

PART I: STEREOSELECTIVE SYNTHESSES OF (+)-KOMARVIQUINONE AND (+)-
KOMAROVISPIRONE

PART II: STUDIES TOWARD THE SYNTHESSES OF DOLASTANE NATURAL
PRODUCTS

by

JIANHUA YU

(Under the Direction of George Majetich)

ABSTRACT

In part I, the first total synthesis of (+)-komaroviquinone and (+)-komarovispirone were achieved. The key reaction for the preparation of (+)-komaroviquinone featured a bromohydrin reaction to install the benzylic oxygen. (+)-komarovispirone was successfully rearranged to (+)-komaroviquinone under photochemical condition.

In part II, studies toward the synthesis of dolastane natural products were carried out.

INDEX WORDS: (+)-komaroviquinone, (+)-komarovispirone, bromohydrin, dolastane

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LIST OF ABBREVIATIONS

Abbreviation	Full name
AIBN	azo- <i>bis</i> -isobutyronitrile
CAN	ceric ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	<i>N,N'</i> -dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
HMPA	hexamethylphosphoramide
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
DIBAL-H	diisobutylaluminium hydride
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid

Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NBSH	<i>ortho</i> -nitrobenzenesulfonylhydrazine
NMM	<i>N</i> -methylmorpholine
PCC	pyridium chlorochromate
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
<i>p</i> -TSA	<i>para</i> -toluenesulfonic acid
BRSM	based on recover of starting material
DMP	Dess–Martin periodinane
PDC	pyridinium dichromate
TFA	trifluoroacetic acid
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
r.t.	room temperature
TBAI	tetrabutylammonium iodide
h	hour
pyn.	pyridine
TBAF	tetra- <i>n</i> -butylammonium fluoride

PART I:

STEREOSELECTIVE SYNTHESSES OF (+)-KOMAROVICINONE AND (+)-KOMAROVISPIRONE

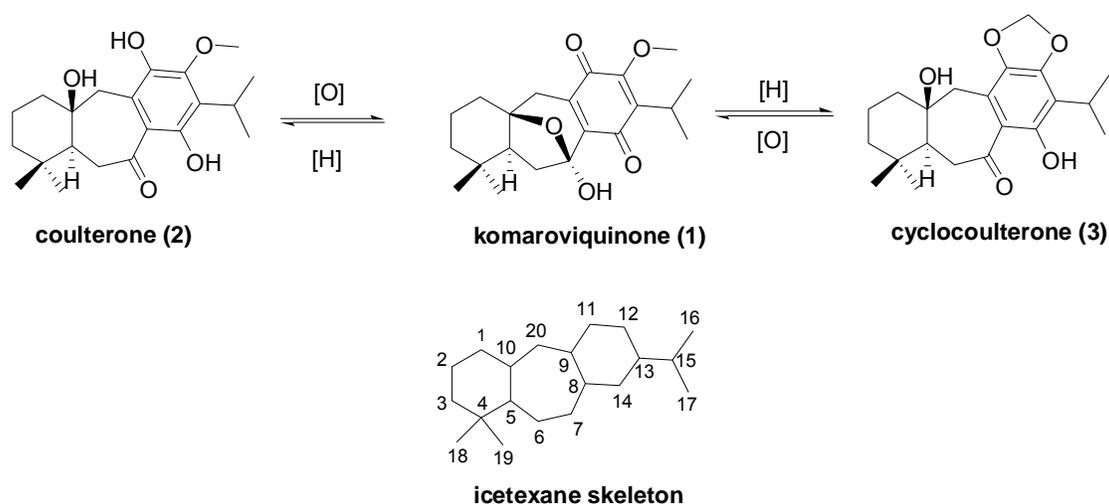
1. (+)-Komarovicinone Isolation and Biological Activity

Chagas' disease is a major public health problem widespread in Central and South American countries, with 18–20 million infected people, 25% of the human population at risk of infection, together with 21,000 deaths per year.¹ This disease's causative agent is *Trypanosoma cruzi*, a parasitic protozoan transmitted to mammalian hosts by blood-sucking triatomine bugs.² Infections by *T. cruzi* result in a life-threatening, acute and/or chronic disease with severe cardiac complications. This situation is worsened by the lack of effective vaccines; undesirable side effects of anti-chagasic drugs in use such as nifurtimox and benznidazole, and the emergence of parasite resistance to these drugs. All these made the development of new chemotherapeutic agents urgently needed.

The *Dracocephalum* is an annual or perennial herb of the Labiatae family, widely spread in Southern Europe and temperate Asia. Some of its species are used as an astringent and a carminative,³ and are reported to show antihyperlipidemic effect,⁴ immunomodulatory effect⁵ and antinociceptive effect.⁶ *Dracocephalum komarovi* Lipsky is a perennial semishrub that grows at around 2300–3600 meters above sea level in the West Tien Shan mountain system.⁷ It

is called ‘buzbosh’ in Uzbekistan and the local people use the above ground parts in a tea to treat various disorders such as inflammatory diseases and hypertony.

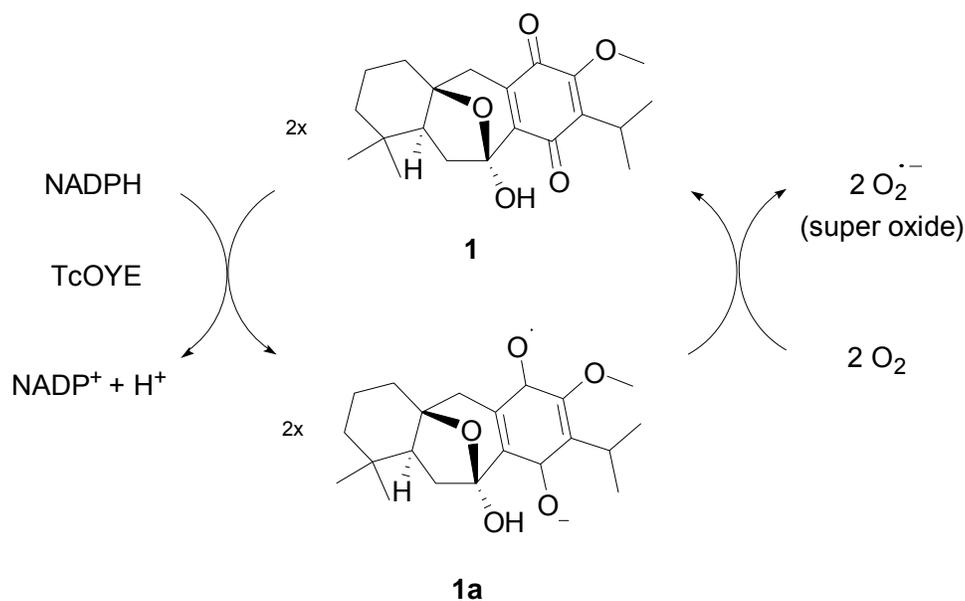
This plant also showed trypanocidal activity. Several compounds were isolated from the plant,⁸ as shown in scheme 1. All these compounds belong to the icetexane family of natural products.



Scheme 1

Of all these compounds, komaroviquinone **1** showed the strongest trypanocidal activity against epimastigotes of *T. cruzi*, with a minimum lethal concentration (MLC) of 0.4 μM , compared to the MLC of gentian violet, the drug currently used to disinfect trypanosomes from transfusion blood in Latin America, which was 6.3 μM under the same assay conditions. Several types of natural quinones have been reported to show trypanocidal activity, and their activities have been partly ascribed to the production of reactive oxygen species in the parasite.^{9,10} The

anti-Chagasic activity of komaroviquinone has been studied in detail by Urade and co-workers.¹¹ They determined that the quinone moiety of **1** catalyzes a redox cycling process which ultimately leads to oxidative stress in the parasite. In the presence of *Trypanosoma cruzi* old yellow enzyme (TcOYE), a NADPH-dependent, single-electron reduction of komaroviquinone yields semi-quinone radical anion **1a** (Scheme 2). This species can then undergo oxidation by molecular oxygen to regenerate **1** and produce superoxide. Interestingly, the later study by Urade et al. identified even more potent activity against *T. cruzi* with an IC₅₀ of 9 nM.¹¹ Komaroviquinone was later found to also inhibit the binding of MIP-1 α to the G protein-coupled CCR5 receptor on Chinese hamster ovary (CHO) cell membranes.¹² Since the CCR5 receptor has been implicated as a principal co-receptor in HIV-1 infection,¹³ this finding suggests a potential role for komaroviquinone in the development of anti-HIV agents.

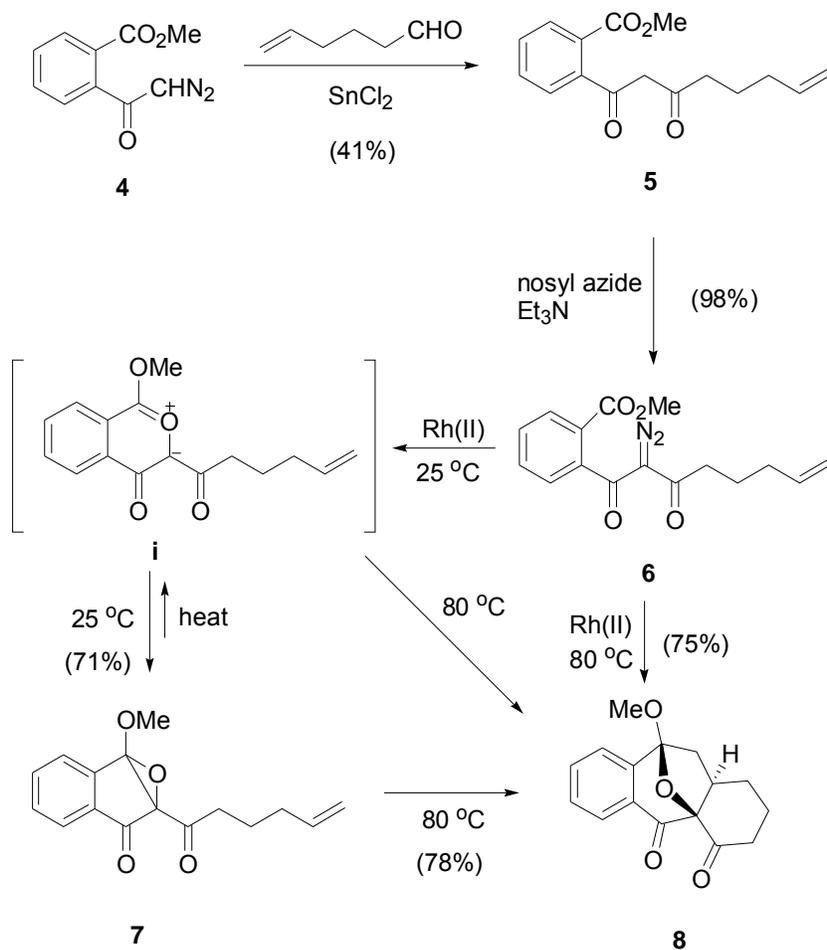


Scheme 2

2. Previous Syntheses of Komaroviquinone

With its complex molecular structures and interesting biological activity, this molecule became a popular target for the synthetic community. Within two years after the isolation of (+)-komaroviquinone **1**, two groups reported their synthetic studies toward this natural structure.¹⁴ Padwa and co-workers achieved an efficient construction of the core structure of komaroviquinone in their study of rhodium-catalyzed cyclization/cycloaddition cascade of an *ortho*-carbomethoxyaryl diazodione.¹⁵

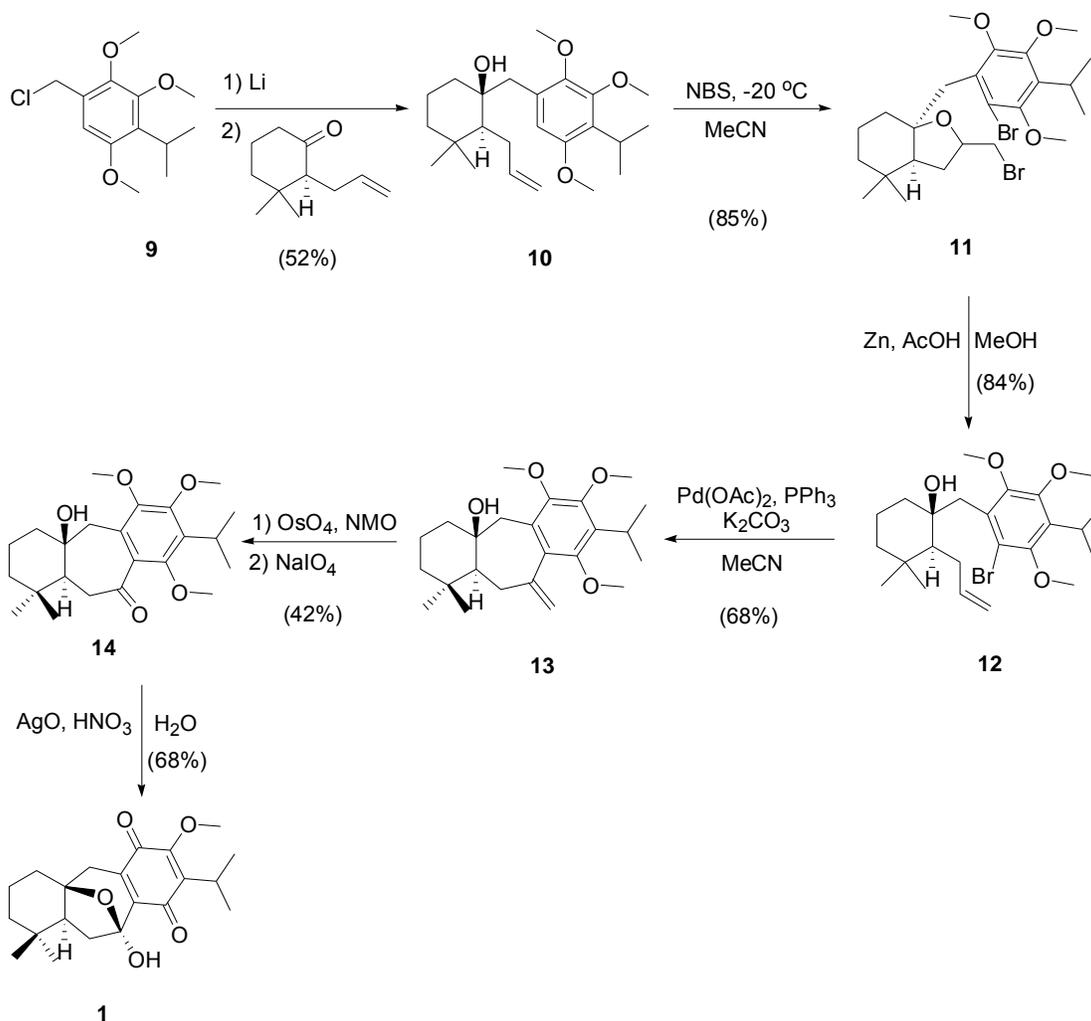
As shown in Scheme 3, Padwa and co-workers started their study using a protocol developed by Holmquist and Roskamp,^{16,17} which converts aldehydes into β -ketone esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride, to make the diketone **5** from **4** in moderate yield. Diazodione **6** was obtained when diketone **5** was treated with nosyl azide and triethylamine under Regitz diazo transfer reaction conditions.¹⁸ Treating a sample of **6** with $\text{Rh}_2(\text{OAc})_4$ in benzene at 80 °C afforded cycloadduct **8** in 75% yield. This reaction mechanism is believed to first produce carbonyl ylide dipole **i**, followed by an intramolecular [3+2]-cycloaddition. Epoxide **7** was isolated when the reaction went at room temperature, and it could also be transformed to **8** upon heating. The Rh(II)-catalyzed intramolecular dipolar cycloaddition efficiently constructs the icetexane core. However, this strategy requires the preparation of a highly substituted aromatic system which led to difficulties. Efforts are still underway to solve this problem.



Scheme 3

Soon after, Banerjee and co-workers reported their synthesis of (\pm)-komaroviquinone (**1**)¹⁹ which featured an intramolecular Heck reaction. Scheme 4 summarizes their synthetic route. Benzyl chloride **9** was prepared and converted into an organolithium reagent and coupled with ketone to give tertiary alcohol **10**. Bromonium ion activation of the terminal alkene, followed by an intramolecular attack by the hydroxyl group, together with an undesired aromatic bromination gave dibromide **11** with 85% yield. Zinc-mediated debromination fragmentation of **11** produced **12** with high yield.²⁰ An intramolecular Heck reaction gave a moderate yield of tricyclic skeleton

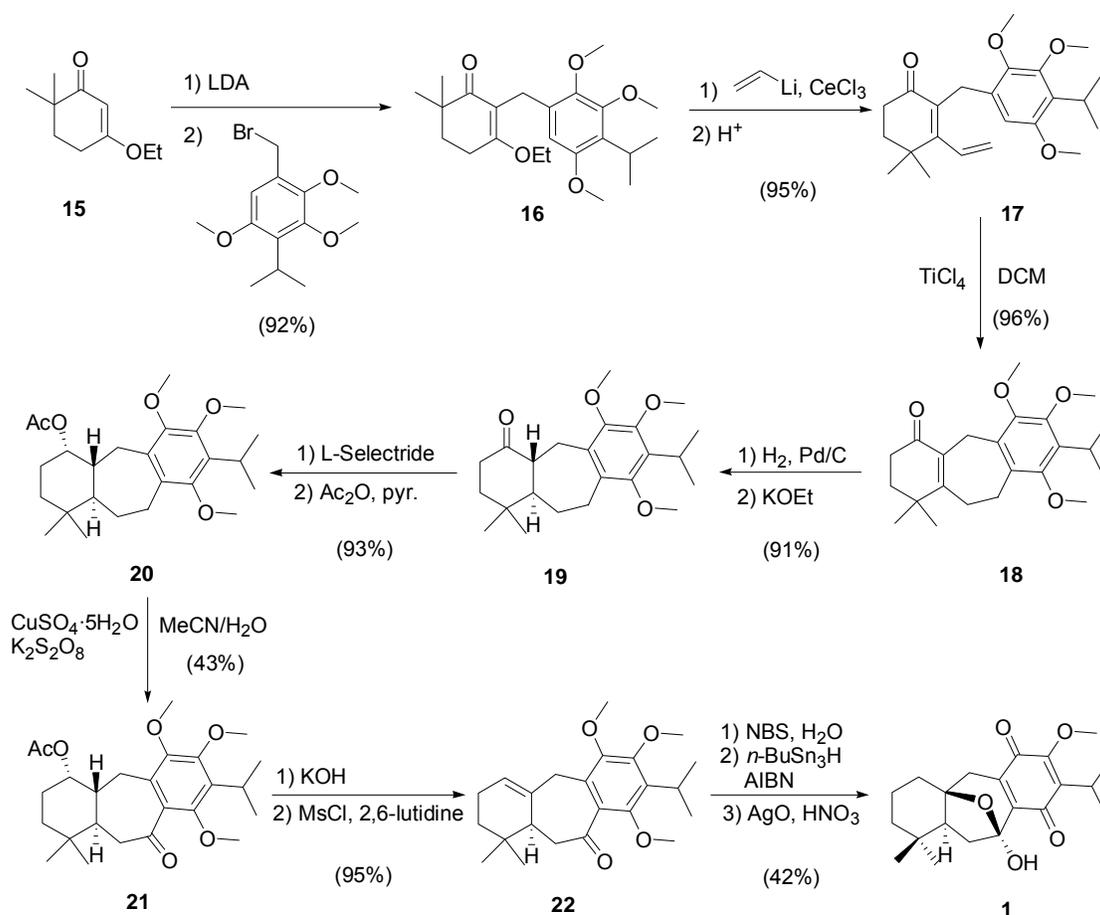
13 from **12**. A standard two-step process to cleave the exocyclic alkene²¹ furnished 42% of ketone alcohol **14** from **13**. The oxidation of hydroquinone **14** was achieved using Ag(II)O²² in dilute HNO₃ producing (±)-komaroviquinone (**1**) in 68% yield.



Scheme 4

Almost at the same time, Majetich and co-workers reported a racemic synthesis of (±)-komaroviquinone (**1**).²³ Their synthesis started with the coupling of the enol ether **15** with a

benzyl bromide. Vinyl lithium produced conjugated dienone **17** which upon treatment with TiCl_4 gave **18** in 96% yields. The biggest obstacle they had to overcome was the selective benzylic oxidation of **18**. Finally, thanks to Yang Li's perseverance, treatment of the acetate **20** with CuSO_4 and $\text{K}_2\text{S}_2\text{O}_8$ produced ketone **21**. The remaining steps of the synthesis were straight forward: hydrolysis, followed by dehydration, gave **22**. Formation of the bromohydrin, followed by dehalogenation, gave the same intermediate as Banerjee's route, and oxidation with the silver salt gave the final natural product.

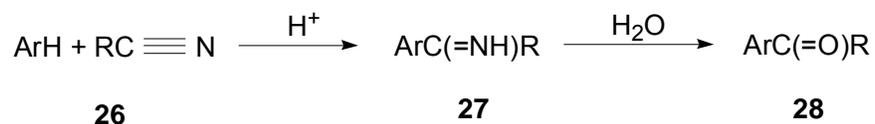


Scheme 5

3. Results and Discussion

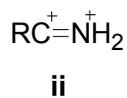
After the completion of our racemic synthesis, we sought to synthesize optically active (+)-komaroviquinone (**1**). In our racemic synthesis we used hydrogenation to install the C(5) hydrogen. We were curious if the C(5) chiral center of alkene **19** could be introduced by an asymmetric hydrogenation of enone **18**. Transition metal complexes, such as Rh, Ru and Ir, with chiral dentates, can hydrogenate enones enantioselectively.²⁴ However, for the asymmetric hydrogenation of hindered enones, high pressures are typically required. Since the special high-pressure apparatus needed for this kind of hydrogenation was not available, we focused on alternative methods.

In our syntheses of (+)-perovskone and (+)-salvadione-A,²⁵ we used functionalized enone **23** to introduce the asymmetric C(5) methine by means of a two-step procedure. Application of a Corey asymmetric reduction, followed by the Myers Mitsunobu-type rearrangement,^{26,27} would produce **25** (Scheme 6). Further transformation of **25** to **22** would permit a total synthesis via three known steps.



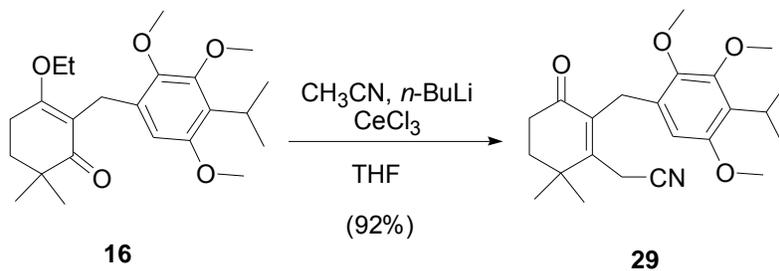
Scheme 7

The mechanism for this reaction is still not well-established. Shudo and co-workers proposed that a dication intermediate is critical for this reaction to take place (Scheme 8) which requires strongly acidic conditions.



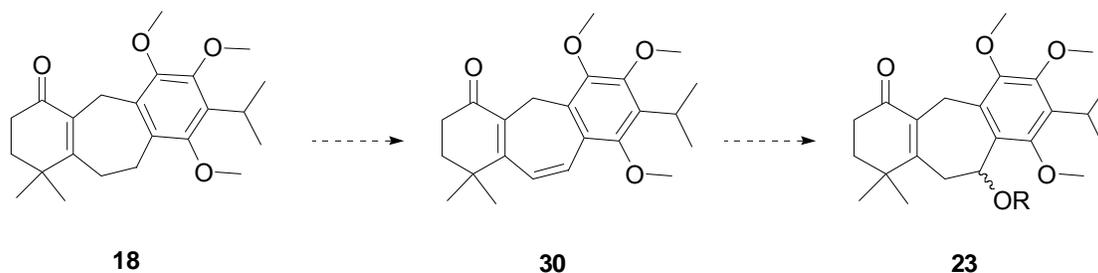
Scheme 8

Treatment of acetonitrile with *n*-BuLi formed the carbanion, which when mixed with ketone **16** gave the nitrile compound **29** in 92% percent yield (Scheme 9). The ring closing step turned out to be very difficult due to the low reactivity of the nitrile group. Under the different conditions tried, it either gave no reaction when using weak Lewis acids or decomposition of the starting material when strong acids were applied.



Scheme 9

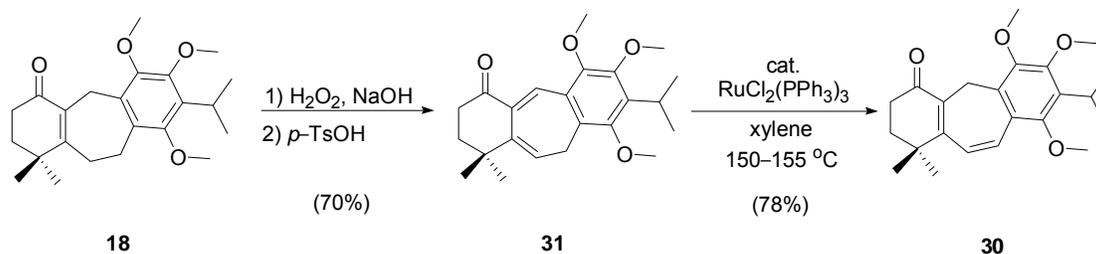
We next tried to extend the conjugation of enone **18** to produce dienone **30** (Scheme 10). We fully expected to be able to differentiate the two double bonds presented in the molecule and selectively introduce an oxygenated functionality at the C(7) position. Once we prepared ketone **23**, we would be able to make (+)-komaroviquinone (**1**) using chemistry already familiar to our research group.



Scheme 10

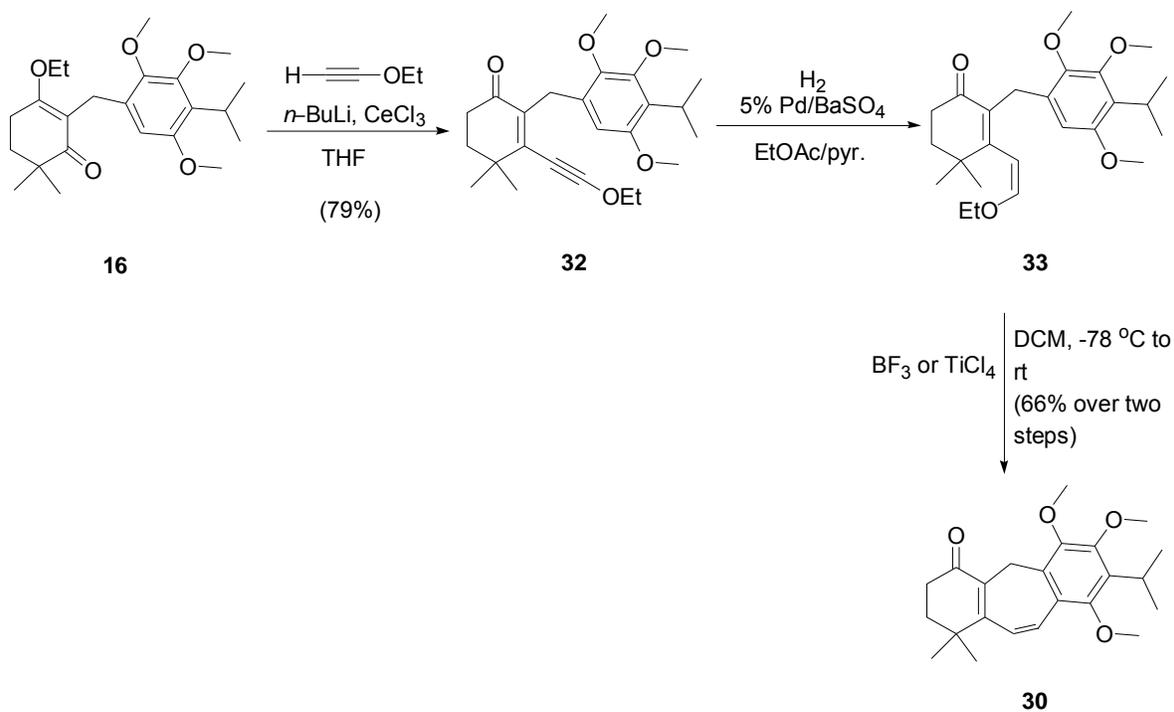
Three routes were used to make the dienone **30**. The first route is shown in Scheme 11. We found that by stirring enone **18** with 30% aqueous hydrogen peroxide and 6 M aqueous NaOH, epoxidation took place over three days. Treatment of this epoxide with *para*-toluenesulfonic acid in refluxing dichloromethane for three days gave diene **31**. Rearrangement of diene **31** to **30**

was accomplished by using $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ in refluxing xylene. This route took advantage of the availability of cyclized product **18**, but it required three extra steps and suffered from the long reaction times required for the first two steps.



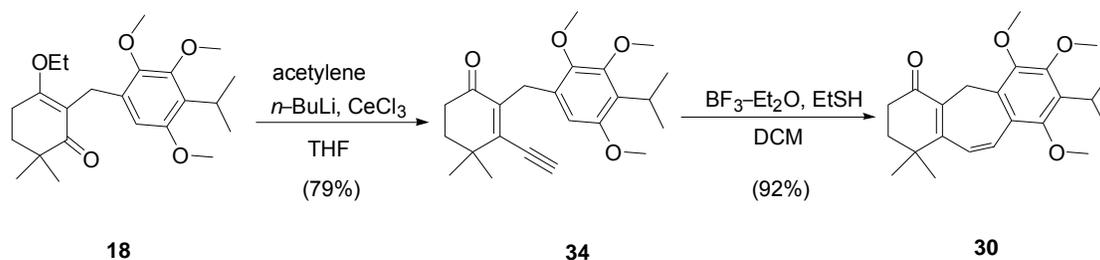
Scheme 11

A new cyclialkylation strategy was developed in order to prepare dienone **30** more efficiently (Scheme 12). Addition of Aren's reagent to **16**, followed by the Lindlar reduction of the alkyne gave dienone **33**. Lewis acid-catalyzed Friedel-Crafts reaction gave the dienone **30** in 52% overall yield.



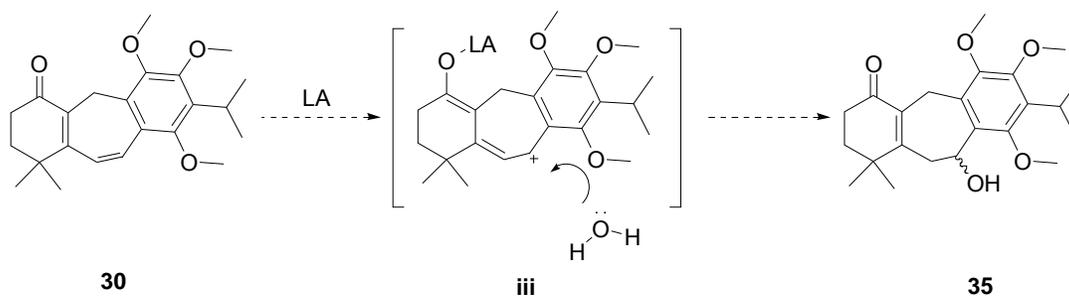
Scheme 12

Unfortunately, Aren's reagent is expensive and was difficult to prepare. Hence, a more cost-efficient route was developed. Instead of using Aren's reagent, we prepared the lithium acetylide and used it as the nucleophile. Treatment with Lewis acid in the presence of ethanethiol gave **30** in high yield (Scheme 13).



