-H27	122.7	C31-C32-C28	107.29(14)

Table 1.13 (Cont'd)

C27-C32-C28	60.11(11)	C39-C38-H38	119.8
C31-C32-H32	122.1	C37-C38-H38	119.8
C27-C32-H32	122.1	C38-C39-C40	118.89(19)
C28-C32-H32	122.1	C38-C39-H39	120.6
C33-O5-H5O	108.6(18)	C40-C39-H39	120.6
C41-O6-H6O	106.7(19)	C35-C40-C39	121.00(19)
O5-C33-C45	114.17(15)	C35-C40-C41	112.35(16)
O5-C33-C34	107.82(13)	C39-C40-C41	126.60(18)
C45-C33-C34	112.59(14)	O6-C41-C40	112.26(15)
O5-C33-C41	113.08(13)	O6-C41-C42	109.39(15)
C45-C33-C41	102.65(13)	C40-C41-C42	113.63(16)
C34-C33-C41	106.29(14)	O6-C41-C33	114.04(14)
C35-C34-C33	105.79(14)	C40-C41-C33	104.13(14)
C35-C34-H34A	110.6	C42-C41-C33	103.04(14)
C33-C34-H34A	110.6	C43-C42-C41	110.00(16)
C35-C34-H34B	110.6	C43-C42-C46	96.99(16)
C33-C34-H34B	110.6	C41-C42-C46	103.91(14)
H34A-C34-H34B	108.7	C43-C42-H42	114.7
C36-C35-C40	119.90(18)	C41-C42-H42	114.7
C36-C35-C34	128.68(17)	C46-C42-H42	114.7
C40-C35-C34	111.30(17)	C48-C43-C42	108.11(18)
C35-C36-C37	118.9(2)	C48-C43-C44	59.92(13)
C35-C36-H36	120.6	C42-C43-C44	104.45(16)
C37-C36-H36	120.6	C48-C43-H43	122.6
C38-C37-C36	120.9(2)	C42-C43-H43	122.6
C38-C37-H37	119.5	C44-C43-H43	122.6
C36-C37-H37	119.5	C48-C44-C45	107.77(17)
C39-C38-C37	120.41(19)	C48-C44-C43	59.69(13)

Table 1.13 (Cont'd)

C45-C44-C43	104.07(17)	C49-O7-H7O	107(2)
C48-C44-H44	122.8	C57-O8-H8O	110.1(19)
C45-C44-H44	122.8	O7-C49-C61	113.13(13)
C43-C44-H44	122.8	O7-C49-C50	108.52(13)
C44-C45-C33	111.43(14)	C61-C49-C50	112.63(13)
C44-C45-C46	97.23(15)	O7-C49-C57	112.48(13)
C33-C45-C46	103.08(15)	C61-C49-C57	102.90(12)
C44-C45-H45	114.4	C50-C49-C57	106.98(13)
C33-C45-H45	114.4	C51-C50-C49	105.44(13)
C46-C45-H45	114.4	C51-C50-H50A	110.7
C47-C46-C42	104.57(16)	C49-C50-H50A	110.7
C47-C46-C45	104.91(17)	C51-C50-H50B	110.7
C42-C46-C45	94.43(14)	C49-C50-H50B	110.7
C47-C46-H46	116.7	H50A-C50-H50B	108.8
C42-C46-H46	116.7	C56-C51-C52	119.96(16)
C45-C46-H46	116.7	C56-C51-C50	111.81(15)
C48-C47-C46	97.54(16)	C52-C51-C50	128.22(16)
C48-C47-H47A	112.3	C53-C52-C51	119.27(17)
C46-C47-H47A	112.3	C53-C52-H52	120.4
C48-C47-H47B	112.3	C51-C52-H52	120.4
C46-C47-H47B	112.3	C52-C53-C54	120.68(18)
H47A-C47-H47B	109.9	C52-C53-H53	119.7
C47-C48-C43	107.1(2)	C54-C53-H53	119.7
C47-C48-C44	107.60(17)	C55-C54-C53	120.37(17)
C43-C48-C44	60.38(13)	C55-C54-H54	119.8
C47-C48-H48	122.0	C53-C54-H54	119.8
C43-C48-H48	122.0	C54-C55-C56	118.81(17)
C44-C48-H48	122.0	C54-C55-H55	120.6

Table 1.13 (Cont'd)

C56-C55-H55	120.6	C60-C61-C49	110.14(13)
C51-C56-C55	120.90(16)	C60-C61-C62	97.08(13)
C51-C56-C57	112.01(14)	C49-C61-C62	104.10(13)
C55-C56-C57	127.08(15)	C60-C61-H61	114.6
O8-C57-C56	111.60(13)	C49-C61-H61	114.6
O8-C57-C58	109.94(13)	C62-C61-H61	114.6
C56-C57-C58	113.84(13)	C63-C62-C58	104.93(13)
O8-C57-C49	114.49(13)	C63-C62-C61	104.78(14)
C56-C57-C49	103.62(13)	C58-C62-C61	94.32(12)
C58-C57-C49	103.02(12)	C63-C62-H62	116.6
C59-C58-C57	111.23(13)	C58-C62-H62	116.6
C59-C58-C62	96.91(13)	C61-C62-H62	116.6
C57-C58-C62	102.72(13)	C64-C63-C62	97.30(13)
C59-C58-H58	114.7	C64-C63-H63A	112.3
C57-C58-H58	114.7	C62-C63-H63A	112.3
C62-C58-H58	114.7	C64-C63-H63B	112.3
C64-C59-C60	59.46(11)	C62-C63-H63B	112.3
C64-C59-C58	107.90(14)	H63A-C63-H63B	109.9
C60-C59-C58	104.57(13)	C60-C64-C63	107.23(14)
C64-C59-H59	122.7	C60-C64-C59	60.47(11)
C60-C59-H59	122.7	C63-C64-C59	107.42(15)
C58-C59-H59	122.7	C60-C64-H64	122.0
C64-C60-C61	108.46(14)	C63-C64-H64	122.0
C64-C60-C59	60.07(11)	C59-C64-H64	122.0
C61-C60-C59	104.20(14)	C2A-C1A-H1A1	109.5
C64-C60-H60	122.5	C2A-C1A-H1A2	109.5
C61-C60-H60	122.5	H1A1-C1A-H1A2	109.5
C59-C60-H60	122.5	C2A-C1A-H1A3	109.5

Table 1.13 (Cont'd)

H1A1-C1A-H1A3	109.5	C5A-C4A-H4A1	110.3
H1A2-C1A-H1A3	109.5	C3A-C4A-H4A2	110.3
C3A-C2A-C1A	108.4(5)	C5A-C4A-H4A2	110.3
C3A-C2A-H2A1	110.0	H4A1-C4A-H4A2	108.6
C1A-C2A-H2A1	110.0	C4A-C5A-H5A1	109.5
C3A-C2A-H2A2	110.0	C4A-C5A-H5A2	109.5
C1A-C2A-H2A2	110.0	H5A1-C5A-H5A2	109.5
H2A1-C2A-H2A2	108.4	C4A-C5A-H5A3	109.5
C2A-C3A-C4A	110.6(4)	H5A1-C5A-H5A3	109.5
C2A-C3A-H3A1	109.5	H5A2-C5A-H5A3	109.5
C4A-C3A-H3A1	109.5	Cl2-C1B-Cl1	112.3(4)
C2A-C3A-H3A2	109.5	Cl2-C1B-H1BA	109.1
C4A-C3A-H3A2	109.5	Cl1-C1B-H1BA	109.1
H3A1-C3A-H3A2	108.1	Cl2-C1B-H1BB	109.1
C3A-C4A-C5A	107.0(5)	Cl1-C1B-H1BB	109.1
C3A-C4A-H4A1	110.3	H1BA-C1B-H1BB	107.9

Table 1.14 Anisotropic displacement parameters ($Å^2$x 10^3) for **4c**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	24(1)	14(1)	23(1)	-2(1)	1(1)	-7(1)
O2	19(1)	19(1)	25(1)	-12(1)	-1(1)	-3(1)
C1	22(1)	13(1)	18(1)	-4(1)	2(1)	-5(1)
C2	21(1)	18(1)	24(1)	-4(1)	3(1)	-4(1)
C3	27(1)	12(1)	22(1)	-4(1)	-1(1)	-5(1)
C4	32(1)	14(1)	34(1)	-2(1)	-9(1)	-4(1)
C5	52(1)	17(1)	29(1)	4(1)	-18(1)	-8(1)
C6	54(1)	24(1)	19(1)	1(1)	-5(1)	-13(1)
C7	35(1)	21(1)	20(1)	-4(1)	3(1)	-11(1)
C8	27(1)	13(1)	19(1)	-4(1)	1(1)	-8(1)
C9	20(1)	14(1)	18(1)	-5(1)	2(1)	-6(1)
C10	24(1)	21(1)	19(1)	-7(1)	3(1)	-11(1)
C11	24(1)	23(1)	30(1)	-12(1)	-4(1)	-6(1)
C12	34(1)	20(1)	21(1)	-5(1)	-5(1)	-9(1)
C13	27(1)	17(1)	18(1)	-7(1)	3(1)	-7(1)
C14	29(1)	15(1)	22(1)	-5(1)	1(1)	-7(1)
C15	37(1)	21(1)	28(1)	-10(1)	-1(1)	-12(1)
C16	34(1)	26(1)	27(1)	-11(1)	-7(1)	-11(1)
O3	13(1)	14(1)	24(1)	-2(1)	-3(1)	-4(1)
O4	21(1)	14(1)	22(1)	-3(1)	-7(1)	-3(1)
C17	13(1)	12(1)	20(1)	-2(1)	-2(1)	-3(1)
C18	17(1)	14(1)	22(1)	0(1)	-5(1)	-2(1)
C19	15(1)	13(1)	27(1)	-4(1)	-4(1)	-4(1)
C20	18(1)	12(1)	40(1)	-2(1)	-6(1)	-3(1)

Table 1.14 (Cont'd)

C21	17(1)	16(1)	47(1)	-10(1)	-1(1)	-3(1)
C22	21(1)	22(1)	37(1)	-12(1)	7(1)	-7(1)
C23	22(1)	17(1)	26(1)	-5(1)	1(1)	-6(1)
C24	15(1)	13(1)	25(1)	-5(1)	-2(1)	-4(1)
C25	13(1)	12(1)	18(1)	-2(1)	-3(1)	-2(1)
C26	19(1)	12(1)	23(1)	-2(1)	-3(1)	-4(1)
C27	21(1)	12(1)	25(1)	-3(1)	-6(1)	-1(1)
C28	19(1)	14(1)	25(1)	-6(1)	-4(1)	-2(1)
C29	18(1)	14(1)	19(1)	-3(1)	-4(1)	-4(1)
C30	17(1)	15(1)	26(1)	-4(1)	-6(1)	-4(1)
C31	26(1)	16(1)	32(1)	-7(1)	-8(1)	-7(1)
C32	26(1)	14(1)	28(1)	-6(1)	-6(1)	-3(1)
O5	23(1)	20(1)	14(1)	-2(1)	-2(1)	1(1)
O6	32(1)	15(1)	21(1)	2(1)	8(1)	-2(1)
C33	28(1)	16(1)	14(1)	-1(1)	-1(1)	-3(1)
C34	28(1)	15(1)	19(1)	-1(1)	-5(1)	-4(1)
C35	35(1)	21(1)	14(1)	2(1)	-7(1)	-8(1)
C36	42(1)	29(1)	27(1)	5(1)	-18(1)	-9(1)
C37	48(1)	44(1)	35(1)	5(1)	-26(1)	-16(1)
C38	60(2)	38(1)	24(1)	-1(1)	-16(1)	-25(1)
C39	51(1)	26(1)	16(1)	-4(1)	-3(1)	-16(1)
C40	40(1)	22(1)	11(1)	0(1)	-2(1)	-10(1)
C41	34(1)	14(1)	15(1)	-1(1)	3(1)	-5(1)
C42	48(1)	19(1)	20(1)	-6(1)	11(1)	-10(1)
C43	44(1)	19(1)	28(1)	0(1)	19(1)	-1(1)
C44	30(1)	23(1)	24(1)	1(1)	7(1)	0(1)
C45	30(1)	17(1)	17(1)	0(1)	1(1)	-5(1)
C46	43(1)	23(1)	16(1)	-1(1)	4(1)	-12(1)

Table 1.14 (Cont'd)

C47	55(1)	28(1)	20(1)	-4(1)	14(1)	-16(1)
C48	44(1)	23(1)	32(1)	-2(1)	19(1)	-4(1)
O7	20(1)	18(1)	15(1)	-4(1)	-1(1)	-1(1)
O8	13(1)	22(1)	18(1)	-1(1)	-1(1)	-3(1)
C49	15(1)	16(1)	15(1)	-4(1)	-2(1)	-2(1)
C50	19(1)	19(1)	18(1)	-3(1)	-6(1)	-4(1)
C51	17(1)	20(1)	19(1)	-5(1)	-2(1)	-3(1)
C52	24(1)	22(1)	27(1)	-4(1)	-9(1)	0(1)
C53	30(1)	18(1)	35(1)	-4(1)	-8(1)	2(1)
C54	33(1)	18(1)	39(1)	-9(1)	-8(1)	-4(1)
C55	24(1)	21(1)	28(1)	-6(1)	-7(1)	-4(1)
C56	15(1)	18(1)	17(1)	-3(1)	-1(1)	-3(1)
C57	14(1)	17(1)	16(1)	-4(1)	-1(1)	-3(1)
C58	16(1)	21(1)	15(1)	-5(1)	-2(1)	-5(1)
C59	19(1)	23(1)	13(1)	-1(1)	-3(1)	-6(1)
C60	19(1)	19(1)	16(1)	-3(1)	0(1)	-5(1)
C61	15(1)	19(1)	15(1)	-4(1)	-1(1)	-5(1)
C62	15(1)	21(1)	17(1)	-5(1)	0(1)	-5(1)
C63	21(1)	28(1)	17(1)	-6(1)	3(1)	-9(1)
C64	24(1)	23(1)	15(1)	0(1)	-1(1)	-7(1)
C1A	56(4)	64(4)	52(4)	-19(3)	7(4)	-4(4)
C2A	75(5)	43(3)	40(3)	-12(2)	11(3)	-25(3)
C3A	51(4)	65(3)	33(2)	-4(2)	-4(3)	-27(4)
C4A	46(3)	41(3)	67(3)	-23(3)	-30(3)	10(2)
C5A	100(5)	58(4)	25(3)	-5(2)	-10(3)	-10(4)
Cl1	53(1)	37(1)	36(1)	-3(1)	-10(1)	-1(1)
Cl2	42(1)	37(1)	34(1)	-11(1)	-2(1)	-4(1)

Table 1.15 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **4c**.

	x	y	z	U(eq)
H2A	5020	7145	2787	26
H2B	5249	8364	2926	26
H4	4293	8842	1609	31
H5	5028	9162	427	38
H6	7033	8598	35	38
H7	8342	7692	823	30
H10	9051	8252	2046	25
H11	9958	6536	2926	29
H12	8382	6377	4022	29
H13	6562	8001	3799	24
H14	7133	9329	2676	26
H15A	9026	9616	3023	33
H15B	8047	9522	3709	33
H16	9799	7827	3877	33
H18A	5814	6165	1159	21
H18B	5109	5391	855	21
H20	3277	7079	1541	28
H21	1900	7015	2551	32
H22	2231	5558	3489	32
H23	3963	4143	3427	26
H26	4991	2386	2616	21
H27	7255	1523	2453	23
H28	8104	2264	1186	23

Table 1.15 (Cont'd)

H29	6345	3566	608	20
H30	4426	3343	1430	22
H31A	4863	1145	1615	28
H31B	5391	1602	826	28
H32	7132	439	1450	26
H34A	9536	517	4473	25
H34B	10018	870	3669	25
H36	12052	627	4406	38
H37	13155	1942	4610	48
H38	12309	3891	4635	45
H39	10336	4563	4472	36
H42	8050	3984	5157	36
H43	6289	4585	4440	42
H44	5878	2680	4125	34
H45	7396	969	4667	27
H46	8460	1765	5452	33
H47A	6329	1618	5916	43
H47B	6585	2804	6103	43
H48	4961	3347	5315	44
H50A	12848	2913	2504	22
H50B	11772	2877	3133	22
H52	13056	462	3057	29
H53	12589	-1201	2775	34
H54	11175	-1040	2049	35
H55	10217	798	1586	28
H58	10764	2858	733	20
H59	9517	4948	799	22
H60	10688	6053	1381	21

Table 1.15 (Cont'd)

H61	12596	4607	1677	19
H62	12782	2804	1092	21
H63A	13180	4616	280	27
H63B	12461	3931	-88	27
H64	11189	5951	68	25
H1A1	755	8347	892	89
H1A2	2085	8264	508	89
H1A3	1109	7936	145	89
H2A1	1158	10244	378	62
H2A2	1424	9823	-369	62
H3A1	-814	9972	516	57
H3A2	-562	9443	-196	57
H4A1	-247	11301	-833	59
H4A2	-475	11834	-120	59
H5A1	-2228	10932	-627	92
H5A2	-2289	12278	-601	92
H5A3	-2459	11400	103	92
H1BA	5287	-1111	4644	45
H1BB	6360	-443	4582	45
H1O	7330(30)	5560(30)	3358(15)	53(8)
H2O	8040(20)	5690(20)	1952(14)	44(7)
H3O	7890(20)	4130(20)	1603(13)	33(7)
H4O	6530(20)	4460(20)	2853(12)	24(6)
H5O	7660(30)	2690(30)	3284(14)	49(8)
H6O	9140(20)	4180(20)	3385(14)	42(7)
H7O	9970(20)	4860(20)	2390(15)	45(8)
H8O	9090(20)	2900(20)	2403(15)	47(8)

Table 1.16 Torsion angles [°] for **4c**.

O1-C1-C2-C3	-120.24(14)	C2-C1-C9-C8	-2.69(16)
C13-C1-C2-C3	113.61(15)	O1-C1-C9-C10	-125.25(15)
C9-C1-C2-C3	1.64(17)	C13-C1-C9-C10	-2.70(16)
C1-C2-C3-C8	0.15(18)	C2-C1-C9-C10	116.31(14)
C1-C2-C3-C4	177.96(16)	O2-C9-C10-C11	-50.41(17)
C8-C3-C4-C5	1.5(3)	C8-C9-C10-C11	-176.97(14)
C2-C3-C4-C5	-176.11(17)	C1-C9-C10-C11	71.28(16)
C3-C4-C5-C6	-1.0(3)	O2-C9-C10-C14	-153.40(14)
C4-C5-C6-C7	0.0(3)	C8-C9-C10-C14	80.04(17)
C5-C6-C7-C8	0.5(3)	C1-C9-C10-C14	-31.71(16)
C6-C7-C8-C3	0.0(3)	C9-C10-C11-C12	-70.14(16)
C6-C7-C8-C9	178.85(16)	C14-C10-C11-C12	37.59(15)
C4-C3-C8-C7	-1.0(2)	C9-C10-C11-C16	-132.53(15)
C2-C3-C8-C7	176.96(15)	C14-C10-C11-C16	-24.81(17)
C4-C3-C8-C9	179.96(15)	C10-C11-C12-C16	-103.20(16)
C2-C3-C8-C9	-2.04(19)	C16-C11-C12-C13	103.00(16)
C7-C8-C9-O2	-52.4(2)	C10-C11-C12-C13	-0.20(17)
C3-C8-C9-O2	126.56(15)	C16-C12-C13-C1	132.90(15)
C7-C8-C9-C10	72.8(2)	C11-C12-C13-C1	69.94(17)
C3-C8-C9-C10	-108.28(16)	C16-C12-C13-C14	25.57(17)
C7-C8-C9-C1	-175.99(16)	C11-C12-C13-C14	-37.39(15)
C3-C8-C9-C1	2.93(17)	O1-C1-C13-C12	55.76(18)
O1-C1-C9-O2	-6.7(2)	C2-C1-C13-C12	178.95(14)
C13-C1-C9-O2	115.89(15)	C9-C1-C13-C12	-66.70(17)
C2-C1-C9-O2	-125.10(15)	O1-C1-C13-C14	158.79(14)
O1-C1-C9-C8	115.75(15)	C2-C1-C13-C14	-78.03(17)
C13-C1-C9-C8	-121.70(14)	C9-C1-C13-C14	36.33(16)

Table 1.16 (Cont'd)

C12-C13-C14-C15	-46.59(16)	C20-C19-C24-C23	0.2(2)
C1-C13-C14-C15	-160.48(14)	C18-C19-C24-C23	-179.17(15)
C12-C13-C14-C10	59.74(14)	C20-C19-C24-C25	178.91(15)
C1-C13-C14-C10	-54.14(16)	C18-C19-C24-C25	-0.49(19)
C11-C10-C14-C15	46.48(16)	C22-C23-C24-C19	0.6(3)
C9-C10-C14-C15	158.91(14)	C22-C23-C24-C25	-177.92(16)
C11-C10-C14-C13	-60.10(14)	C19-C24-C25-O4	123.69(15)
C9-C10-C14-C13	52.33(16)	C23-C24-C25-O4	-57.7(2)
C13-C14-C15-C16	48.95(17)	C19-C24-C25-C26	-111.46(16)
C10-C14-C15-C16	-49.50(17)	C23-C24-C25-C26	67.1(2)
C14-C15-C16-C12	-31.05(18)	C19-C24-C25-C17	-0.25(17)
C14-C15-C16-C11	32.17(18)	C23-C24-C25-C17	178.33(16)
C11-C12-C16-C15	100.31(17)	O3-C17-C25-O4	-3.37(18)
C13-C12-C16-C15	3.34(19)	C29-C17-C25-O4	119.55(14)
C13-C12-C16-C11	-96.97(16)	C18-C17-C25-O4	-121.47(14)
C12-C11-C16-C15	-100.40(17)	O3-C17-C25-C24	118.96(14)
C10-C11-C16-C15	-4.5(2)	C29-C17-C25-C24	-118.12(13)
C10-C11-C16-C12	95.88(16)	C18-C17-C25-C24	0.86(16)
O3-C17-C18-C19	-122.70(14)	O3-C17-C25-C26	-122.94(14)
C29-C17-C18-C19	110.80(15)	C29-C17-C25-C26	-0.02(15)
C25-C17-C18-C19	-1.13(16)	C18-C17-C25-C26	118.96(14)
C17-C18-C19-C24	1.03(18)	O4-C25-C26-C27	-53.49(18)
C17-C18-C19-C20	-178.30(16)	C24-C25-C26-C27	-179.29(14)
C24-C19-C20-C21	-0.8(3)	C17-C25-C26-C27	68.96(16)
C18-C19-C20-C21	178.49(17)	O4-C25-C26-C30	-156.53(13)
C19-C20-C21-C22	0.6(3)	C24-C25-C26-C30	77.67(16)
C20-C21-C22-C23	0.2(3)	C17-C25-C26-C30	-34.08(15)
C21-C22-C23-C24	-0.8(3)	C25-C26-C27-C32	-132.62(14)