Scheme 13

With dienone **30** in hand, we tried several ways to introduce the oxygen at the C(7) position. Based on the structure of **30**, we assumed that in at least one conformation the C(6), C(7)–double bond would be in conjugation with the C(1), C(10), C(5)–system. We hoped that treatment of **30** with a strong Lewis acid would form a carbocation at the C(7) benzylic position which would be trapped by water to give us benzylic alcohol **35** (Scheme 14).³² However, under the various conditions tried, we always observed no reaction. In hindsight, a model of dieneone **30** caused us to realize that the C(6), C(7)–double bond is not planar with the C(1), C(10), C(5)–conjugated system; thus the energy barrier to form enol **iii** is very high.

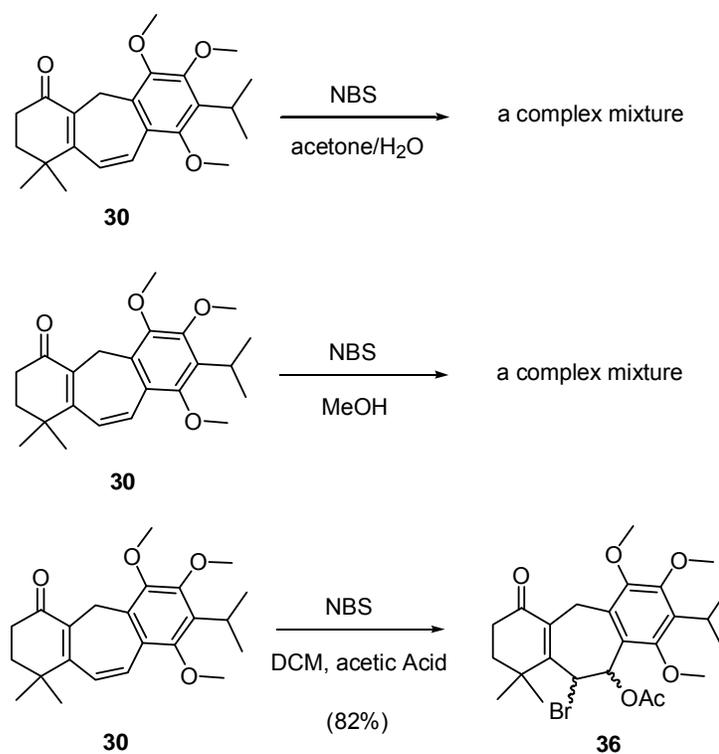


Scheme 14

We then turned to a reaction I studied extensively during my first few months in the Majetich research group. In particular, we wondered if bromohydrin formation be selective for the C(10), C(5)–tetrasubstituted double bond or would the C(6), (7)–disubstituted double bond react? We predicted that the styrenyl double bond should be more reactive toward NBS because it is next to the electron–rich aromatic ring while the C(10), C(5)–double bond is in conjugation with the C(1) carbonyl group which lowers its electron density and hence its reactivity. In

addition, we hoped that after the bromonium ion formation, the benzylic C(7) position would be the more electrophilic site.

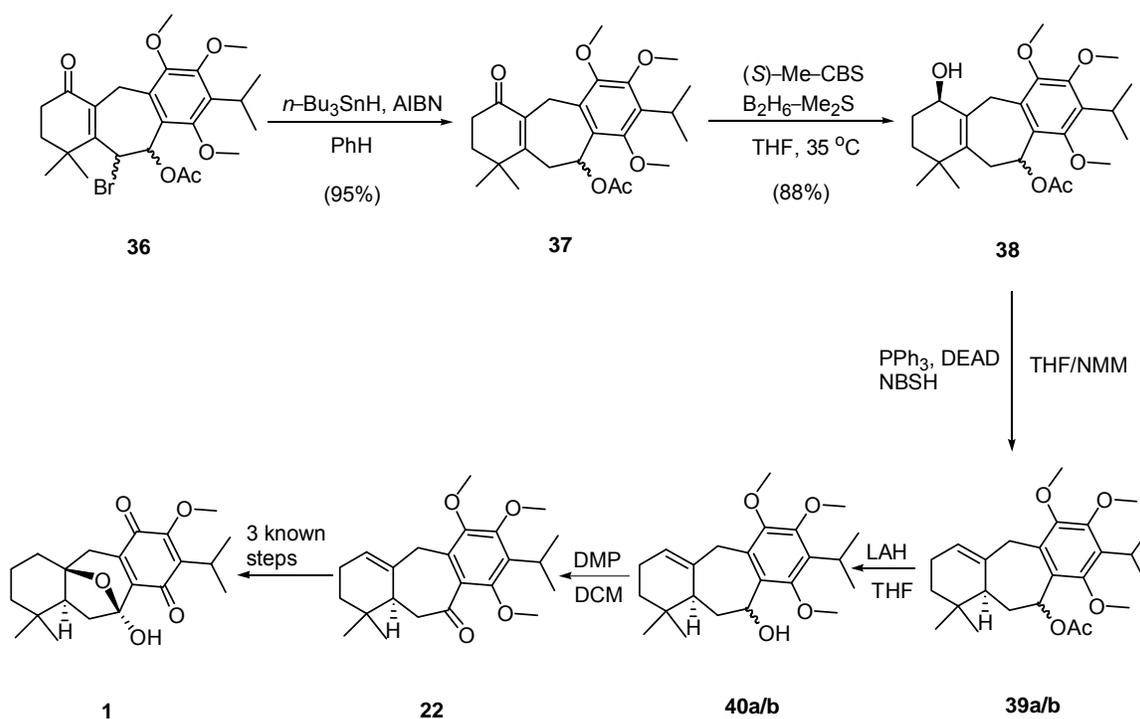
Unfortunately treatment of the diene **30** with NBS followed by the addition of water or methanol produced unknown mixtures (Scheme 15). Fortunately, when we used acetic acid as the nucleophile, bromide **36** was produced in very good yield.



Scheme 15

Removal of the bromide was achieved by treatment with tri-*n*-butyltin hydride under radical conditions (Scheme 16). We worried about the CBS reduction since the selectivity between the α,β -unsaturated ketone and the acetate group might be tricky. Luckily, by slow addition of the borane using the syringe pump, only the ketone reduced to gave two separable

diastereoisomeric allylic alcohols. We then applied Meyers' allylic transposition procedure on the two alcohols to install the desired α C-5 methine. The remaining steps were straightforward. Reduction of acetates **39a/b** with LAH gave benzylic alcohols **40a/b**. However, oxidation with Dess–Martin periodinane gave only ketone **22** in enantiomerically pure form. The application of the final three steps we developed during our racemic synthesis allowed us to complete an enantioselective synthesis of (+)-komaroviquinone.



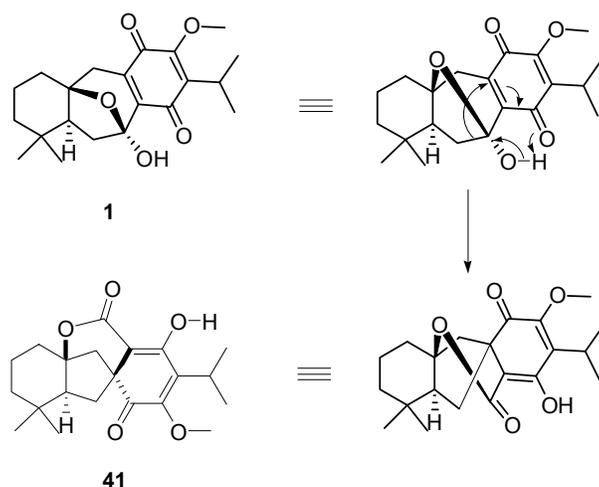
Scheme 16

4. Isolation of (+)-Komarovispirone and its Biological Activity

After we finished the synthesis of (+)-komaroviquinone, we then turned our focus to (+)-komarovispirone (Scheme 17). (+)-komarovispirone (**41**) is isolated from the same species

as (+)-komaroviquinone³³ and has moderate trypanocidal activity against epimastigote of *T. cruzi* with a minimum lethal concentration (MLC) of 23 μ M.

Based on their structural similarity, it was proposed that (+)-komarovispirone was derived from (+)-komaroviquinone via an acid-catalyzed rearrangement.³³

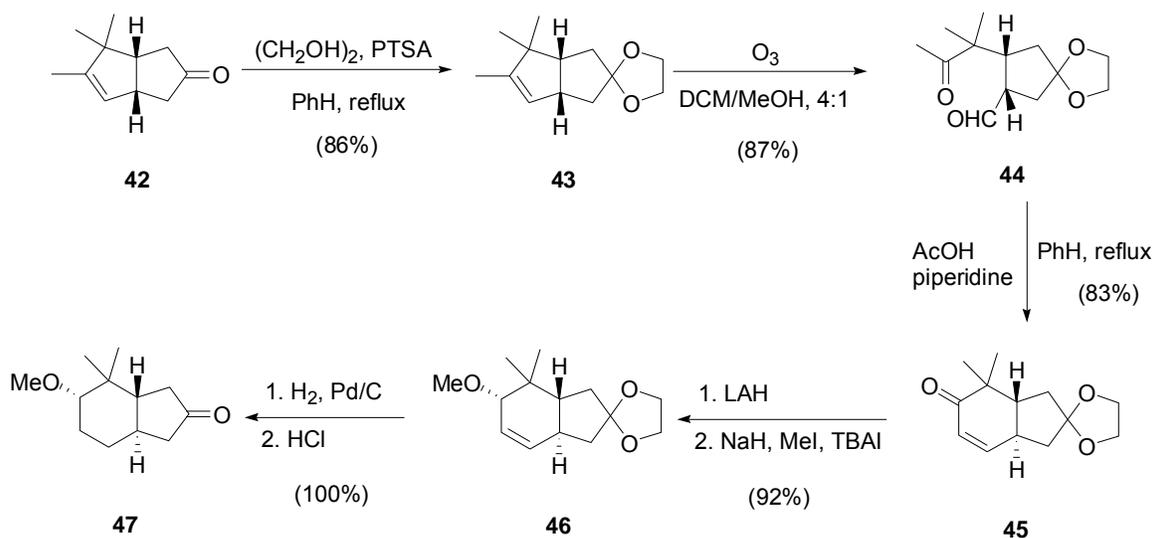


Scheme 17

5. Previous Syntheses of the Komarovispirone

The novel tricyclic structure containing an unusual cyclohexane spiro fused to a bicyclo[4.3.0]nonane carbon framework, coupled with its biological activity has made komarovispirone **41** an interesting and challenging synthetic target. To date only one approach to the komarovispirone skeleton was reported in 2007.³⁴ This synthesis commenced with bicycle **42**, which was previously prepared in their laboratory in enantiomerically pure form (Scheme 18).³⁵ Protection of the carbonyl group of **42** as a ketal was applied in order to avoid potential regiochemical problems. Ozonolysis of **43**, followed by an intramolecular aldol condensation,

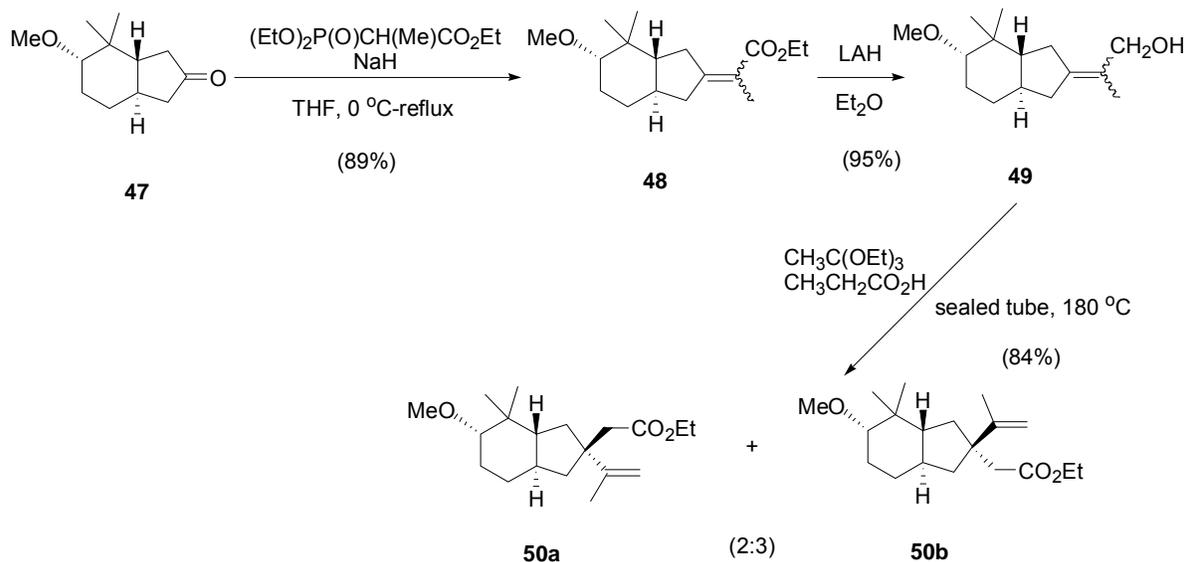
generated ring-expanded bicyclic enone **45** containing the requisite trans-ring junction. Reduction of the carbonyl group with LAH gave the alcohol in a highly regio- and stereoselective manner. Methylation of the resulting alcohol delivered allylic ether **46**. Alkene hydrogenation and ketal cleavage yielded ketone **47**.



Scheme 18

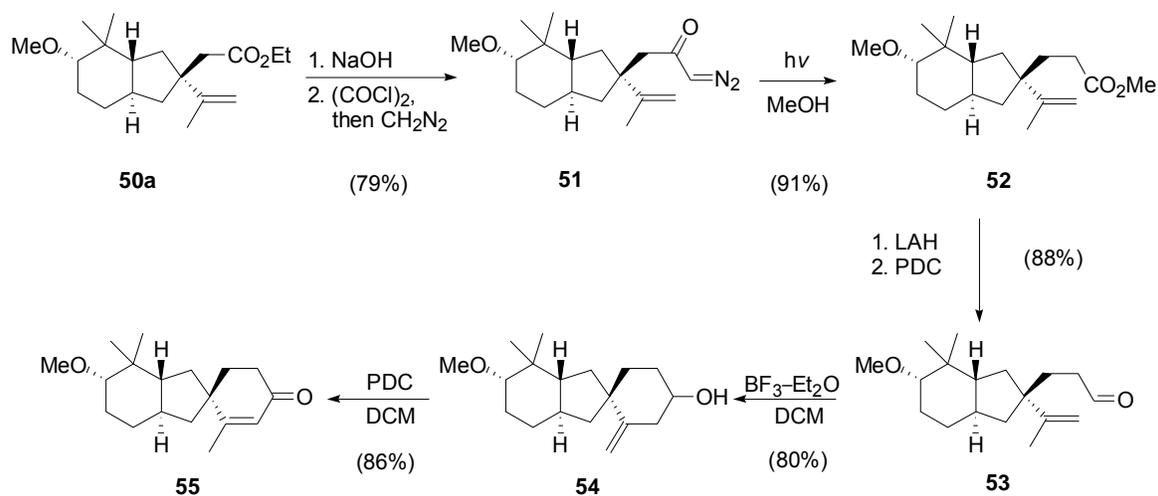
As shown in Scheme 19, a Horner–Wadsworth–Emmons reaction of ketone **47** with triethyl phosphonopropionate and sodium hydride in refluxing THF furnished an *E,Z*-mixture of the unsaturated ester **48** in 89% yield, which on regioselective reduction with LAH in ether at low temperature furnished an *E,Z*-mixture of allyl alcohol **49**. The orthoester Claisen rearrangement of the allyl alcohol **49** with triethyl orthoacetate and a catalytic amount of propionic acid at 180 °C in a sealed tube furnished a 2:3 diastereomeric mixture of esters **50a** and **50b** containing the requisite quaternary carbon atom, which were separated by column chromatography. Each of

these diastereomers was subsequently advanced to the tricyclic komarovispirone skeleton via a different strategy.



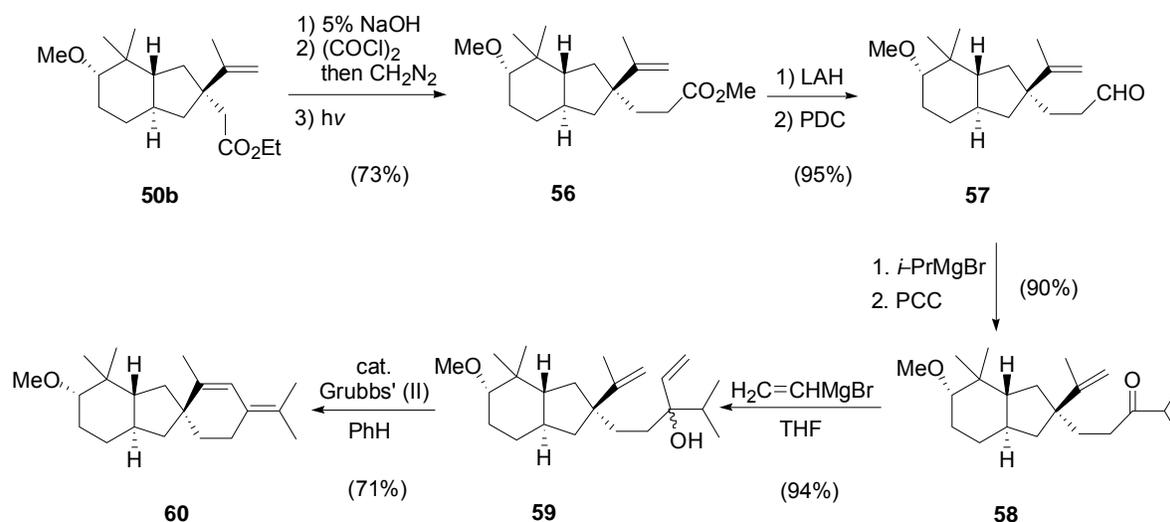
Scheme 19

In one approach, alkene **50a** was homologated to ester **52** by a classical Arndt–Eistert sequence (Scheme 20). Reduction of ester **52** to aldehyde **53** set the stage for a Lewis acid-mediated intramolecular ene cyclization, which following oxidation of the intermediate alcohol and *in situ* olefin isomerization gave tricyclic enone **54**.



Scheme 20

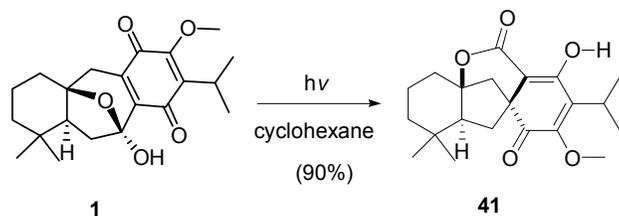
Alkene **50b** was similarly advanced in five steps to an aldehyde intermediate that underwent addition of isopropylmagnesium bromide to provide alcohol **59** (Scheme 21). Oxidation followed by addition of vinylmagnesium bromide delivered a diene that was converted to tricyclic diene **60** by ring-closing metathesis with Grubbs' second generation catalyst in refluxing benzene and subsequent dehydration.



Scheme 21

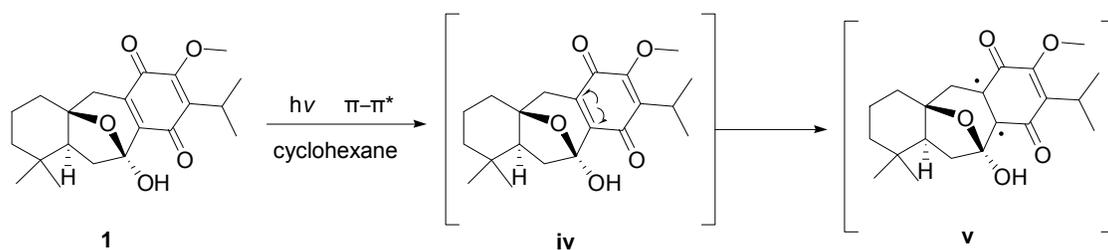
6. Results and Discussion

We doubted that (+)-komaroviquinone isomerizes into (+)-komarovispirone under acidic or basic conditions. Indeed, when using common mineral acids, trifluoroacetic acid, TEA, or DBU no isomerization occurred. At the same time, we noticed that (+)-komaroviquinone was unstable in the NMR sample. The (+)-komaroviquinone in deuterated chloroform reacted to give two major compounds after two days. After careful separation and characterization, we found one of them was the (+)-komarovispirone which suggested to us that a photochemically promoted isomerization had occurred. We then irradiated pure **1** in benzene with the low-pressure mercury lamp and found that after one hour the reaction was completed and **41** was the only product (Scheme 22). Using cyclohexane as the solvent gave a slightly better yield. In order to preclude the other possibilities, a sample of (+)-komaroviquinone in deuterated chloroform was stored in the dark for seven days, and no decomposition or isomerization was observed.



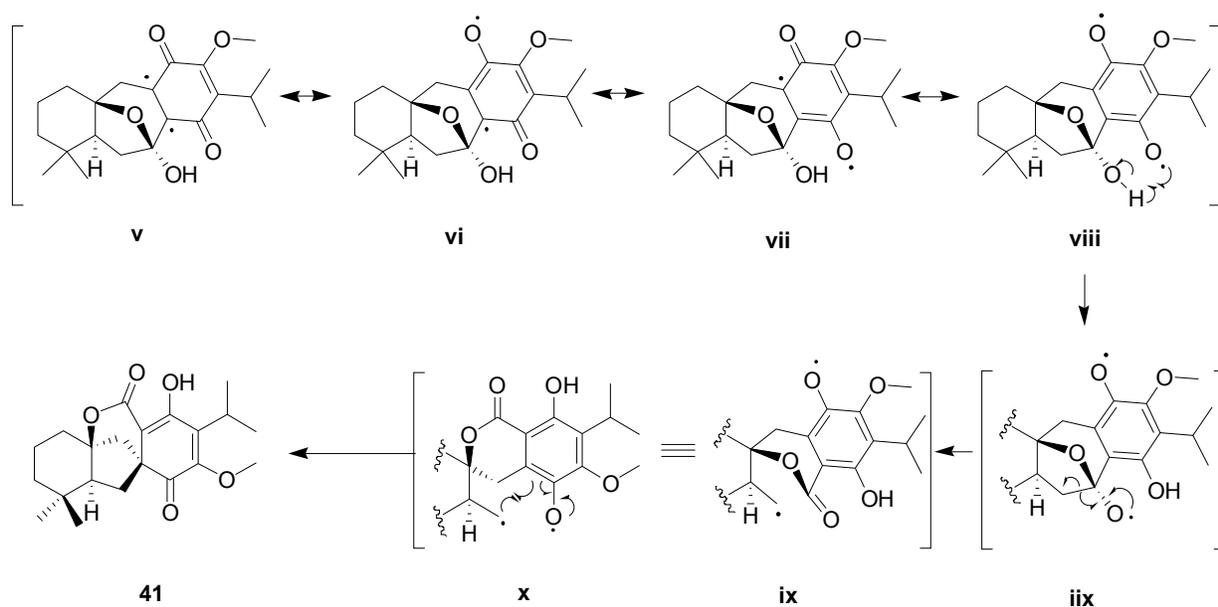
Scheme 22

Since **1** cleanly photolyzes to only **41**, we were unable to isolate, or trap, any intermediates to verify the mechanism. Based on our observations, the reaction mechanism was deduced in the following way. The first question we needed to answer is what is the first step? Is it a $\pi\text{-}\pi^*$ or $n\text{-}\pi^*$ transition? The absorption spectrum of 1,4-benzoquinone in saturated hydrocarbons normally shows bands at 240, 290 and 450 nm with ϵ approximately 20,000, 250 and 20 respectively. The first two bands are due to, respectively, ‘allowed’ and ‘forbidden’ $\pi\text{-}\pi^*$ transitions, which the third band is due to a ‘forbidden’ $n\text{-}\pi^*$ first singlet transition.³⁶ Since we used a 254 nm lamp, it is very likely that the first step is an allowed $\pi\text{-}\pi^*$ transition as shown in Scheme 23.



Scheme 23

After the formation of the diradical species **v**, it can be represented by a number of different resonance structures as shown in Scheme 24. Intramolecular hydrogen atom abstraction would yield **ix**, which would then undergo carbon–carbon bond fragmentation to generate lactone **ix**. A molecular model of **ix** reveals that the C(6) free radical is positioned directly above the sp²-hybridized C(9) carbon atom, thereby facilitating the creation of the C(6)–C(9) σ bond and the C(9) asymmetric center.



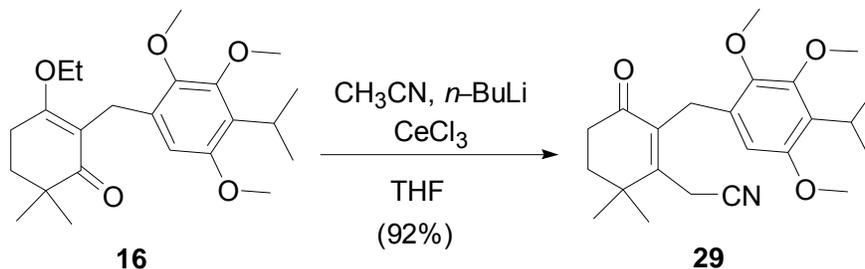
Scheme 24

Storage of komaroviquinone in deuteriochloroform in the dark for seven days at room temperature confirmed that **1** was stable under these conditions; however, exposing this same solution to daylight at room temperature for 2 days produced **41** and trace quantities of an unknown. These observations, together with our photochemically promoted isomerization of

komaroviquinone, suggest that komarovspirone is most likely an artifact of the isolation process.

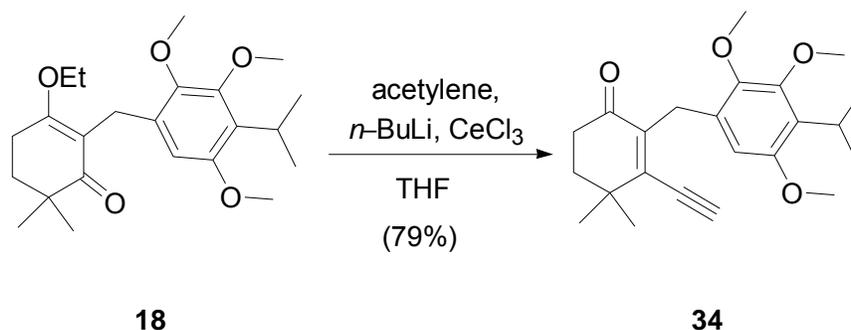
7. Experimental Section

General Procedures. All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at room temperature with water. The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was extracted with diethyl ether twice, combined organic layer was washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230–400 mesh ASTM) and elution with distilled reagent grade petroleum ether and diethyl ether. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in CDCl_3 and were calibrated using trace CHCl_3 present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in CDCl_3 and were calibrated using trace CHCl_3 present (δ 77.23) as an internal reference. The IR spectra were obtained using an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution MS were taken using a LCT Premier from Waters.



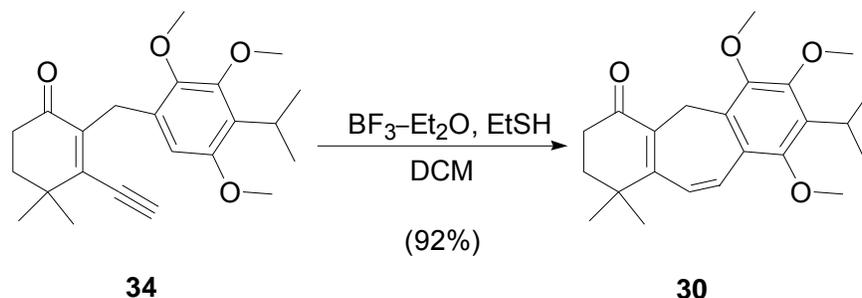
Nitrile 29 from ketone 16: To a solution of diisopropylamine (1.15 mL, 8.15 mmol) in freshly distilled THF (20 mL) at $-78\text{ }^\circ\text{C}$ was added *n*-butyllithium (3.28 mL, 1.31 mmol) over a 2-min period. The resulting mixture was stirred at rt for 5 minutes. To the above LDA solution was then added anhydrous acetonitrile (410 μL , 1.97 mmol) and anhydrous cerium chloride (50.0 mg, 0.203 mmol). The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 30 minutes. A solution of ketone **16** (790 mg, 2.03 mmol) in THF (20 mL) was cannulated into the above solution over a period of 5 minutes. The resulting mixture was allowed to warm to rt and then stirred for an additional 8 h. The reaction mixture was then cooled to $0\text{ }^\circ\text{C}$ and water (25 mL) was added slowly, followed by 6 M HCl (10 mL). After warming the resulting solution to rt, it was stirred for 1 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), gave 711 mg (92%) of nitrile **29** as a light yellow oil (hexane/EtOAc, 4:1, R_f **29** = 0.41): ^1H (400 MHz) δ 6.20 (s, 1H), 3.77 (s, 6H), 3.63 (bs, 5H), 3.42 (s, 2H), 2.52 (t, $J = 6.0$ Hz, 2H), 1.86 (t, $J = 6.0$ Hz, 2H), 1.23 (d, $J = 6.8$ Hz, 6H), 1.11 (s, 6H); ^{13}C NMR (100 MHz) δ 202.9 (s), 154.9 (s), 151.9 (s), 144.7 (s), 136.0 (s), 129.9 (s), 128.8 (s), 116.6 (s), 106.8 (d), 60.9 (q), 60.8 (q), 55.7 (q), 40.6 (s), 35.3 (t), 27.2 (t), 25.2 (d), 24.5 (t), 24.5 (q), 22.9 (t), 21.4 (q) ppm;

HRMS: $[M+H]^+$ observed = 386.2338, $[M+H]^+$ calculated = 386.2331; IR (film) λ_{\max} 2931, 2250, 1672 cm^{-1} .