Table 1.16 (Cont'd)

C30-C26-C27-C32	-25.45(16)	C28-C27-C32-C31	-100.34(16)
C25-C26-C27-C28	-70.00(16)	C26-C27-C32-C31	-3.90(19)
C30-C26-C27-C28	37.17(15)	C26-C27-C32-C28	96.44(15)
C26-C27-C28-C32	-102.65(15)	C27-C28-C32-C31	100.45(16)
C32-C27-C28-C29	102.91(15)	C29-C28-C32-C31	3.90(19)
C26-C27-C28-C29	0.26(16)	C29-C28-C32-C27	-96.55(15)
C32-C28-C29-C17	132.19(14)	O5-C33-C34-C35	120.55(14)
C27-C28-C29-C17	69.62(16)	C45-C33-C34-C35	-112.62(16)
C32-C28-C29-C30	25.08(16)	C41-C33-C34-C35	-0.98(17)
C27-C28-C29-C30	-37.49(15)	C33-C34-C35-C36	-177.27(18)
O3-C17-C29-C28	53.70(18)	C33-C34-C35-C40	-1.36(19)
C18-C17-C29-C28	176.96(13)	C40-C35-C36-C37	-1.4(3)
C25-C17-C29-C28	-68.79(15)	C34-C35-C36-C37	174.20(19)
O3-C17-C29-C30	156.53(13)	C35-C36-C37-C38	0.1(3)
C18-C17-C29-C30	-80.22(16)	C36-C37-C38-C39	0.7(3)
C25-C17-C29-C30	34.03(15)	C37-C38-C39-C40	-0.2(3)
C27-C26-C30-C31	47.22(15)	C36-C35-C40-C39	1.9(3)
C25-C26-C30-C31	160.64(13)	C34-C35-C40-C39	-174.38(15)
C27-C26-C30-C29	-59.91(13)	C36-C35-C40-C41	179.69(16)
C25-C26-C30-C29	53.51(14)	C34-C35-C40-C41	3.4(2)
C28-C29-C30-C31	-46.75(16)	C38-C39-C40-C35	-1.1(3)
C17-C29-C30-C31	-160.28(13)	C38-C39-C40-C41	-178.55(17)
C28-C29-C30-C26	59.97(13)	C35-C40-C41-O6	-127.64(16)
C17-C29-C30-C26	-53.55(14)	C39-C40-C41-O6	50.0(2)
C26-C30-C31-C32	-49.70(16)	C35-C40-C41-C42	107.56(17)
C29-C30-C31-C32	49.33(16)	C39-C40-C41-C42	-74.8(2)
C30-C31-C32-C27	31.80(17)	C35-C40-C41-C33	-3.79(18)
C30-C31-C32-C28	-31.49(17)	C39-C40-C41-C33	173.81(16)

Table 1.16 (Cont'd)

O5-C33-C41-O6	7.3(2)	C41-C33-C45-C44	67.42(18)
C45-C33-C41-O6	-116.15(16)	O5-C33-C45-C46	-158.63(14)
C34-C33-C41-O6	125.45(15)	C34-C33-C45-C46	78.00(17)
O5-C33-C41-C40	-115.35(15)	C41-C33-C45-C46	-35.88(17)
C45-C33-C41-C40	121.16(14)	C43-C42-C46-C47	-46.69(18)
C34-C33-C41-C40	2.76(16)	C41-C42-C46-C47	-159.35(17)
O5-C33-C41-C42	125.79(16)	C43-C42-C46-C45	59.98(16)
C45-C33-C41-C42	2.30(18)	C41-C42-C46-C45	-52.68(18)
C34-C33-C41-C42	-116.10(16)	C44-C45-C46-C47	46.38(17)
O6-C41-C42-C43	50.8(2)	C33-C45-C46-C47	160.43(15)
C40-C41-C42-C43	177.17(15)	C44-C45-C46-C42	-59.99(16)
C33-C41-C42-C43	-70.81(18)	C33-C45-C46-C42	54.06(17)
O6-C41-C42-C46	153.77(16)	C42-C46-C47-C48	49.75(19)
C40-C41-C42-C46	-79.91(19)	C45-C46-C47-C48	-48.99(18)
C33-C41-C42-C46	32.11(19)	C46-C47-C48-C43	-32.2(2)
C41-C42-C43-C48	132.66(16)	C46-C47-C48-C44	31.4(2)
C46-C42-C43-C48	25.06(19)	C42-C43-C48-C47	4.3(2)
C41-C42-C43-C44	70.06(18)	C44-C43-C48-C47	100.87(18)
C46-C42-C43-C44	-37.54(17)	C42-C43-C48-C44	-96.54(17)
C42-C43-C44-C48	102.81(18)	C45-C44-C48-C47	-3.9(2)
C48-C43-C44-C45	-102.58(18)	C43-C44-C48-C47	-100.1(2)
C42-C43-C44-C45	0.22(18)	C45-C44-C48-C43	96.22(18)
C48-C44-C45-C33	-132.19(16)	O7-C49-C50-C51	125.50(14)
C43-C44-C45-C33	-69.97(18)	C61-C49-C50-C51	-108.44(15)
C48-C44-C45-C46	-25.04(18)	C57-C49-C50-C51	3.90(16)
C43-C44-C45-C46	37.19(16)	C49-C50-C51-C56	-3.40(19)
O5-C33-C45-C44	-55.3(2)	C49-C50-C51-C52	177.86(17)
C34-C33-C45-C44	-178.70(15)	C56-C51-C52-C53	-1.3(3)

Table 1.16 (Cont'd)

C50-C51-C52-C53	177.38(17)	O8-C57-C58-C62	159.03(13)
C51-C52-C53-C54	0.5(3)	C56-C57-C58-C62	-74.92(16)
C52-C53-C54-C55	0.4(3)	C49-C57-C58-C62	36.58(15)
C53-C54-C55-C56	-0.5(3)	C57-C58-C59-C64	132.00(14)
C52-C51-C56-C55	1.2(3)	C62-C58-C59-C64	25.43(15)
C50-C51-C56-C55	-177.69(15)	C57-C58-C59-C60	69.88(16)
C52-C51-C56-C57	-179.72(15)	C62-C58-C59-C60	-36.68(14)
C50-C51-C56-C57	1.4(2)	C58-C59-C60-C64	102.43(14)
C54-C55-C56-C51	-0.3(3)	C64-C59-C60-C61	-103.37(14)
C54-C55-C56-C57	-179.27(17)	C58-C59-C60-C61	-0.94(16)
C51-C56-C57-O8	-122.58(15)	C64-C60-C61-C49	-132.44(14)
C55-C56-C57-O8	56.5(2)	C59-C60-C61-C49	-69.70(16)
C51-C56-C57-C58	112.25(16)	C64-C60-C61-C62	-24.56(16)
C55-C56-C57-C58	-68.7(2)	C59-C60-C61-C62	38.18(14)
C51-C56-C57-C49	1.11(17)	O7-C49-C61-C60	-49.96(18)
C55-C56-C57-C49	-179.85(16)	C50-C49-C61-C60	-173.49(13)
O7-C49-C57-O8	-0.40(19)	C57-C49-C61-C60	71.68(15)
C61-C49-C57-O8	-122.47(14)	O7-C49-C61-C62	-153.11(13)
C50-C49-C57-O8	118.67(15)	C50-C49-C61-C62	83.36(15)
O7-C49-C57-C56	-122.18(14)	C57-C49-C61-C62	-31.47(15)
C61-C49-C57-C56	115.75(13)	C59-C58-C62-C63	-47.04(15)
C50-C49-C57-C56	-3.11(16)	C57-C58-C62-C63	-160.70(13)
O7-C49-C57-C58	118.94(14)	C59-C58-C62-C61	59.52(13)
C61-C49-C57-C58	-3.13(15)	C57-C58-C62-C61	-54.15(14)
C50-C49-C57-C58	-121.99(14)	C60-C61-C62-C63	46.26(15)
O8-C57-C58-C59	56.32(17)	C49-C61-C62-C63	159.15(13)
C56-C57-C58-C59	-177.63(13)	C60-C61-C62-C58	-60.42(13)
C49-C57-C58-C59	-66.13(16)	C49-C61-C62-C58	52.46(14)

Table 1.16 (Cont'd)

C58-C62-C63-C64	49.48(15)	C62-C63-C64-C59	-31.58(16)
C61-C62-C63-C64	-49.20(15)	C58-C59-C64-C60	-96.68(14)
C61-C60-C64-C63	-4.54(18)	C60-C59-C64-C63	100.31(15)
C59-C60-C64-C63	-100.64(15)	C58-C59-C64-C63	3.63(18)
C61-C60-C64-C59	96.10(15)	C1A-C2A-C3A-C4A	-175.1(6)
C62-C63-C64-C60	32.09(16)	C2A-C3A-C4A-C5A	-179.0(5)

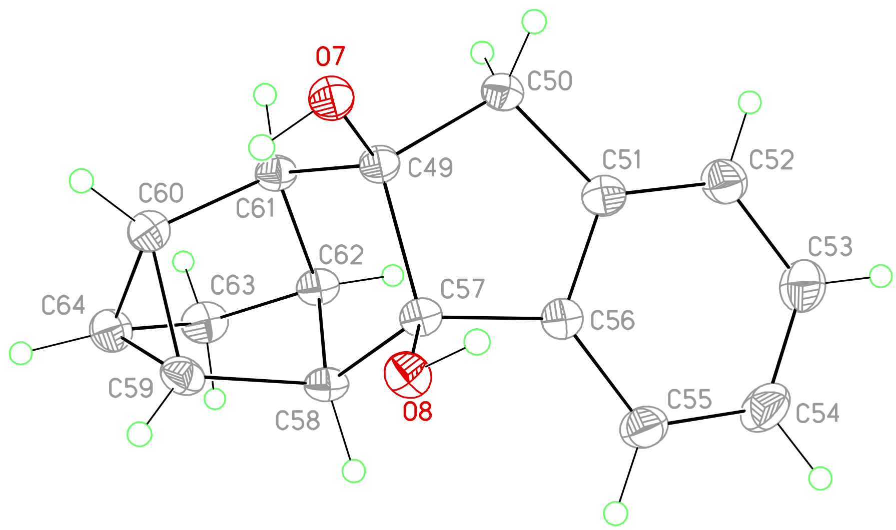
Table 1.17 Hydrogen bonds for **4c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O4-H4O...O1	0.79(2)	2.04(2)	2.8133(19)	167(2)
O6-H6O...O7	0.83(3)	1.95(3)	2.7655(19)	167(3)
O8-H8O...O5	0.82(3)	2.06(3)	2.8686(19)	169(3)
O3-H3O...O8	0.81(3)	1.98(3)	2.7566(19)	161(2)
O5-H5O...O4	0.88(3)	1.95(3)	2.7831(19)	157(3)
O1-H1O...O6	0.86(3)	2.00(3)	2.805(2)	157(3)
O7-H7O...O2	0.79(3)	2.09(3)	2.841(2)	159(3)
O2-H2O...O3	0.84(3)	1.98(3)	2.8134(18)	167(3)
C13-H13...Cl2#1	1.00	2.90	3.820(2)	153.6
C26-H26...Cl1	1.00	2.99	3.791(2)	137.8

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1

Figure 1.5 View of molecule 4 of **4c** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



Chapter 2: Ongoing Effort and Progress Toward the Total Synthesis of Andrographolide*

2.1 INTRODUCTION

Terpenoid natural products are a large class of natural products secreted by plants, animals and bacteria.[1] These secondary metabolites have been widely used in medicine, agriculture and fragrance industry.[1-3] They are found to be used in traditional medicine and Ayurveda along with modern pharmaceutical drugs such as paclitaxel, phorbol etc.[3] These important applications of terpenoids have kept chemist interested towards an efficient synthesis of these compounds.

Molecular complexity of terpenoids because of multicyclic structures and dense functional groups is another reason for the continued interest from organic chemists. The backbone for terpenes is formed biosynthetically via carbocationic cyclization and rearrangement reactions.[4-7] Therefore, the chemical synthesis for this compound is dependent mainly on cascade poly-cyclization of polyolefins.[8-9] These methods have allowed organic chemists to access complicated products from basic building blocks but suffers significantly because of lack of convergence and practical applications. So, a streamlined protocol for terpenoid products in a concise route has been a challenge.

In 2014, Krische group developed *tert*-(hydroxy) prenylation[10] reaction with an aim to access terpenoid natural products. Using cyclometallated π-allyliridium complex, a

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*This chapter is based on the ongoing efforts to synthesize andrographolide:
The work was performed in collaboration with Jiajie Feng and Thomas Wurm. B. S. contributed in synthesis and route modifications/improvements of Fragment A; route designs, different approaches and synthesis of Fragment B.

catalytic method for direct alcohol C−H functionalization via C−C bond-forming transfer hydrogenation was used for regio-, diastereo- and enantioselective C−H *tert*-(hydroxy)prenylation.[10] Following this methodology, a modular approach was used in the successful synthesis of terpenoid natural products Oridamycin A, Tryptoquinone B &C and Isoiresin.[11] Using the common intermediate used in the synthesis of these terpenoid natural products, structurally similar terpenoids can be accessed. We were then interested if the same approach can be used in the synthesis of Andrographolide.

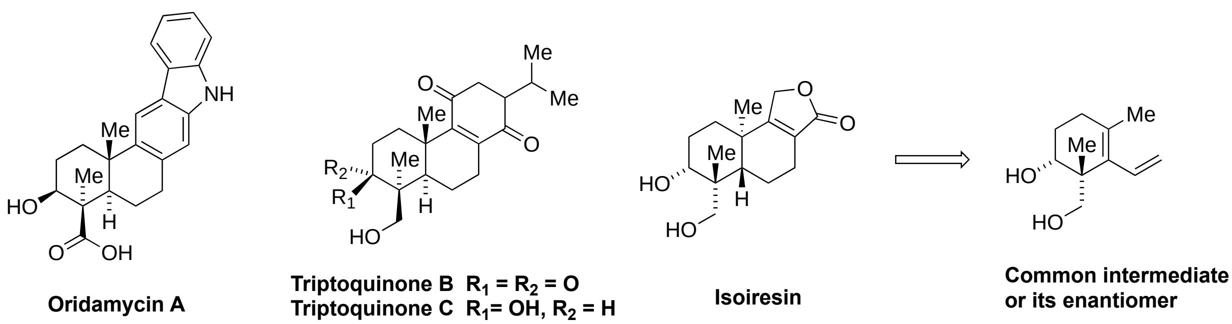
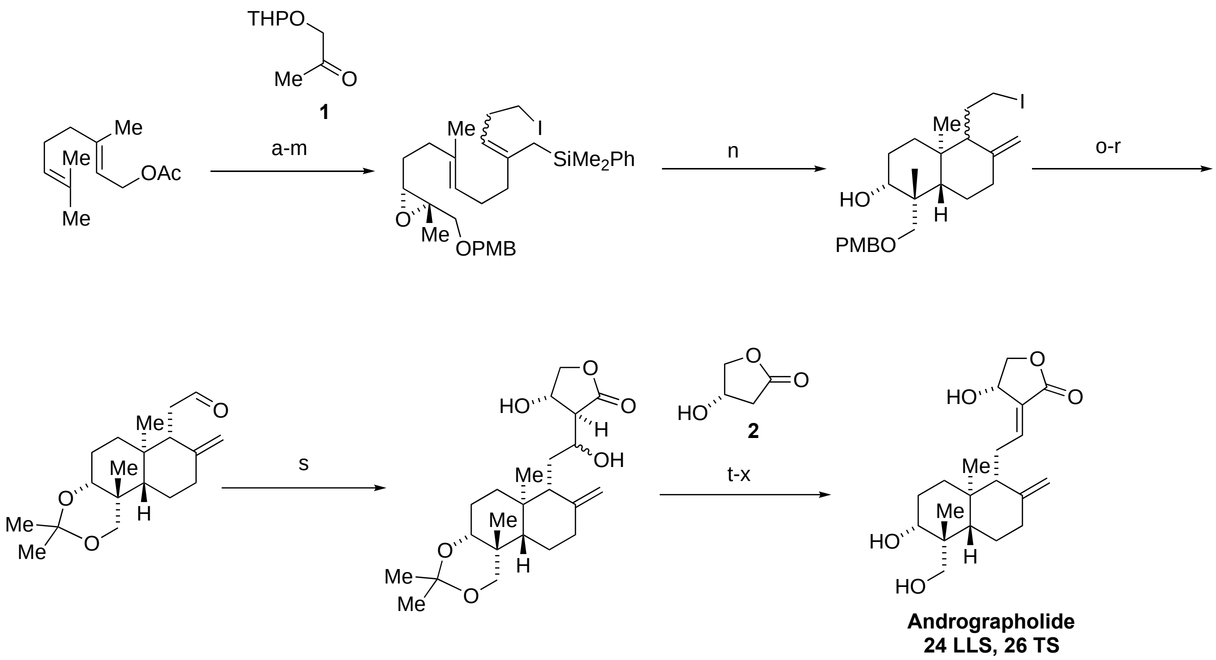


Figure 2.1 Terpenoid natural products synthesized via modular construction strategy.

Andrographolide is a diterpenoid lactone isolated from the stem and leaves of *Andrographis paniculata.*[12] The chemical structure was first elucidated in 1965 by Cava and co-workers.[13] A main bitter component of traditional herb; studies have been performed to understand the binding of andrographolide to different protein targets.[14-15] Andrographolide and congeners are known to exhibit antitumor,[16] antiinflammatroy,[17] immunostimulatory[18] and antipyretic properties.[19] One prior asymmetric total synthesis of andrographolide is known in literature.[20]

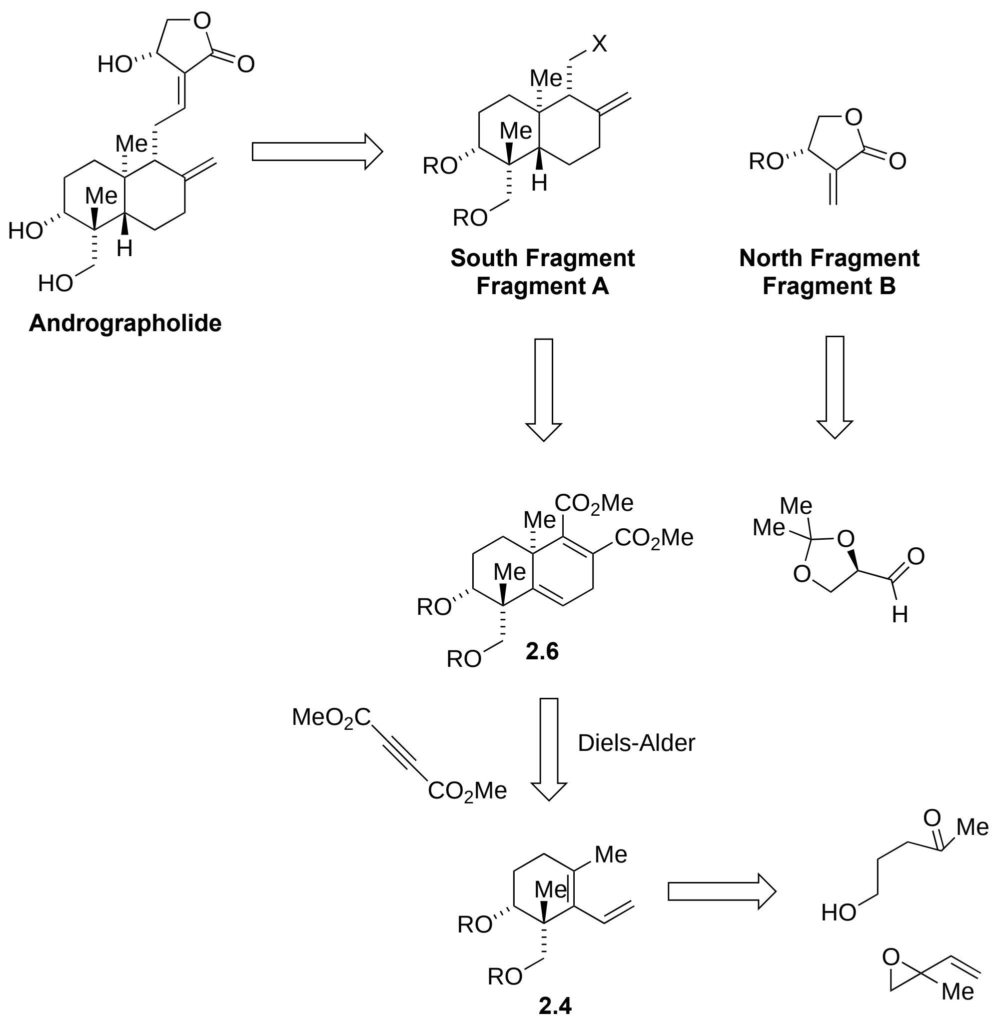


Key: (a) O_3, pyridine, then $NaBH_4$, MeOH; (b) I_2, PPh_3, imid; (c) K_2CO_3, MeOH; (d) PPh_3; (e) n-BuLi, then **1**; (f) I_2, Ph_3P, imid; (g) cyclopropyl methyl ketone, LDA; (h) PTSA; (i) $Ti(O\text{-}iPr)_4$, L-(+)-DIPT, *t*-BuOOH, CaH_2, silica gel, 4A MS; (j) PMBBr, NaH, TBAI; (k) $PhMe_2SiCH_2MgCl$, $CeCl_3$; (l) $MgI_2.(OEt_2)_n$; (m) K_2CO_3; (n) $SnCl_4$; (o) DDQ; (p) K_2CO_3; (q) $Me_2C(OMe)_2$, PPTS; (r) DMSO, $NAHCO_3$; (s) LDA, **2**; (t) TBSCL, imid; (u) MsCl, Et_3N; (v) DIPEA; (w) TBAF; (x) $HOAc/H_2O$

Scheme 2.1 Prior asymmetric synthesis of andrographolide

The prior synthesis was achieved via the biomimetic cyclization of an epoxy homoiodo allylsilane precursor. The two fragments were joined using classical aldol condensation reaction; however, it took too many steps for the assembly of the main decalin core. So, a more concise and step economic approach can be possible to access the natural product.