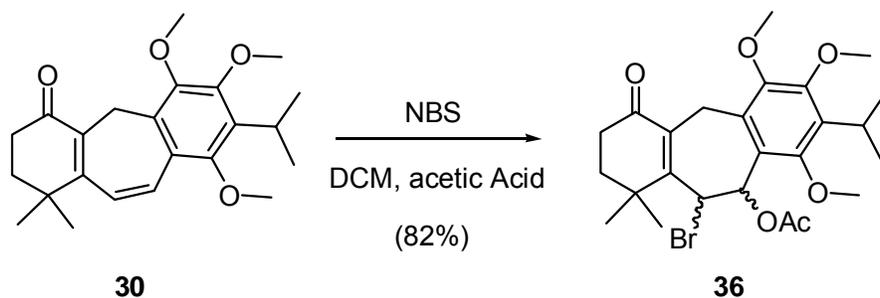


Enynone 34 from enone 18: To a solution of acetylene (4.30 mL, 114 mmol) in freshly distilled THF (40 mL) at $-78\text{ }^{\circ}\text{C}$, *n*-butyllithium (2.5 M, 41.2 mL, 104 mmol) in freshly distilled THF (100 mL) was added over a 15-min period. After stirring for 0.5 h at $-78\text{ }^{\circ}\text{C}$, enone **18** (7.70 g, 19.7 mmol) in THF (15 mL) was added slowly. The resulting mixture was allowed to warm to rt and then stirred at rt for an additional 8 h. Aqueous 1.0 M HCl (20.0 mL) was added dropwise at $0\text{ }^{\circ}\text{C}$ and the resulting mixture was stirred for 30 minutes. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 8:1), gave 2.90 g of unreacted enone **18** and 4.01 g (79%, brsm) of enynone **34** as a white solid (hexane/EtOAc, 4:1, R_f **34** = 0.45): mp = $92.0\text{--}92.9\text{ }^{\circ}\text{C}$; ^1H (400 MHz) δ 6.29 (s, 1H), 3.87 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 3.70 (s, 1H), 3.68 (s, 3H), 3.45 (septet, $J = 7.2\text{ Hz}$, 1H), 2.51 (t, $J = 6.8\text{ Hz}$, 2H), 1.93 (t, $J = 6.8\text{ Hz}$, 2H), 1.34 (s, 6H), 1.27 (d, $J = 7.2\text{ Hz}$, 6H); ^{13}C NMR (100 MHz) δ 197.3 (s), 154.3 (s), 151.9 (s), 147.1 (s), 145.5 (s), 142.0 (s), 130.1 (s), 128.3 (s), 106.5 (d), 91.9 (s), 80.7 (s), 61.0 (q), 60.5 (q), 55.7 (q),

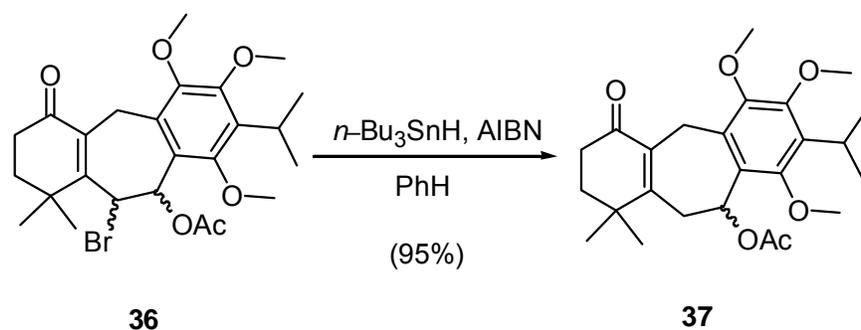
36.5 (t), 35.8 (s), 34.7 (t), 28.1 (t), 27.9 (q), 25.3 (d), 21.6 (q) ppm; HRMS: $[M+H]^+$ observed = 371.2227, $[M+H]^+$ calculated = 371.2222; IR (film) λ_{\max} 3264, 2957, 1672 cm^{-1} .



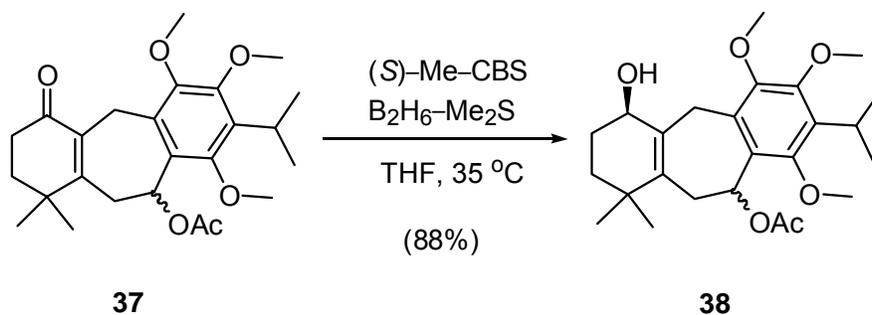
Cyclized dienone 30 from enynone 34: To a solution of **34** (4.36 g, 11.8 mmol) and ethanethiol (97%, 0.500 mL, 6.57 mmol) in freshly distilled CH_2Cl_2 (50 mL) at 0 °C was added dropwise 5.0 mL of $\text{BF}_3\text{-Et}_2\text{O}$ (40.0 mmol). The resulting mixture was stirred for 1 h at 0 °C and 72 h at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), gave 4.01 g (92%) of dienone **30** (hexane/EtOAc, 4:1, R_f **34** = 0.65) as a light yellow oil: ^1H (400 MHz) δ 7.46 (d, J = 12.4 Hz, 1H), 6.75 (d, J = 12.4 Hz, 1H), 3.91 (s, 3H), 3.86 (d, J = 23.2 Hz, 1H), 3.83 (s, 3H), 3.76 (d, J = 23.2 Hz, 1H), 3.67 (s, 3H), 3.44 (septet, J = 7.2 Hz, 1H), 2.49 (t, J = 7.2 Hz, 2H), 1.84 (t, J = 7.2 Hz, 2H), 1.33 (d, J = 7.2 Hz, 6H), 1.23 (bs, 6H); ^{13}C (100 MHz) 196.61 (s), 157.32 (s), 154.21 (s), 151.86 (s), 146.23 (s), 133.90 (d), 133.55 (s), 132.33 (s), 130.38 (s), 127.66 (d), 124.93 (s), 62.11 (q), 61.17 (q), 60.47 (q), 37.06 (t), 34.81 (s), 34.58 (t), 27.69 (q), 27.69 (q), 25.66 (d), 22.34 (t), 22.06 (q), 22.06 (q) ppm; HR-MS: $[M+H]^+$ observed = 371.2231; $[M+H]^+$ calculated = 371.2222; IR (neat): 2957, 2926, 2869, 1664, 1455, 1342, 1122, 1043, 910, 734 cm^{-1} .



Bromohydrin 36 from dienone 30: To a solution of **30** (1.00 g, 2.70 mmol) in CH₂Cl₂ (60 mL) was added acetic acid (10 mL), followed by NBS (577 mg, 3.24 mmol). The resulting mixture was stirred for 1 h at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 8:1), gave 1.13 g (82%) of bromohydrin **36** as a white solid (hexane/EtOAc, 4:1, R_f **36** = 0.35): mp: 96.9 °C turned red, 106.0–106.5 °C melted; ¹H (400 MHz) δ 6.44 (d, *J* = 5.2 Hz, 1H), 5.04 (d, *J* = 5.2 Hz, 1H), 4.82 (d, *J* = 17.6 Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 3.69 (d, *J* = 17.2 Hz, 1H), 3.67 (s, 3H), 3.31 (septet, *J* = 6.8 Hz, 1H), 2.52 (m, 2H), 2.02 (s, 3H), 1.93 (m, 1H), 1.86 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.35 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H); ¹³C NMR (100 MHz) δ 197.6 (s), 170.4 (s), 157.5 (s), 154.2 (s), 154.2 (s), 147.9 (s), 138.1 (s), 133.5 (s), 129.9 (s), 123.0 (s), 71.1 (d), 62.6 (q), 60.5 (q), 60.4 (q), 43.8 (d), 37.5 (t), 37.3 (s), 34.3 (t), 28.0 (q), 26.4 (d), 25.5 (q), 22.1 (q), 22.1 (q), 21.7 (t), 21.5 (q) ppm; HRMS: [M+H]⁺_{observed} = 509.1529, [M+H]⁺_{calculated} = 509.1539; IR (film) λ_{max} 2963, 1739, 1223, 1038 cm⁻¹.

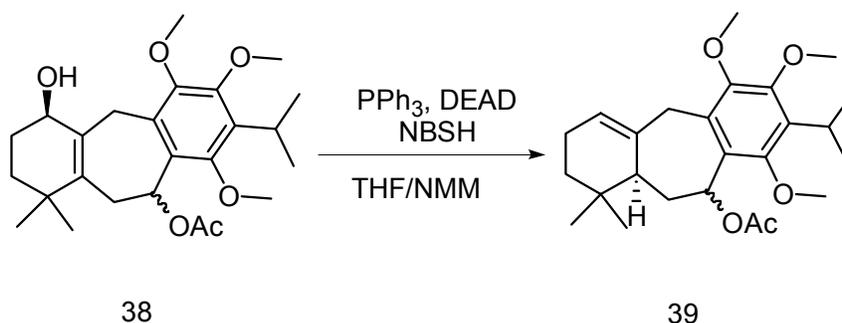


Enone 37 from debromination of 36: To a solution of bromide **36** (859 mg, 1.69 mmol) in anhydrous benzene (20 mL) under nitrogen atmosphere were added tri-*n*-butyltin hydride (*n*-Bu₃SnH) (1.20 mL, 4.46 mmol) and azo-*bis*-isobutyronitrile (AIBN) (50 mg, 0.30 mmol). The resulting mixture was refluxed for 2 h. The resulting solution was concentrated using a rotary evaporator. Column chromatographic purification of the resulting residue (elution with pet ether/EtOAc, 8:1) afforded 689 mg (95%) of **37** as a white solid (hexane/EtOAc, 4:1, R_f **37** = 0.35): mp = 173.5–174.0 °C; ¹H (400 MHz) δ 6.28 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.4$ Hz, 1H), 4.37 (d, $J = 15.6$ Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 3.53 (d, $J = 16.4$ Hz, 1H), 3.30 (septet, $J = 6.8$ Hz, 1H), 3.03 (dd, $J_1 = 8.8$ Hz, $J_2 = 15.2$ Hz, 1H), 2.89 (dd, $J_1 = 5.2$ Hz, $J_2 = 14.8$ Hz, 1H), 2.47 (m, 2H), 2.01 (s, 3H), 1.83 (m, 2H), 1.32 (d, 3H), 1.29 (d, 3H), 1.21 (s, 3H), 1.18 (s, 3H); ¹³C NMR (100 MHz) δ 196.8 (s), 170.8 (s), 161.7 (s), 153.7 (s), 153.7 (s), 147.6 (s), 136.9 (s), 133.6 (s), 132.1 (s), 124.9 (s), 67.6 (d), 62.5 (q), 60.7 (q), 60.4 (q), 37.1 (t), 36.2 (s), 34.4 (t), 33.9 (t), 27.5 (q), 26.2 (d), 25.6 (q), 22.2 (q), 22.1 (q), 21.7 (q), 20.6 (t) ppm; HRMS: $[M+H]^+$ observed = 509.1529, $[M+H]^+$ calculated = 509.1539; IR (film) λ_{max} 2963, 1739, 1223, 1038 cm⁻¹.



Allylic alcohol 38 from CBS reduction of 37: (*S*)-Methyl-CBS-oxazaborolidine (1.0 M, 1.35 mL, 1.35 mmol) and borane methyl sulfide complex (0.65 mL, 6.7 mmol) were dissolved in freshly distilled anhydrous THF (50 mL). Enone **37** (2.90 g, 6.70 mmol) in anhydrous THF (25 mL) was added using a syringe pump over a period of 2 h at rt. The resulting mixture was stirred for 4 h at rt and then cooled to 0 °C. Cold methanol (25 mL) was added dropwise to destroy excess hydride. Standard ethereal workup and chromatography (elution with pet ether/EtOAc, 8:1) afforded 1.30 g (45%) **38a** as a colorless oil (hexane/EtOAc, 2:1, R_f **38a** = 0.50): $[\alpha]^{24} = -40.0^\circ$ ($c = 0.018\text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 6.20 (dd, $J_1 = 6.4\text{ Hz}$, $J_2 = 9.2\text{ Hz}$, 1H), 4.09 (bs, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.66 (d, $J = 3.6\text{ Hz}$, 2H), 3.61 (s, 3H), 3.31 (septet, $J = 7.2\text{ Hz}$, 1H), 2.79 (dd, $J_1 = 7.2\text{ Hz}$, $J_2 = 14.4\text{ Hz}$, 1H), 2.73 (dd, $J_1 = 6.0\text{ Hz}$, $J_2 = 14.4\text{ Hz}$, 1H), 2.07 (s, 3H), 1.86 (m, 1H), 1.71 (m, 1H), 1.56 (m, 1H), 1.41 (m, 1H), 1.34 (d, $J = 7.2\text{ Hz}$, 3H), 1.29 (d, $J = 7.2\text{ Hz}$, 3H), 1.10 (s, 3H), 1.00 (s, 3H); HRMS: $[\text{M}+\text{Na}]^+$ observed = 455.2412, $[\text{M}+\text{H}]^+$ calculated = 455.2412; IR (film) λ_{max} 2936, 1732, 1239, 1040 cm^{-1} . and 1.20 g (43%). Continued elution afforded 1.20 g (43%) **38b** as colorless oil (hexane/EtOAc, 2:1, R_f **38b** = 0.35): $[\alpha]^{24} = +29.3^\circ$ ($c = 0.013\text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 6.15 (dd, $J_1 = 5.6\text{ Hz}$, $J_2 = 9.6\text{ Hz}$, 1H), 4.03 (bs, 1H), 3.87 (s, 3H), 3.78 (d, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 3.54 (d, $J = 14.4\text{ Hz}$, 1H), 3.28 (septet, $J =$

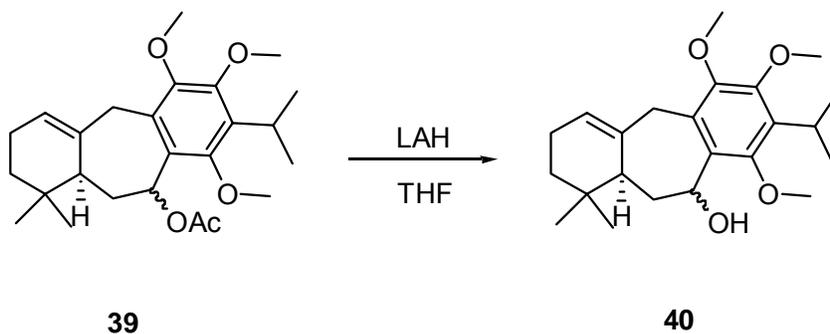
7.2 Hz, 1H), 2.82 (dd, $J_1 = 9.6$ Hz, $J_2 = 14.0$ Hz, 1H), 2.69 (dd, $J_1 = 5.6$ Hz, $J_2 = 14.8$ Hz, 1H), 2.04 (s, 3H), 1.84 (m, 1H), 1.61 (m, 2H), 1.36 (m, 1H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz) δ 170.8 (s), 154.5 (s), 153.2 (s), 147.0 (s), 140.0 (s), 138.2 (s), 133.3 (s), 133.0 (s), 125.4 (s), 69.2 (d), 68.2 (d), 62.2 (q), 60.6 (q), 60.4 (q), 35.0 (t), 35.0 (s), 31.7 (t), 29.4 (t), 27.5 (q), 27.4 (q), 26.2 (d), 26.1 (t), 22.2 (q), 22.1 (q), 21.7(q) ppm; IR (film) λ_{max} 2937, 1731, 1239, 1040 cm^{-1} . (Note: In this step, we separated the diastereoisomers having different stereochemistry at the benzylic position. For convenience we simply labeled the less polar alcohol as **38a** and the more polar alcohol as **38b**. The absolute stereochemistry of these compounds were not determined since this stereocenter would be removed at a later stage. For the next two steps, **39a** and **40a** simply mean that these compounds were derived from **38a**).



Diene 39 from allylic alcohol 38: Triphenylphosphine (2.20 g, 8.4 mmol) was dissolved in anhydrous *N*-methyl morpholine (NMM) (6.00 mL) at -30 °C. Diethylazodicarboxylate (DEAD) (1.20 mL, 7.60 mmol) was added dropwise. The orange color of DEAD faded immediately after each drop of reagent was added to the solution. After 10 minutes a viscous yellow solution was

formed. A solution of optically active allylic alcohol **38a** (1.10 g, 2.54 mmol), dissolved in freshly distilled THF (6 mL), was added dropwise and the resulting mixture was stirred at $-30\text{ }^{\circ}\text{C}$ for 30 minutes. The reaction mixture was allowed to warm to $-15\text{ }^{\circ}\text{C}$ over a 30-min period. Solids began to form at $-15\text{ }^{\circ}\text{C}$ and soon the entire reaction mixture was solidified. This solid was vigorously shaken by hand every 5 minutes for 30 minutes, and then cooled to $-30\text{ }^{\circ}\text{C}$ and *o*-nitrobenzenesulfonylhydrazine (NBSH) (1.55 g, 7.60 mmol) was added in one portion. The solid mixture “melted” upon the addition of NBSH, and a clear solution was formed within a 10-min period. The resulting solution was stirred at $-30\text{ }^{\circ}\text{C}$ for 1 h, and then the temperature was raised to $-20\text{ }^{\circ}\text{C}$ and stirred for 1 hour. After stirring at $-10\text{ }^{\circ}\text{C}$ for 1 h, the orange colored mixture was allowed to slowly warm to rt and stirred overnight. Ether (30 mL) was added to the resulting solution, followed by addition of 10 mL 5% aqueous H_2O_2 and the resulting mixture was stirred for 15 minutes. The organic layer was separated, washed with water (15 mL) and brine (15 mL). The organic phase was dried over anhydrous MgSO_4 , filtered and then concentrated using a rotary evaporator. The crude yellow solid was dissolved in 30 mL of diethyl ether and petroleum ether (10 mL) was added to precipitate out the triphenylphosphine oxide. The ethereal phase was concentrated and purified by means of flash column chromatography (elution with pet ether/EtOAc, 12:1) to afford 535 mg (75%) pure alkene **39a** as a colorless oil (hexane/EtOAc, 4:1, R_f **39a** = 0.75): $[\alpha]^{24} = +10.0^{\circ}$ ($c = 0.018\text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 6.65 (d, $J = 6.4\text{ Hz}$, 1H), 5.48 (s, 1H), 3.89 (s, 3H), 3.87 (d, $J = 14.0\text{ Hz}$, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.37 (septet, $J = 7.2\text{ Hz}$, 1H), 3.25 (d, $J = 13.2\text{ Hz}$, 1H), 2.60 (m, 1H), 2.11 (s, 3H), 1.86–2.10 (m, 2H), 1.10–1.60 (m, 4H), 1.33 (d, $J = 1.6\text{ Hz}$, 3H), 1.32 (d, $J = 2.0\text{ Hz}$, 3H), 0.96 (s,

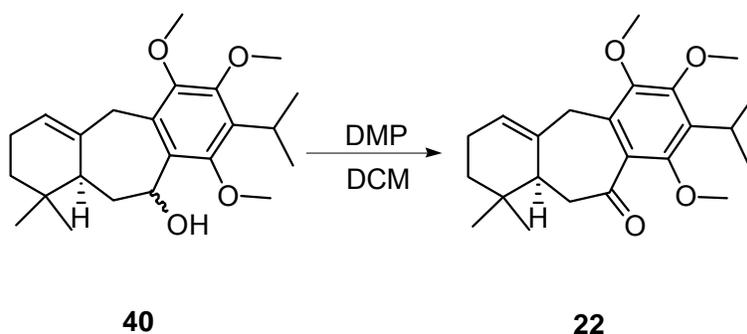
3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz) δ 170.4 (s), 153.6 (s), 152.1 (s), 146.8 (s), 138.5 (s), 135.2 (s), 132.5 (s), 126.7 (s), 122.5 (d), 69.7 (d), 63.3 (q), 60.6 (q), 60.4 (q), 46.1 (d), 34.5 (t), 33.3 (t), 32.0 (t), 31.6 (s), 27.5 (q), 26.2 (d), 23.4 (t), 22.4 (q), 22.3 (q), 22.3 (q) ppm; IR (film) λ_{max} 2955, 1734, 1238, 1034 cm^{-1} . Allylic alcohol **38b** (550 mg, 1.27 mmol) gave 370 mg (70%) **39b** (hexane/EtOAc, 4:1, R_f **39b** = 0.75): $[\alpha]^{24} = -83.6^\circ$ ($c = 0.037 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 6.47 (dd, $J_1 = 5.6 \text{ Hz}$, $J_2 = 8.8 \text{ Hz}$, 1H), 5.56 (bs, 1H), 3.91 (s, 3H), 3.77 (d, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.52 (d, $J = 14.8 \text{ Hz}$, 1H), 3.36 (septet, $J = 7.2 \text{ Hz}$, 1H), 2.56 (dd, $J_1 = 9.2 \text{ Hz}$, $J_2 = 12.0 \text{ Hz}$, 1H), 2.04 (s, 3H), 2.00 (m, 1H), 1.60 (m, 2H), 1.35 (d, $J = 2.4 \text{ Hz}$, 3H), 1.33 (d, $J = 2.8 \text{ Hz}$, 3H), 1.29 (m, 1H), 0.94 (s, 3H), 0.87 (m, 1H), 0.78 (s, 3H); ^{13}C NMR (125 MHz) δ 169.4 (s), 152.7 (s), 152.0 (s), 146.3 (s), 135.8 (s), 131.8 (s), 131.3 (s), 123.3 (s), 119.5 (d), 69.7 (d), 61.6 (q), 59.5 (q), 59.3 (q), 41.4 (d), 35.0 (t), 31.7 (t), 31.3 (t), 30.9 (s), 27.8 (q), 25.0 (d), 22.0 (t), 21.1 (q), 21.0 (q), 20.5 (q) ppm; HRMS: $[\text{M}+\text{Na}]^+$ observed = 439.2456, $[\text{M}+\text{Na}]^+$ calculated = 439.2461; IR (film) λ_{max} 2957, 1735, 1237, 1035 cm^{-1} .



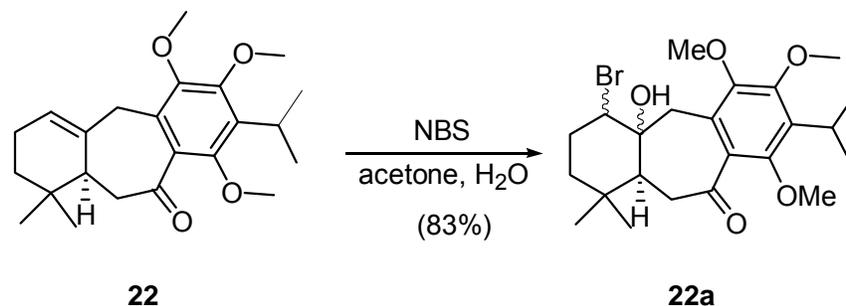
LAH reduction of acetates 39a/b to alcohol 40a/b: To a solution of acetate **39a** (100 mg, 0.24 mmol) in anhydrous THF (10 mL) at 0 °C was added LAH (11 mg, 0.29 mmol). The resulting

reaction mixture was stirred at 0 °C for 30 minutes before water was added dropwise to quench the reaction. Ethereal workup, followed by silica gel chromatography (elution with pet ether/EtOAc, 10:1), afforded 83 mg (93%) pure **40a** as a colorless oil (hexane/EtOAc, 4:1, R_f **40a** = 0.52): $[\alpha]^{24} = -59.1^\circ$ ($c = 0.016 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 5.53 (m, 1H), 5.48 (s, 1H), 3.88 (s, 3H), 3.76 (d, $J = 13.6 \text{ Hz}$, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.44 (d, $J = 14.0 \text{ Hz}$, 1H), 3.37 (septet, $J = 6.8 \text{ Hz}$, 1H), 2.35 (m, 2H), 2.00 (m, 2H), 1.35–1.55 (m, 1H), 1.34 (d, $J = 4.8 \text{ Hz}$, 3H), 1.32 (d, $J = 5.2 \text{ Hz}$, 3H), 1.16 (m, 1H), 0.98 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz) δ 152.8 (s), 151.9 (s), 147.2 (s), 138.9 (s), 133.7 (s), 132.5 (s), 130.0 (s), 121.6 (d), 67.5 (d), 63.4 (q), 60.8 (q), 60.5 (q), 44.6 (d), 36.1 (t), 34.0 (t), 31.9 (q), 31.8 (t), 27.6 (q), 27.4 (q), 26.1 (d), 23.4 (t), 22.4 (q), 22.3 (q) ppm; IR (film) λ_{max} 2954, 1734, 1456, 1340, 1042 cm^{-1} .

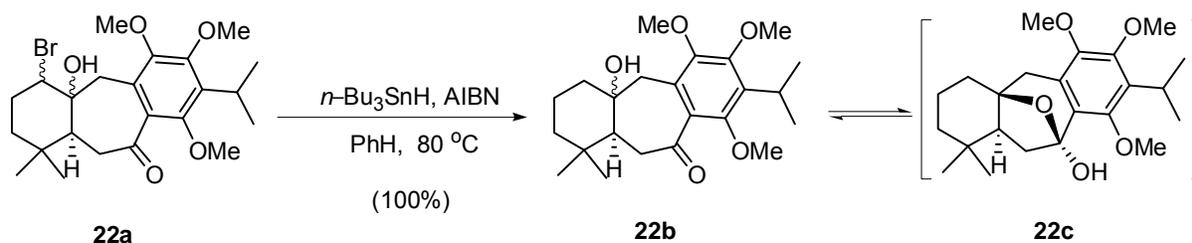
Acetate **39b** (100 mg, 0.240 mmol) gave 84 mg (93%) **40b** as a colorless oil (hexane/EtOAc, 4:1, R_f **40b** = 0.52): $[\alpha]^{24} = -31.9^\circ$ ($c = 0.016 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 5.63 (s, 1H), 5.26 (t, $J = 6.4 \text{ Hz}$, 1H), 3.89 (s, 3H), 3.74 (d, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 3.58 (d, $J = 17.6 \text{ Hz}$, 1H), 3.36 (septet, $J = 7.2 \text{ Hz}$, 1H), 2.31 (m, 1H), 2.05 (m, 2H), 1.76 (m, 2H), 1.44 (m, 1H), 1.36 (d, $J = 7.2 \text{ Hz}$, 3H), 1.32 (d, $J = 7.2 \text{ Hz}$, 3H), 0.96 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz) δ 153.1 (s), 152.7 (s), 147.8 (s), 137.6 (s), 133.4 (s), 130.9 (s), 129.1 (s), 121.5 (d), 69.8 (d), 63.1 (q), 60.6 (q), 60.5 (q), 43.3 (d), 35.2 (t), 34.8 (t), 33.3 (t), 32.2 (q), 28.6 (s), 26.3 (d), 23.4 (t), 22.3 (q), 22.2 (q) ppm; HRMS: $[\text{M}+\text{Na}]^+$ observed = 397.2352, $[\text{M}+\text{Na}]^+$ calculated = 397.2355; IR (film) λ_{max} 2956, 1453, 1120, 1037 cm^{-1} .



Ketone 22 from the oxidation of benzylic alcohols 40a/b: To a solution of alcohol **40a** (83 mg, 0.22 mmol) in DCM (5.0 mL) was added DMP (113 mg, 0.268 mmol) at 0 °C. The resulting mixture was stirred at rt for 0.5 h. Water (2.0 mL) was added slowly to quench the reaction. Ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 15:1), afforded 80 mg (98%) ketone **22** as a light yellow oil (hexane/EtOAc, 4:1, R_f **22** = 0.74): $[\alpha]^{23} = -60.0^\circ$ ($c = 0.016 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 5.70 (s, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.69 (d, $J = 14.4 \text{ Hz}$, 1H), 3.41 (d, $J = 7.2 \text{ Hz}$, 1H), 3.11 (d, $J = 14.4 \text{ Hz}$, 1H), 2.84 (dd, $J_1 = 2.4 \text{ Hz}$, $J_2 = 18.8 \text{ Hz}$, 1H), 2.40 (dd, $J_1 = 13.2 \text{ Hz}$, $J_2 = 18.8 \text{ Hz}$, 1H), 2.19 (d, $J = 13.2 \text{ Hz}$, 1H), 1.98–2.05 (m, 2H), 1.35–1.40 (m, 2H), 1.32 (d, $J = 7.2 \text{ Hz}$, 6H), 0.96 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (400 MHz) 206.53 (s), 155.26 (s), 152.57 (s), 146.10 (s), 134.96 (s), 134.06 (s), 129.59 (s), 128.27 (s), 122.48 (d), 63.31 (q), 60.84 (q), 60.55 (q), 43.17 (t), 42.65 (d), 36.46 (t), 33.50 (t), 31.74 (s), 29.12 (q), 25.58 (d), 22.95 (t), 21.89 (q), 21.79 (q), 20.70 (q) ppm; HR-MS: $[\text{M}+\text{H}]^+$ observed = 373.2384; $[\text{M}+\text{H}]^+$ calculated = 373.2379; IR (neat): 2958, 1701, 1458, 1412, 1331, 1287, 1201, 1121, 1032 cm^{-1} . Benzylic alcohol **40b** (84 mg, 0.22 mmol) gave 81 mg (97%) ketone **22**: $[\alpha]^{23} = -68.0^\circ$ ($c = 0.016 \text{ g mL}^{-1}$, CHCl_3).

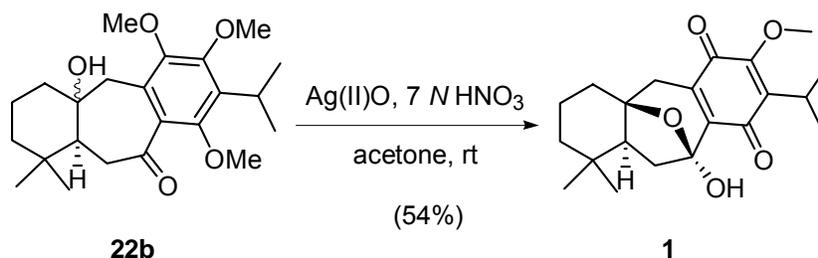


Bromohydrin from alkene 22: To a solution of alkene **22** (57.4 mg, 0.155 mmol) in acetone (10 mL) and H₂O (3 mL) was added *N*-bromosuccinimide (NBS) (35.8 mg, 0.201 mmol, 1.3 equivalents) in one portion. The resulting mixture was stirred at rt for 1.5 h and was quenched with water (5 mL). The acetone was removed under vacuum using a rotary evaporator, followed by standard ethereal workup, to give 100 mg of a crude oil. Column chromatographic purification (elution with pet ether/ether, 8:1) afforded 60 mg (83%) of bromide **22a** (hexane/EtOAc, 4:1, R_f = 0.56). ¹H NMR showed a mixture of several compounds, and it was used in the next step without an attempt to further purify it or characterize it.