2.2 RETROSYNTHETIC ANALYSIS

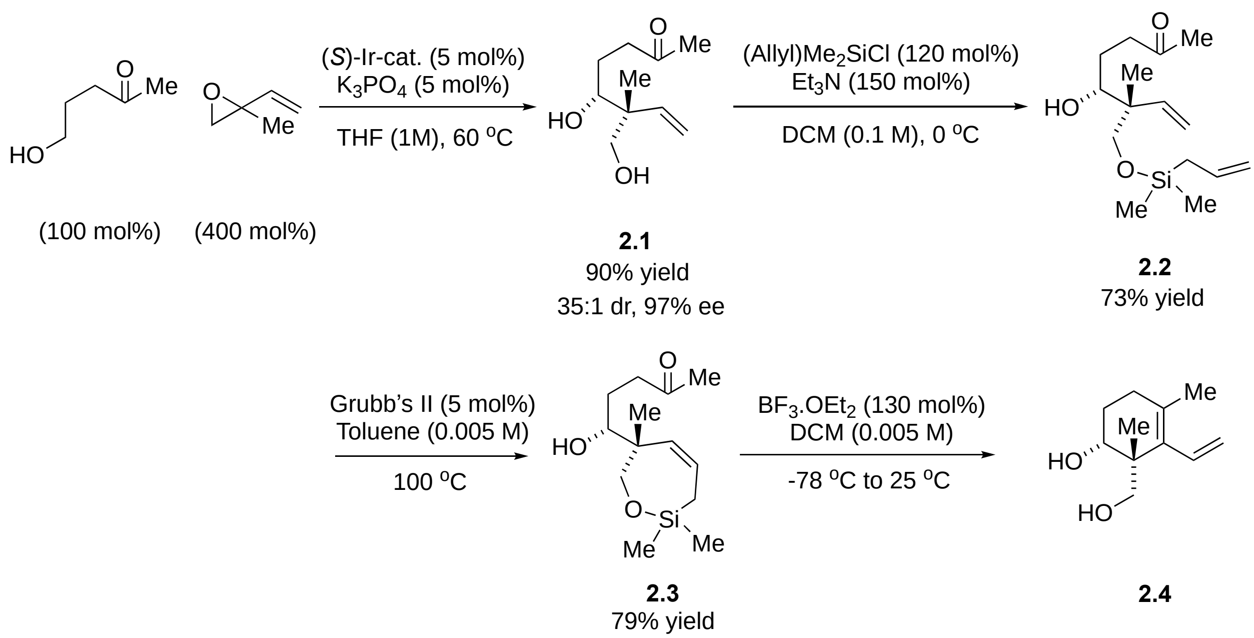


Scheme 2.2 Retrosynthetic scheme and analysis of andrographolide

We were encouraged to apply the similar modular strategy[11] previously used by our group for the synthesis of terpenoids. We envisioned that Andrographolide, can be synthesized after combining two fragments where northern fragment is a lactone with an exomethylene group or a vinyl halide and the southern fragment consisting of a homo allylic halide containing the majority of framework for the natural product. The halide where presumably the external double bond is more thermodynamically stable[21] than the internal double bond can be obtained from the few functional group conversions of the diester. The diester **2.6** can be envisioned via a Diels-Alder reaction constructing the six-membered ring from the diene **2.4** intermediate. The diene **2.4** can be synthesized using previous reported method from the group utilizing the *tert*-(hydroxy)-prenylation reaction. The norther fragment, lactone can be constructed different ways where one possibility is from the aldehyde using Corey-Fuchs followed by the metal catalyzed carbonylative lactonization reaction.

2.3 CURRENT PROGRESS TOWARD THE SYNTHESIS OF ANDROGRAPHOLIDE

Our main focus was to utilize the previously reported intermediate for modular construction of terpenoid natural products. Diene intermediate **2.4** was successfully synthesized via previously reported route.

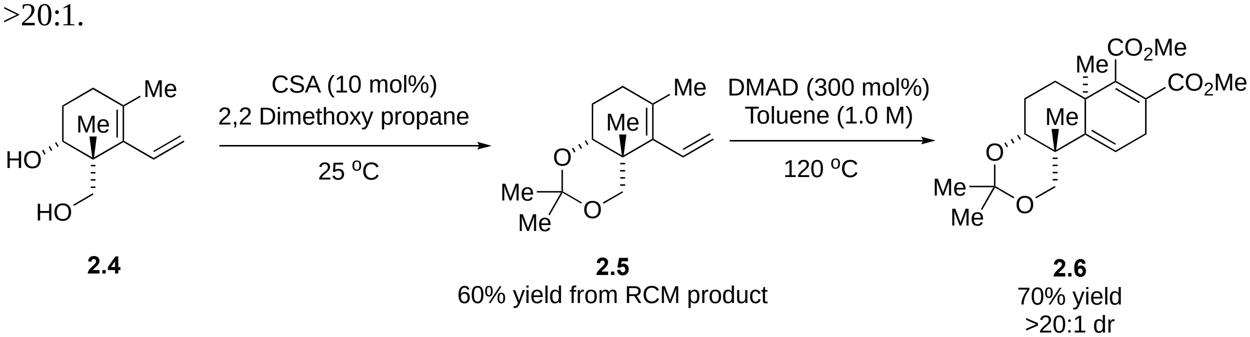


Scheme 2.3 Synthesis of diene **2.4** via prior method.[11]

The synthesis started from the C−C bond-forming transfer hydrogenation reaction for regio-, diastereo- and enantioselective C−H *tert*-(hydroxy)prenylation.[10] The commercially available alcohol is exposed to isoprene oxide in the presence of the π-allyliridium C,O-benzoate complex derived from 4-CN-3-NO_2-benzoic acid and (*S*)-Tol-BINAP. The desired product of enantioselective *tert*-(hydroxy)prenylation **2.1** is formed in 90% yield with excellent diastereoselectivity (35:1) and enantioselectivity (97% ee).

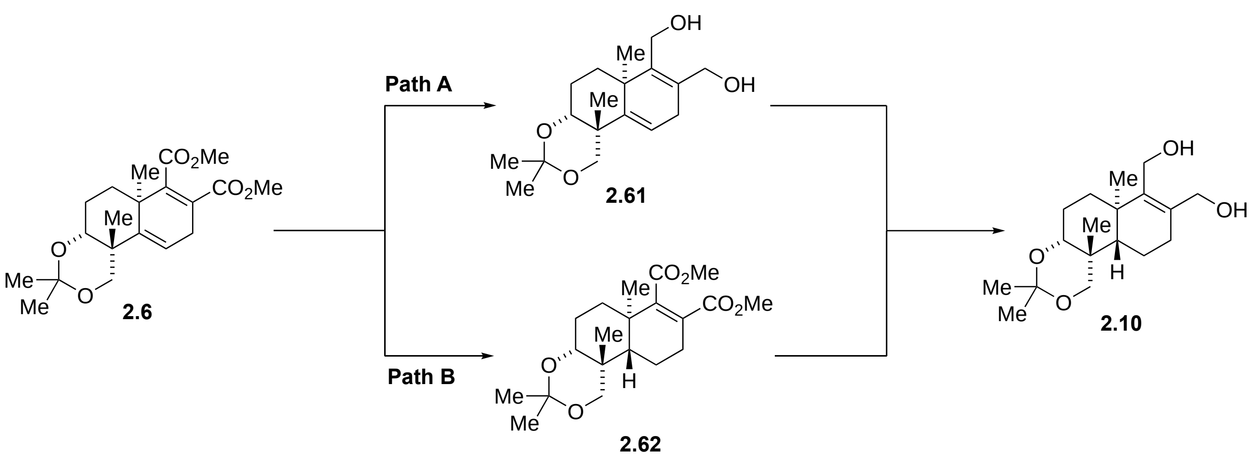
Reaction of **2.1** with allyldimethylsilyl chloride results in chemoselective functionalization of the primary alcohol to provide silyl ether **2.2** in 73% yield, which upon ring-closing metathesis (RCM) using Grubb's II delivers the cyclic allylsilane **2.3** in 79% yield.[11] Compound **5** exist in equilibrium with 5-membered lactols, suggesting the [2.2.1]oxabicycle formation upon intramolecular Sakurai allylation by way of an endocyclic oxacarbenium ion and elimination in situ to **2.4** (Scheme 2.3).

The intermediate **2.4** was used for further synthesis. Diels-Alder reaction directly with **2.4** is not successful because of the instability of unprotected dienol at high temperature. So, the intermediate is subjected for acetonide protection using camphor sulfonic acid in 2,2 dimethoxy propane to obtain **2.5** in 60% yield over two steps. The protected diol **2.5** was reacted with dimethyl acetylene dicarboxylate (DMAD); cycloadduct **2.6** was obtained with an excellent facial selectivity with diastereomeric ratio >20:1.



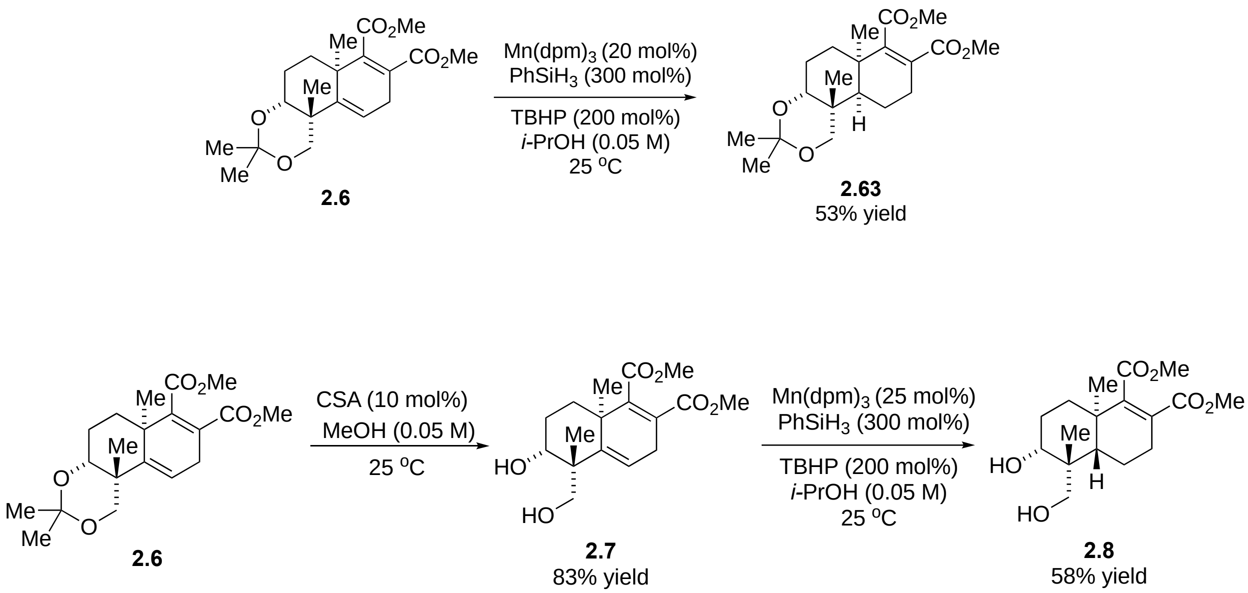
Scheme 2.4 Diels-Alder reaction between diene **2.5** and DMAD.

Attempt to reduce only one methyl carboxylate in Diels-Alder adducts **2.6** was unsuccessful due to a tendency to form an α,β-unsaturated γ-lactone. So, there were two strategies remaining to continue the synthesis: reduce both methyl esters first to form **2.61**, and subsequently hydrogenate the trisubstituted olefin to access **2.10** (Scheme 2.5, Path A); or perform hydrogenation on alkene to generate **2.62**, and then reduce the carboxylates to primary alcohols to form the **2.10** (Scheme 2.5, Path B). LAH reduction of **2.6** resulted unto **2.61**; however, olefin reduction on **2.61** did not gave the product under many attempted conditions, and the compound was very unstable presumably due to conformational strain (Scheme 2.5). Hence, it was decided that path B would be a more reasonable approach to continue the synthesis.



Scheme 2.5 Approach and strategy for the selective reduction of olefin.

Cycloadduct **2.6** was subjected to the best known Shenvi conditions for the selective reduction of the olefin. To our surprise, *cis*-decalin was formed instead of the desired *trans*-decalin. Despite of the typically more stable *trans*- fusion of the two six membered rings we recovered *cis*- fused rings. It was envisioned that the third ring formed via the protected acetonide is restricting the conformational flexibility for the reduction reaction. So, the cycloadduct **2.6** was deprotected to afford diol **2.7** and then subjected to the previous attempted Shenvi conditions. To our delight, the desired *trans*-decalin was obtained in an acceptable yield and excellent diastereomeric ratios.



Scheme 2.6 Shenvi reduction for construction of decalin.

The selectively reduced product **2.8** can be re-subjected to acetonide protection to get **2.9** in 85% yield. The methyl esters in **2.9** was subjected to DIBAL-H reduction to reduce two esters providing the diol **2.10** in 70% yield. The diol was subjected to reductive transposition conditions reported by Myers[21] to obtain 2.11 in 55% yield. Initial 1D/2D NMR studies indicates the synthesis of desired diastereomer of the alcohol; however, a definite conclusion cannot be made until a crystal structure of **2.11** or after successful synthesis of the natural product. The remaining alcohol in **2.11** can be subjected to Appel type halogenation to obtain **2.12** which is the desired southern fragment.

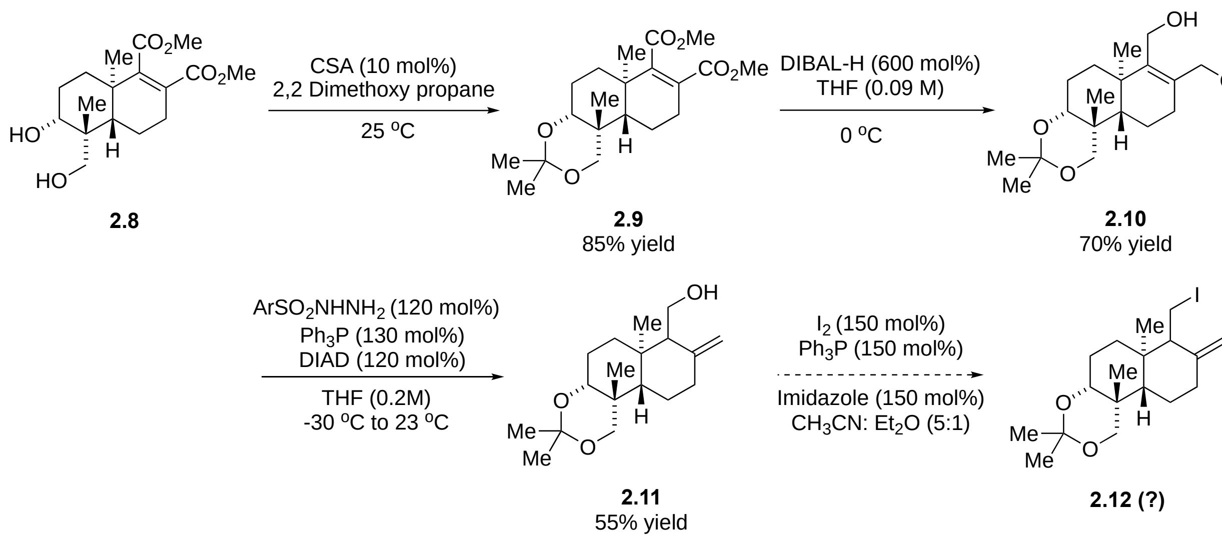


Figure 2.2 Construction of the southern fragment.

On the other hand, in order to understand the possible end game strategy a model system was designed and synthesized. The model system was designed to mimic the actual southern fragment **2.12**. A homoallylic iodide with a six-membered ring and a gem-dimethyl group adjacent to the branched iodide was synthesized **2.13e**. Boronic ester **2.13f** was also synthesized from the corresponding iodide to further analyze the classical Suzuki type coupling conditions.

The commercially available enone was reacted with methyl cuprate synthesized *in-situ* via methyl Grignard and copper iodide and then quenched with formaldehyde gas to obtain the alcohol **2.13a**.[22] Synthesis of homoallylic alcohol **2.13d** was performed after silyl protection to obtain **2.13b** followed by Wittig olefination to afford **2.13c** then deprotection using tetrabutyl ammonium fluoride (TBAF). The homoallylic alcohol **2.13d** was subjected to Appel type reaction condition to obtain homoallylic iodide **2.13e**. Another model system, boronic ester, **2.13f** was synthesized from the corresponding iodide in a single step using copper iodide and bispinacolato diboron.[23]

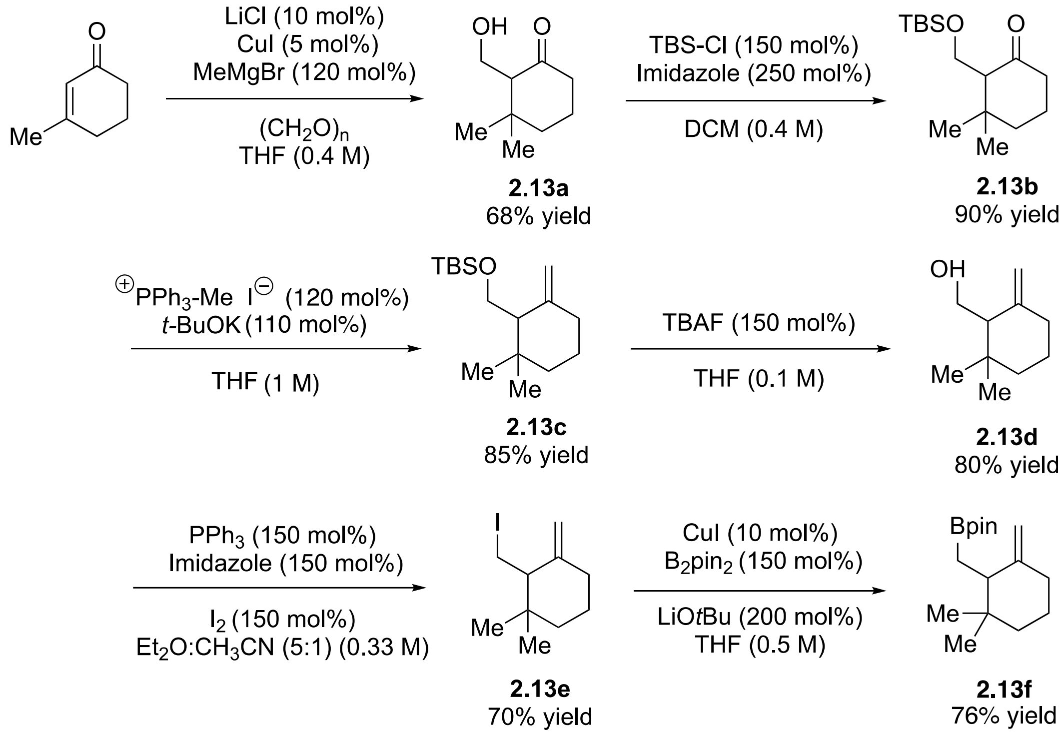
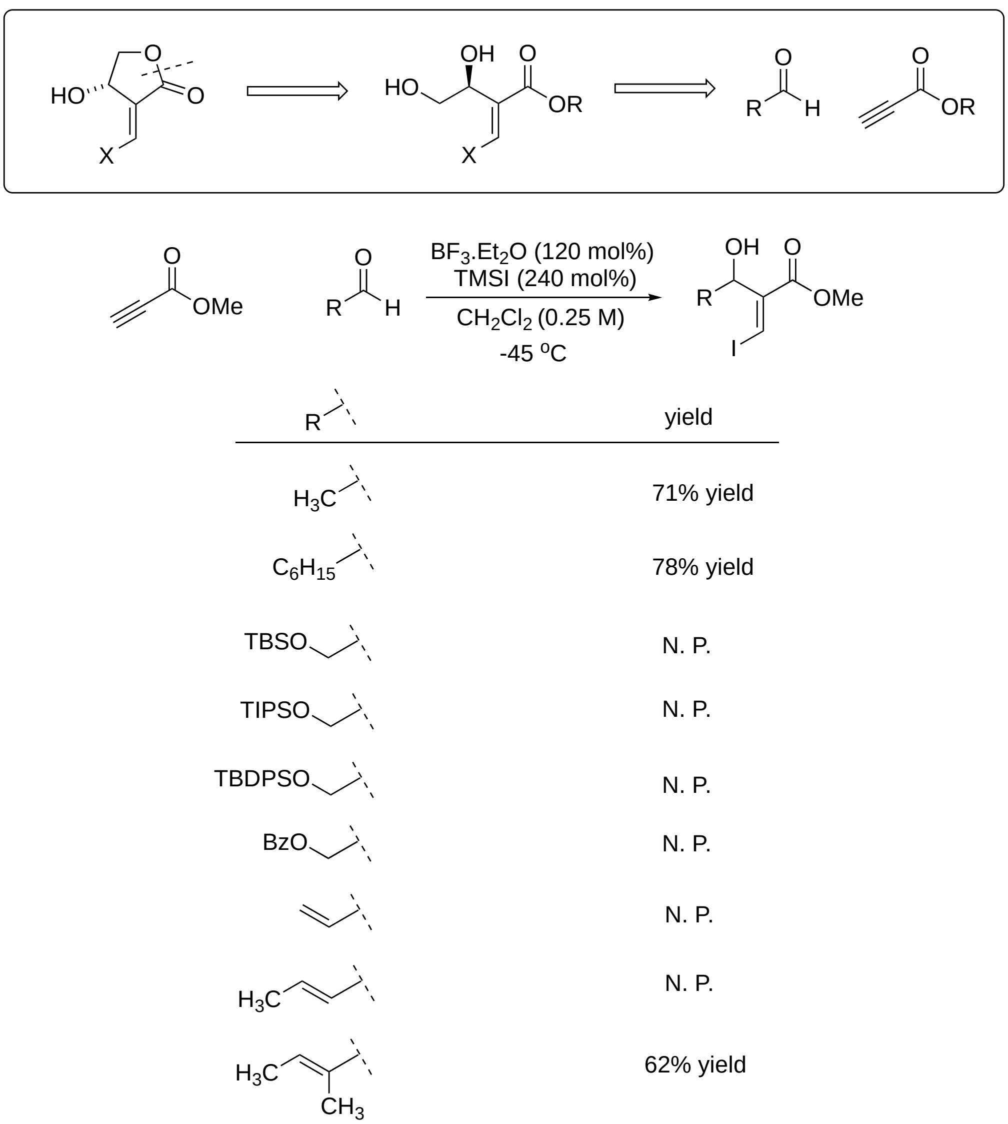


Figure 2.3 Synthetic route for the model system homoallylic iodide **2.13e.**

Even though the northern fragment is a lactone and looks relatively simple compared to the southern fragment. A significant challenge was faced to synthesize the compound. The open form of lactone with an unsaturated ester calls for a Morita-Baylis-Hillman type approach. Our initial strategy was based on the variants of this approach. Various reactions were attempted with methyl propiolate and different aldehydes to obtain the vinyl iodide. Regular aldehydes seem to work fine under the reported conditions with boron trifluoro etherate and trimethylsilyl iodide; however, any type of protected alcohols did not survive the harsh reaction condition or give the desired product. Presumably, the oxophilic nature of the $BF_3{\cdot}OEt_2$ and the harsh TMSI condition was responsible for the problem in this reaction. Even the aldehyde with α,β unsaturation did not give the product; anticipating a possible cleavage of the double bond in later stage would have provided similar products to that of the protected alcohol. Surprisingly, methyl substituted olefin works for this reaction; but, is not feasible for our approach.