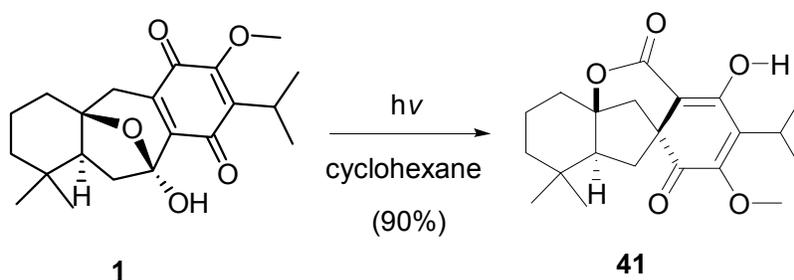
Alcohol from the photochemical reduction of bromide: To a solution of bromide **22a** (55.0 mg, 0.117 mmol) in anhydrous benzene (10 mL) under nitrogen atmosphere were added *n*-Bu₃SnH (315 μL, 1.17 mmol, 10.0 equivalents) and AIBN (9.6 mg, 0.058 mmol, 0.5 equiv).

The resulting mixture was refluxed for 2 h. The resulting dark yellow solution was concentrated under vacuum using a rotary evaporator. Column chromatographic purification (elution with pet ether/ether, 8:1) afforded 46.0 mg of a residue which contained alcohol **22b** and hemiacetal **22c** (hexane/EtOAc, 4:1, $R_f = 0.52$). The ^1H NMR showed a mixture of three compounds.



(+)-Komaroviquinone from alcohol 22b: To the crude alcohol **22b** (46.0 mg, 0.117 mmol) dissolved in acetone (8 mL) was added Ag(II)O (36.8 mg, 0.468 mmol, 4.0 equivalents) and 7 *N* HNO_3 (3 drops). The resulting mixture was stirred at rt for 5 minutes and more 7 *N* HNO_3 (three drops) was added. This operation was repeated and monitored by TLC analysis until alcohol **22b** was consumed. The resulting dark yellow solution was concentrated under vacuum using a rotary evaporator to remove the acetone, followed by standard ethereal workup. Column chromatographic purification (elution with pet ether/ether, 8:1) afforded 23 mg (54%) of (+)-komaroviquinone **1** as a light orange oil: $[\alpha]^{23} = +28.9^\circ$ ($c = 0.006 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 6.00 (s, 1H), 3.99 (s, 3H), 3.24 (septet, $J = 7.2 \text{ Hz}$, 1H), 2.55 (d, $J = 19.2 \text{ Hz}$, 1H), 2.30 (dd, $J_1 = 7.2 \text{ Hz}$, $J_2 = 13.6 \text{ Hz}$, 1H), 2.25 (d, $J = 19.6 \text{ Hz}$, 1H), 1.98–2.08 (m, 2H), 1.83–1.92 (m, 1H), 1.68–1.76 (m, 2H), 1.56–1.64 (m, 3H), 1.22 (d, $J = 0.8 \text{ Hz}$, 3H), 1.20 (d, $J = 1.2 \text{ Hz}$, 3H),

1.12–1.18 (m, 1H), 0.96 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz) 189.4, 183.8, 156.3, 142.4, 139.2, 137.3, 101.1, 79.6, 61.4, 51.7, 46.0, 39.3, 32.3, 31.5, 30.6, 30.0, 27.3, 24.6, 20.6, 20.7, 20.7, 15.9 ppm.



(+)-Komarospirone from (+)-Komaroviquinone: (+)-Komaroviquinone (6.0 mg, 0.017 mmol) was dissolved in of dry and deoxygenated cyclohexane (1 mL). The resulting solution was placed in an ACE glass microscale photochemical reactor and irradiated for 1 h at rt using a Pen-Ray, 5.5 W low pressure, cold cathode, mercury lamp. Standard ethereal workup, followed by column chromatography (elution with petroleum ether/ethyl acetate, 10:1), gave 5.4 mg (90%) of **41** (hexane/EtOAc, 4:1, R_f **41** = 0.55) as a light yellow oil: $[\alpha]^{24} = +201.0^\circ$ ($c = 0.005 \text{ g mL}^{-1}$, CHCl_3); ^1H (400 MHz) δ 13.32 (s, 1H), 3.71 (s, 3H), 3.57 (septet, $J = 7.2 \text{ Hz}$, 1H), 2.06 (d, $J = 11.6 \text{ Hz}$, 1H), 1.89–2.00 (m, 2H), 1.75 (bd, $J = 13.2 \text{ Hz}$, 1H), 1.47 (m, 1H), 1.36–1.39 (m, 7H), 1.20–1.25 (m, 3H), 0.89 (m, 1H), 0.87 (s, 3H), 0.75 (td, $J_1 = 13.6 \text{ Hz}$, $J_2 = 4.0 \text{ Hz}$, 1H), 0.53 (s, 3H); ^{13}C NMR (125 MHz) 195.3, 169.5, 160.2, 154.5, 143.4, 107.0, 91.4, 59.7, 55.3, 51.5, 43.5, 40.3, 40.2, 34.3, 33.3, 31.5, 25.9, 20.4, 20.3, 18.4 ppm.

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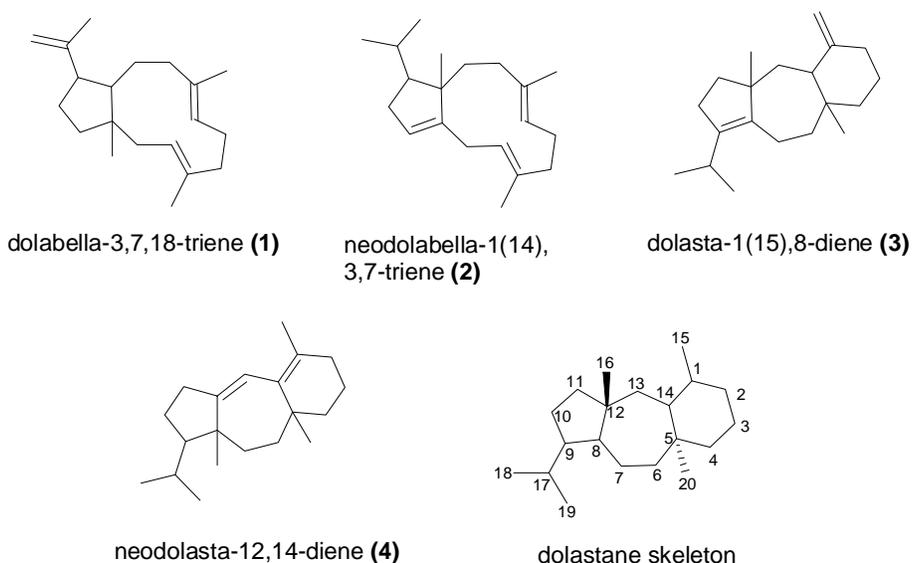
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PART II:
STUDIES TOWARD THE SYNTHESSES OF DOLASTANE NATURAL PRODUCTS

1. Dolastane Diterpenes: Isolation; Biological Activity

Fifty years ago, the diterpenoids were considered rare components of the marine environment. However, there are now over 1,900 compounds known, representing more than 125 diterpenoids.¹ Dolabellanes, neodolabellanes, dolastanes and neodolastanes are four groups of structurally related bi- or tri-cyclic diterpenes whose carbocyclic skeletons are shown in Scheme 1.



Scheme 1

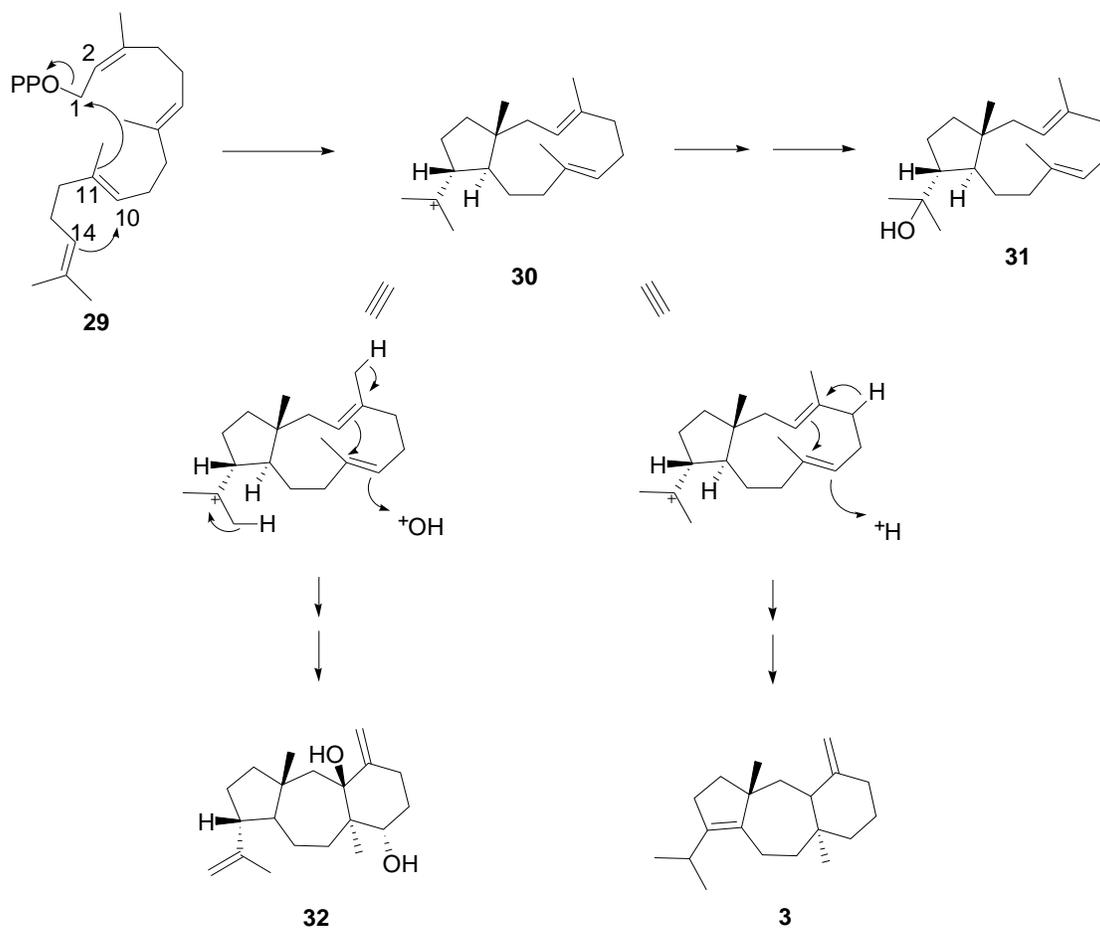
The dolastanes comprise about twenty-five known compounds **4–28**, as shown in Scheme 2. The first dolastane isolated was dolatriol **17**, which was isolated in 1976 from extracts of

digestive gland of the poisonous Indian Ocean sea hare *Dolabella auricularia*.² Further work established that this unusual diterpene was actually produced by a brown algae genus *Dictyota* and only concentrated by *Dolabella* through its diet. All the dolastanes have this distinctive 5–7–6 linear fused tricyclic framework. Their structural diversity rests on the following features: (1) the number and the position of the hydroxyl and double bonds groups; (2) the trans configuration of the two angular methyl groups at C(5) and C(12); (3) the BC–ring system is usually trans fused; and (4) the relative stereochemical configurations have been safely assigned based on X–ray crystal structure analysis and NMR studies. The absolute configuration was determined by X–ray analysis of **17** and **25**^{2,3} the c.d. data of **5**⁴, as well as by the enantioselective total synthesis of **5** and **27**^{5,6}.

Several of the dolastane diterpenes exhibit promising biological activity. For example, compound **5** has antimicrobial activity against *Mucor mucedo* and *Staphylococcus aureus*.⁷

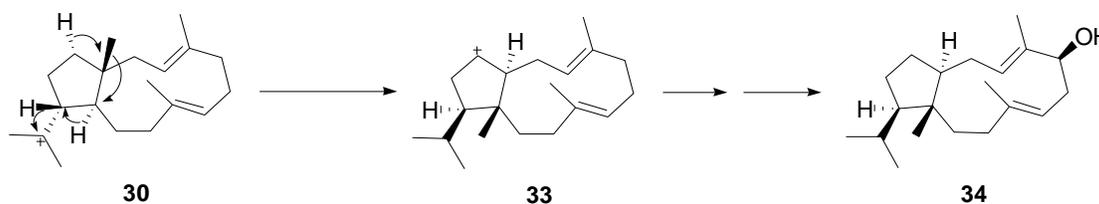
2. Biogenesis

The dolastane carbocyclic skeleton can be logically derived from geranylgeraniol **29** via the intermediacy of the bicyclic dolabelladiene ring system (Scheme 3).^{8, 9} The dolabelladiene system results from C(1)–C(11) and C(10)–C(14) cyclization of geranylgeraniol pyrophosphate **29**, in a concerted process.¹⁰ Hydroxylation or protonation of the dolabelladiene precursor **30**, followed by transannular cyclization at C(2)–C(7) generates the 5–7–6 linear fused claularane **32** or dolastane skeleton **3**, respectively.



Scheme 3

The co-occurrence of several dolastane diterpenoids and the dolabelladienol **31** from extracts of the brown alga *Dictyota dichomata* and from the herbivorous mollusk *Dolabella californica* suggests that these metabolites arise from the same biogenetic precursor **30**.^{11, 12} The co-occurrence of the clavularane **32** and the methyl-rearranged bicyclic diterpene **34** (Scheme 4) from the indo-pacific stoloniferan soft-coral *Clavularia inflate*,^{8, 9} with the structural similarity of the clavularanes and the dolastanes, lends support to the hypothesis that all of these marine metabolites arise from the same biogenetic precursor.



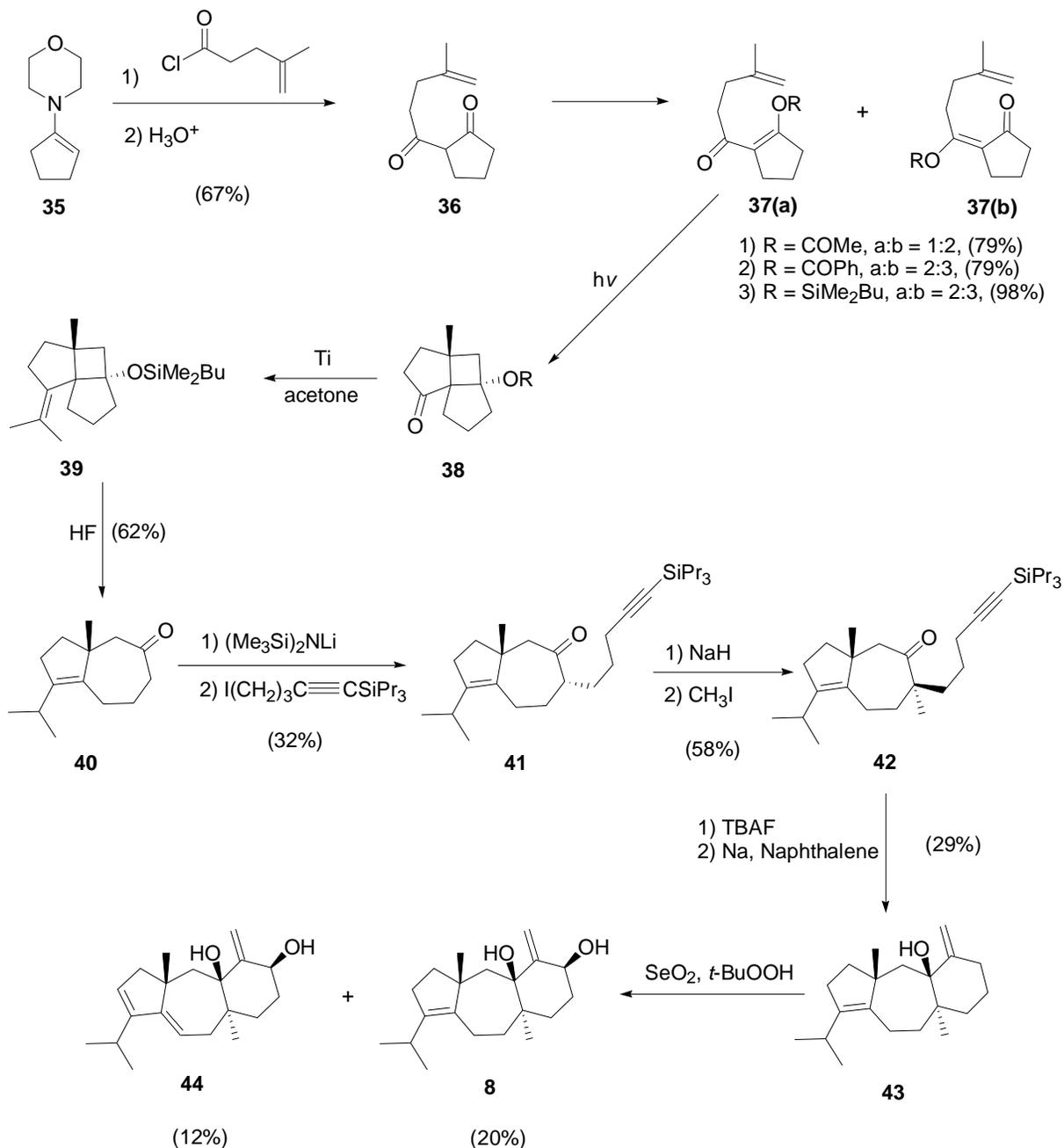
Scheme 4

3. Previous Syntheses of the Dolastanes.

Since 1983, the research group of Pattenden,^{13, 14} Paquette,¹⁵⁻¹⁷ Piers,¹⁸⁻²⁰ Mehta,^{21, 22} Majetich,^{5, 23} and Williams²⁴ have completed total syntheses of various dolastanes.

The first total synthesis of a racemic dolastane, rac-**8**, was communicated by Pattenden in 1986¹⁴ followed by a full paper in 1988.¹³ Their strategy is shown as in Scheme 5 using only seven carbon-carbon bond forming reactions. The first key step was the [2+2]-intramolecular photocycloaddition-cyclobutane fragmentation sequence to form compound **36**→**37**→**38**. A McMurray olefination was used to install the isopropyl functionality. Treatment with HF opened

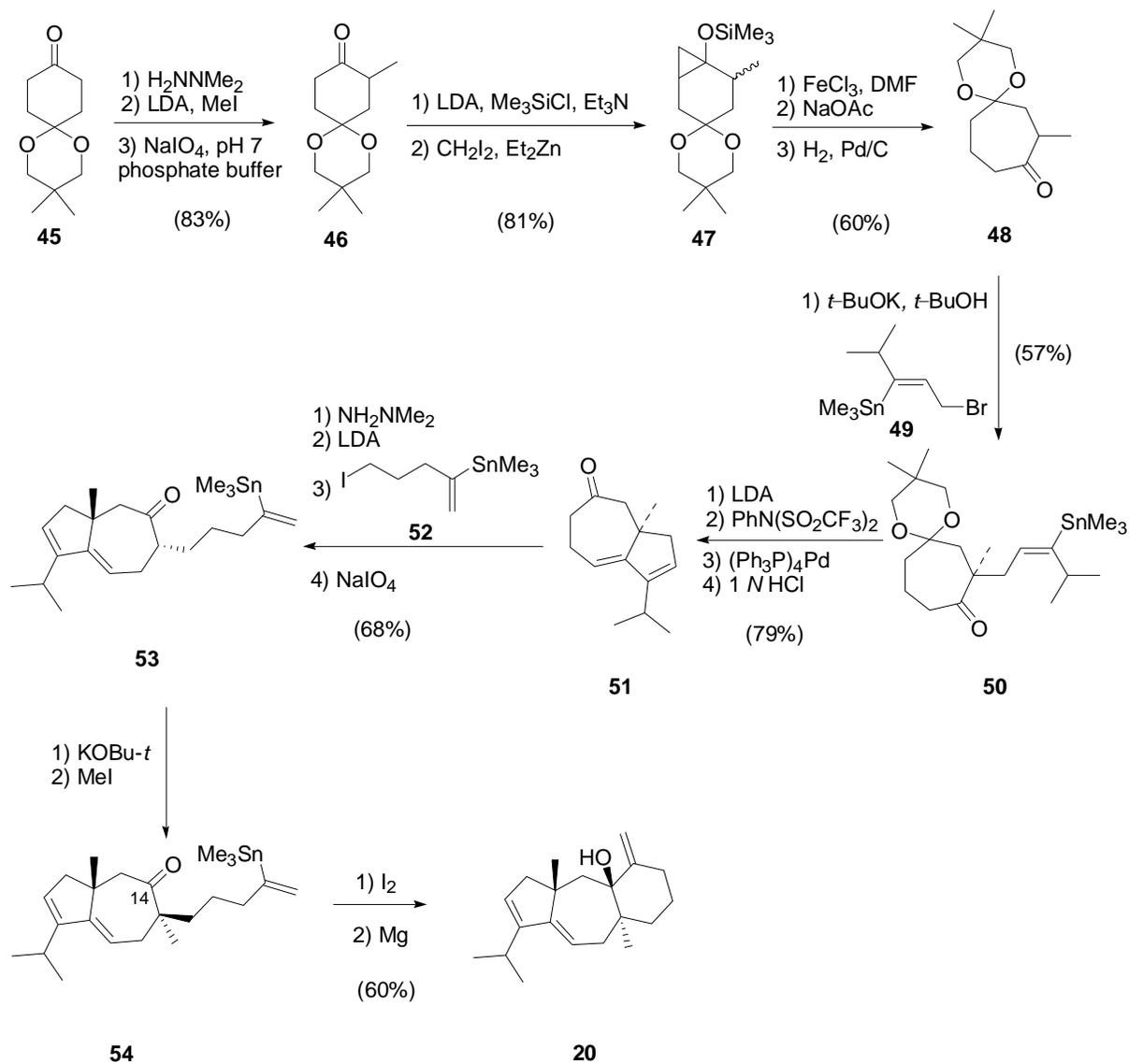
the cyclobutane ring to produce hydroazulenone **40**; alkylation of **40** gave exclusively the α -epimer of **41** due to the steric hindrance of the angular methyl group, which also controls the introduction of the C(20) angular methyl group. The final stages featured a deprotection of the silyl group, then an intramolecular reductive coupling of ketone **42** using sodium naphthalene radical anion in THF to give the methylenecyclohexane annulation products **43**. Allylic oxidation of **43** gave natural product **8**. This procedure is obviously hampered by a very low yield and the formation of the non-natural (\pm)-1(15),7,9-dolastatrien-2,14-diol (**44**). Furthermore, the separation of the two dolastanes could not be achieved by Pattenden and coworkers.



Scheme 5

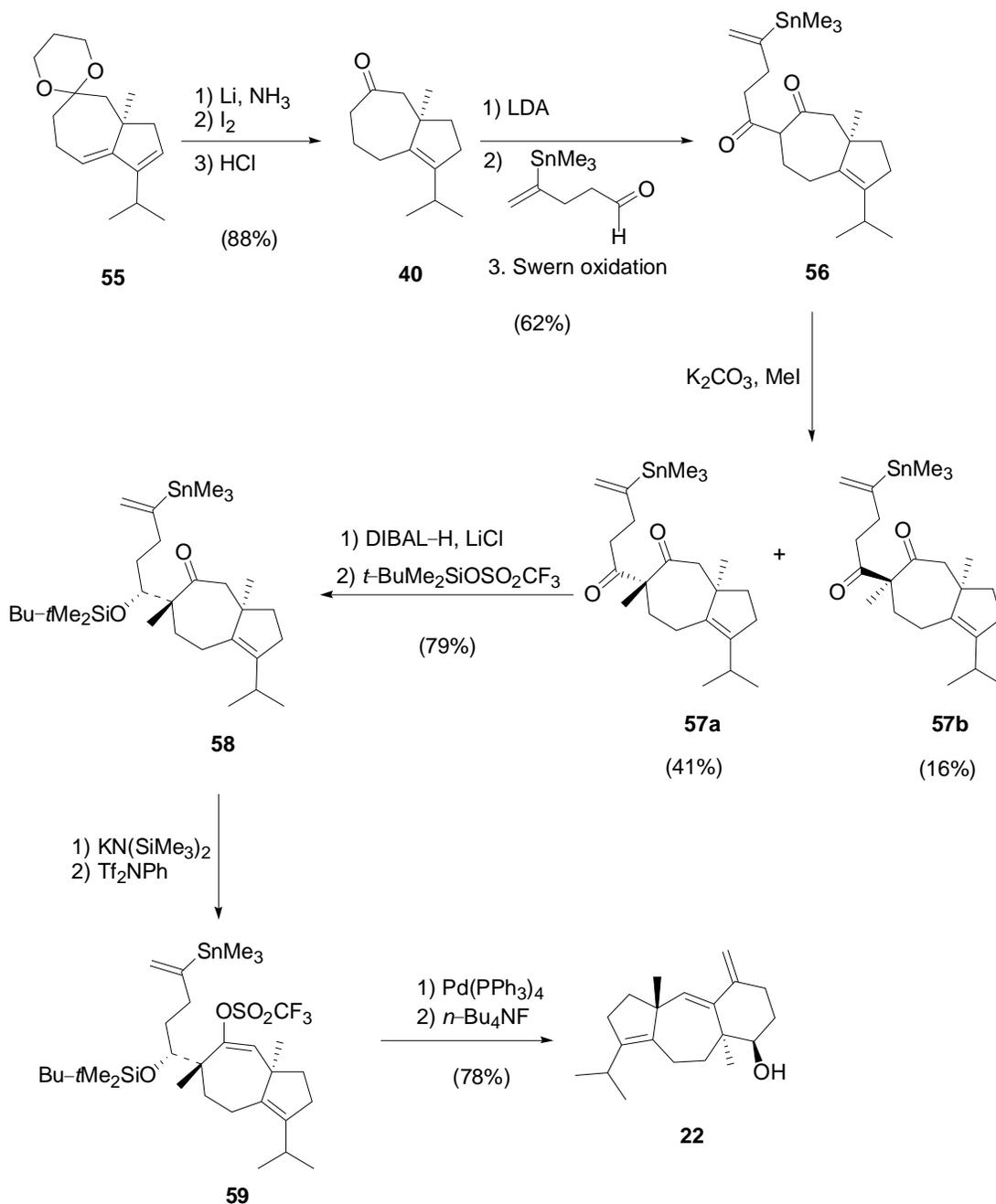
In the same year, Piers and Friesen reported the total synthesis of the natural (\pm)-1(15),7,9-dolastatrien-14-ol (\pm)**20** (Scheme 6).¹⁸ Their synthesis used an annulation pathway in which ketone **48** is alkylated with vinyltrimethylstannane **49**. Ketone **50** is converted

into the corresponding enol triflate then cyclized to yield a diene system **51**. Ketone **51** is then regioselectively alkylated with **52** to give the key intermediate **53**. Vinylstannane **53** was converted into Grignard reagent which adds to the C(14) carbonyl to yield the desired dolastane (\pm)-**20** in moderate yield as a single diastereomer.



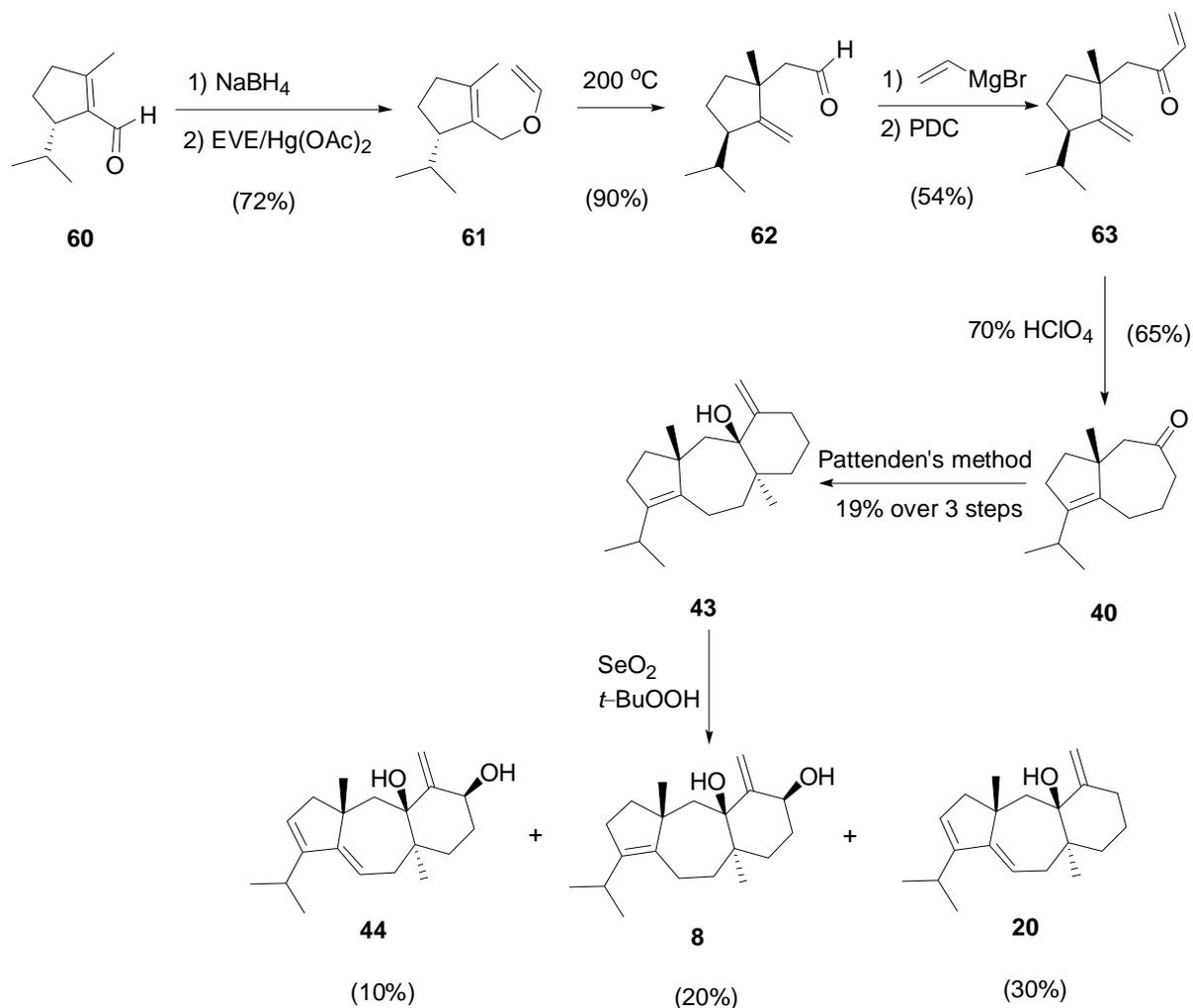
Scheme 6

Several years later, the Piers group reported the total synthesis of dolastane natural product **22** using the same key intermediate **55** as their first route (Scheme 7). However, in this synthesis they utilized a different strategy to make the C-ring.