Table 2.1 Attempts to form lactone via modified Morita-Baylis-Hillman approach.



A second approach was based on the use of chiral pool via the reaction of commercially available aldehyde with dithiane then oxidation and olefination. Initial stage of addition and oxidation worked in excellent yield; however, the crucial olefination stage suffered due to the high steric hindrance of the ketone or the extremely low pka of the dithiane proton under common basic olefination conditions. Various types of olefination conditions including Wittig, Takai etc. were attempted but unsuccessful to afford the desired vinyl halide.

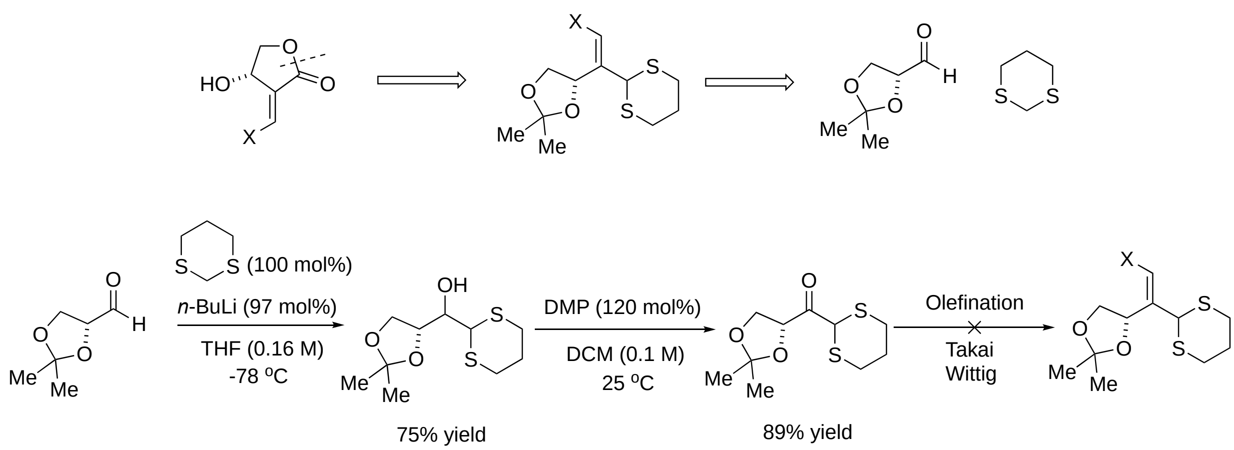


Figure 2.4 Dithiane approach for construction of lactone.

Another approach was based on the bromination-dehydrobromination of the olefin after Morita-Baylis-Hillman reaction. The first step worked with a specifically designed ester to obtain in a reasonable time frame. Using corresponding methyl or ethyl ester took weeks for a decent conversion of the starting material. Even though the bromination step seemed to run smoothly, the dehydrobromination attempt was unsuccessful despite using various approaches under basic conditions probably due to the unstable nature of the intermediates or the product.

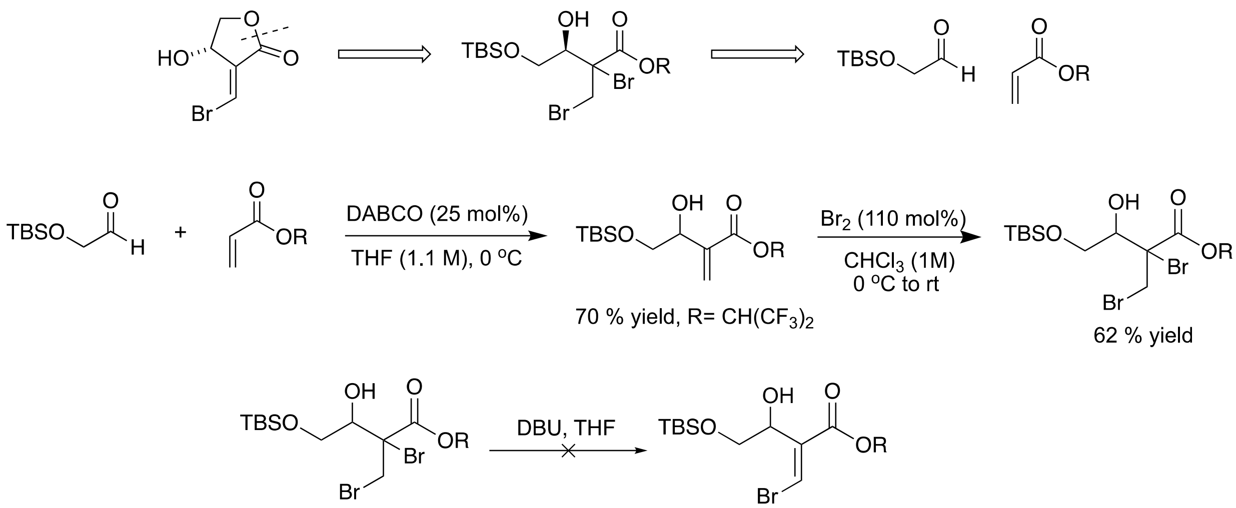
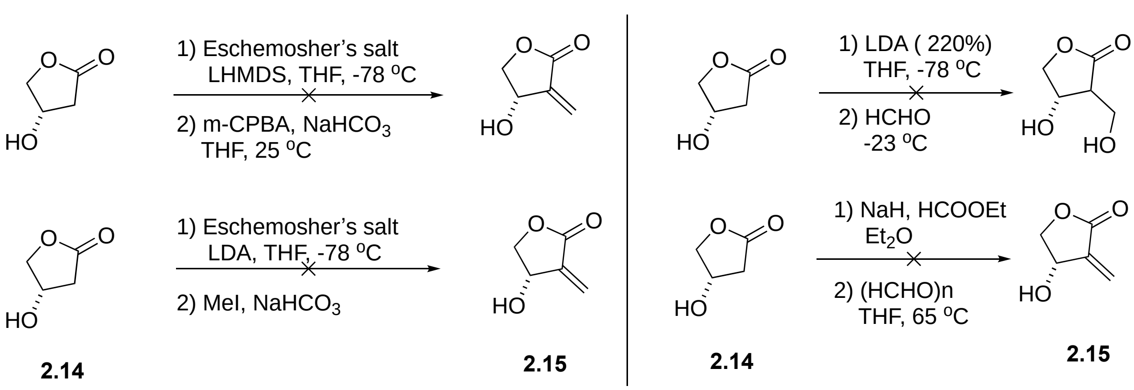


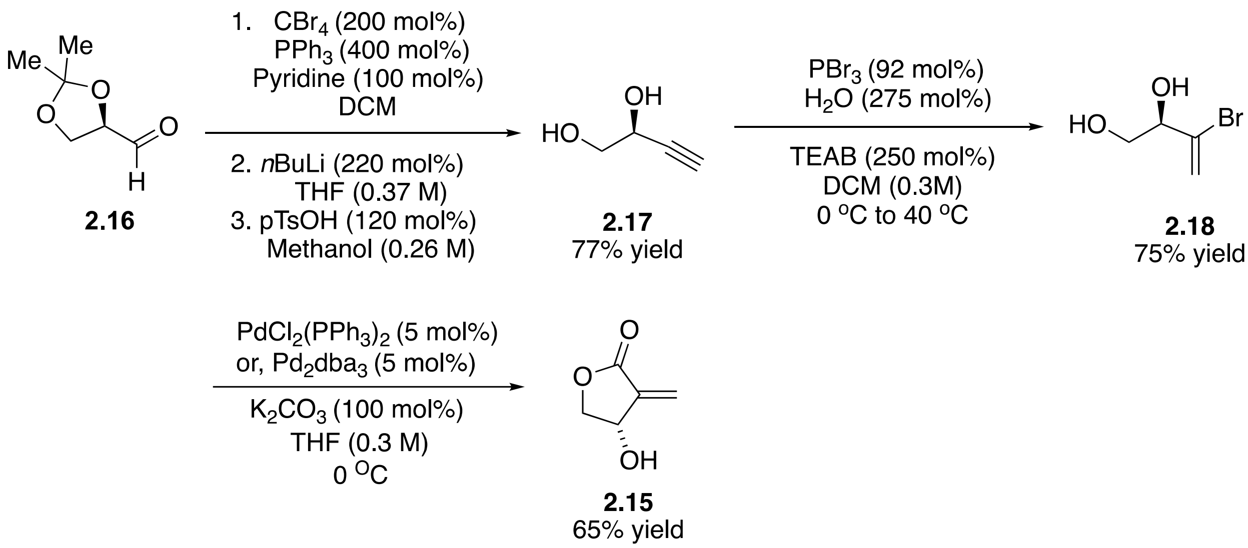
Figure 2.5 Bromination and dehydrobromination approach to synthesize vinyl bromo lactone.

A different strategy was started, and the approach was changed to access the exomethylene lactone **2.15** instead of the vinyl halide. First attempt was to use the commercially available lactone **2.14**. Approaches using Eschemosher's salt under basic conditions or the quenching with formaldehyde gas did not gave the desired product. The stability of lactone under the reaction conditions, β-hydroxy alcohol with a possibility for retro-aldol and the unstable intermediates under the highly basic reaction conditions were the major problems faced in this approach.

Table 2.2 Initial attempts to synthesize exomethylene lactone **2.15.**

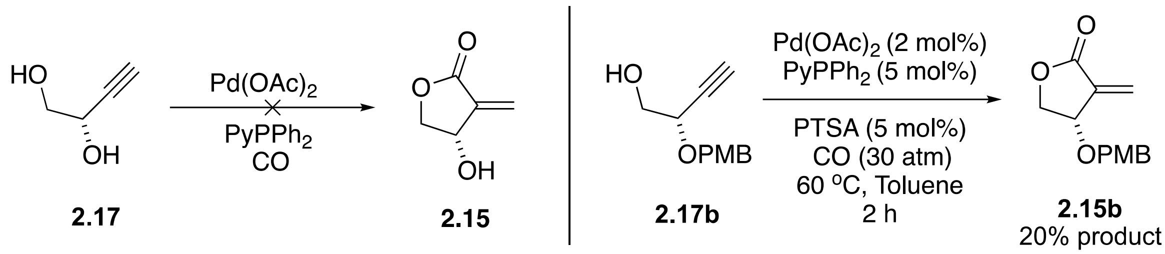


Finally, the strategy starting from commercially available aldehyde **2.16** worked for the synthesis of lactone **2.15** (Scheme 2.6)**.** Initially, Corey-Fuchs reaction of the aldehyde and the deprotection of acetonide using *p*-toluenesulfonic acid afforded the acetylenic alcohol **2.17** in excellent yield. Hydrogen bromide (HBr) gas was freshly synthesized using phosphorus tribromide (PBr_3) in water and passed through tetraethyl ammonium bromide (TEAB). It was then reacted with diol **2.17** to afford the vinyl bromide **2.18.** Using carbonylative lactonization under catalytic palladium, base and CO, the vinyl bromide **2.18** was converted to the desired lactone **2.15** in a good yield.



Scheme 2.7 Synthesis of exomethylene lactone **2.15.**

When a more direct approach was applied to synthesize the lactone **2.15** directly from acetylenic alcohol **2.17** using carbonylative lactonization, the product was not obtained. Despite attempting with protected alcohol, the reaction suffered from low yield and π-allyl formation of the metal was observed that kicks out the alcohol with the protecting group. So, the above explained approach (Scheme 2.6) with vinyl bromide seemed to be most effective despite containing more steps.



Scheme 2.8 Initial attempts of carbonylative lactonization to construct lactone **2.15.**

So far, this is the progress for the synthesis of andrographolide. Various coupling conditions, end game strategy or another approach are currently being investigated using model system to solve the problems faced during the synthesis.

2.4 CONCLUSION

Asymmetric synthesis of andrographolide is attempted and a significant progress has been made to synthesize the diterpenoid lactone with an estimation to complete in 14-15 LLS. The synthesis will showcase a modular approach that was initiated by the *tert*-(hydroxy) prenylation reaction discovered prior in our lab and then subsequently applied to synthesize various diterpenoid natural products. Various coupling reactions and other approaches to join the two fragments are currently under investigation *en route* to the natural product.

2.5 EXPERIMENTAL DETAILS AND PROCEDURE

General Information

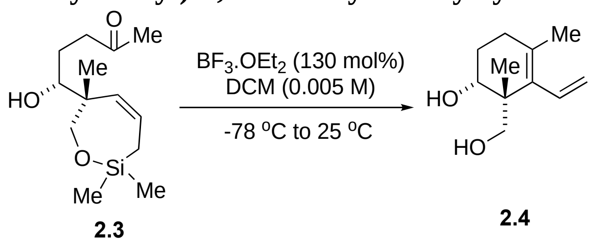
All reactions were performed under an atmosphere of argon, unless specifically noted in detailed procedures. Tetrahydrofuran, diethyl ether and toluene were distilled from sodium-benzophenone immediately prior to use. Dichloromethane, 1,2-dichloroethane were distilled from calcium hydride prior to use. Anhydrous solvents were transferred via oven-dried syringes and needles. Reagents purchased from commercial sources were used as received or purified via distillation over appropriate drying agent or after recrystallization. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F254). Visualization was accomplished with UV light followed by dipping in appropriate stain solution then heating. Flash column chromatography was performed on Sorbent silica gel (40-63 μm, unless indicated specifically).

Spectroscopy, Spectrometry, and Data Collection

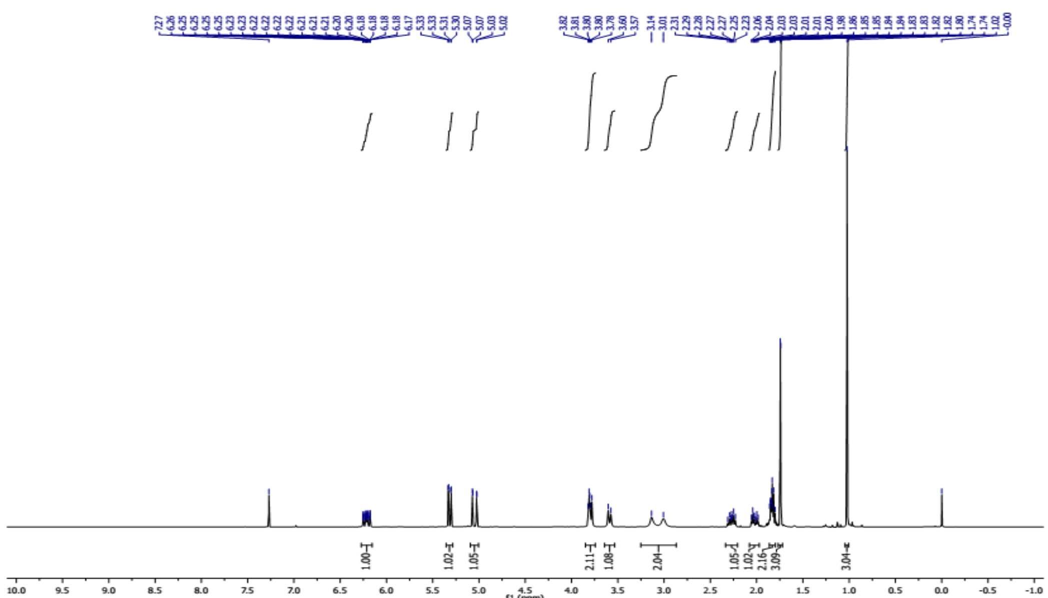
Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS instrument for electrospray ionisation (ESI) or a Micromass Autospec Ultima instrument for chemical ionization (CI), and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M, M+H, M-H or M+Na), or a suitable fragment ion. 1H Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400 MHz), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ solution. Coupling constants are reported in

Hertz (Hz) with one decimal place, and chemical shifts are reported as parts per million (ppm) relative to residual solvent peaks (CDCl3 δ_H 7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using an Agilent MR (400 MHz), Varian DirectDrive (400), or Varian INOVA (500 MHz) spectrometer in $CDCl_3$ or CD_3OD solution, and chemical shifts are reported as parts per million (ppm) relative to solvent peaks ($CDCl_3$ δ_C 77.0 ppm; CD3OD δ_C 49.0 ppm). Specific optical rotations ([α]D) were obtained on an Atago AP-300 automatic polarimeter at the sodium line (589.3 nm) in $CHCl_3$ or CH_3OH solution. Melting points were taken on a Stuart SMP3 melting point apparatus or SRS OptiMelt automated melting point system.

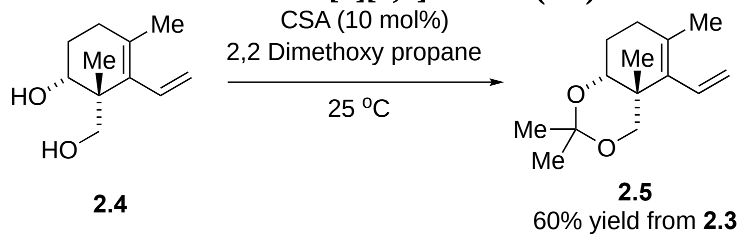
(1*R*,2*R*)-2-(hydroxymethyl)-2,4-dimethyl-3-vinylcyclohex-3-en-1-ol (2.4)



The compound was prepared as reported in literature[11] with slightly modified conditions as described. To a solution of the RCM product **2.3** (0.50 g, 1.95 mmol, 100 mol%) in DCM (400 mL) at -78 °C, freshly distilled $BF_3{\cdot}OEt_2$ (0.72 mL, 5.84, 130 mol%) was added dropwise via syringe. The resulting solution was allowed to stir at this temperature and slowly warming to room temperature, then for further 18 hours. The reaction was quenched with $NaHCO_3$ (aq. 300 mL) and extracted with DCM (100mL x 2). The combined organic layer was washed with brine (150 ML) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure (water bath room temperature) and subjected to quick flash chromatography on neutral alumina ($MeOH/Et_2O$ = 1:15 to 1:5). The compound **2.4** was obtained as brown oil and it was directly subjected to next step for further transformations.



(4a*R*,8a*R*)-2,2,4a,6-tetramethyl-5-vinyl-4a,7,8,8a-tetrahydro-4*H*-benzo[*d*][1,3]dioxine (2.5)



To a solution of diol (0.0821 g, 0.45 mmol, 100 mol%) in 2,2-dimethoxy propane (2,2-DMP, 1.0 mL) was added camphorsulfonic acid 10 mol% at ambient temperature. The resulted mixture was allowed to stir at the same temperature for 5 hours. The reaction was diluted with Et_2O (1.0 mL) and quenched by addition of saturated $NaHCO_3$ (aq., 1.0 mL). The organic layer was separated and washed with water (1.0 mL × 2). After dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/ether = 99:1). The title compound **2.5** was obtained as a colorless oil (0.0644 g, 0.29 mmol) in 60% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.17 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.24 (dd, *J* = 11.3, 2.4 Hz, 1H), 5.00 (dd, *J* = 17.8, 2.4 Hz, 1H), 3.80 – 3.75 (m, 2H), 3.45 (d, *J* = 11.8 Hz, 1H), 2.29 (td, *J* = 14.8, 13.7, 9.4 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.72 (s, 3H), 1.69 – 1.64 (m, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 0.90 (s, 3H).

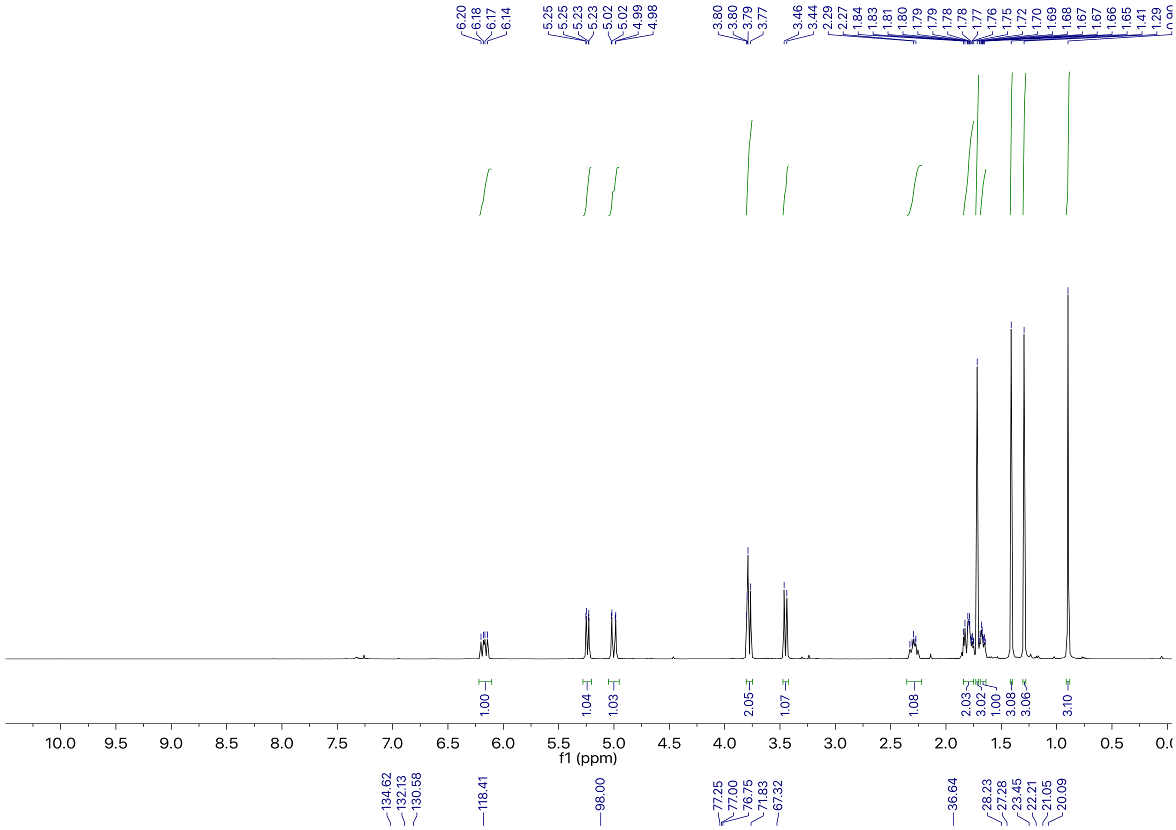
^{13}C NMR (126 MHz, Chloroform-*d*) δ 134.62, 132.13, 130.58, 118.41, 98.00, 71.83, 67.32, 36.64, 28.23, 27.28, 23.45, 22.21, 21.05, 20.09.