Scheme 7

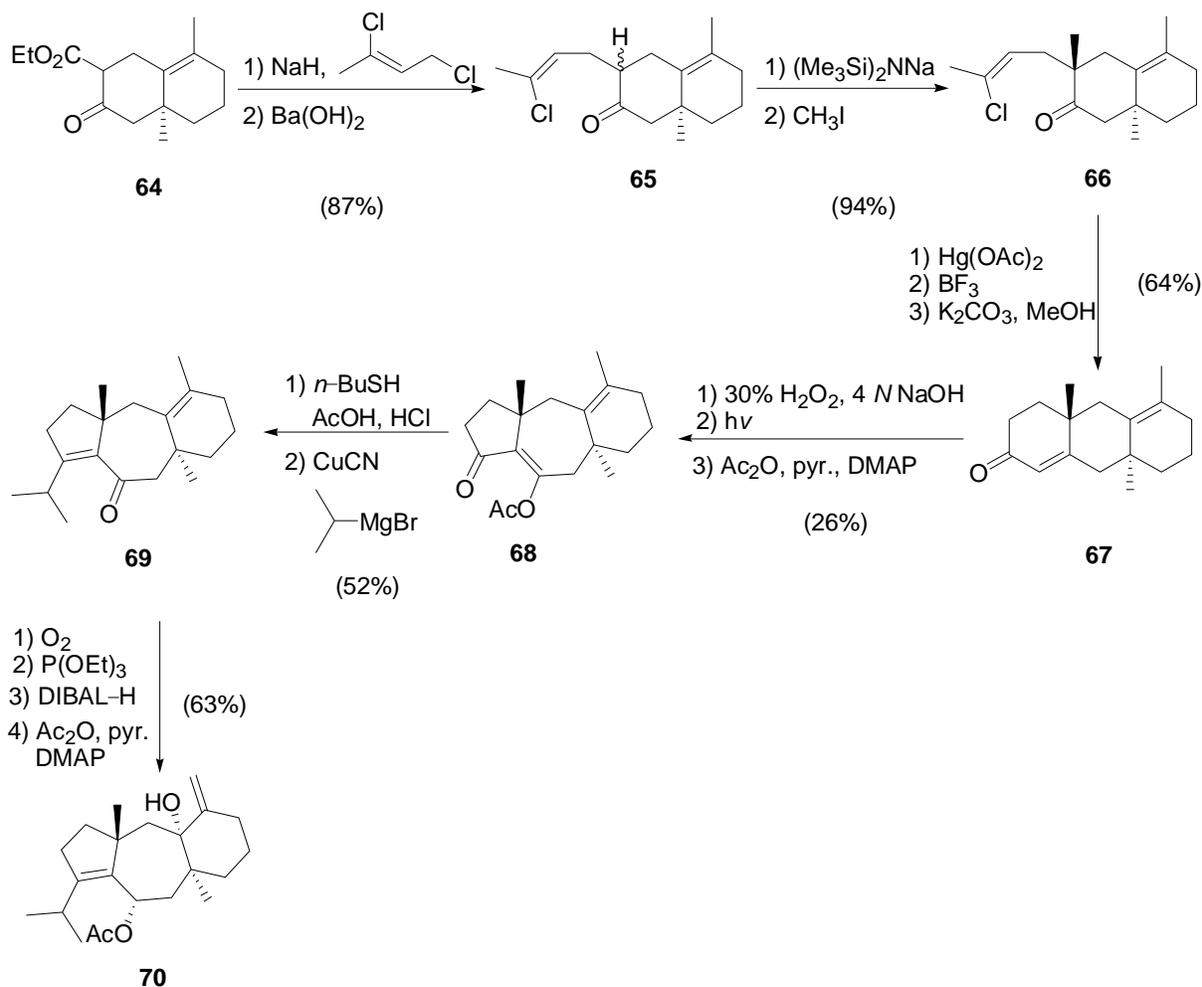
The enantioselective ex-chiral-pool synthesis of the enantiomer of the natural (+)-dolasta-1(15),7,9-trien-14-ol **20** was achieved by Mehta and coworkers in 1987, as summarized in Scheme 8. Their key step featured a stereospecific Claisen rearrangement (i.e., **61** → **62**) followed by an acid-catalyzed olefin-enone cyclization (i.e., **63** → **40**) to give the same bicyclic ketone as Pattenden and Piers (cf. **40**). However, in contrast to Pattenden's work, they were able to separate the three dolastanes **44**, **8** and **20** through "repeated column chromatography on AgNO₃-SiO₂." As we can see, these three groups used a similar A+B→AB+C→ABC strategy which utilized the C(16) methyl group to install the C-14 hydroxyl group.



Scheme 8

The synthesis of the non-natural (\pm)-7,14-*epi*-1(15),8-dolastadien-7,14-ol (*rac*-7,14-*epi*-**70**) was published by Paquette in 1986 (Scheme 9). Their synthesis highlighted a photochemical rearrangement of the 6,6,6-tricyclic α,β -epoxy ketone **67** into the 5,7,6-tricyclic dolastane skeleton. The succeeding hydroxylation of the double bond by photooxygenation with singlet oxygen as well as the DIBAL-H reduction proceeded with an undesired

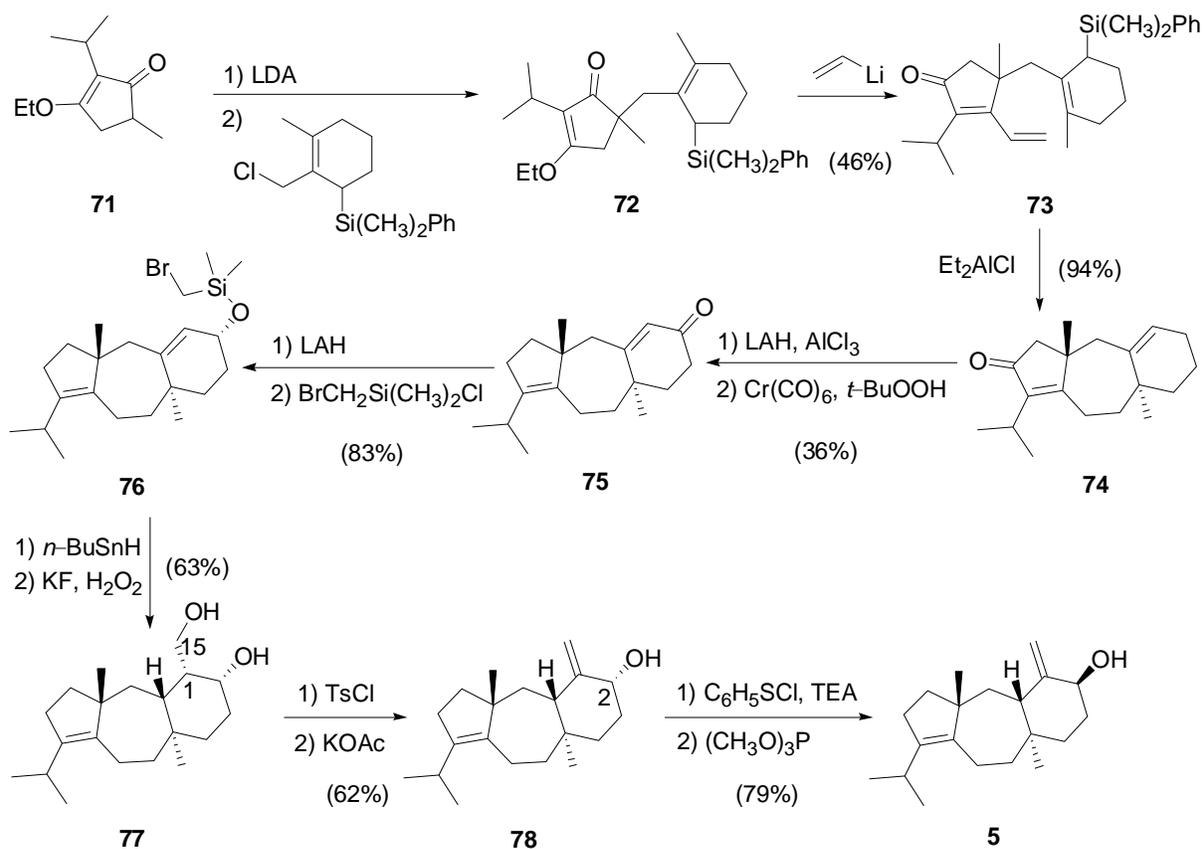
substrate-induced diastereoselectivity to provide the racemic 7,14-epimer of the natural dolastane **70**.



Scheme 9

An $A + C \rightarrow AC \rightarrow ABC$ strategy was applied by Majetich and coworkers for their synthesis of the natural (\pm) -1(15),8-dolastadien-2-ol (\pm) -**5** (Scheme 10). A Lewis acid-mediated intramolecular allylsilane 1,6-addition of the dienone **73** afford the 5,7,6-tricyclic carbon framework including the desired stereochemistry of the angular methyl groups. The

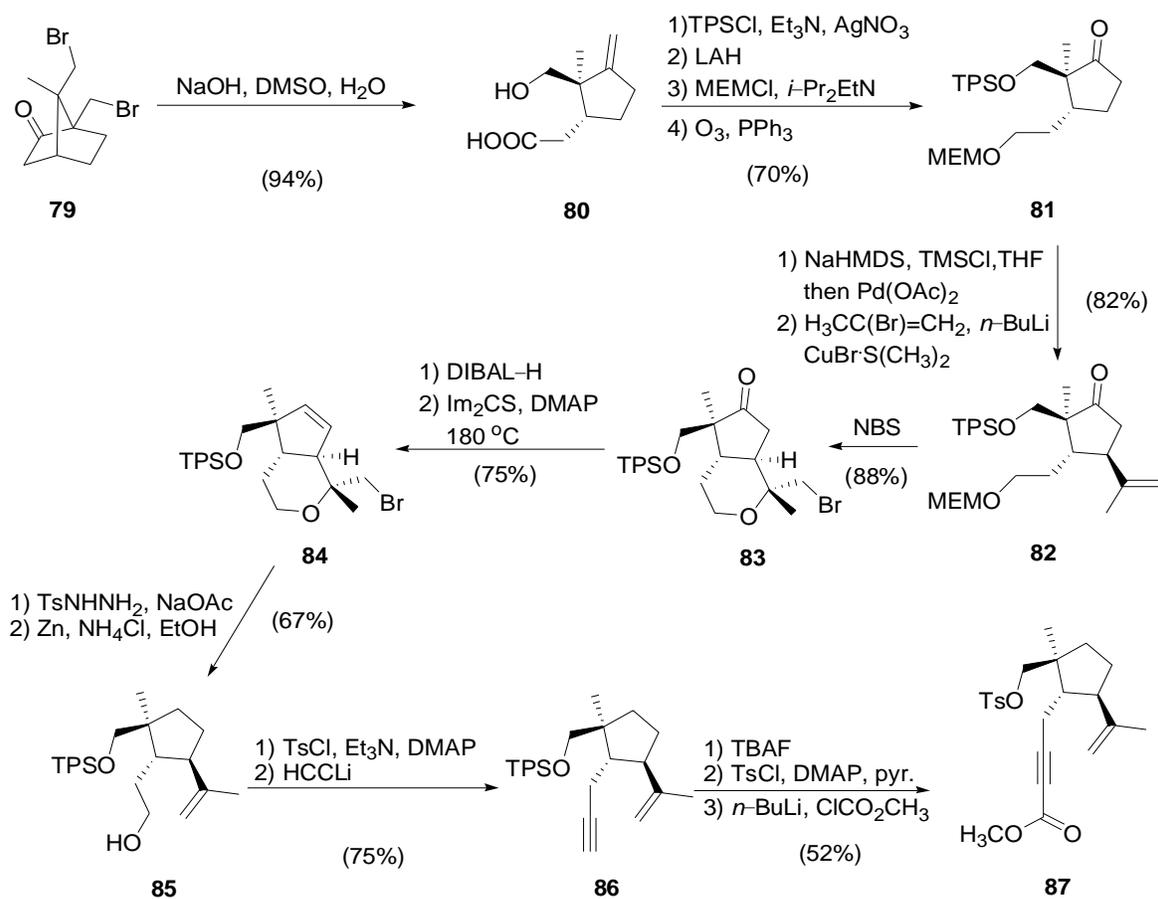
missing C(15) atom was introduced by an intramolecular addition of a radical generated from the silicon tethered bromomethylene moiety in **76** onto C(1) of the C-ring double bond. The stereochemistry of the hydroxyl function at C(2) was inverted by a sulfoxide–sulfenate rearrangement.



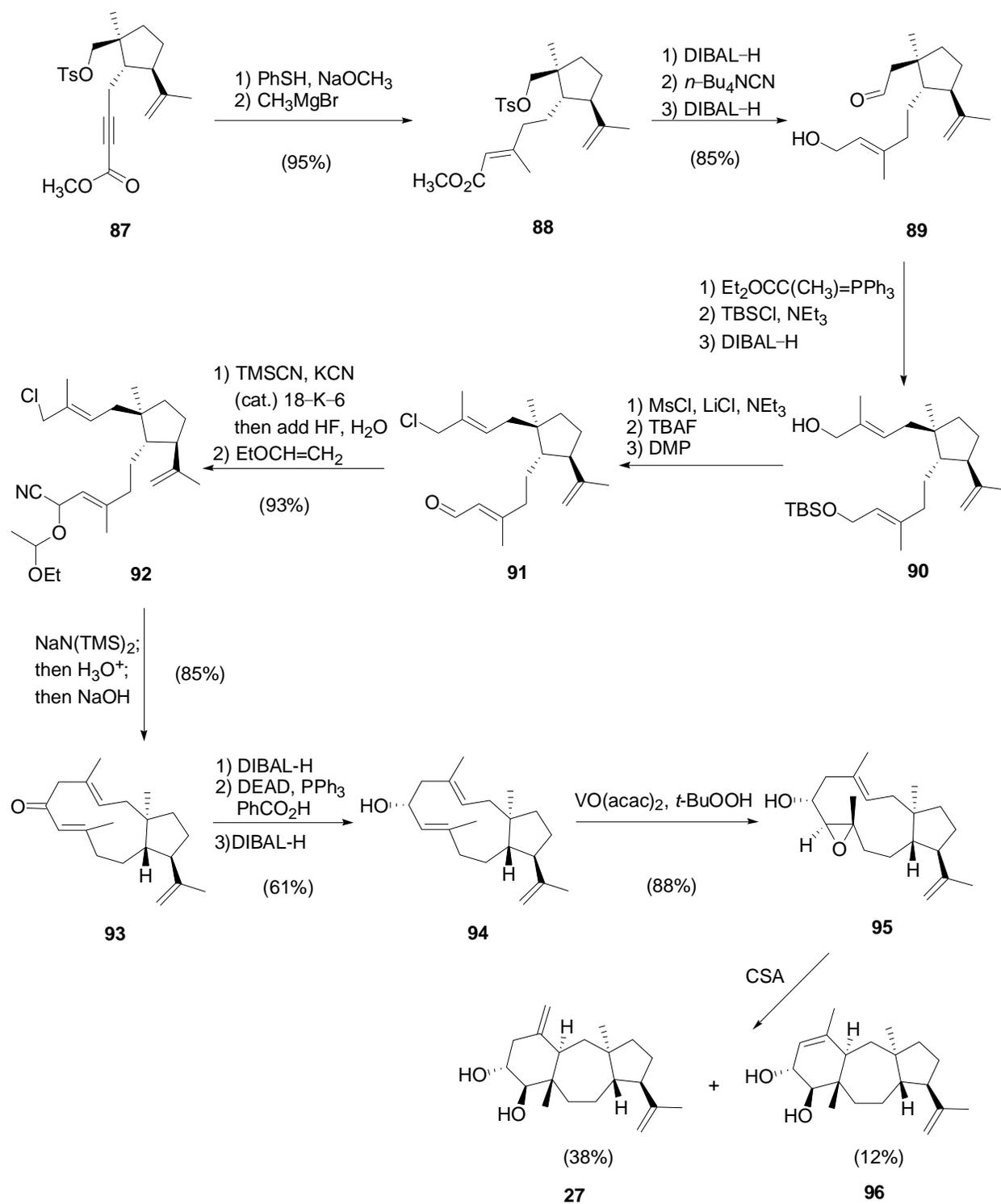
Scheme 10

The most recent total synthesis of a dolastane diterpene was published by Williams and coworkers in 1993 (Scheme 11). (–)-Clavulara-1(15),17-dien-3,4-diol **27** was synthesized using a strategy that relied on the availability of the enantiomerically pure building block **80**,

which was prepared from (+)-9,10-dibromocamphor **79** following Money's procedure.²⁵ *Bis*-silylation and hydride reduction gave a primary alcohol, followed by protection. Ozonolysis gave the ketone **81**. Saegusa oxidation,²⁶ followed by a diastereoselective 1,4-addition of an isopropenyl cuprate, afforded the cyclopentanone **82**. The reduction of the ketone was problematic; it was protected to the isopropenyl double bond as bromohydrin **83**. Twenty-two transformations were required to prepare cyanohydrin **92** for the key macrocyclization step (Scheme 11). The final step is an acid catalyzed transannular cyclization of **95** which gave 38% of the natural product **27** together with some olefin isomer **96**.



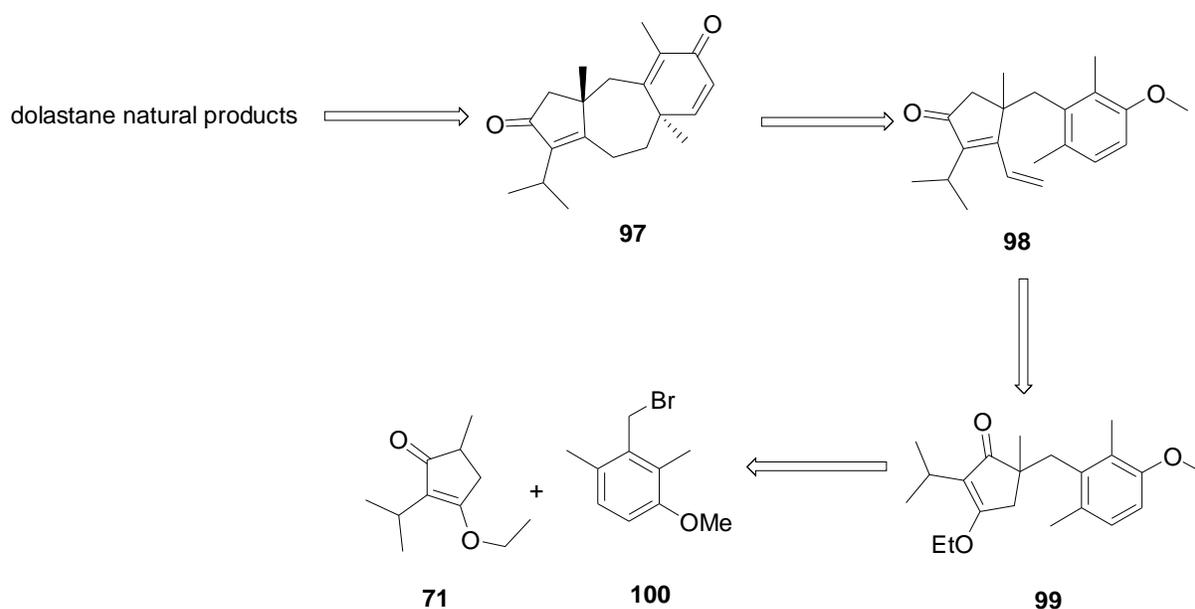
Scheme 11



Scheme 11 continued

4. Results and Discussion.

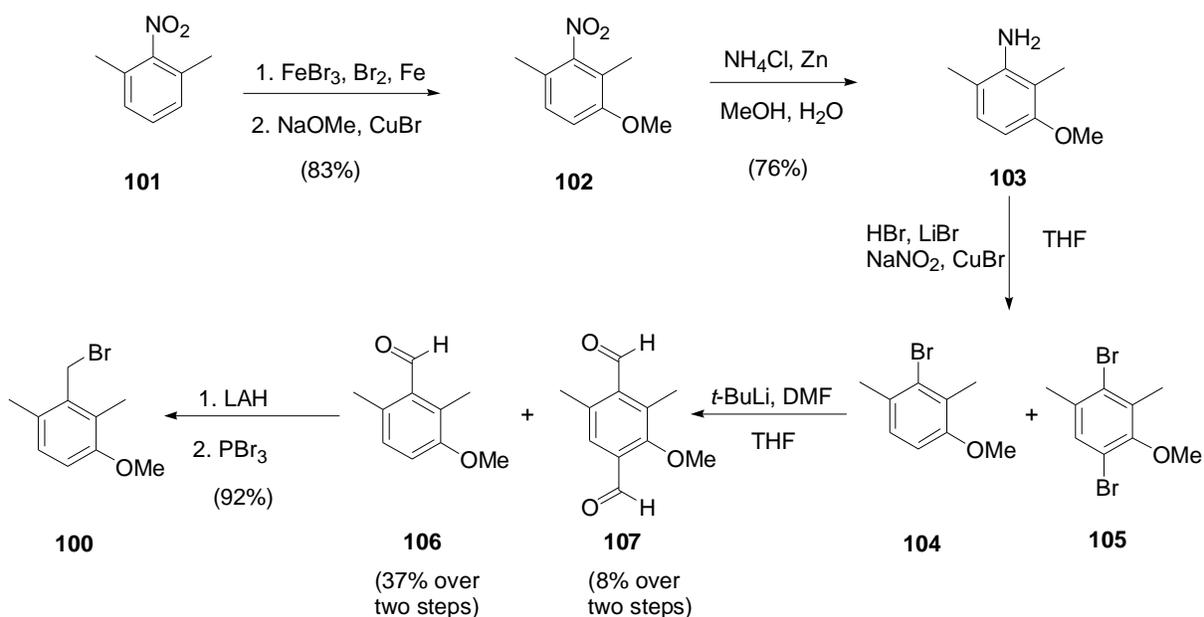
Our general dolastane synthetic plan is shown in Scheme 12. By manipulating the functionality of the key cyclized product **97**, we should be able to prepare multiple dolastanes. The cyclization precursor **98** was easily prepared by adding vinyl lithium to ketone **99**. Intermediate **99** was quickly prepared by the alkylation of the ketone **71** with benzyl bromide **100**.



Scheme 12

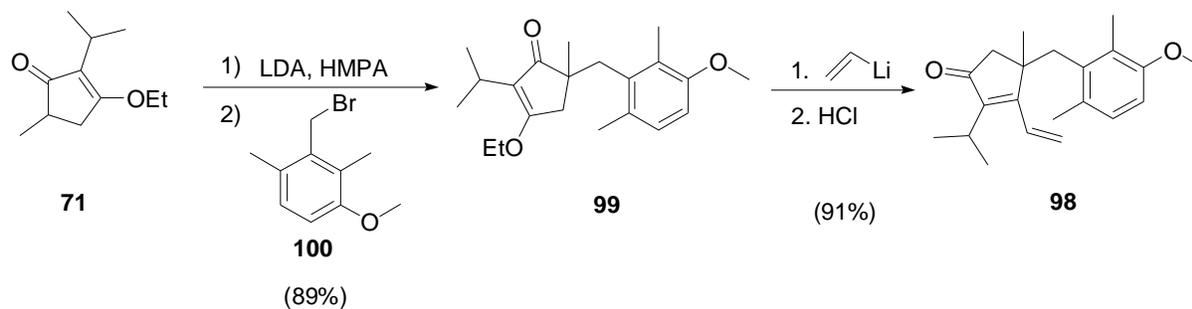
Our study started with the preparation of the A ring and C ring pieces. For the A-ring synthesis, we took advantage of our previous published work.²⁷ For the C ring synthesis, we start with the commercially available 2,6-dimethyl-nitrobenzene **101** (Scheme 13). Monobromination followed by nucleophilic aromatic substitution gave anisole derivative **102**. Zinc metal reduction of the nitro group provided aniline compound **103**. The next step, a Sandmeyer reaction, always

gave an inseparable mixture of mono- and dibromination products, i.e., **104** and **105**, respectively. Fortunately, carrying this mixture to the next step produced two easily separable aldehydes. Reduction of the aldehyde **106** to an alcohol with LAH was followed by the conversion of the alcohol to the corresponding benzyl bromide **100** by treatment with PBr₃.



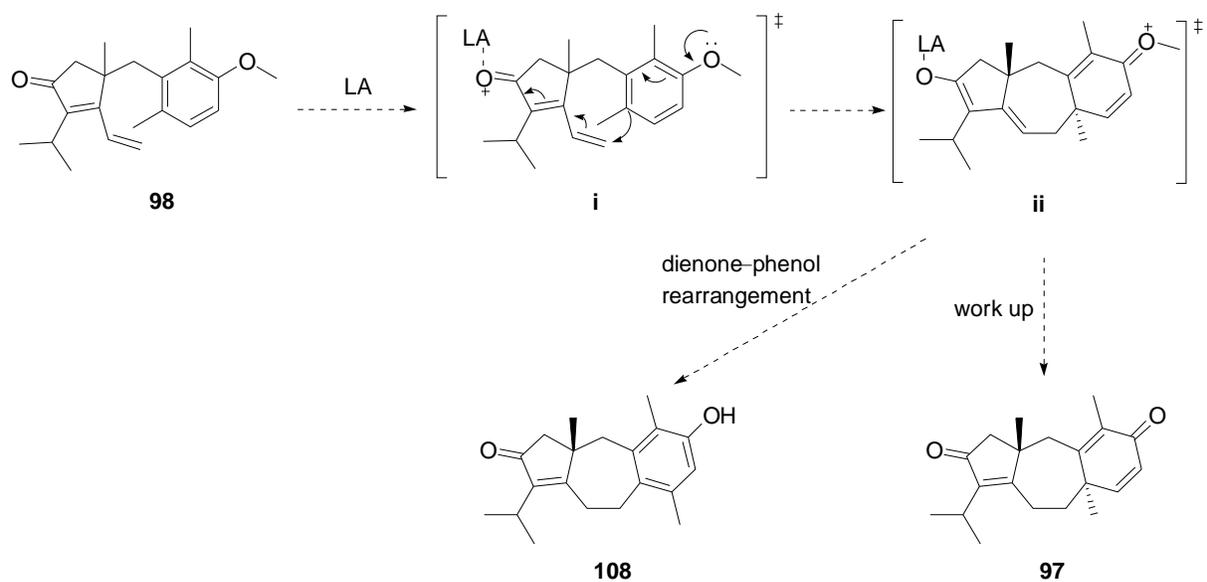
Scheme 13

With the A- and C-rings in hand, we then set out to explore the key cyclization step. Coupling of **71** and **100** gave adduct **99** in excellent yield. Vinyl lithium reaction, followed by acidic workup, gave dienone **98** in excellent yield (Scheme 14).

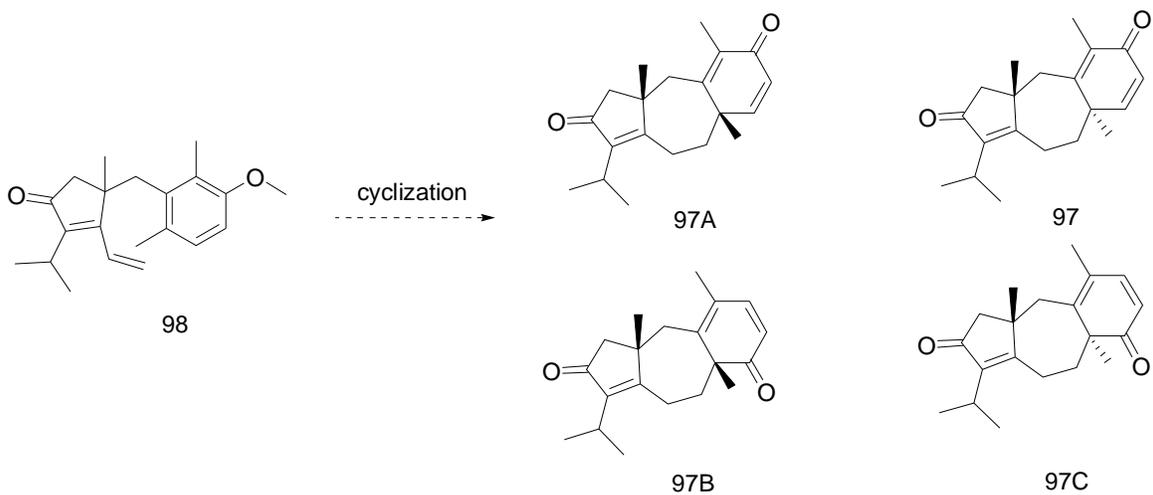


Scheme 14

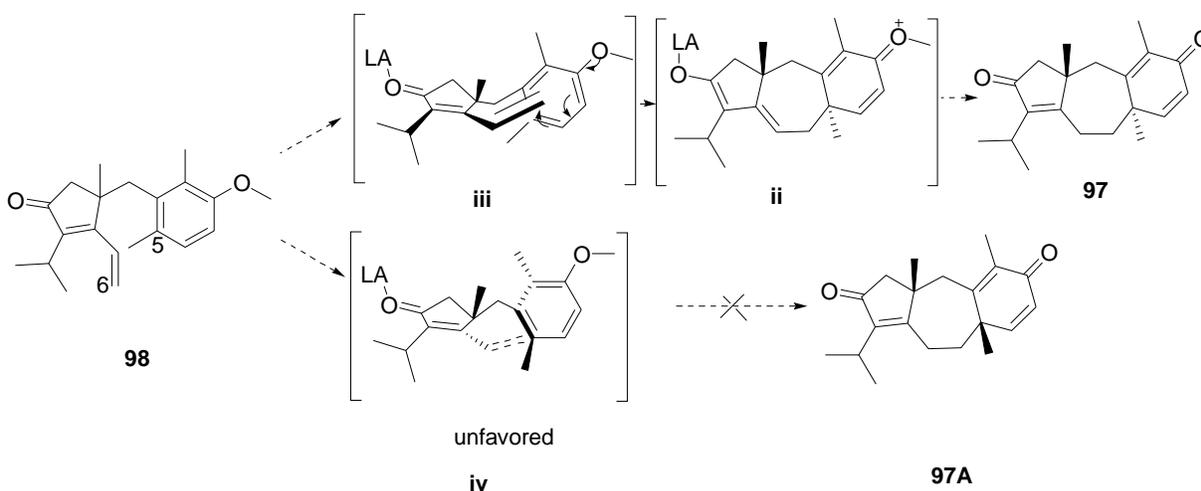
Though the Friedel–Crafts acylation reaction has been known for more than a century,²⁸ there are few examples whereby substituting the arene ring leads to the loss of the aromatic system. Scheme 15 shows our proposed mechanism for this cyclization step which is different from the Friedel–Crafts acylation reaction mechanism since a new quaternary carbon center will be created which makes the rearomatization inaccessible. In theory intermediate **ii** could produce phenol **108** if a dienone–phenol rearrangement occurs.²⁹ We could also predict that a stronger Lewis acid was needed since ring closure would require higher activation energy.



Another issue we need to address here is the selectivity for this step. Based on the possible regio-selectivity and facial-selectivity, there are four possible products from this transformation as depicted in Scheme 16.