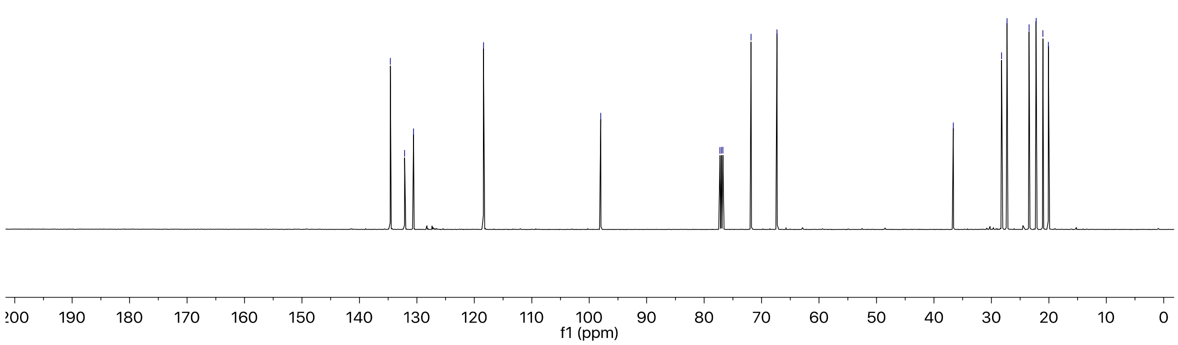
R_f 0.59 (hexanes/EtOAc = 9:1, UV/p-anisaldehyde)

HRMS (CI) Calcd. for $C_{14}H_{22}O_2$: 222.1620, Found: 222.1615.

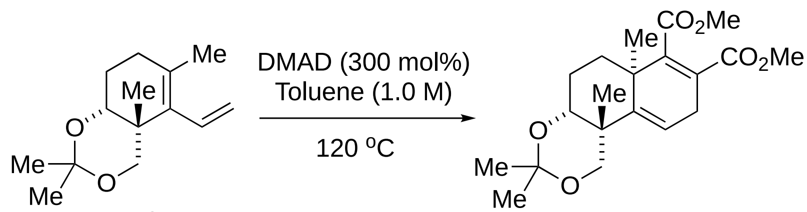
FTIR (neat): 2989, 2932, 2864, 1447, 1240, 1227, 1197, 1122, 1085 cm^{-1}.

Optical Rotation $[\alpha]_D$ = -124° (c=1, $CHCl_3$)


f1 (ppm)


f1 (ppm)

Dimethyl (4a*R*,6a*R*,10b*R*)-3,3,6a,10b-tetramethyl-4a,5,6,6a,9,10b-hexahydro-1*H*-naphtho[2,1-*d*][1,3]dioxine-7,8-dicarboxylate (2.6)



2.5

2.6
70% yield
>20:1 dr

To a solution of diene **2.5** (100 mg, 0.45 mmol, 100 mol%) in toluene (0.45 mL) was added dimethyl acetylenedicarboxylate (DMAD, 1.35 mmol, 300 mol%). The mixture was heated to 120℃ in seal tube for 18 hours. After cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/EtOAc = 15:1 to 5:1). The title compound was obtained as a colorless oil (114 mg, 0.315 mmol) in 70% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.78 (dd, *J* = 6.4, 1.9 Hz, 1H), 3.90 (d, *J* = 12.0 Hz, 1H), 3.75 (s, 3H), 3.73 (d, *J* = 1.9 Hz, 1H), 3.67 (s, 3H), 3.44 (d, *J* = 12.0 Hz, 1H), 3.11 (d, *J* = 6.3 Hz, 1H), 2.82 (dd, *J* = 22.1, 1.9 Hz, 1H), 2.06 (td, *J* = 7.6, 2.8 Hz, 1H), 1.85 – 1.65 (m, 2H), 1.57 – 1.46 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 0.94 (s, 3H).

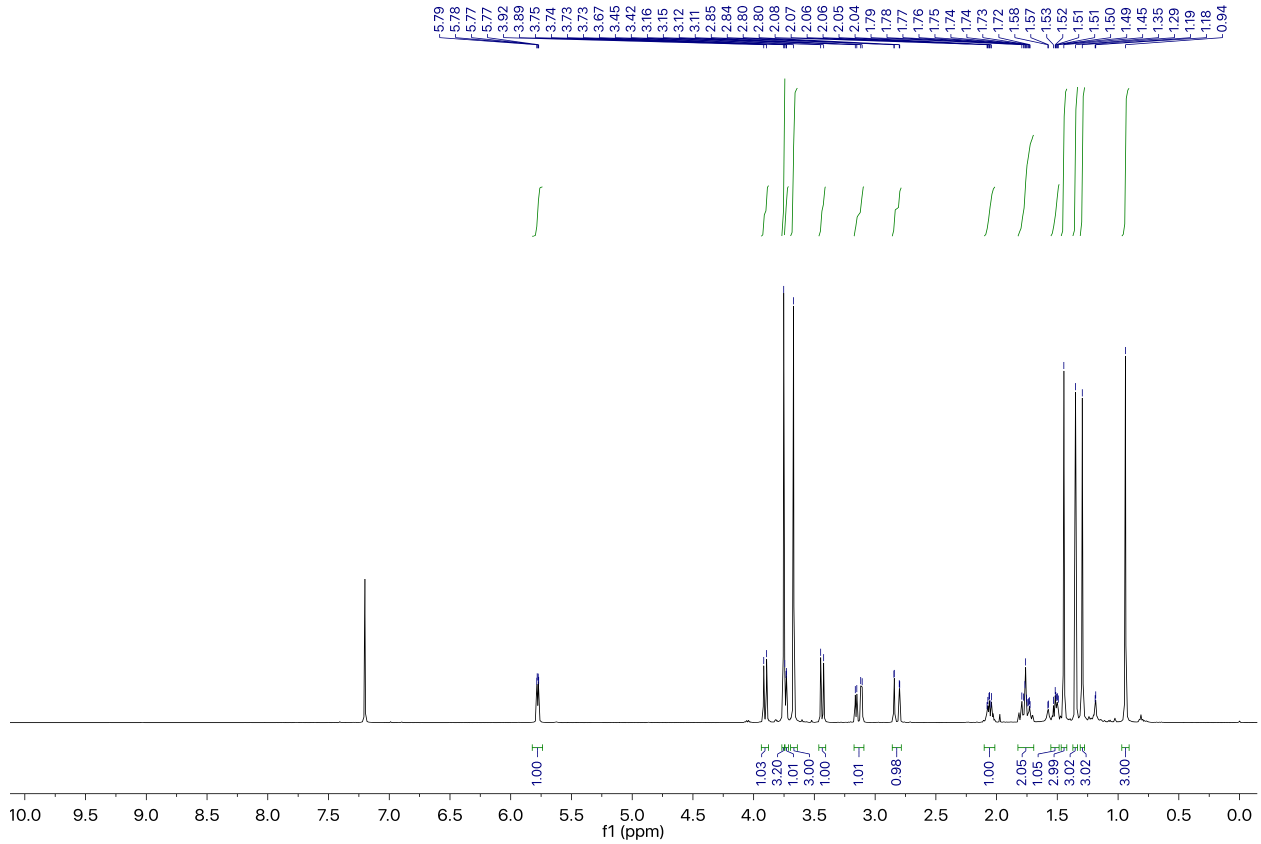
^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.51, 166.10, 152.07, 144.63, 126.36, 119.64, 98.49, 77.20, 72.25, 68.22, 52.04, 38.55, 28.17, 28.12, 26.81, 26.06, 25.01, 24.51, 20.73.

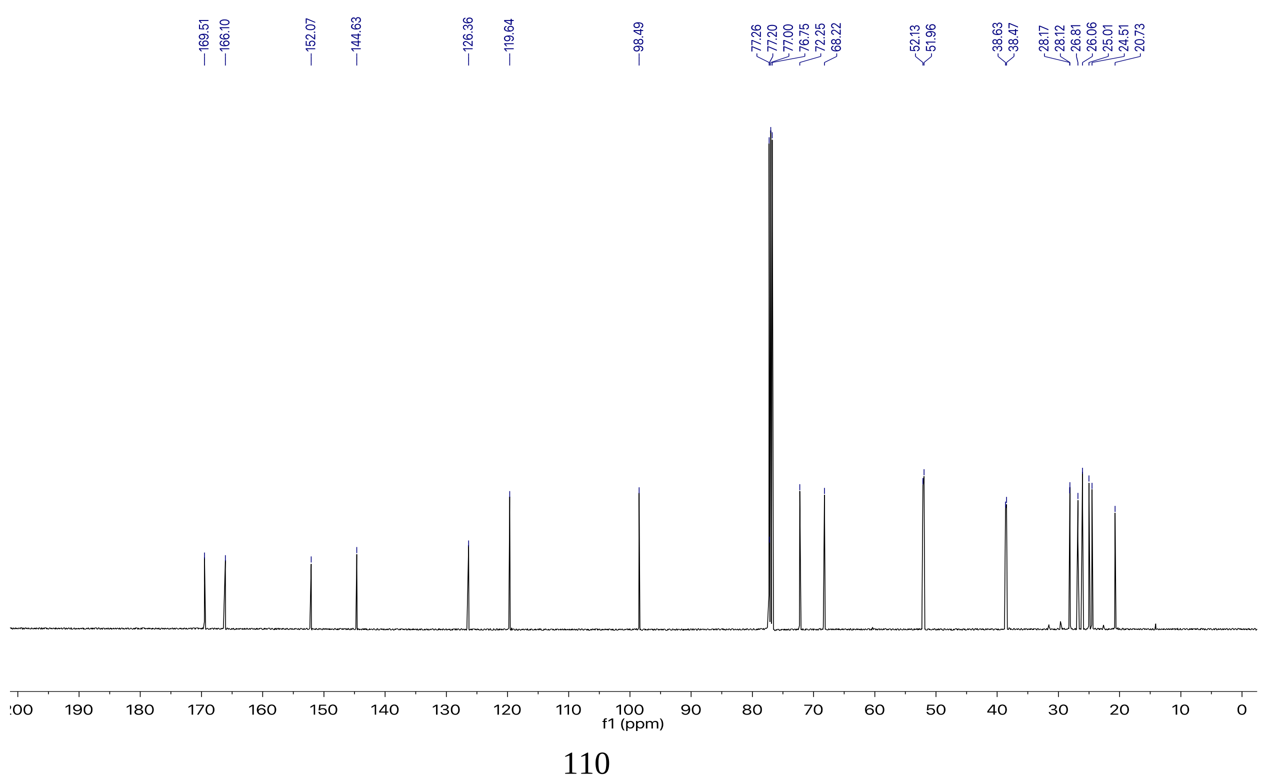
R_f 0.35 (hexanes/ethylacetate = 7:3, UV/p-anisaldehyde)

HRMS (ESI) Calcd. for (M+Na)+ 387.1778, Found: 387.1779

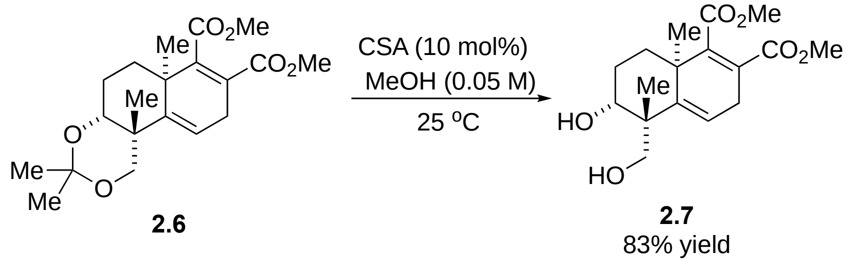
FTIR (neat): 3465, 2953, 1731, 1438, 1378, 1262, 1203 cm^{-1}

Optical Rotation $[\alpha]_D$ = +84° (c=1, $CHCl_3$)





Dimethyl (5*R*,6*R*,8a*R*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate (2.7)



To a solution of acetonide **2.6** (300 mg, 0.82 mmol, 100 mol%) in methanol (8.2 mL) was added camphorsulfonic acid 10 mol% at ambient temperature. The resulted mixture was allowed to stir at the same temperature for 3 hours. The solvent was removed and subjected to flash column chromatography on silica gel (hexanes/ethyl acetate = 7:3 to 1:1). The title compound **2.7** was as a white solid (223 mg, 0.68) in 83% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.80 (dd, *J* = 5.8, 2.1 Hz, 1H), 4.13 (d, *J* = 11.1 Hz, 1H), 3.84 (d, *J* = 32.7 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.44 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.27 (d, *J* = 11.0 Hz, 1H), 3.14 (dd, *J* = 22.7, 5.8 Hz, 1H), 2.00 – 1.85 (m, 1H), 1.81 – 1.73 (m, 1H), 1.61 (td, *J* = 13.6, 3.7 Hz, 1H), 1.51 (dt, *J* = 13.3, 3.7 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H).

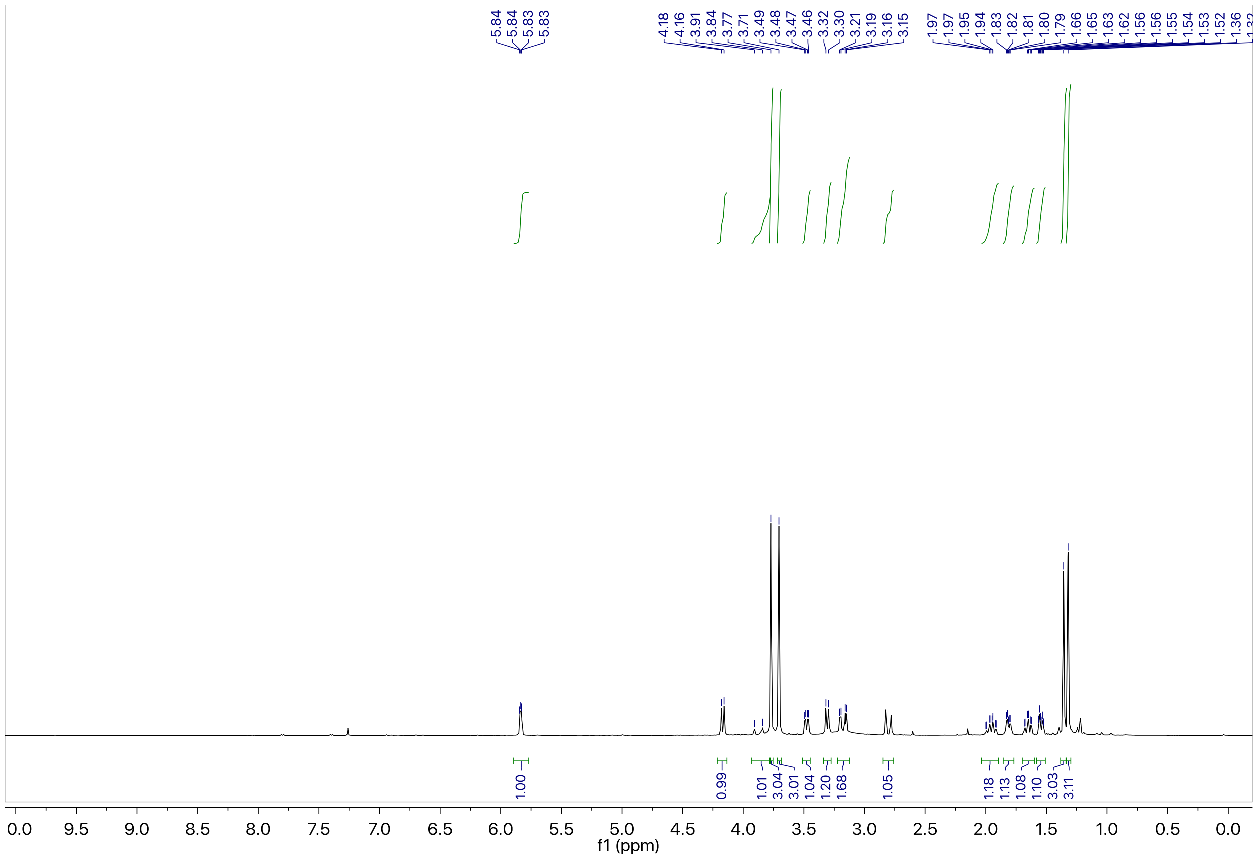
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.25, 166.05, 149.64, 143.37, 125.41, 122.63, 77.53, 77.02, 68.52, 52.27, 52.13, 46.45, 38.06, 32.59, 27.08, 26.86, 25.98, 22.17.

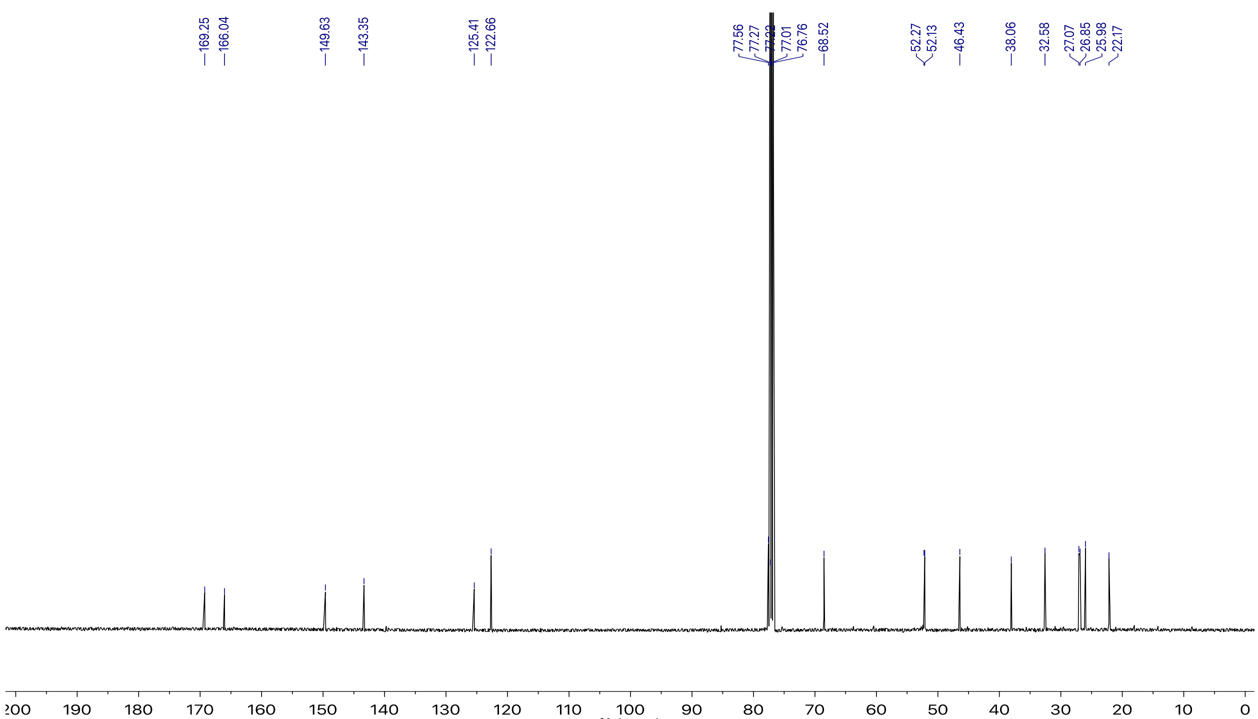
R_f 0.2 (hexanes/ethyl acetate = 1:1, UV/p-anisaldehyde)

HRMS (ESI) Calcd. for (M+Na)+ 347.1465, Found: 347.1474

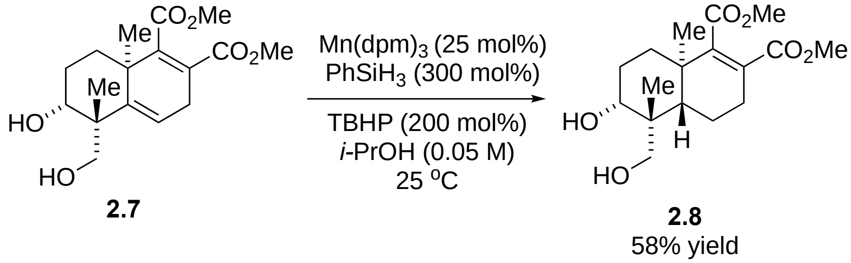
FTIR (neat): 3426, 2949, 2880, 2360, 1720, 1668, 1634, 1434, 1259.

Optical Rotation $[\alpha]_D$ = +180° (c=1, $CHCl_3$)





Dimethyl (4a*S*,5*R*,6*R*,8a*R*)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate (2.8)



To a degassed solution of 100 mg **2.7** (0.3 mmol, 100 mol%) in anhydrous 2-propanol (3 mL) was added a degassed solution of $PhSiH_3$ (97.2 mg, 0.9 mmol, 300 mol%) in 2-propanol (1 mL), tert-butyl hydroperoxide (5.5 M in decane, 0.6 mmol, 200 mol%) and a degassed solution of $Mn(dpm)_3$ (0.06 mmol, 20 mol%) in 2-propanol (2 mL). The resulted mixture was degassed by bubbling with argon for 5 seconds, and was allowed to stir at ambient temperature for 5 hours. After completion, the solvent was removed and subjected to flash column chromatography on silica gel (hexanes/ethyl acetate = 7:3 to 1:1). The title compound **2.8** was obtained as a colorless oil. (56 mg, 0.174 mmol) in 58% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.20 (d, *J* = 11.2 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.63 (d, *J* = 4.3 Hz, 1H), 3.46 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.38 – 3.28 (m, 1H), 2.95 (s, 1H), 2.87 – 2.77 (m, 1H), 2.47 (ddd, *J* = 19.0, 6.5, 1.2 Hz, 1H), 2.35 (ddd, *J* = 19.0, 11.2, 7.5 Hz, 1H), 1.98 – 1.72 (m, 3H), 1.59 – 1.40 (m, 3H), 1.26 (s, 3H), 1.20 (s, 3H).

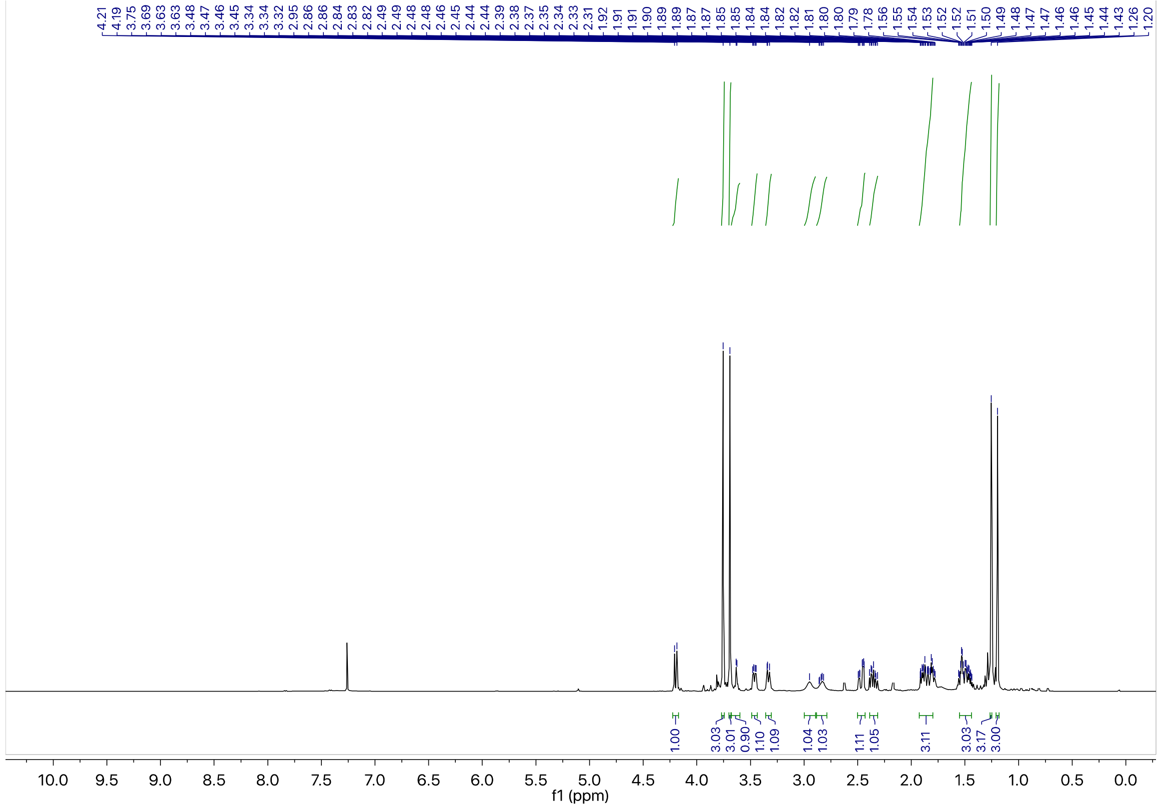
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.03, 167.20, 150.64, 126.96, 77.23, 52.12, 51.96, 49.60, 42.78, 37.22, 33.71, 27.60, 26.56, 22.37, 20.94, 17.73.

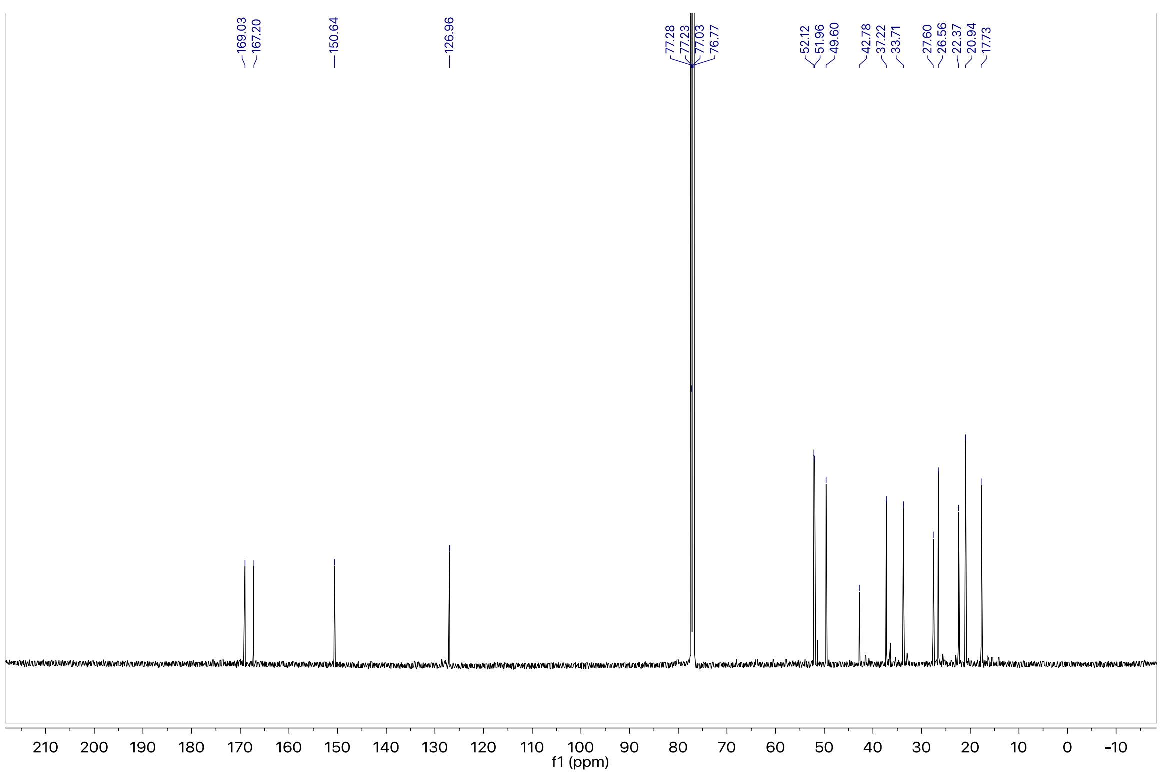
R_f 0.2 (hexanes/ethyl acetate = 1:1, UV/p-anisaldehyde)

HRMS (ESI) Calcd. for (M+Na)+ 349.1622, Found: 349.1632

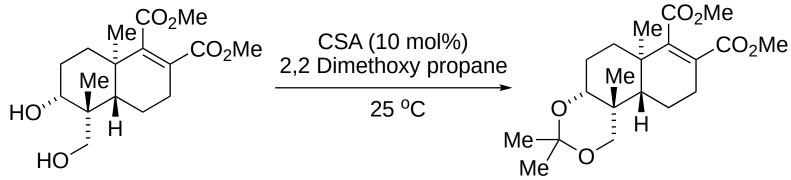
FTIR (neat): 3400, 2950, 1726, 1434, 1379, 1255, 1039.

Optical Rotation $[\alpha]_D$ = +76° (c=1, $CHCl_3$)


1.00
3.03
3.01
0.90
1.10
1.09
1.04
1.03
1.11
1.05
3.11
3.03
3.17
3.00
f1 (ppm)


169.03
167.20
150.64
126.96
77.28
77.23
77.03
76.77
52.12
51.96
49.60
42.78
37.22
33.71
27.60
26.56
22.37
20.94
17.73
f1 (ppm)

Dimethyl (4a*R*,6a*R*,10a*S*,10b*R*)-3,3,6a,10b-tetramethyl-4a,5,6,6a,9,10,10a,10b-octahydro-1*H*-naphtho[2,1-*d*][1,3]dioxine-7,8-dicarboxylate (2.9)



2.8 **2.9** 85% yield

To a solution of diol **2.8** (146 mg, 0.45 mmol, 100 mol%) in 2,2-dimethoxypropane (2,2-DMP, 4.5 mL) was added camphorsulfonic acid 10 mol% at ambient temperature. The resulted mixture was allowed to stir at the same temperature for 5 hours. The reaction was diluted with Et_2O and quenched by addition of sat $NaHCO_3$ The organic layer was separated, and washed with water After dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (hexanes/ethyl acetate = 95:5). The title compound was obtained as a colorless oil **2.9** (139 mg, 0.38 mmol) in 85% yield.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.04 (d, *J* = 11.7 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.64 (d, *J* = 7.0 Hz, 1H), 3.48 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.26 (d, *J* = 11.7 Hz, 1H), 2.54 – 2.30 (m, 2H), 2.08 (dt, *J* = 9.6, 5.0 Hz, 1H), 1.88 – 1.71 (m, 2H), 1.65 – 1.49 (m, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.24 (s, 3H).

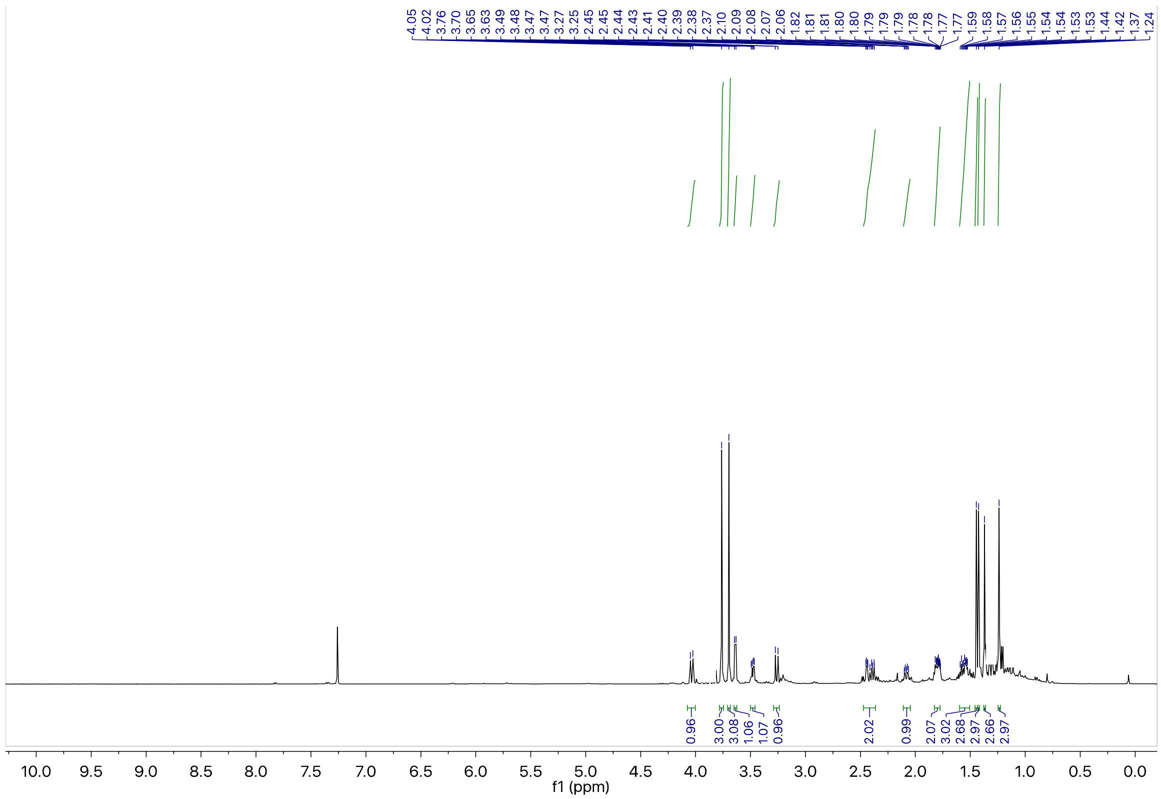
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.04, 167.40, 150.93, 127.04, 99.01, 77.23, 76.77, 63.38, 52.09, 51.92, 47.23, 37.42, 36.84, 31.77, 27.47, 26.21, 26.06, 25.78, 25.03, 21.88, 17.22.

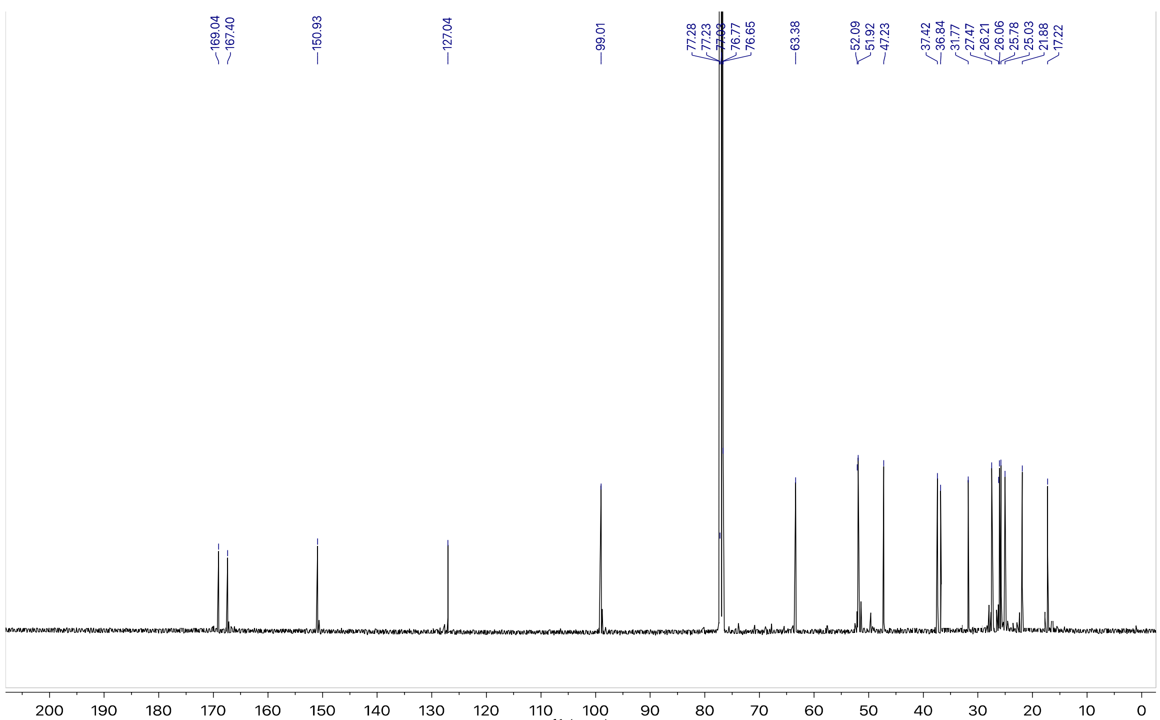
R_f 0.35 (hexanes/ethyl acetate = 7:3, UV/p-anisaldehyde)

HRMS (CI) Calcd. for $C_{20}H_{29}O_6$ $(M+H)^+$: 367.2121, Found: 367.2126.

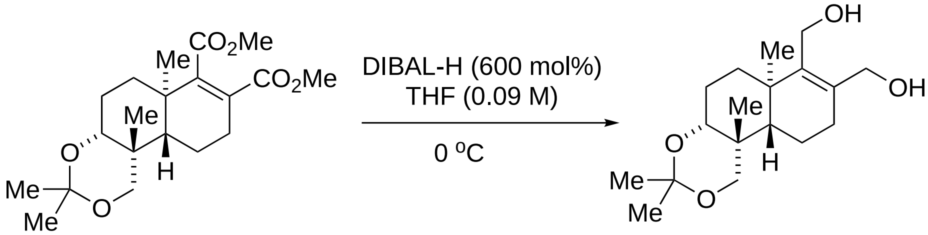
FTIR (neat): 2950, 1724, 1433, 1377, 1249, 1200, 1154 cm^{-1}

Optical Rotation $[\alpha]_D$ = -31° (c=1, $CHCl_3$)





((4a*R*,6a*R*,10a*S*,10b*R*)-3,3,6a,10b-tetramethyl-4a,5,6,6a,9,10,10a,10b-octahydro-1*H*-naphtho[2,1-*d*][1,3]dioxine-7,8-diyl)dimethanol (2.10)



2.9

2.10
70% yield

To an ice-cooled solution of dicarboxylate (80 mg, 0.218 mmol, 100 mol%) in THF (2.42 mL) was added diisobutylaluminum hydride (DIBAL-H, 1.0 M solution in hexane, 1.3 mL, 600 mol%) slowly. The resulted mixture was allowed to stir at 0℃ for 2 hour. The reaction was diluted with DCM and quenched by addition of Rochelle salt solution (1.0 M aqueous solution). The two layers were separated, and the aqueous phase was extracted with DCM. The combined organic phases were washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to flash column chromatography on silica gel (hexanes/acetone = 10:1 to 3:1). The title compound was obtained as a white solid (47.3 mg, 0.152 mmol) in 70% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.32 – 3.80 (m, 5H), 3.57 – 3.47 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.73 (broad s, 2H), 2.22 (dd, *J* = 8.7, 4.1 Hz, 2H), 2.01 – 1.90 (m, 1H), 1.89 – 1.73 (m, 2H), 1.71 – 1.64 (m, 1H), 1.59 (dd, *J* = 12.7, 6.6 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H).

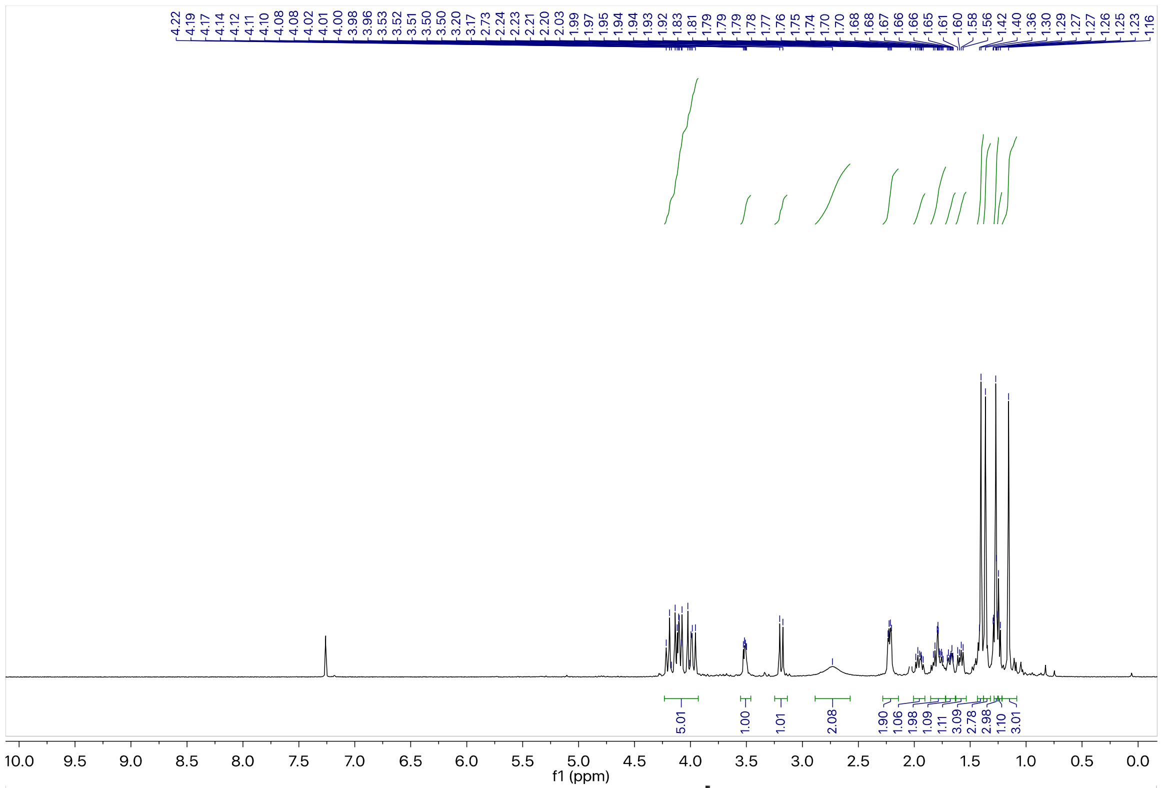
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.60, 129.57, 101.51, 80.29, 64.81, 64.16, 60.44, 51.28, 42.64, 37.15, 33.39, 29.29, 27.75, 23.80, 23.69, 22.48, 19.69, 18.27.

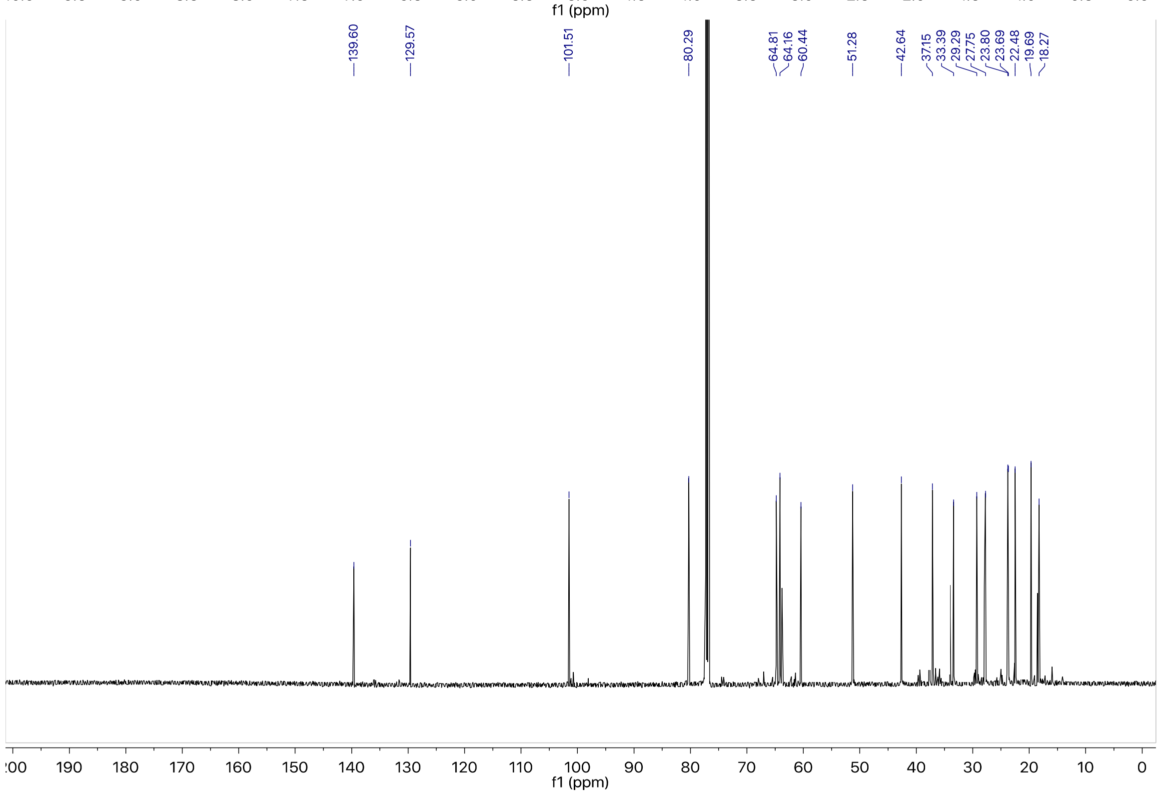
R_f 0.12 (hexanes/ethyl acetate = 1:1, UV/p-anisaldehyde)

HRMS (ESI) Calcd. for (M+Na)+ 333.2036, Found: 333.2042

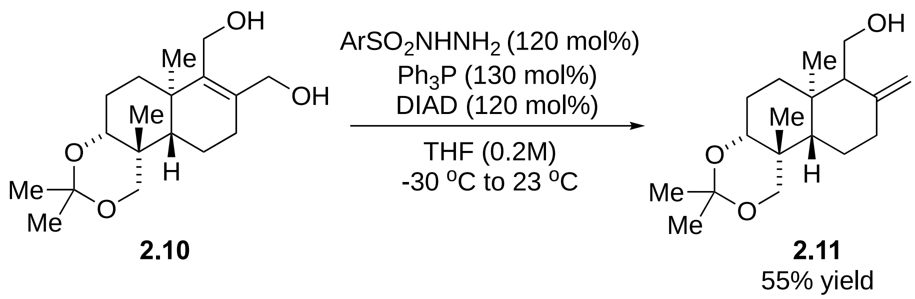
FTIR (neat): 3382, 2933, 1378, 1220, 1089, 1036 cm^{-1}.