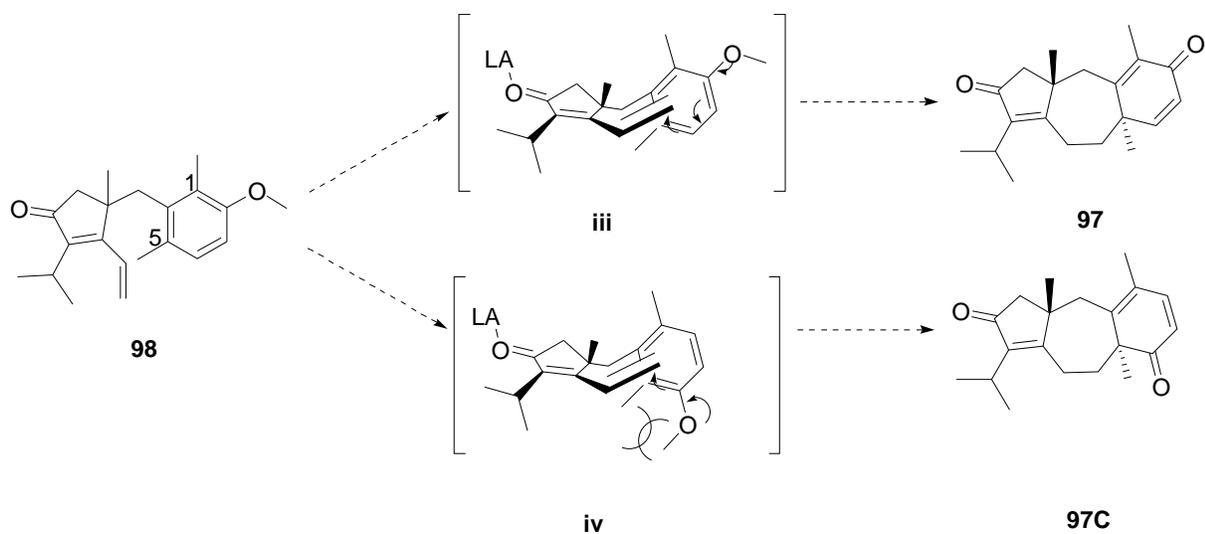


We predicted that the product with trans angular methyl groups would dominate based on our previous result on the allylsilane addition result. As shown in Scheme 17, when the parallel orientation of the planar units is achieved, C(5) would attack C(6) from the less sterically hindered face of the aromatic ring and intramolecular 1,6-conjugate addition generates a cationic intermediate **ii** in which the two angular methyl groups possess a trans relationship.



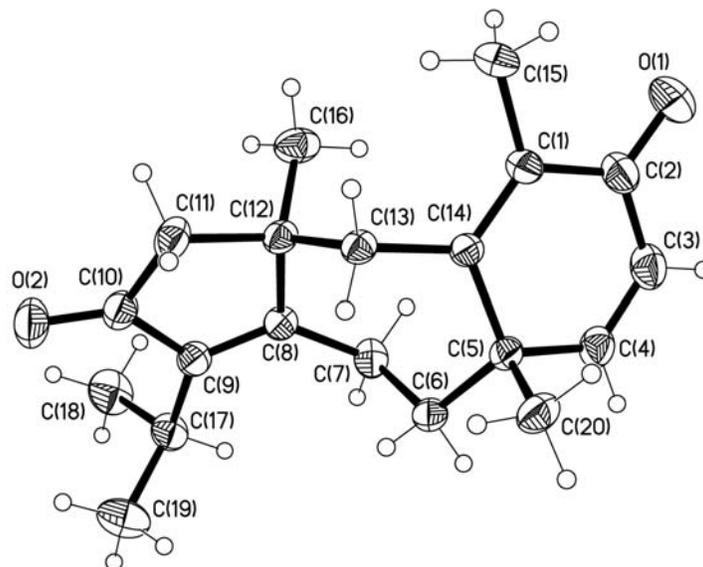
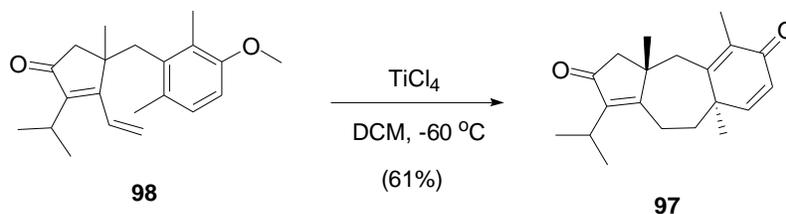
Scheme 17

In terms of regioselectivity, the *para* position should be favored because of the electronic and the steric effects (Scheme 18). Since C(1) is *ortho* to the methoxy and C(5) is *para* to the methoxy group. Based on these considerations we know that the *para*- and the *ortho*-position should be very close. Study of molecular models of **98** suggests the conformation leading to intermediate **iii** should be favored since the conformation represented by intermediate **iv** introduces steric congestion between the vinyl and methoxy moieties.



Scheme 18

After extensive screening of different Lewis acids, we found out that TiCl_4 was the most effective catalyst. After stirring at $-60\text{ }^\circ\text{C}$ for 30 minutes we obtained only enone **97** in good yield (Scheme 19). An X-ray crystal structure confirmed the trans-conformation of the two angular methyl groups.



Scheme 19

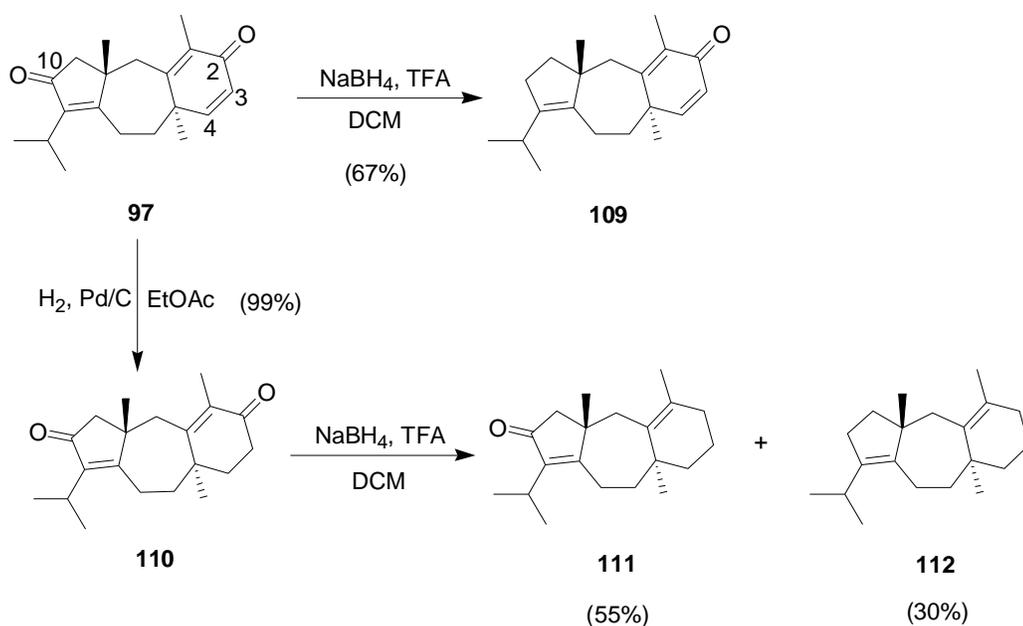
Comparison of the key cyclized intermediate **97** with numerous dolastanes reveals that the major differences lie in the following molecular sites:

- none of the natural products have a C(10) carbonyl group;
- several of the natural products have a β -hydroxyl group at C(2) or a methylene unit there;
- most of the natural products have a C(1), C(15)-exocyclic double bond;
- most of the natural products have a C(14) β -hydroxyl group; and

- several of the natural products have a hydroxyl group or an acetyl group at the C(4) position.

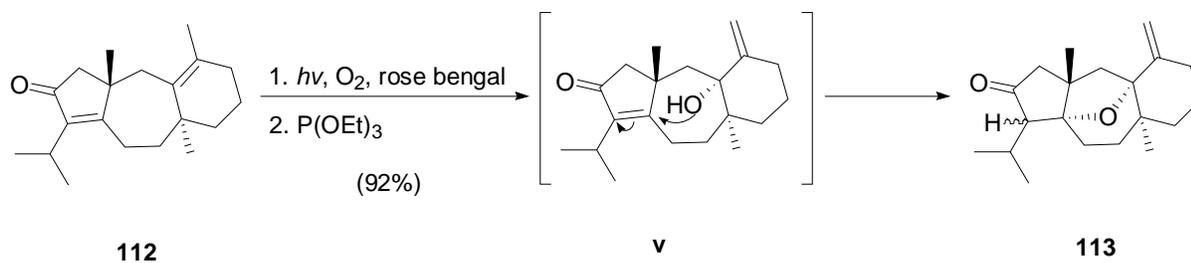
In order to achieve these goals, we needed to solve several problems. The most obvious one is how to differentiate the C(10) and C(2) carbonyl groups.

We believed that the A-ring enone would be more reactive than the C-ring dienone, because in compound **97** there are two double bonds in conjugation with the C(2) carbonyl group, which reduces its electron density thereby making it less reactive. Indeed, treatment of compound **97** with sodium borohydride in the presence of TFA using dichloromethane as the solvent selectively reduced the C(10) carbonyl to a methylene unit (Scheme 20). However, if we first reduced the C(3)–C(4) double bond, the C(2) carbonyl group was found to be more reactive. We speculate that it is due to the steric hindrance of the isopropyl group, since based on electron density predictions, the C(10) carbonyl group would be more reactive.



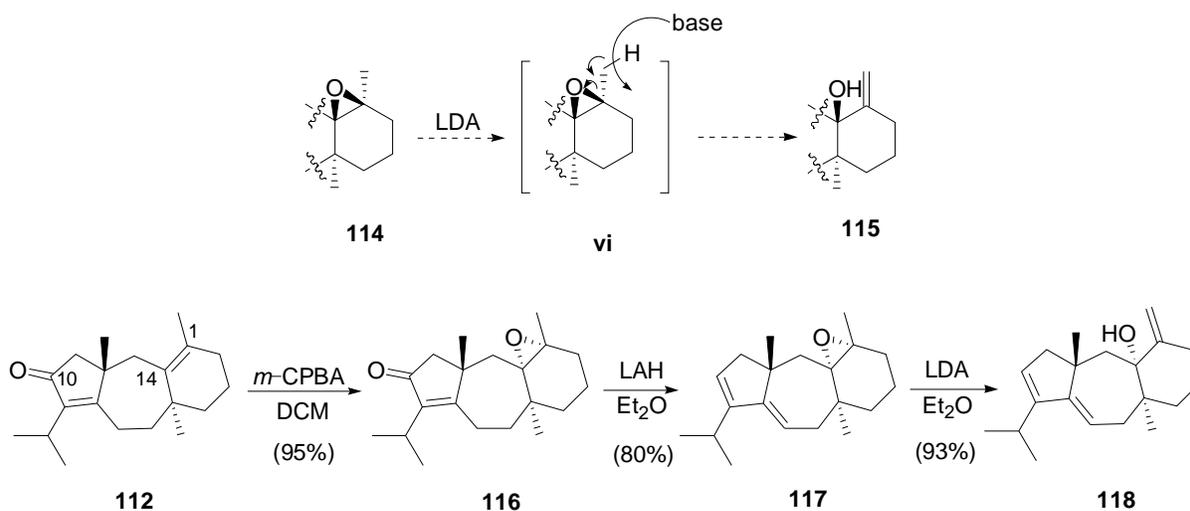
Scheme 20

Next we tried to install the C(14) α -hydroxyl group and the C(1), C(15)-double bond using Paquette's photochemical oxidation.¹⁷ Not surprisingly, due to steric hindrance of the C(16) methyl group, only the α -alcohol was produced. However, in our case, an intramolecular Michael addition took place and the furan **113** was formed as the only product (Scheme 21).



Scheme 21

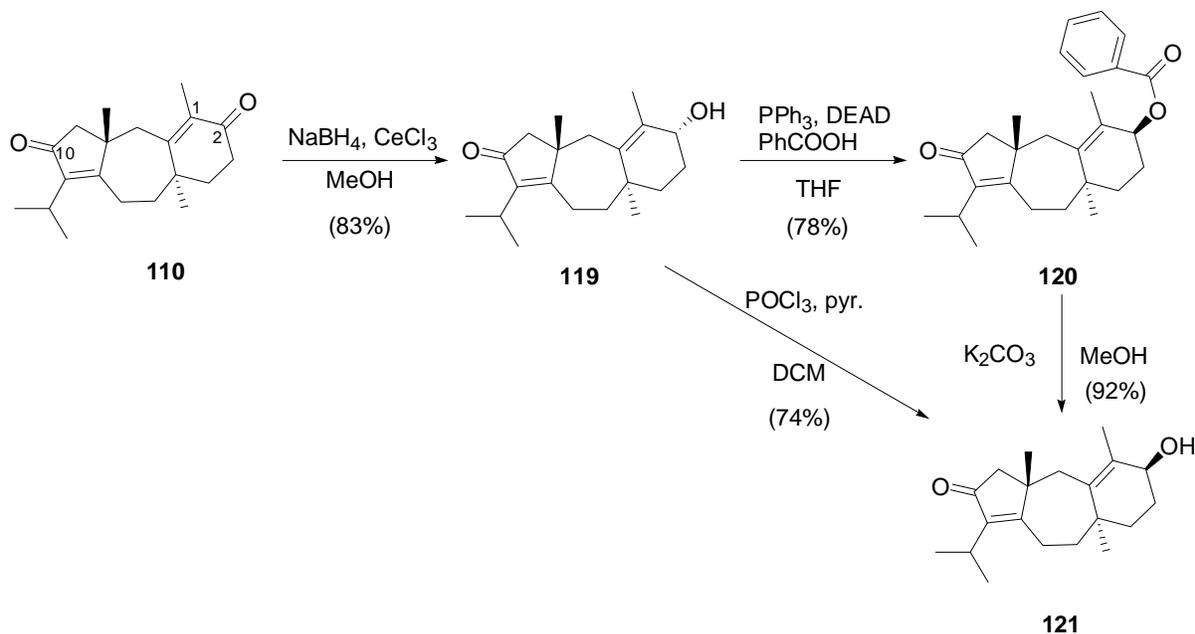
Another way to prepare this allylic alcohol was by opening of the C(1), C(15)- β -epoxide. We first tested this idea on the α -epoxide since epoxidation of **112** gave only the α -epoxide. The reduction of the C(10) carbonyl gave the allylic alcohol, which was very labile to acidic conditions and would automatically dehydrate to form diene **117**. Epoxide **117** was treated with LDA and the resulting mixture was placed in a sealed tube and heated at 50 °C overnight to give the desired product **118** in 90% yield, albeit only the α -alcohol was formed. Thus we were confident if we could prepare the corresponding β -epoxide, we would be able to introduce the C(14) β -alcohol (Scheme 22).



Scheme 22

We first tried a hydroxyl directed epoxidation to prepare the C(1), C(14)- β -epoxide. This strategy required a C(2) β -oriented hydroxyl group, since the Luche reduction of compound **110** gave only the α -C(14) alcohol due to the steric hindrance of the C(20) methyl group. In order to

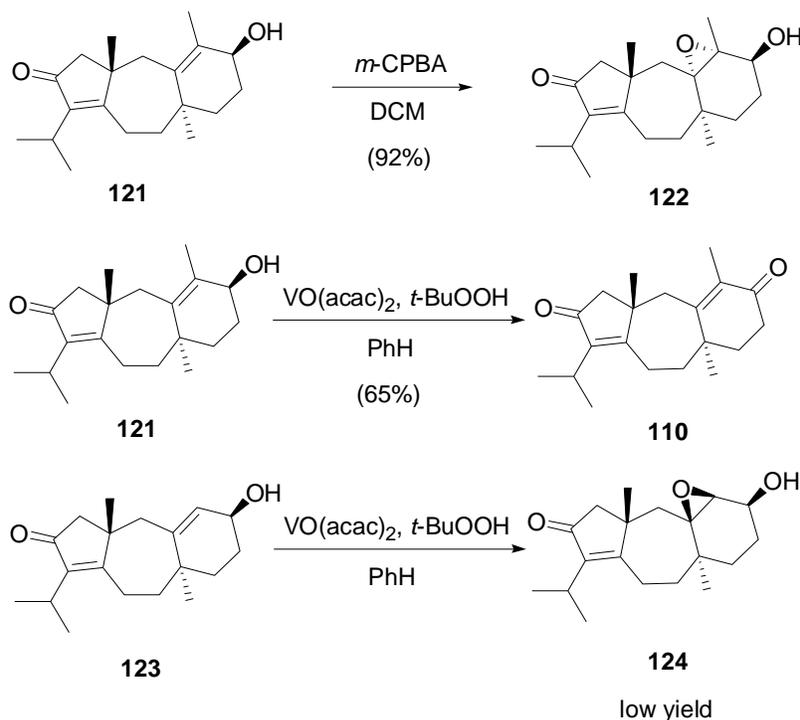
invert the stereochemistry of the C(2) hydroxyl, we used the Mitsunobu reaction followed by hydrolysis. Later we found that using phosphorus oxychloride and a quick aqueous workup would also give the same β -alcohol **121** in a one step process (Scheme 23).



Scheme 23

With the required β -allylic alcohol compound **121** in hand, we then tried two well-established epoxidation conditions to prepare the β -epoxide (Scheme 24). It was hoped that the alcohol oxygen would chelate with *m*-CPBA to induce the desired facial selectivity. However, in our case, since the steric hindrance of the C(16) angular methyl group was so overwhelming, only α -epoxide **122** was formed. When $\text{VO}(\text{acac})_2$ was used to catalyze the epoxidation of **121**, only enone **110** was formed presumably due to the steric hindrance of the

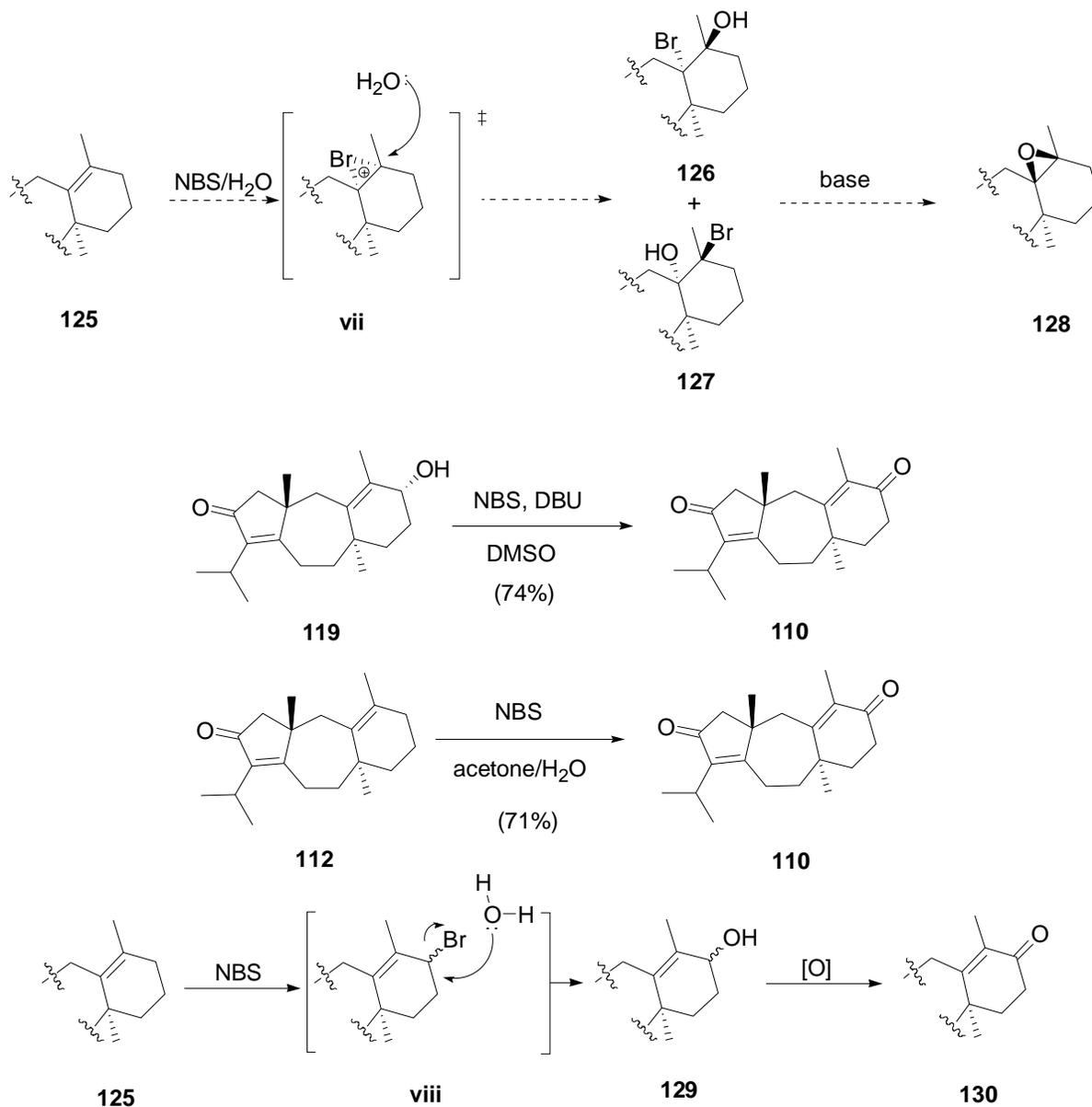
C(15) methyl group. In our previous study, the oxidation of the trisubstituted compound **123** produced desired β -epoxide **124** although in low yield.



Scheme 24

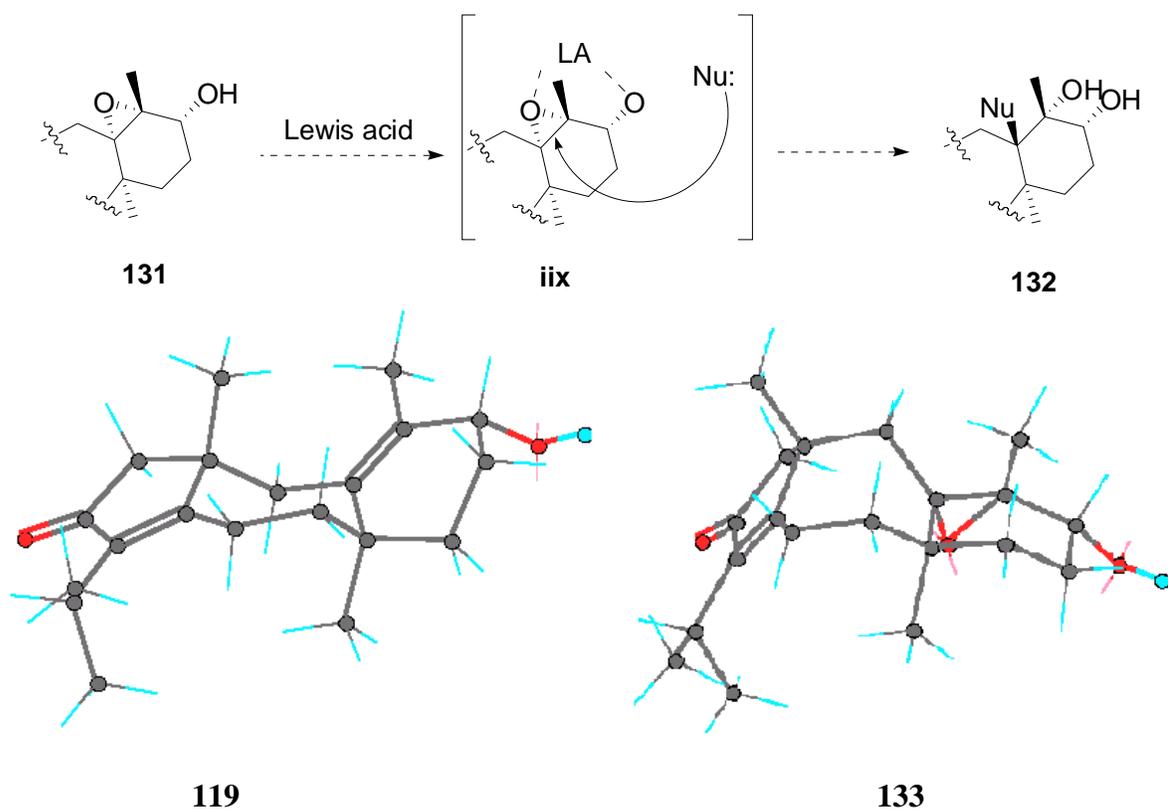
A classic way to prepare an epimeric epoxide is to make the bromohydrin from the alkene and then treat it with base. We concluded that since the C(16) methyl blocks the β face of the C(1), C(14)-double bond, bromium ion formation would be selective from the α face; the addition of water would come from the opposite face; treatment of the resulting bromohydrin with base would give the desired β epoxide **128**. However, when **119** was treated with NBS, only enone **110** was produced (Scheme 25). We thought this occurred because the allylic alcohol **119** is easy to oxidize. To our surprise, treatment of **112** under similar conditions, however, gave only

enone **110**. Presumably allylic halogenation occurred first, followed by hydrolysis then further oxidation to produce enone **110**.

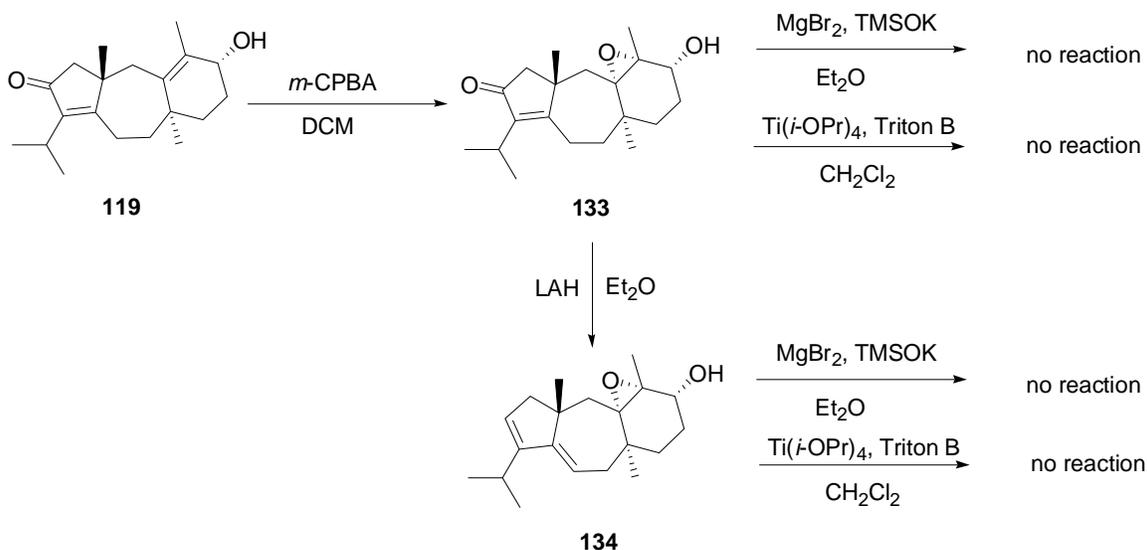


Scheme 25

Since the C(16) methyl blocks the β face of the C(1), C(14)–double bond, we next tried the Lewis acid–mediated opening of hydroxyl epoxide **133** (Scheme 26). Examination of a model of **133** revealed that its conformation was different from **119** so much that it made the C(14) position became more accessible. Unfortunately, as shown in Scheme 26, no nucleophile opened the C(1), C(14)–epoxide from the β face.

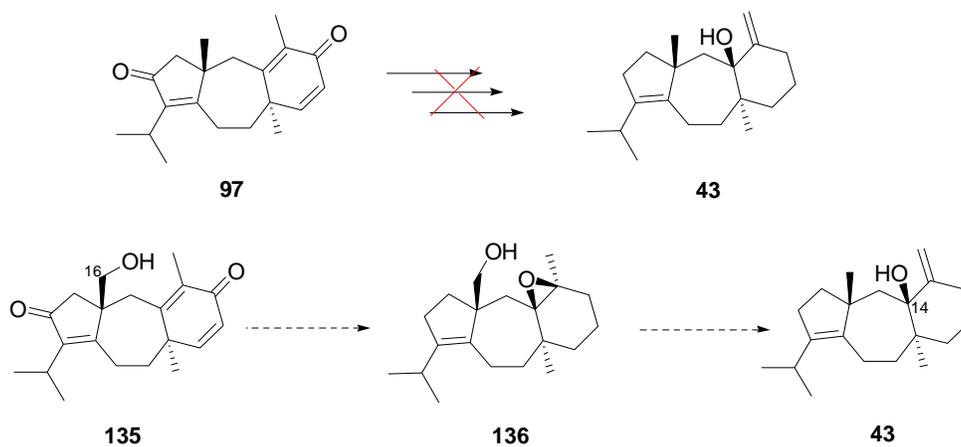


Scheme 26



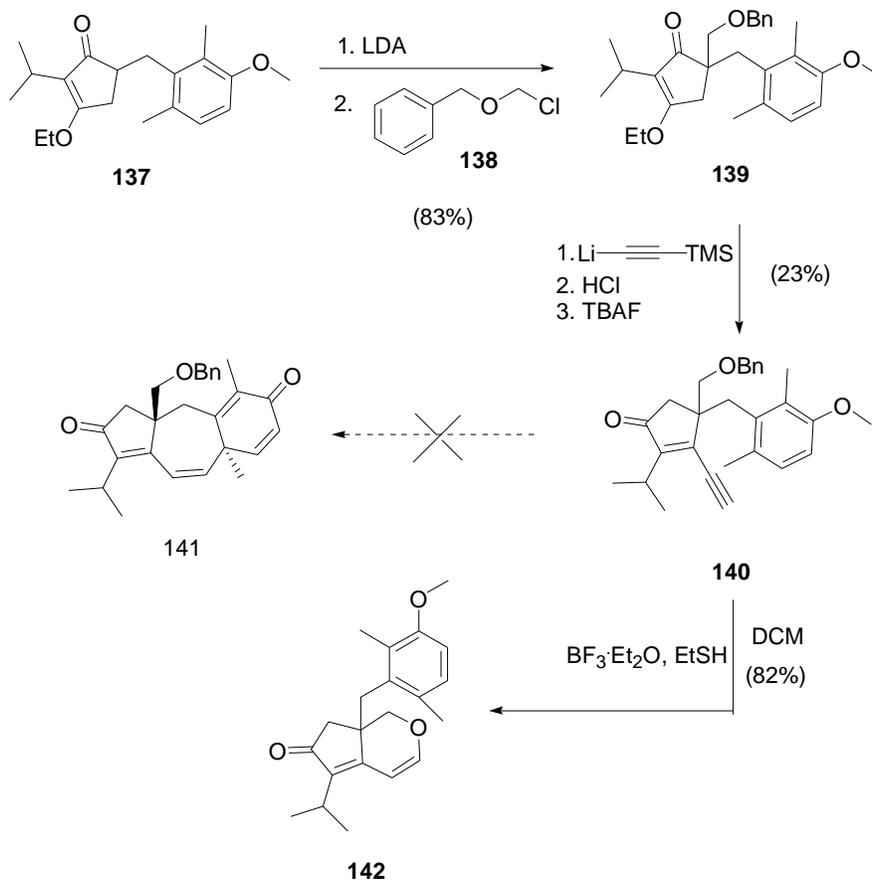
Scheme 26 continued

Further study of the X-ray structure of tricycle **97** reveals that the distance between the C(16) methyl group and the C(1), C(14)–double bond is roughly one carbon–carbon bond distance (Scheme 27). The comparison of the molecular structure of **97** with the natural dolastane natural products, exhibits major conformational differences in the central seven member ring conformation. We decided to use the C(16) methyl group to introduce the β -oriented C(14) hydroxyl group by having a hydroxymethylene unit at C(16) which would install the C(14) hydroxyl group selectively from the β -face.