Optical Rotation $[\alpha]_D$ = -81º (c=1, $CHCl_3$)


4.22
4.19
4.17
4.14
4.12
4.11
4.10
4.08
4.08
4.02
4.01
4.00
3.98
3.96
3.53
3.52
3.51
3.50
3.50
3.20
3.17
2.73
2.24
2.23
2.21
2.20
2.03
1.99
1.97
1.95
1.94
1.94
1.93
1.93
1.92
1.83
1.81
1.79
1.79
1.79
1.78
1.77
1.76
1.75
1.74
1.70
1.70
1.68
1.68
1.67
1.66
1.66
1.65
1.61
1.60
1.58
1.56
1.42
1.40
1.36
1.30
1.29
1.27
1.27
1.26
1.25
1.23
1.16
5.01
1.00
1.01
2.08
1.90
1.06
1.98
1.09
1.11
3.09
2.78
2.98
1.10
3.01
10.0 9.5 9.0 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)


139.60
129.57
101.51
80.29
64.81
64.16
60.44
51.28
42.64
37.15
33.39
29.29
27.75
23.80
23.69
22.48
19.69
18.27
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

((4a*R*,6a*R*,10a*S*,10b*R*)-3,3,6a,10b-tetramethyl-8-methylenedecahydro-1*H*-naphtho[2,1-*d*][1,3]dioxin-7-yl)methanol (2.11)



Diisopropylazodicarboxylate (DIAD, 0.158 mmol, 120 mol%) was added to a solution of triphenylphosphine (44 mg, 0.168 mmol, 130 mol%) in THF (0.4 mL) at -30 °C. After 5 min, diol (40 mg, 0.129 mmol, 100 mol%) in 0.15 ml THF was added to the cold reaction mixture, followed 10 min later by solid NBSH (0.158 mmol, 120 mol%). The reaction mixture was held at-30 °C for 2 hr, after which the reaction mixture was warmed to 23 °C then stirred at this temp for another 2 h. After completion, the solvent was removed and subjected to flash silica gel chromatography (hexanes/acetone 9:1) to obtain the product as colorless oil (21 mg, 0.07 mmol) in 55% yield.

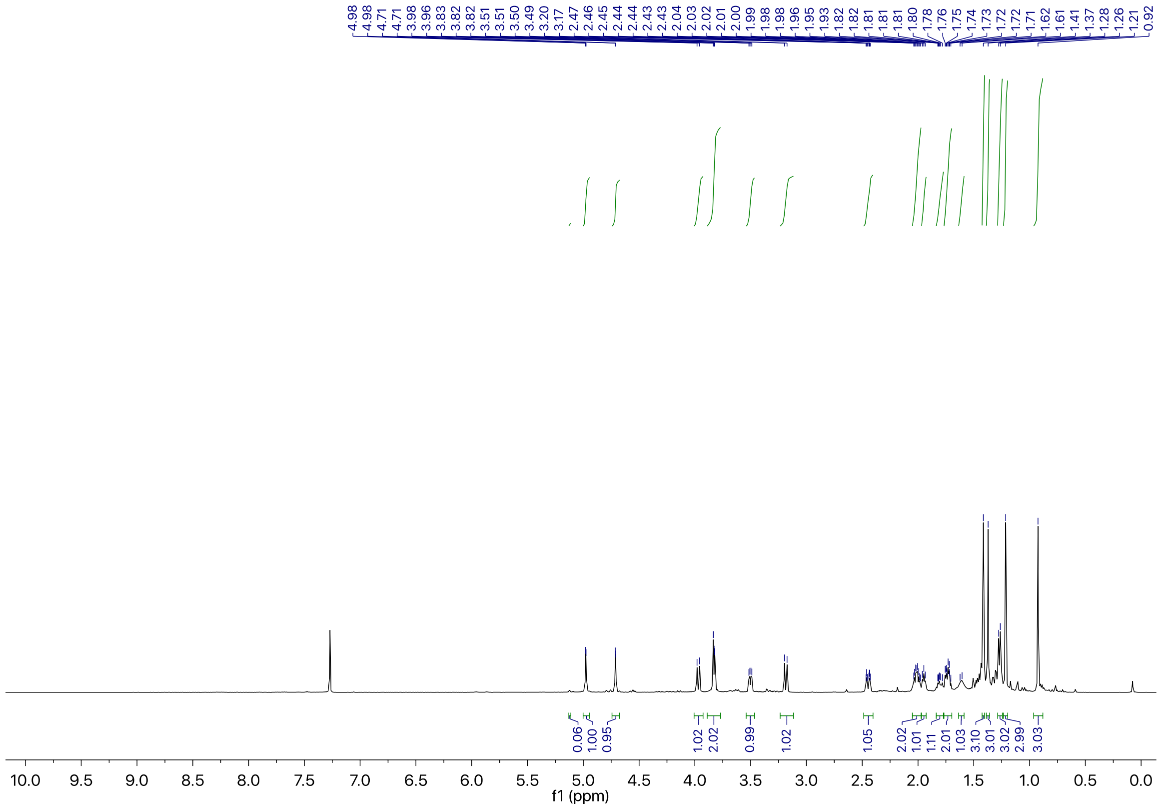
^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.13 – 4.89 (m, 1H), 4.76 – 4.58 (m, 1H), 3.97 (d, *J* = 11.6 Hz, 1H), 3.90 – 3.75 (m, 2H), 3.50 (dd, *J* = 9.0, 4.1 Hz, 1H), 3.18 (d, *J* = 11.6 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.02 (td, *J* = 8.6, 4.3 Hz, 2H), 1.95 (t, *J* = 6.4 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.73 (dt, *J* = 12.6, 3.5 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.21 (s, 3H), 0.92 (s, 3H).

R_f 0.5 (hexanes/ethyl acetate = 1:1, UV/p-anisaldehyde)

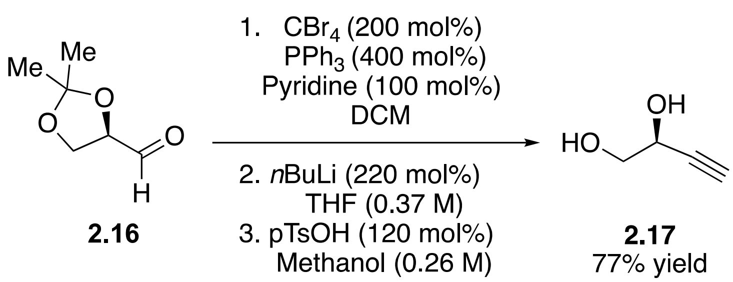
HRMS (CI) Calcd. for $C_{20}H_{29}O_6$ (M+H)+ : 295.2273, Found: 295.2261.

FTIR (neat): 3328, 2931, 2865, 1446, 1037 cm^{-1}.

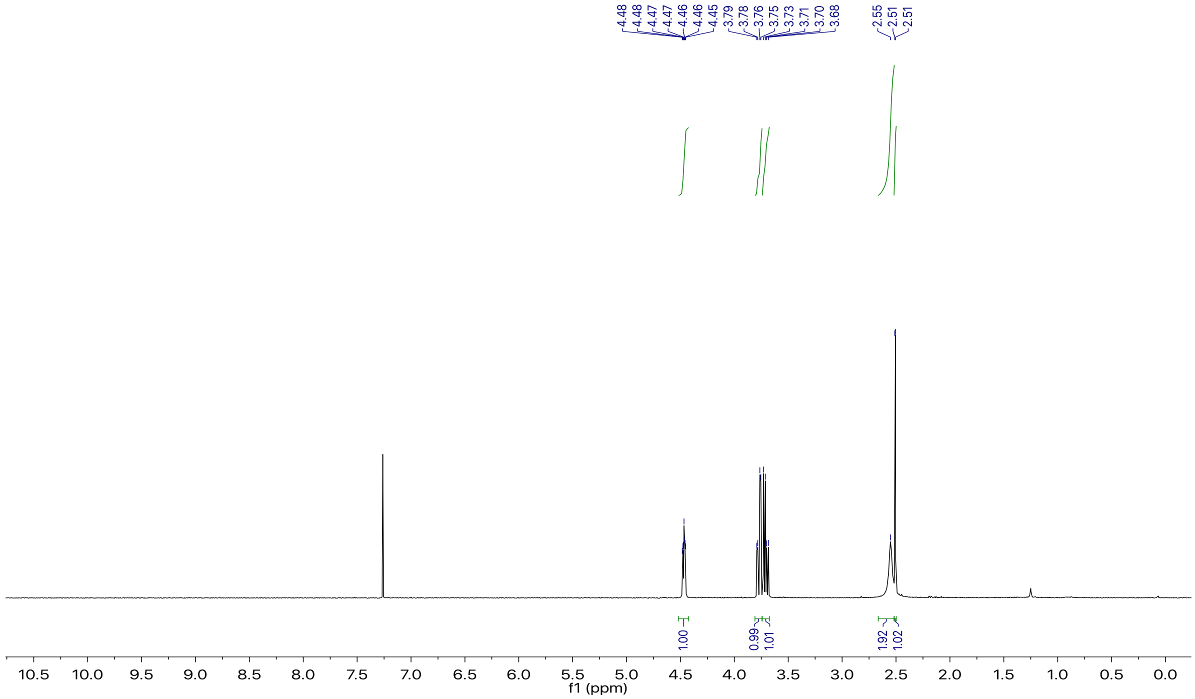
Optical Rotation $[\alpha]_D$ = +101° (c=0.25, $CHCl_3$).



(*S*)-but-3-yne-1,2-diol (2.17)



Propyn-1,2-diol was prepared similar to the procedure described in the literature.[24] The proton and carbon spectra of the product was obtained as expected when compared to the values in the report.


4.48
4.48
4.47
4.47
4.46
4.46
4.45
3.79
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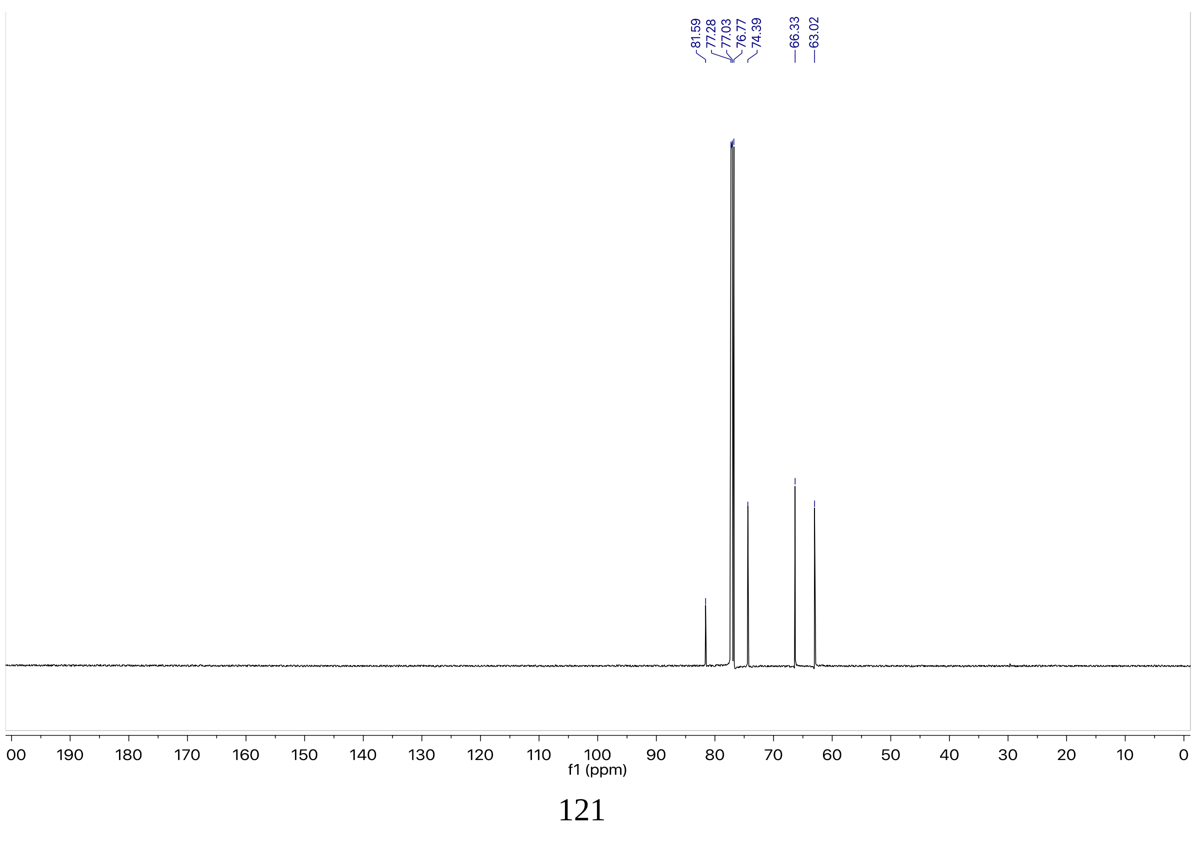
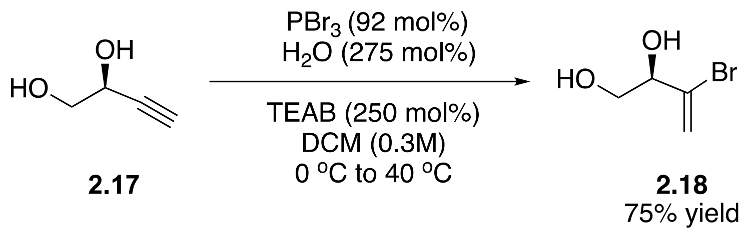
3.76
3.75
3.73
3.71
3.70
3.68
2.55
2.51
2.51
1.00
0.99
1.01
1.92
1.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


81.59
77.28
77.03
76.77
74.39
66.33
63.02
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*R*)-3-bromobut-3-ene-1,2-diol (2.18)



HBr gas was produced by adding PBr_3 (0.73 mL, 5.5 mmol) dropwise to water (0.29 mL, 16 mmol).[25] The HBr gas thus produced was bubbled through tetraethyl ammonium bromide (3.1 g) in 20 mL of dichloromethane at 0 °C after which it was absorbed by tetraethyl ammonium bromide solution. To this solution inject 3-Butyn-1,2-diol **2.17** (516 mg, 6 mmol) the reaction mixture was heated at 40 °C overnight. Cooled to 0 °C, quenched with triethylamine and extracted with ether, dried over Na_2SO_4, solvent was removed in vacuo. The crude product was then subjected to flash silica gel chromatography 7:3 to 1:1 Hexanes:Et_2O to afford 745 mg (75%) of the vinyl bromide **2.18** as a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.98 (t, J = 1.6 Hz, 1H), 5.62 (d, J = 2.0 Hz, 1H), 4.30 – 4.17 (m, 1H), 3.75 (dd, J = 11.5, 3.8 Hz, 1H), 3.67 (dd, J = 11.4, 6.3 Hz, 1H), 2.54 (s, 2H).

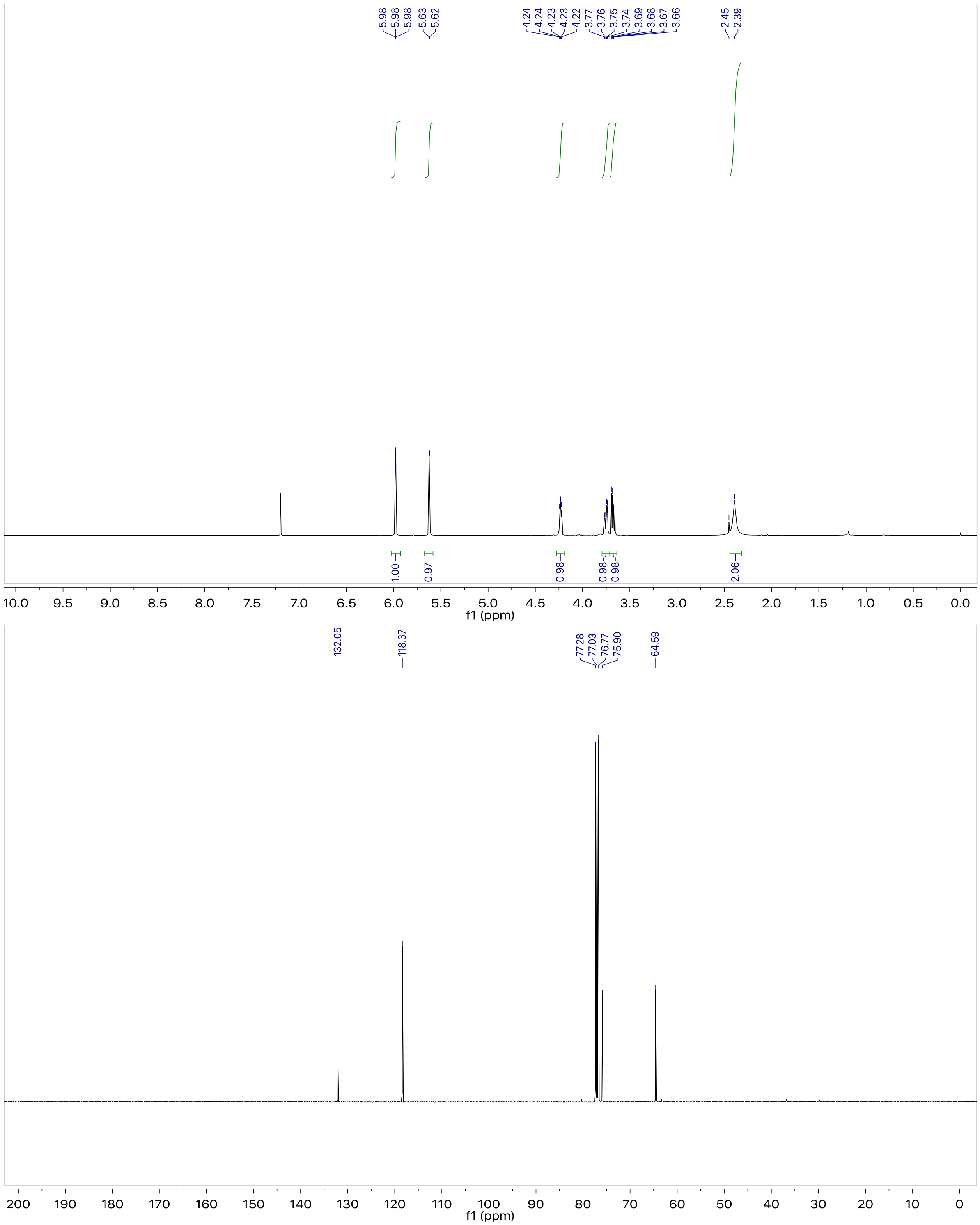
^{13}C NMR (126 MHz, $CDCl_3$) δ 132.03, 118.37, 75.91, 64.61.

R_f 0.28 (hexanes/ethyl acetate = 1:1, $KMNO_4$)

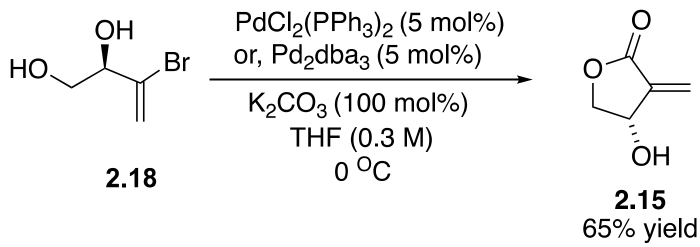
HRMS (CI) Calcd. for $C_4H_8O_2Br$ (M+H)+ : 166.9708, Found: 166.9707.

FTIR (neat): 3330, 2931, 2881, 1626, 1398, 1034, 901 cm^{-1}.

Optical Rotation $[\alpha]_D$ = +100° (c=1, $CHCl_3$).


5.98
5.98
5.98
5.63
5.62
4.24
4.24
4.23
4.23
4.22
3.77
3.76
3.75
3.74
3.69
3.68
3.67
3.66
2.45
2.39
1.00
0.97
0.98
0.98
0.98
2.06
f1 (ppm)
132.05
118.37
77.28
77.03
76.77
75.90
64.59
f1 (ppm)

(*S*)-4-hydroxy-3-methylenedihydrofuran-2(3*H*)-one (2.15)



To a dry reaction tube catalyst (5 mol%) and potassium carbonate (41.4 mg, 100 mol%) was taken. The tube was then flushed with CO for 5 mins. THF (1 ml) was added to the tube followed by the vinyl bromide (49.8 mg, 0.3 mmol, 100 mol%). The tube was capped with PTFE lined cap and heated at 60 °C overnight. The reaction mixture was filtered over celite and solvent was removed under reduced pressure. The crude mixture was subjected to flash silica gel chromatography (pretreated with triethylamine) 7:3 Hexane:ethyl acetate to obtain the *exo*-methylene lactone 22 mg (65% yield) as yellowish oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.40 (d, *J* = 2.1 Hz, 1H), 5.97 (d, *J* = 1.7 Hz, 1H), 4.91 (ddt, *J* = 6.6, 3.8, 1.9 Hz, 1H), 4.45 (dd, *J* = 10.0, 6.6 Hz, 1H), 4.13 (dd, *J* = 10.1, 3.6 Hz, 1H), 2.22 – 1.80 (broad s, 1H).

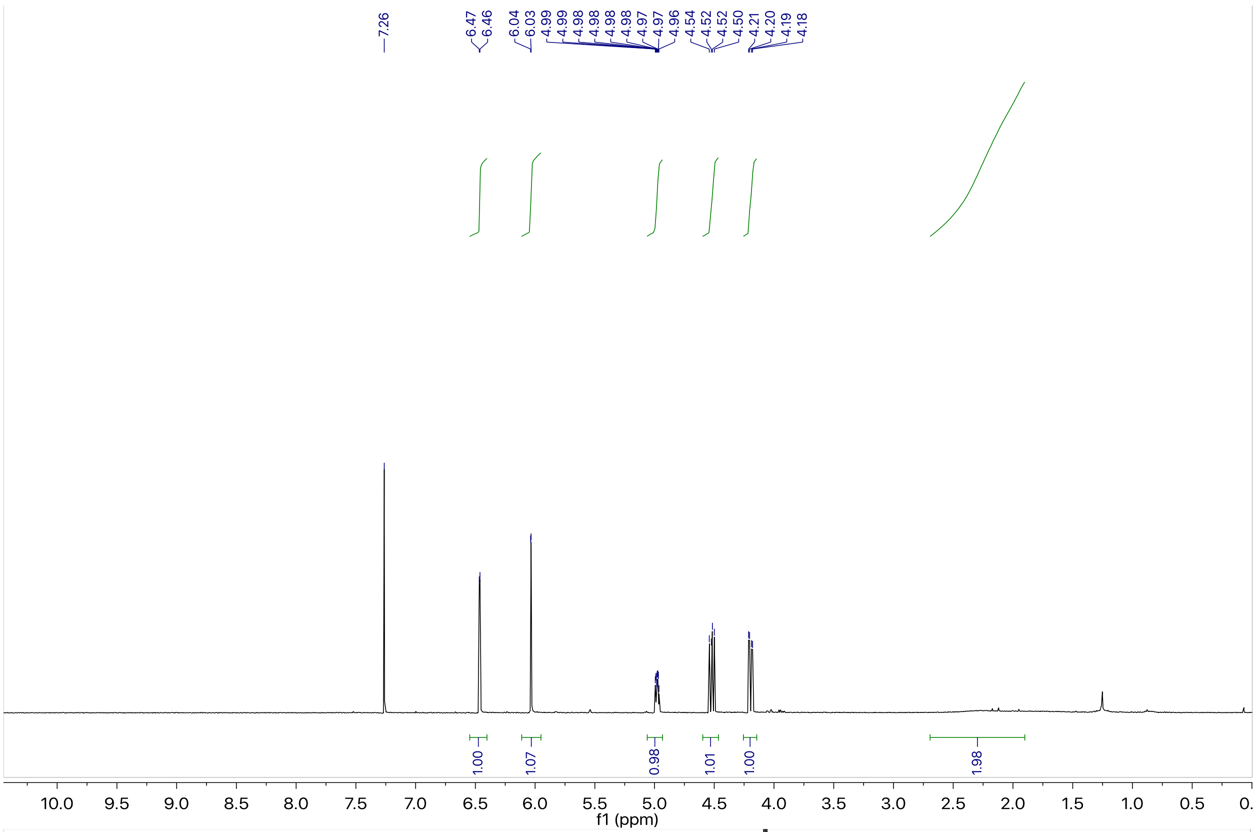
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.02, 137.70, 126.68, 73.36, 67.75.

Rf 0.24 (Hexane: Ethyl acetate = 1:1, $KMNO_4$)

HRMS (CI) Calcd. for $C_5H_7O_3$ (M+H)+ : 115.0395, Found: 115.0392.

FTIR (neat): 3405, 2923, 2852, 1745, 1668, 1411, 1270, 1120.

Optical Rotation $[\alpha]_D$ = -103.6˚ (c = 0.5, CHCl3)


7.26
6.47
6.46
6.04
6.03
4.99
4.98
4.98
4.98
4.98
4.97
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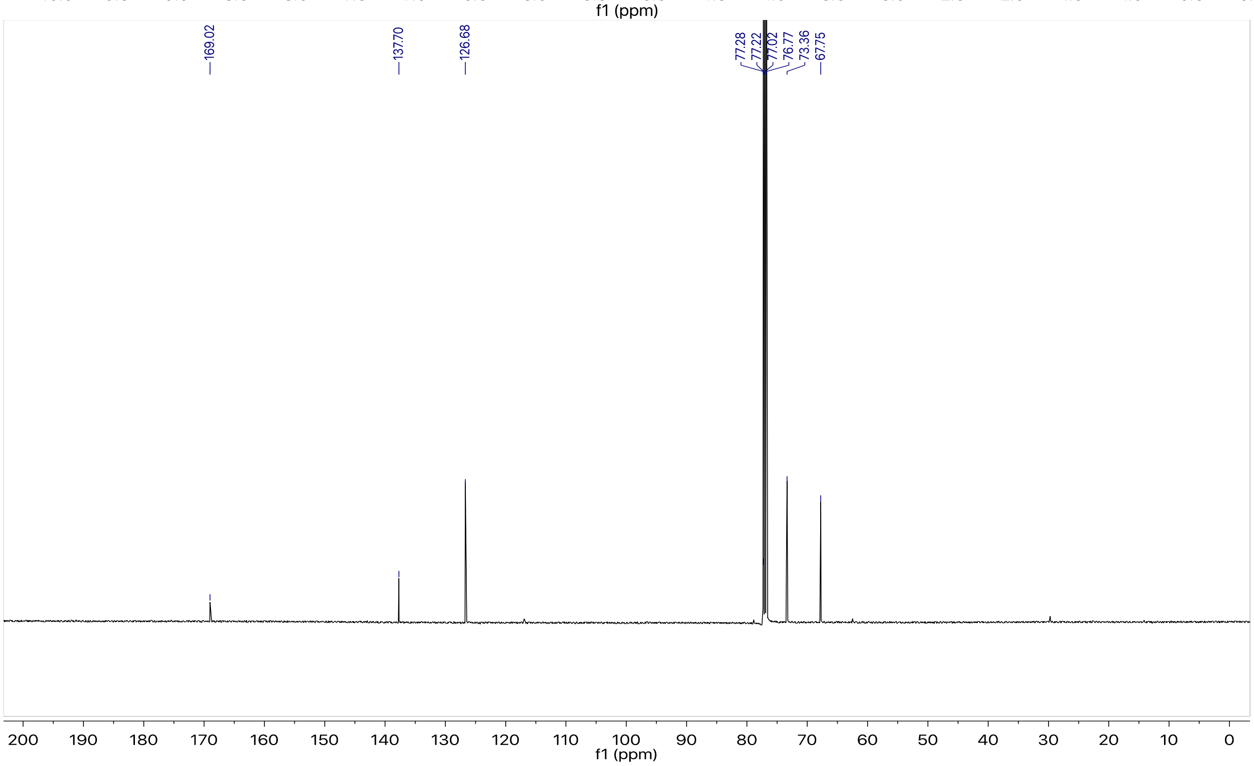
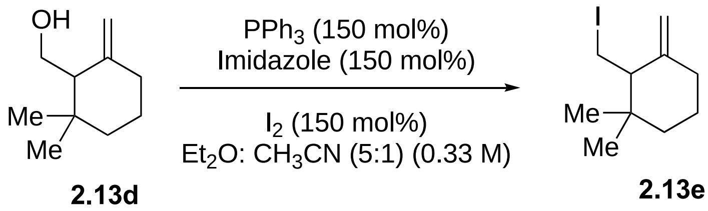
4.96
4.54
4.52
4.52
4.50
4.21
4.20
4.19
4.18
1.00
1.07
0.98
1.01
1.00
1.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


169.02
137.70
126.68
77.28
77.22
77.02
76.77
73.36
67.75
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2-(iodomethyl)-1,1-dimethyl-3-methylenecyclohexane (2.13e)

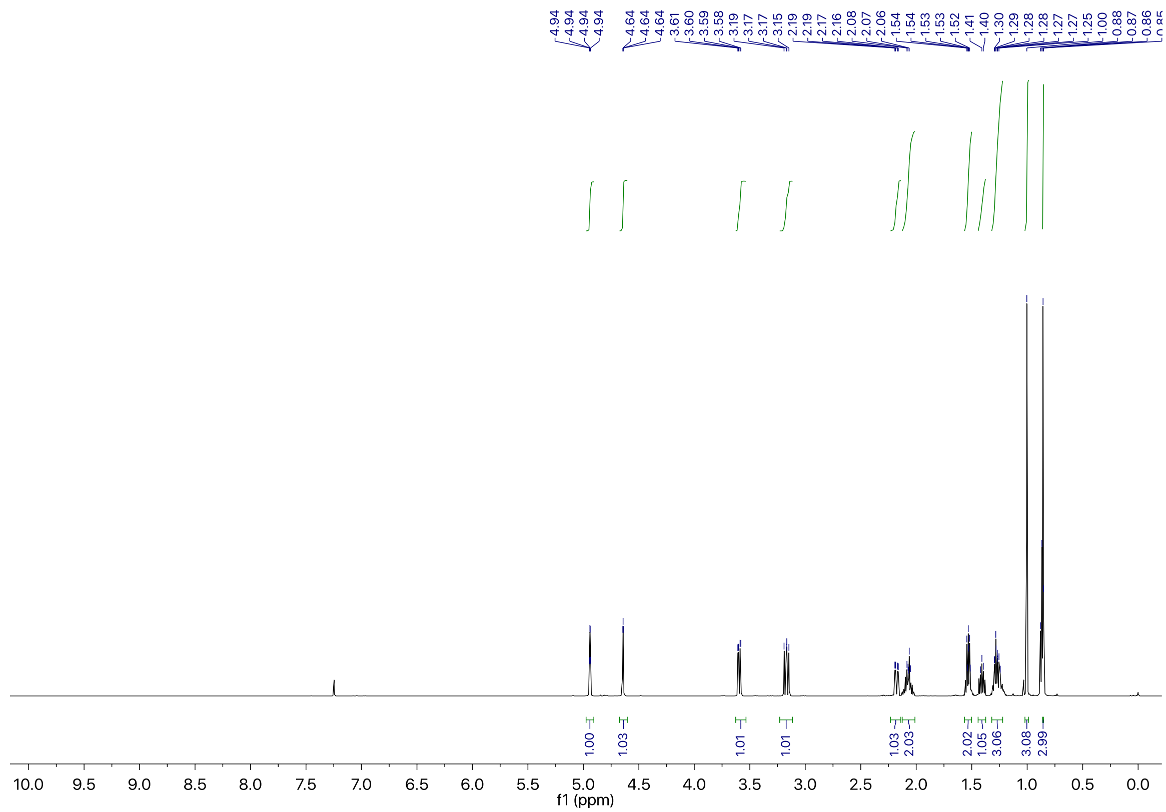


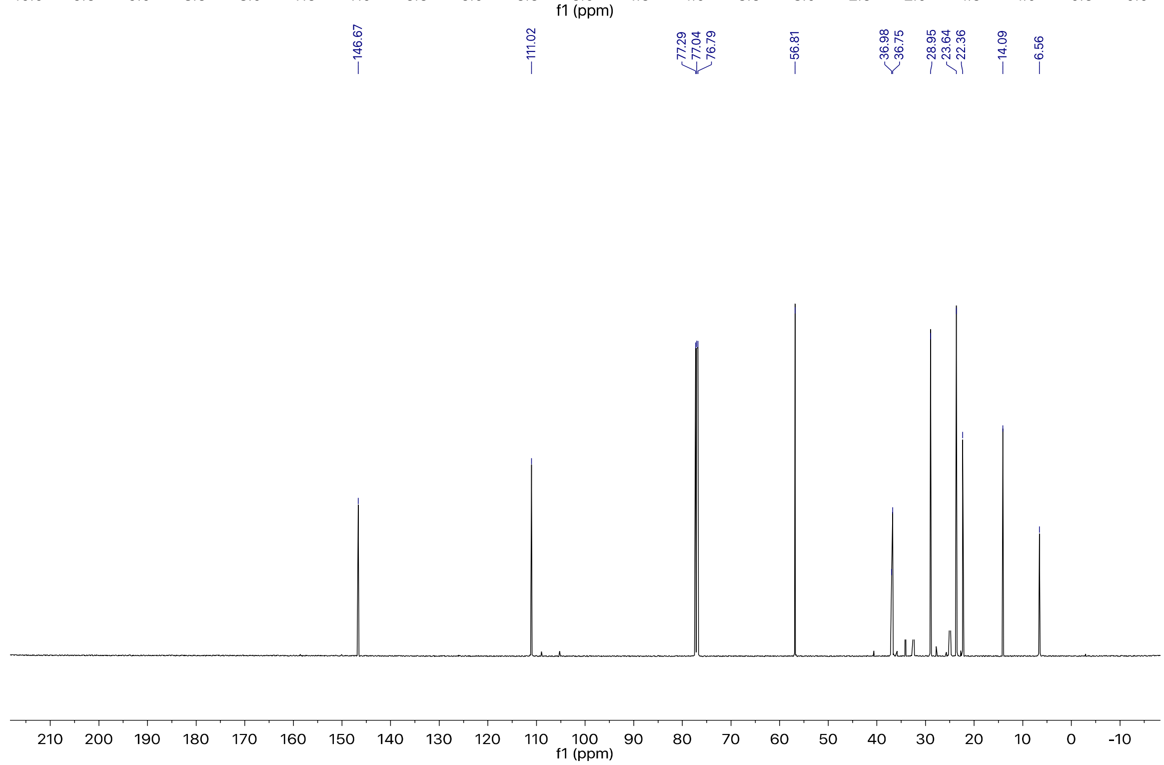
To a dry RB flask, PPh_3 (2.56 g, 9.77 mmol, 150 mol%) and imidazole (665 mg, 9.77 mmol, 150mol%) was taken, followed by freshly distilled diethyl ether 16 ml and acetonitrile 13 ml. Iodine (2.47 g, 9.77 mmol, 150 mol%) was added and cooled to 0 ^{o}C. Alcohol **2.13 d** (1g, 6.49 mmol, 100 mol%) was added dropwise then warmed to room temperature and stirred for 48 hours. After completion, the solvent was removed under reduced pressure and subjected to flash silica gel chromatography 100% pentane to afford **2.13e** as colorless oil 1.2 g (70% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.16 – 4.88 (m, 1H), 4.74 – 4.58 (m, 1H), 3.59 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.17 (dd, *J* = 12.0, 9.9 Hz, 1H), 2.18 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.07 (dd, *J* = 10.8, 5.4 Hz, 2H), 1.65 – 1.49 (m, 2H), 1.49 – 1.35 (m, 1H), 1.36 – 1.20 (m, 3H), 1.00 (s, 3H), 0.86 (s, 3H).

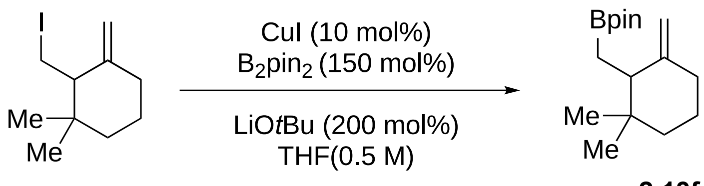
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.67, 111.02, 56.81, 36.98, 36.75, 28.95, 23.64, 22.36, 14.09, 6.56.

R_f 0.8 (Hexane: Ethyl acetate = 98:2, $KMNO_4$)





2-((2,2-dimethyl-6-methylenecyclohexyl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.13f)

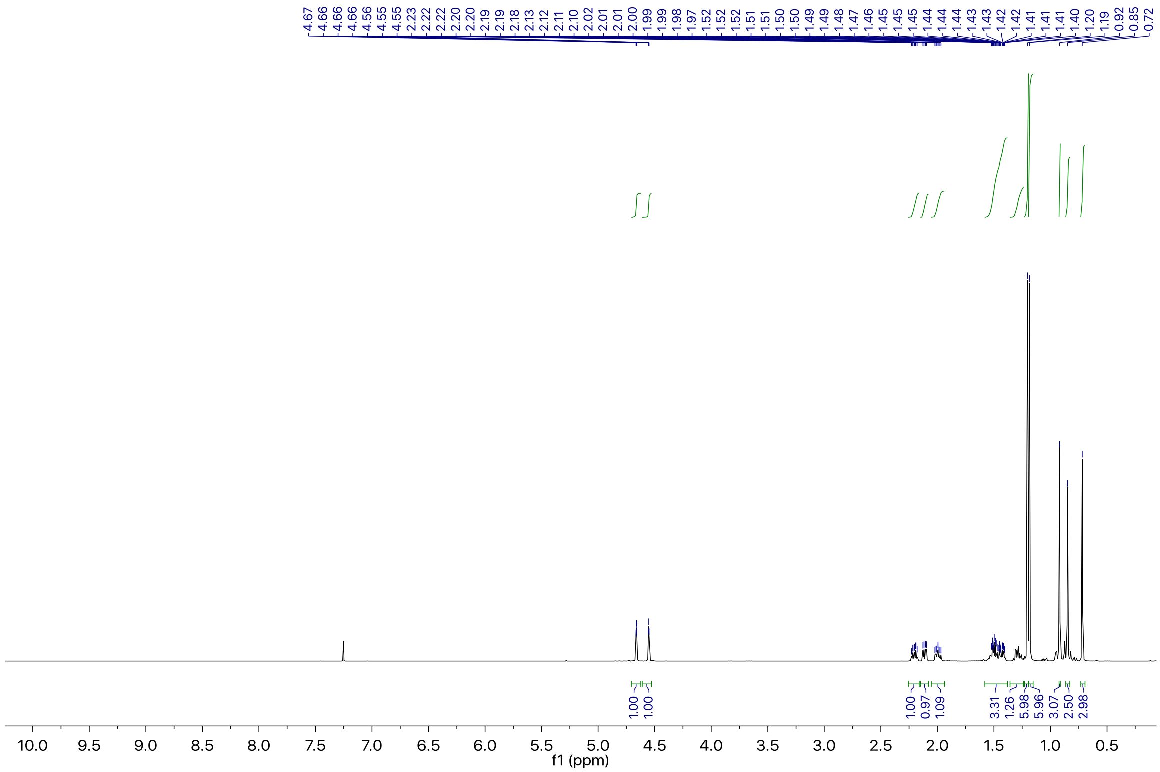


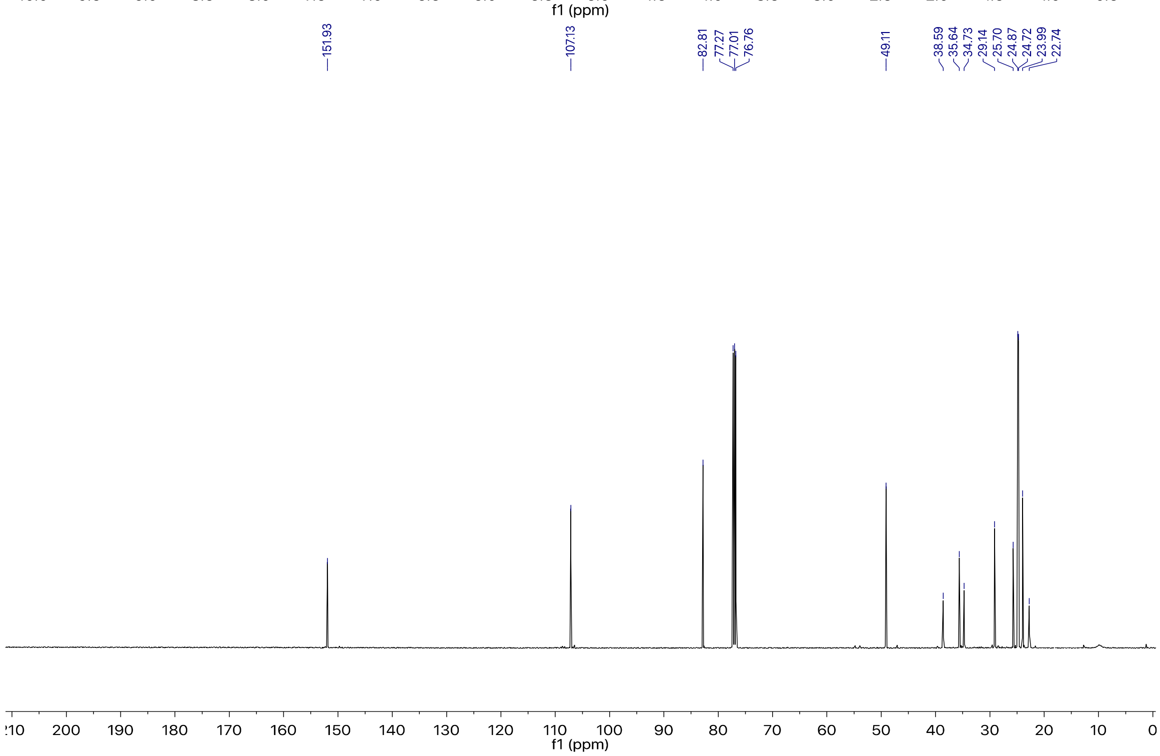
To a dry RB flask, CuI (19.2 mg, 0.1 mmol, 10 mol%) and LiO*t*Bu (160 mg, 2 mmol, 200 mol%) was taken, followed by B_2pin_2 (380 mg, 1.5 mmol, 150 mol%) and freshly distilled THF 2 ml and iodide **2.13e** (264 mg mg, 1 mmol, 100 mol%). The reaction was stirred for 18h and diluted with ethyl acetate and filtered through silica. Then, solvent was removed and subjected to flash silica gel chromatography 98:2 hexanes:EtOAc to afford Bpin compound **2.13f** in 76% yield as colorless oil which turns into white solid when stored in freezer.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.66 (dd, *J* = 2.1, 1.1 Hz, 1H), 4.55 (t, *J* = 1.6 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.11 (dd, *J* = 11.1, 4.8 Hz, 1H), 1.99 (ddd, *J* = 13.4, 9.0, 4.9 Hz, 1H), 1.58 – 1.39 (m, 3H), 1.28 (ddd, *J* = 13.5, 9.1, 4.8 Hz, 1H), 1.20 (s, 6H), 1.19 (s, 6H), 0.92 (s, 4H), 0.72 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.93, 107.13, 82.81, 49.11, 38.59, 35.64, 34.73, 29.14, 25.70, 24.87, 24.72, 23.99, 22.74.

R_f 0.2 (Hexane: Ethyl acetate = 95:5, $KMNO_4$)





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Chapter 1

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