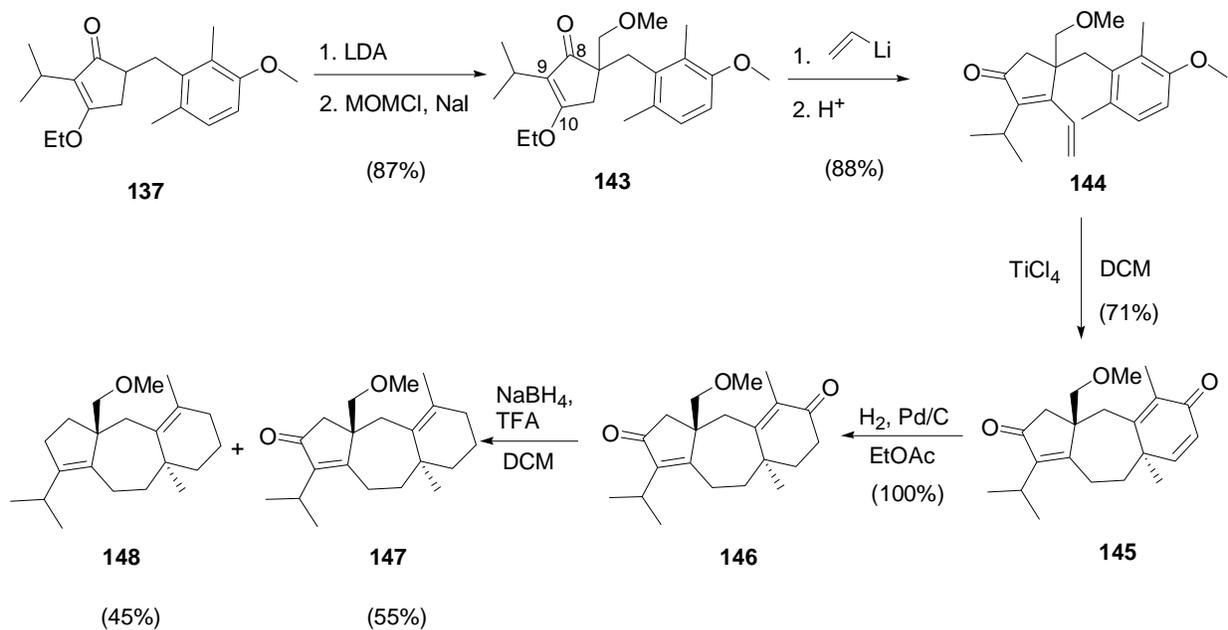
Scheme 27

The alkylation of **137** with benzyl chloromethyl ether **138** gave us intermediate **139** which we homologated to enynone **140**. To our surprise the benzyl protecting group is labile to the Lewis acid used for the cyclization step. After deprotection occurred the free alcohol underwent intermolecular Michael addition to give only pyran **140** (Scheme 28).



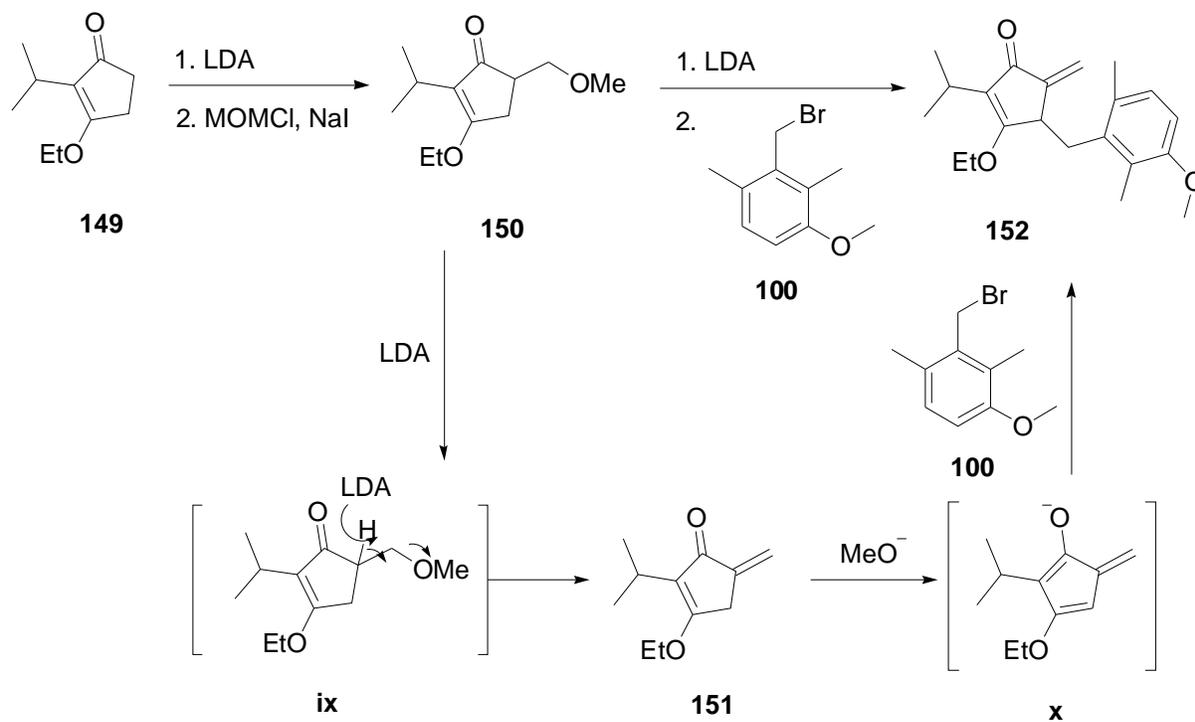
Scheme 28

We were curious if a methyl group would serve as a more stable protecting group. Coupling of enone **137** with MOMCl gave **143** in excellent yield. Addition of vinyl lithium to the sterically congested C(8) carbonyl was problematic. Normally an 1:1 THF/Et₂O mixed solvent system efficiently hydrolyses the enolate to afford a conjugated dienone. However, treating the adduct of vinyl lithium with ketone **143** under these conditions gave low yield with mainly the recover of starting material. Fortunately, removing the THF and using only diethyl ether furnished **144** in excellent yield. This time cyclization occurred. More importantly, cyclization product **145** had similar reactivity as intermediate **97** (Scheme 29).



Scheme 29

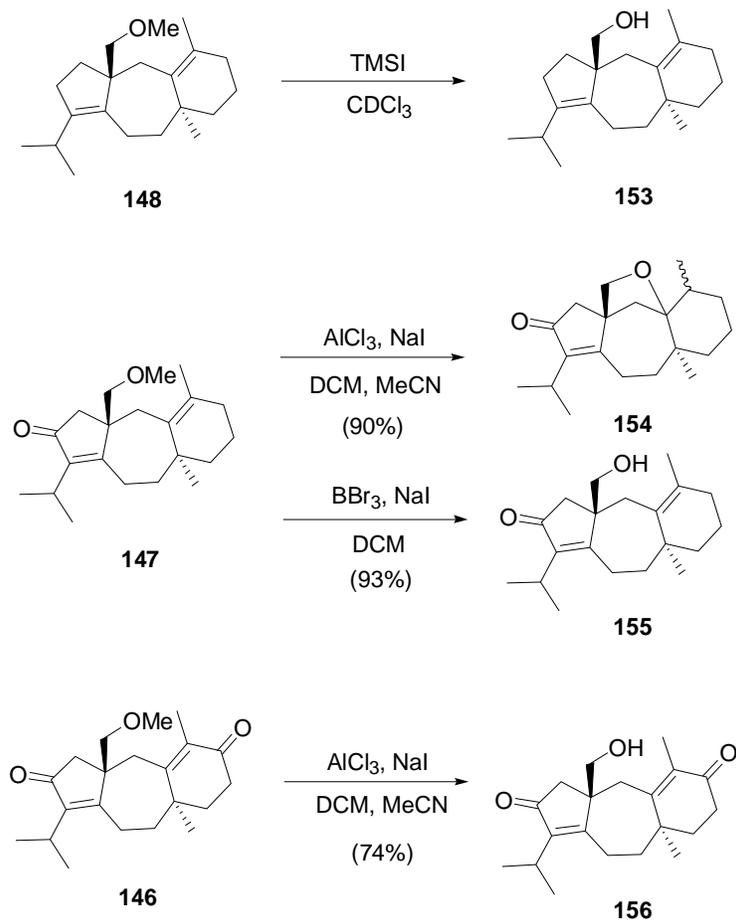
We also explored the possibility of first reacting the A ring compound **149** with MOMCl, and then alkylating it with the C ring bromide **100**. However, treatment of **159** with LDA caused the elimination of the methoxy group to give **151**. Intermediate **151** was easily deprotonated and addition of bromide **100** produced only adduct **152** (Scheme 30).



Scheme 30

Since the deprotection of methyl groups is often difficult, we tested different conditions on three substrates. We placed compound **148** and excess TMSI in a NMR tube and recorded spectra over time, within minutes methyl iodine was detected, suggesting that the deprotection was occurring. However, after workup, a mixture of several compounds was obtained. It might be because TMSI reacts easily with water to form HI, a strong protic acid. For substrates **147** and **146** we obtained compounds **155** and **156** in excellent yield. However, the formation of **154** is surprising (Scheme 31), especially when **146** reacted under same conditions and gave the primary alcohol **156**. One possible reason is that AlCl_3 is a softer Lewis acid than BBr_3 , and that a double bond is a softer Lewis base than a carbonyl group. So when **147** react with AlCl_3 , after the successful deprotection of the methyl group, AlCl_3 will activate the C(1), C(14)–double bond

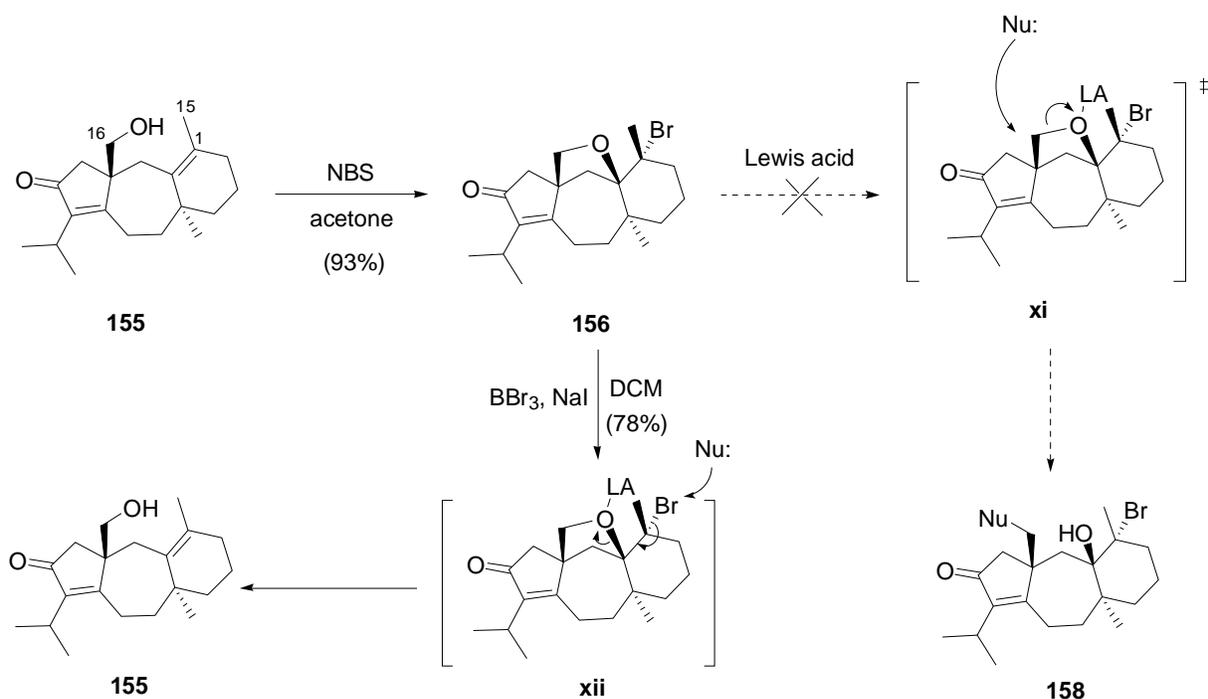
and make it more electrophilic. While in the case of **165**, this activation effect is much weaker so we can get the uncyclized product.



Scheme 31

Having worked out conditions to deprotect alcohol **155**, we were able to investigate whether bromohydrin formation would take place. Furan **156** formed quickly and in 93% yield upon exposure to NBS in acetone. We were excited that bromohydrin formation efficiently introduced the desired C(14)- β oriented oxygen atom and introduced a bromine atom at C(15) which we

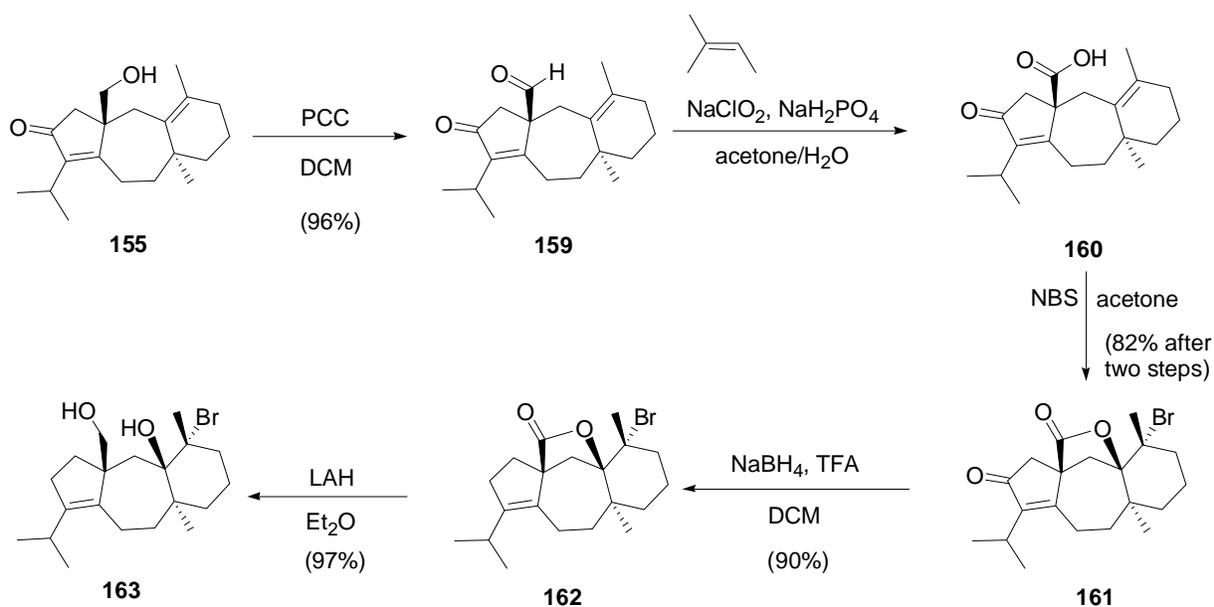
believed would allow us to introduce the C(1), C(15)–double bond. However, the cleavage of the furan carbon oxygen bond turned out to be very difficult. We hoped that treatment with a strong Lewis acid would weaken the C(16)–oxygen bond, so that a nucleophile would displace the C(14) hydroxyl group. Instead nucleophiles attacked the C(1) bromide which gave back enone **155**, the starting material from bromohydrin formation (Scheme 32). We concluded that the C(16) site is inaccessible causing the nucleophile to attack the more accessible bromide.



Scheme 32

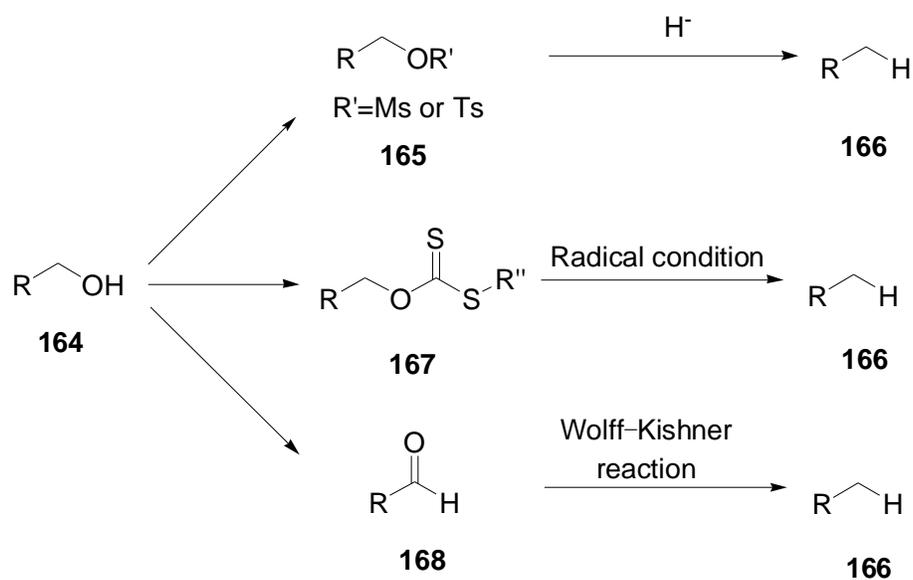
Concurrent with the above strategy, we oxidized the primary alcohol up to the corresponding carboxylic acid; treatment with the NBS formed the lactone bromide **161**. Sodium borohydride and TFA could selectively reduce the C(10) carbonyl group. LAH reduction of the

lactone **162** gave diol **163** which we believed it would be possible to selectively reduce the C(16) hydroxymethylene unit to an angular methyl group (Scheme 33).



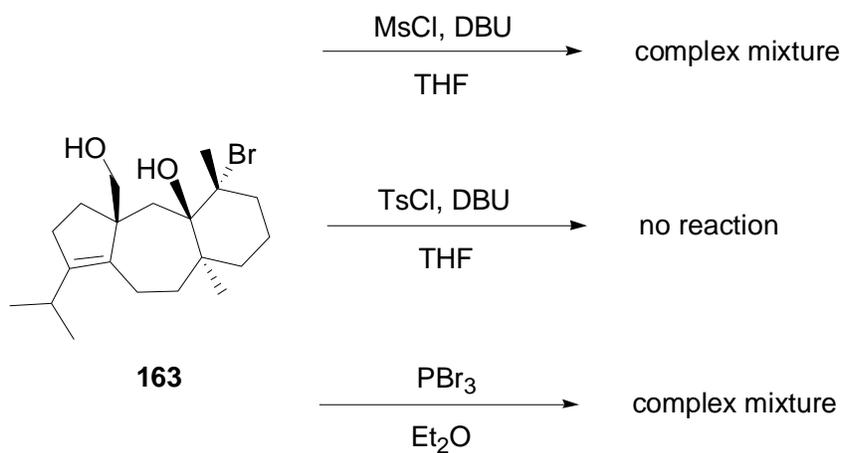
Scheme 33

There are three common ways to achieve the dehydroxylation of a neopentyl primary alcohol. The first method is to convert the primary alcohol into a good leaving group, followed by the hydride displacement. The second way is using a Barton–McCombie deoxygenation reaction. The third popular procedure to achieve this transformation is to carry out a Wolff–Kishner reduction on the corresponding aldehyde (Scheme 34).



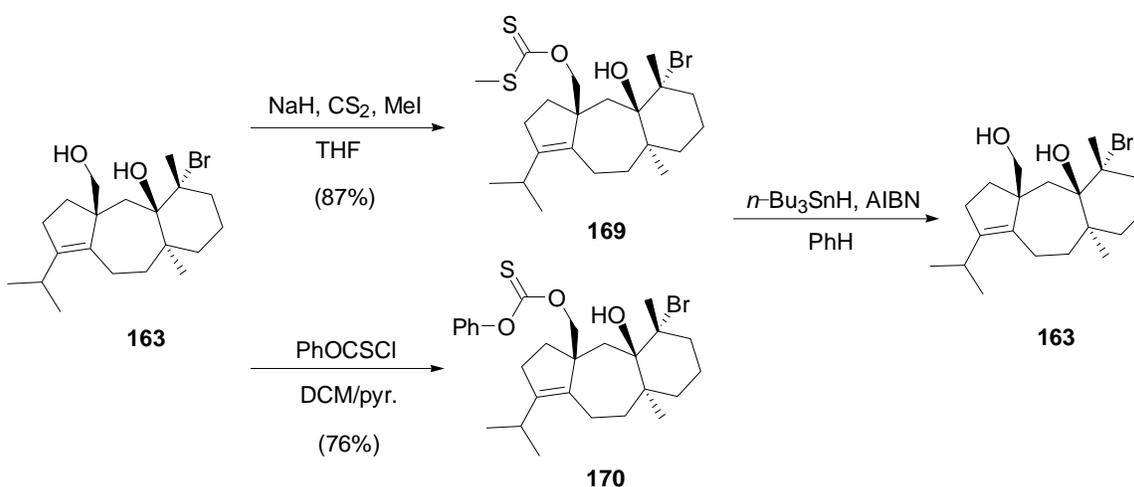
Scheme 34

With the diol **163** in hand, we first tried the hydride displacement sequence. Unfortunately, all attempts to convert the primary alcohol into a mesylate or a tosylate gave either no reaction or complex mixtures; efforts to convert alcohol **163** into a halogen gave similar result (Scheme 35).



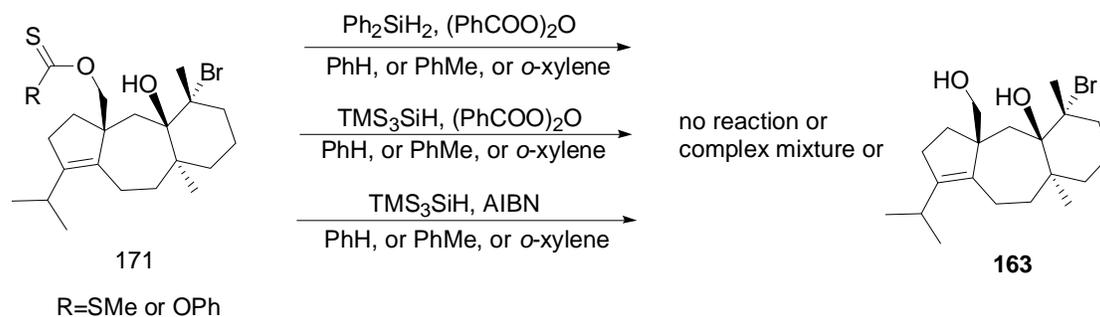
Scheme 35

With the failure of the traditional hydride S_N2 procedure to reduce the C(16) alcohol we turned to free radical-based methods. Several thiocarbonyl derivatives were prepared. However, using tri-*n*-butyltin hydride as the hydride source and AIBN as the radical initiator produced only the starting diol **163** (Scheme 36). In hindsight, these results are not surprising since the radical deoxygenation of the primary alcohol has been a long problem.



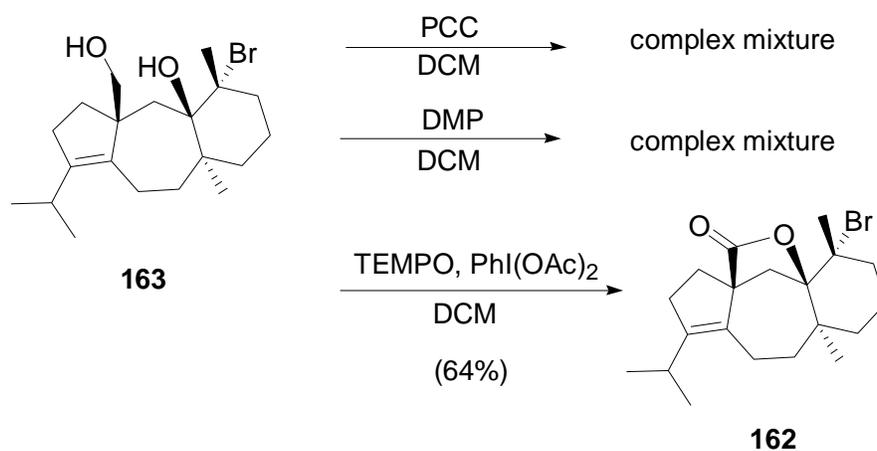
Scheme 36

One of the ways reported to solve this problem was to make the radical at a higher temperature by changing to either different hydride source, a different radical initiator, a different reaction solvent or some combination of these factors. The different conditions we unsuccessfully tried are listed in Scheme 37. Warming the reaction mixture to higher temperature caused the xanthate material to decompose.



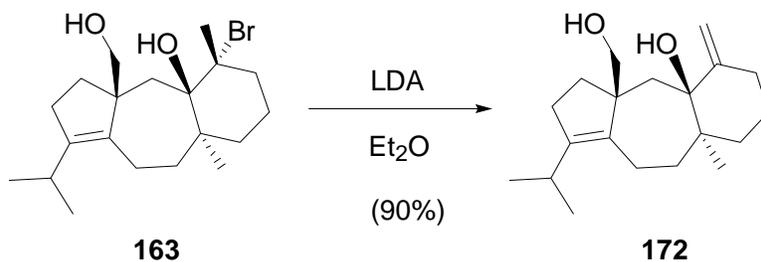
Scheme 37

We also attempted to reduce the C(16) alcohol by first oxidizing it to an aldehyde, followed by a Wolff–Kishner reaction. However, we were not able to prevent overoxidation of the corresponding lactol to lactone **162** (Scheme 38).



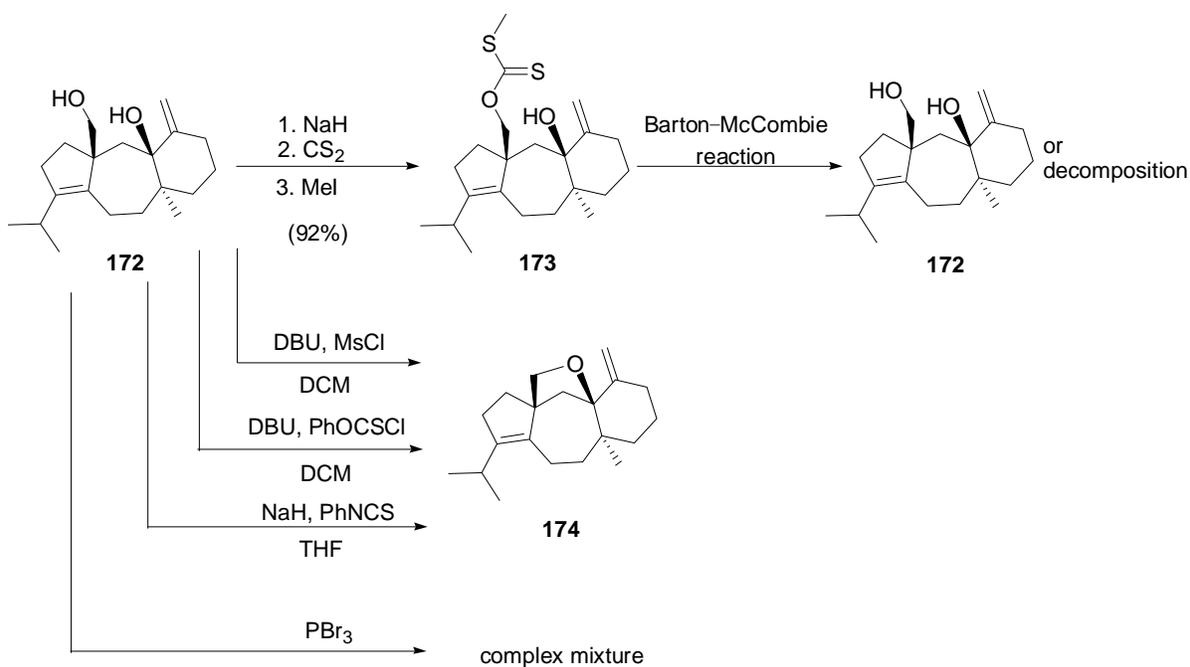
Scheme 38

In light of our inability to deoxygenate compound **163**, we decided to introduce the C(1), C(15)–double bond and then try to deoxygenate the C(16) allylic alcohol. Treatment of compound **163** with LDA gave **172** as the only product in 90% yield (Scheme 39).



Scheme 39

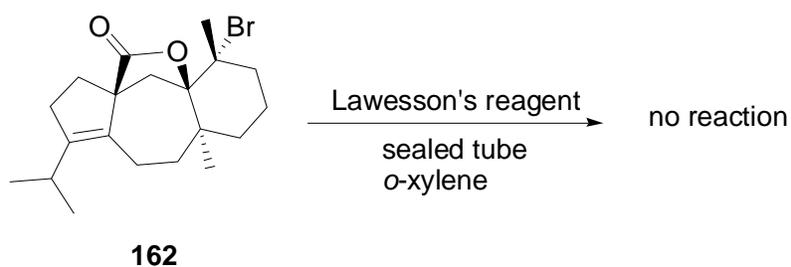
With allylic alcohol **182** in hand, we then re-examined all the previously examined conditions (Scheme 35, 36 and 37) to remove the C(16) alcohol, but without success. Note that furan **174** forms readily (Scheme 40).



Scheme 40

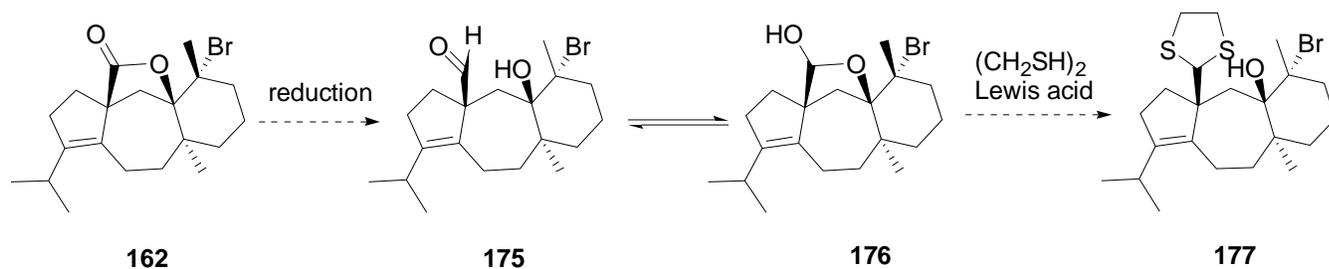
Because of these observations, we concluded that steric congestion of the molecule at the C(16) site would make any nucleophilic attack at C(16) unlikely. Moreover, a use of modified

Barton–McCombie procedure gave either no reaction or decomposition under stronger conditions. These results, although failures, led us to use sulfur to epoxidize the C(1), C(14)–double bond, followed by cleavage of the carbon–sulfur bond using Raney–Nickel or Li/NH₃ to remove the sulfur. We tried to convert lactone **162** to the thio–lactone using Lawesson’s reagent, but no reaction occurred since Lawesson’s reagent works best for ketones or aldehydes and is less reactive toward esters, such as lactone **162** (Scheme 41).



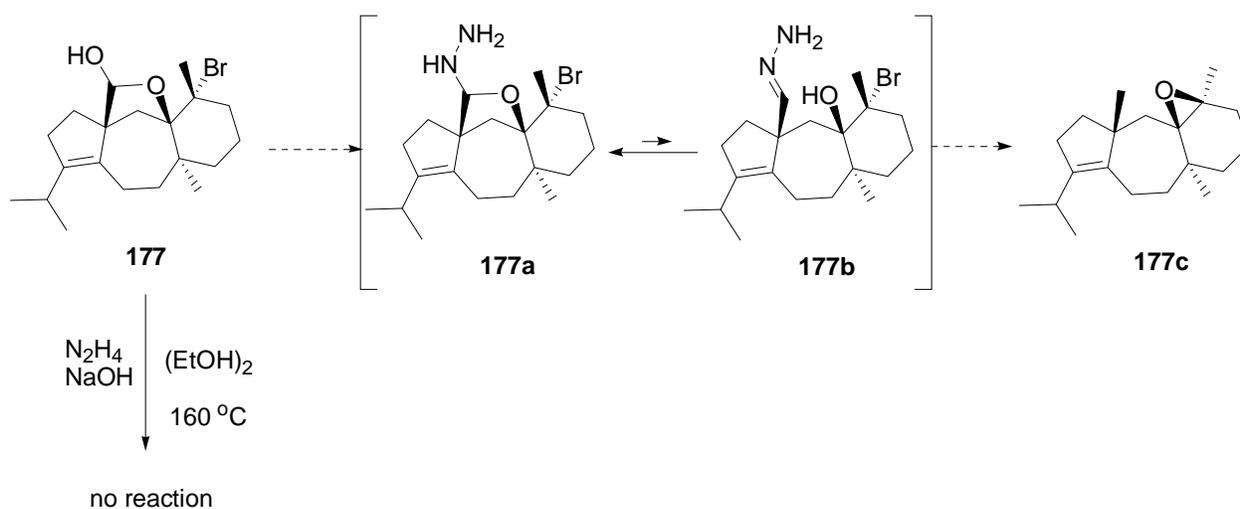
Scheme 41

We also investigated if **162** could be reduced to aldehyde alcohol **175** or the corresponding lactol **176** and then converted into thioacetal **177** (Scheme 42).



Scheme 42

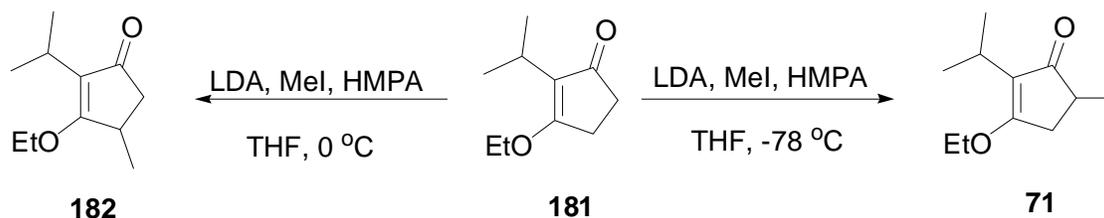
Knowing that the Wolff–Kishner reaction proceeds through several unfavorable intermediates, we hoped that hemi-acetal **177** would reduce to a methyl at C(16) using hydrazine and sodium hydroxide (Scheme 44). The nitrogen atom in hydrazine is a very good nucleophile so it should replace the hydroxy group at C(16) position (i.e. **177a**). However, the formation of hydrazone **177b** might be difficult; however, once formed **177b** must be reduced. Moreover, under the base conditions employed in the Wolff–Kishner reduction we hoped that epoxide **177c** would be produced. Unfortunately, no reaction occurred even after 24 hours refluxing at 160 °C.



Scheme 44

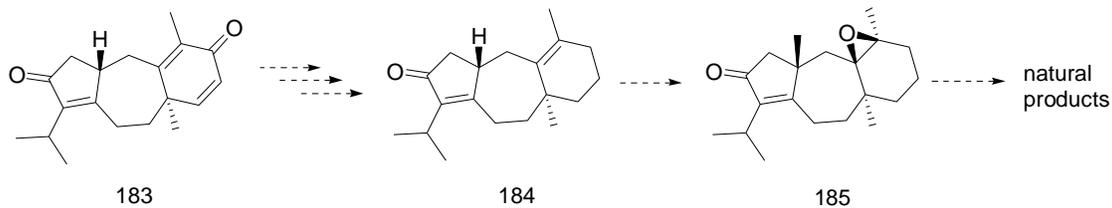
We explored other ways to get around the steric influence of the C(16) methyl group. Since it is known that for cyclopentenone system, the regioselectivity of alkylation reaction is depend

on the reaction temperature.³⁰ As shown in Scheme 45, we found this selectivity potentially useful.



Scheme 45

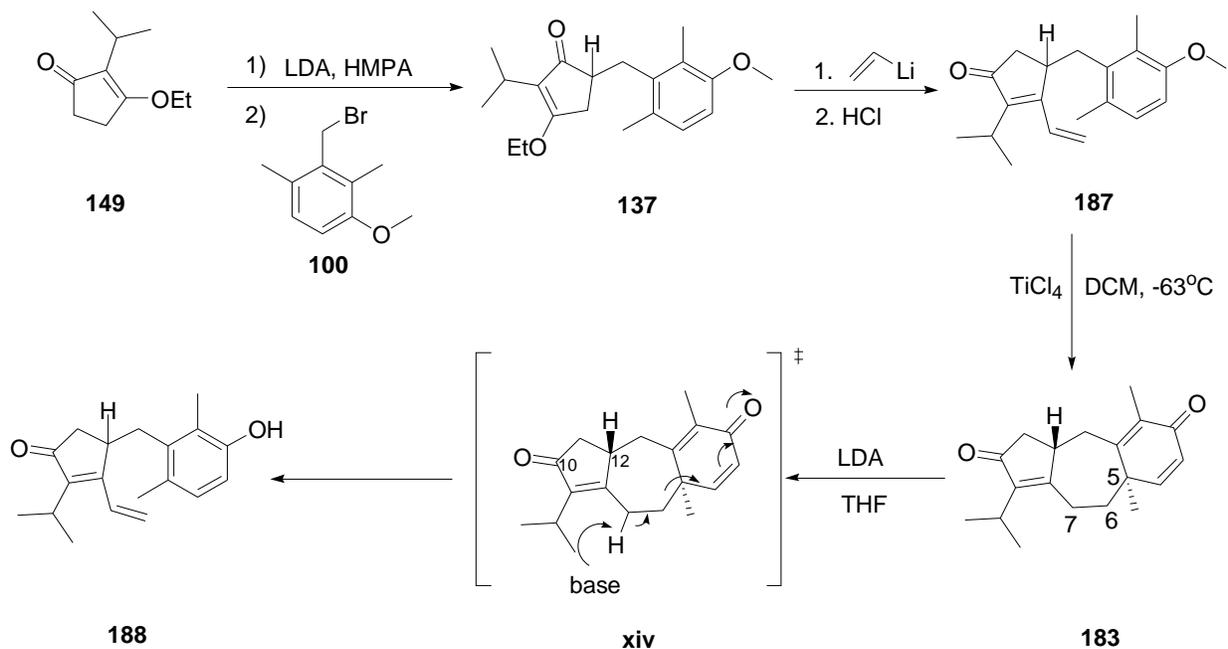
We were curious if in the absence of angular C(16) methyl group, previous strategies could work. Assuming that we could make compound **185**, this strategy required the introduction of the C(16) methyl at a late stage in the synthesis (Scheme 46).



Scheme 46

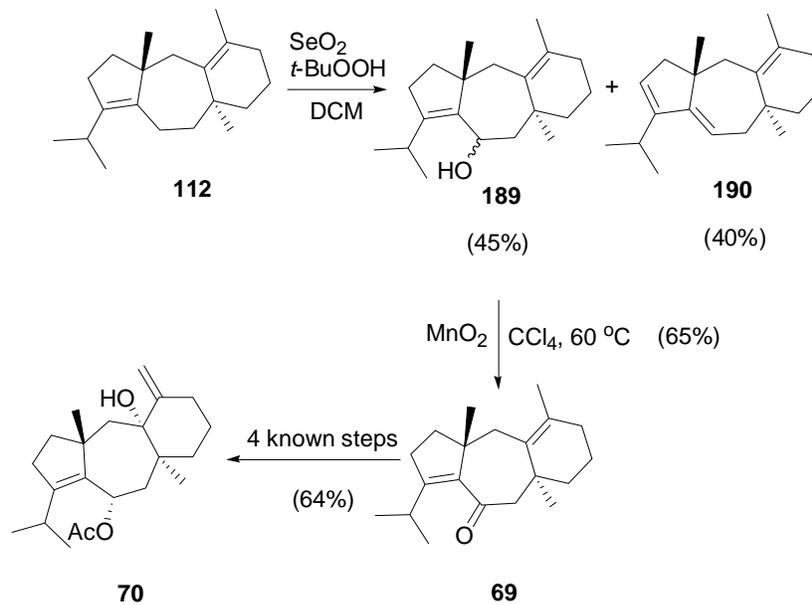
The first few steps of this revised strategy worked well (Scheme 47). Treatment of **183** with LDA at 0 °C was expected to remove the C(12) methine so that alkylation with iodomethane would introduce the desired C(12) angular methyl group. To our surprise, this reaction only gave

188, which results from the deprotonation at the C(7) position which causes the C(5), C(6)-bond to break and results in the rearomatization of the C-ring.



Scheme 47

Scheme 48 presents a formal synthesis of (\pm)-7,14-*epi*-1(15),8-dolastadien-7,14-*ol*. When compound **112** was treated under allylic oxidation condition, it gave two easily separable products **189** and **190**. Compound **189** was easily oxidized to the known enone **69** which represents a formal synthesis of **70**.



Scheme 48

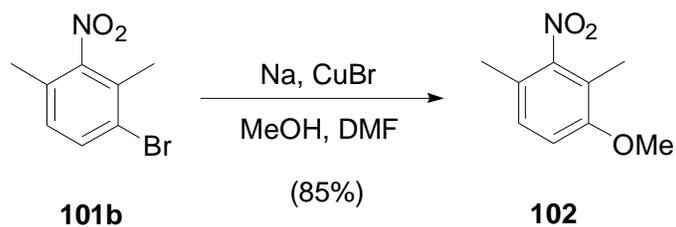
It is my belief that the multitude of results reported herein will one day permit the facile and efficient synthesis of several dolastanes and perhaps permit access to the dolabelladienes. Moreover, the difficulties we encountered to deoxygenate the C(16) neopentyl hydroxyl group may one day lead to a general, practical solution to this seemingly trivial transformation.

5. Experimental Section

General Procedures. All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at room temperature with water. The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was extracted with diethyl ether twice, combined organic layer was washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230–400 mesh ASTM) and elution with distilled reagent grade petroleum ether and diethyl ether. Melting points were recorded on a Laboratory Devices Mel–Temp 3.0. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB–400 and DRX–500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in CDCl_3 and were calibrated using trace CHCl_3 present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in CDCl_3 and were calibrated using trace CHCl_3 present (δ 77.23) as an internal reference. The IR spectra were obtained using an Avatar 360FT–IR and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution MS were taken using a LCT Premier from Waters.

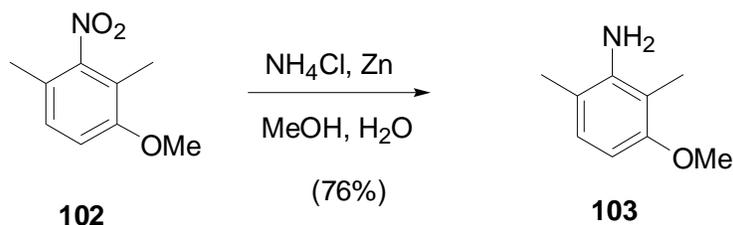


Bromide 101b from nitrobenzene 101: To a solution of **101** (50 g, 331 mmol) in freshly distilled DCM (150 mL) was added FeBr₃ (2.0 g, 6.8 mmol) and Fe (5.0 g, 89 mmol). Molecular bromine (18.6 mL, 361 mmol) was added dropwise and 100 mL of DCM was added to the mixture. The reaction mixture was refluxed for 8 h. The reaction mixture was cooled to rt followed by standard ethereal workup. The organic layer was dried over anhydrous MgSO₄, filtered, and then concentrated under vacuum using rotary evaporator to give 74.3 g (98.0%) of bromide **101b** as a crude red oil: ¹H (400 MHz) δ 7.55 (d, *J* = 4.8 Hz, 1H), 7.02 (d, *J* = 4.8 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H); ¹³C NMR (100 MHz) δ 134.0 (d), 129.9 (d), 129.6 (s), 128.7 (s), 123.2 (s), 18.3 (q), 17.3 (q) ppm; HRMS: [M]⁺_{observed} = 228.9738, [M]⁺_{calculated} = 228.9738; IR (film) λ_{max} 2927, 1517, 1370, 815 cm⁻¹. This crude bromide was used in the next reaction without purification.

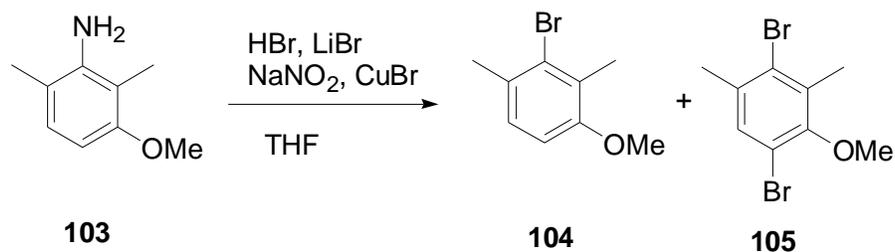


Anisole 102 from bromide 101b: A solution of sodium methoxide was prepared by portion-wise addition of sodium metal (21.0 g, 913 mmol) to anhydrous methanol (300 mL).

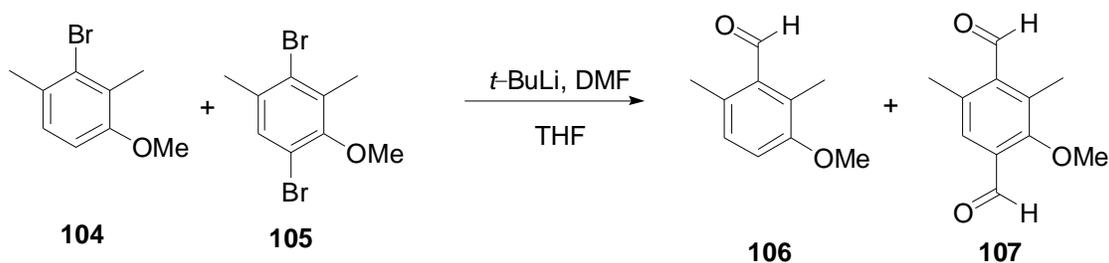
After the complete consumption of the sodium, a solution of **101b** (70.0 g, 304 mmol) in anhydrous DMF (300 mL) was added, followed by addition of CuBr (4.0, 28.0 mmol). The reaction mixture was heated to 110 °C for 12 h, then cooled to rt and H₂O (100 mL) was added dropwise to quench the reaction. Standard ethereal workup gave 46.8 g (85%) of **102** as a crude red oil which was carried to the next step without purification: ¹H (400 MHz) δ 7.06 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 2.23 (s, 3H), 2.14 (s, 3H); ¹³C NMR (100 MHz) δ 181.1 (s), 156.4 (s), 128.9 (d), 120.6 (s), 118.7 (s), 111.8 (d), 56.2 (q), 16.7 (q), 10.9 (q) ppm; HRMS: [M]⁺ observed = 181.0741, [M]⁺ calculated = 181.0739; IR (film) λ_{max} 2930, 1524, 1263, 1071, 810 cm⁻¹.



Aniline 103 from nitrobenzene 102: To a solution of **103** (30.0 g, 166 mmol) in MeOH (270 mL) and H₂O (30 mL) was added NH₄Cl (26.0 g, 486 mmol), followed by Zn powder (110 g, 1.68 mol) portion-wise. The reaction mixture was stirred at rt for 2 h, followed by standard ethereal workup gave 19.0 g (76.0%) of **103** as a crude red oil which was used in the next step without purification: ¹H (400 MHz) δ 6.89 (d, *J* = 8.4 Hz, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H); ¹³C NMR (100 MHz) δ 156.7 (s), 143.8 (s), 127.6 (d), 115.1 (s), 110.9 (s), 101.0 (d), 55.9 (q), 17.4 (q), 9.4 (q) ppm; HRMS: [M]⁺ observed = 152.1074, [M]⁺ calculated = 152.1075; IR (film) λ_{max} 3393, 2910, 1626, 1496, 1262, 791 cm⁻¹.

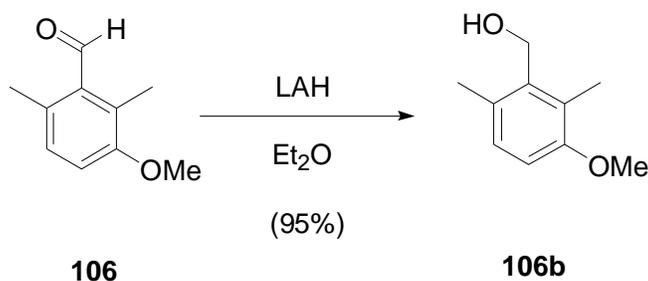


Bromide 104 and 105 from aniline 103: A round bottom flask at 0 °C was charged with HBr (4.67 g, 27.7 mmol), THF (60 mL), LiBr (1.14 g, 13.1 mmol), NaNO₂ (1.0 g, 14.5 mmol), and CuBr (2.26 g, 15.8 mmol). The ice bath was removed, followed by the dropwise addition of the **103** (3.0 g, 2.00 mmol) in THF (15 mL). The reaction mixture was stirred at rt for an additional 1 h followed by standard ethereal workup gave 3.43 g of a crude black oil which was subjected to the next step without attempted purification or characterization.



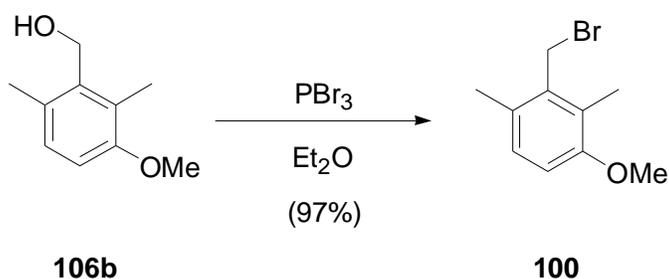
Aldehyde 106 and 107 from bromide 104 and 105: To a solution of **104** and **105** (34 g) in THF (250 mL) at -78 °C was slowly added *t*-BuLi (180 mL, 306 mmol). This mixture was stirred at -78 °C for 2 h followed by the addition of DMF (40 mL). The reaction mixture was warmed to rt and stirred overnight. Water (10 mL) was added slowly to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 1.22 g (37% over two steps) of aldehyde **106** (hexane/EtOAc, 4:1, R_f **106** = 0.66) as a white solid:

^1H (400 MHz) δ 10.6 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 3.83 (s, 3H), 2.51 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz) δ 194.5 (d), 156.4 (s), 133.8 (s), 132.1 (s), 129.8 (s), 129.6 (d), 115.0 (d), 56.1 (q), 20.1 (q), 11.5 (q) ppm; HRMS: $[\text{M}]^+$ observed = 164.0840, $[\text{M}]^+$ calculated = 164.0837; IR (film) λ_{max} 2939, 1691, 1262 cm^{-1} . Further elution gave 0.31 g (8.1% over two steps) of bisaldehyde **107** as a white solid (hexane/EtOAc, 4:1, R_f **107** = 0.45): mp = 82.0–82.3 $^\circ\text{C}$; ^1H (400 MHz) δ 10.6 (s, 1H), 10.4 (s, 1H), 7.54 (s, 1H), 3.85 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz) δ 193.7 (d), 190.1 (d), 160.4 (s), 138.8 (s), 136.2 (s), 134.9 (s), 131.4 (s), 128.9 (d), 63.8 (q), 19.9 (q), 11.8 (q) ppm; HRMS: $[\text{M}]^+$ observed = 192.0790, $[\text{M}]^+$ calculated = 192.0786; IR (film) λ_{max} 2930, 1691, 1409, 1232 cm^{-1} .



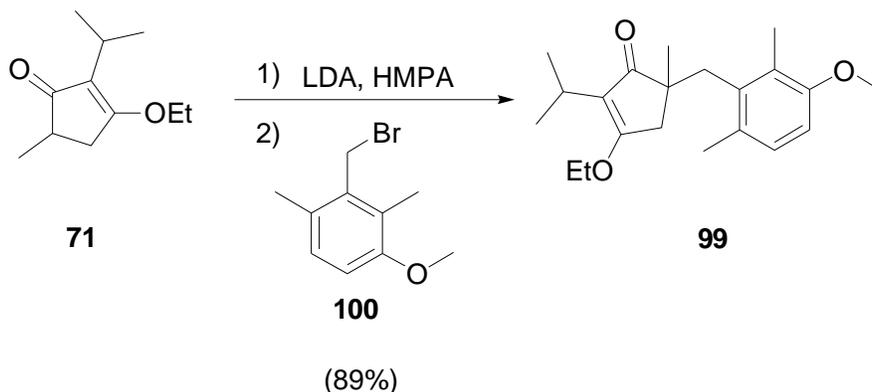
Alcohol 106b from aldehyde 106: A solution of aldehyde **106** (10.0 g, 61.0 mol) in Et_2O (150 mL) was cooled to 0 $^\circ\text{C}$ and LAH (2.55 g, 67.1 mmol) was added portion-wise. The ice bath was removed and the solution was stirred at rt for 1 h. The solution was poured into a big Erlenmeyer flask containing Na_2SO_4 (20 g) and EtOAc (300 mL). Water was added slowly until the heterogeneous mixture turned from grey to white. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc = 4:1), afforded 9.60 g (95%) **106b** as a white

solid (hexane/EtOAc, 4:1, R_f **106b** = 0.25): ^1H (400 MHz) δ 7.02 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz) δ 156.4 (s), 137.8 (s), 129.2 (s), 128.4 (d), 126.4 (s), 110.4 (d), 59.8 (t), 55.9 (q), 19.2 (q), 11.6 (q) ppm; HRMS: $[\text{M}]^+$ observed = 166.0999, $[\text{M}]^+$ calculated = 166.0994; IR (film) λ_{max} 3396, 2957, 1464, 1258 cm^{-1} .



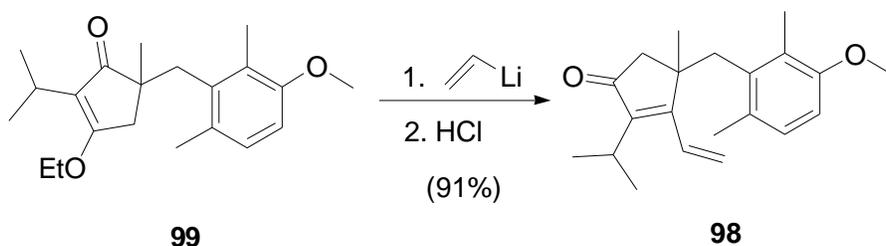
Bromide 100 from alcohol 106b: A solution of **106b** (5.00 g, 30.1 mmol) in Et_2O (150 mL) was cooled to 0 °C and PBr_3 (3.1 mL, 33.1 mmol) was added dropwise. The resulting solution was removed from the ice bath and stirred at rt for 1 h. The resulting solution was cooled to 0 °C and brine (30 mL) was added slowly. The aqueous phase was removed and the organic layer was dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure, and column chromatography (elution with pet ether/EtOAc, 15:1) afforded 6.69 g (97%) of **100** as a white solid (hexane/EtOAc, 4:1, R_f **100** = 0.80): mp = 62.3–62.5 °C; ^1H (400 MHz) δ 7.03 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 4.60 (s, 2H), 3.83 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz) δ 156.4 (s), 135.3 (s), 129.3 (s), 128.4 (d), 126.5 (s), 111.0 (d), 55.9

(q), 29.9 (t), 19.0 (q), 11.4 (q) ppm; HRMS: $[M+H]^+$ observed = 228.0140, $[M+H]^+$ calculated = 228.0150; IR (film) λ_{\max} 3000, 2833, 1486, 1261 cm^{-1} .

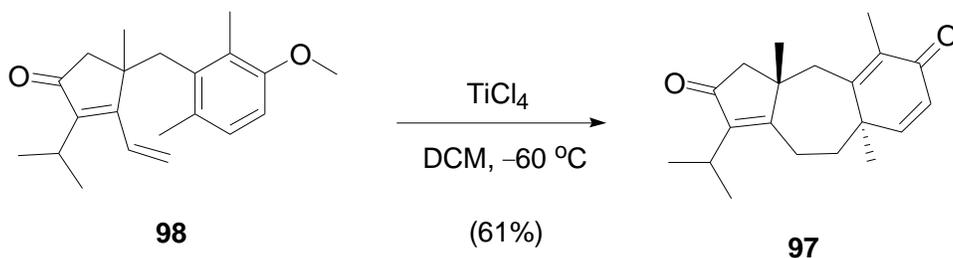


Adduct 99 prepared by coupling 71 with bromide 100: To a solution of diisopropylamine (2.40 mL, 17 mmol) in THF (20 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (6.30 mL, 16 mmol) over a 5-min period. The resulting mixture was stirred at rt for 10 min then cooled to $-78\text{ }^{\circ}\text{C}$. A solution of **71** (2.60 g, 14.3 mmol) and HMPA (2.60 g, 14.3 mmol) in THF (10 mL) was cannulated over a 5-min period. The resulting solution was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ then carefully raised to $-63\text{ }^{\circ}\text{C}$. A solution of **100** (2.94 g, 17.2 mmol) in THF (10 mL) was cannulated into the reaction mixture over a 2-min period. The resulting mixture was allowed to stir overnight. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 4.2 g (97%) of **99** as a light yellow oil (hexane/EtOAc, 4:1, R_f **99** = 0.47): ^1H (400 MHz) δ 6.94 (d, $J = 8.4$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 3.99 (m, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.28 (d, $J = 14.8$ Hz, 1H), 3.74 (d, $J = 14.8$ Hz, 1H), 2.71 (septet, $J = 7.2$ Hz, 1H), 2.38 (d, $J = 17.2$ Hz, 1H), 2.18 (s, 3H), 2.16 (d, $J = 17.2$ Hz, 1H), 2.10 (s, 3H), 1.28 (s, 3H), 1.19 (t, J

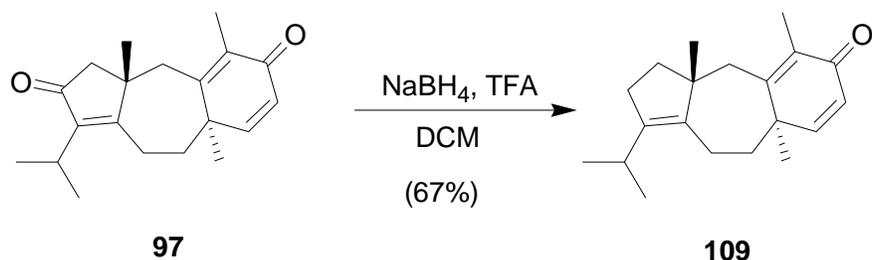
= 7.2 Hz, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz) δ 209.3 (s), 181.9 (s), 156.3 (s), 137.9 (s), 129.7 (s), 128.0 (d), 126.4 (s), 122.9 (s), 108.5 (d), 64.9 (t), 55.8 (q), 46.9 (s), 36.8 (t), 36.4 (t), 27.9 (q), 23.0 (d), 21.0 (q), 20.3 (q), 20.3 (q), 15.1 (q), 13.5 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 331.2266, $[\text{M}+\text{H}]^+$ calculated = 331.2273; IR (film) λ_{max} 2981, 1622, 1342, 1253 cm^{-1} .



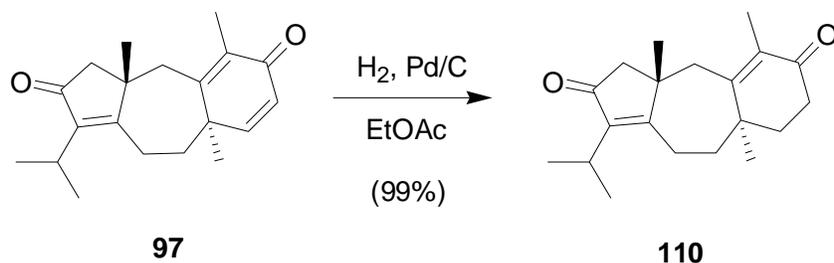
Dienone 98 from enone 99: To a solution of vinyl bromide (3.2 mL, 45 mmol) in freshly distilled Et_2O (60 mL) at -78 °C, *t*-butyllithium (54 mL, 1.7 M, 91 mmol) was added over a 15-min period. After stirring 2.5 h at rt, the vinyl lithium mixture was cannulated into **99** (2.00 g, 6.1 mmol) in THF (60 mL) solution at -78 °C. The resulting mixture was warmed to rt and stirred for an additional 8 h. Hydrochloric acid (20.0 mL, 1.0 M) was added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 8:1), gave 1.76 g (91%) of **99** as a light yellow oil (hexane/EtOAc, 2:1, R_f **99** = 0.75). No spectral data was collected due to the presence of an inseparable impurity.



Cylialkylation product 97 from dienone 98: To a solution of **98** (200 mg, 0.641 mmol) in fresh distilled DCM (2 mL) at $-78\text{ }^{\circ}\text{C}$ was added TiCl_4 (10 μL , 0.91 mmol). The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then the temperature was raised to $-63\text{ }^{\circ}\text{C}$ and stirred for an additional 0.5 h. Water (5 mL) was added dropwise to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 4:1) afforded 115 mg (61%) of **97** as a white solid (hexane/EtOAc, 2:1, R_f **97** = 0.41): ^1H (500 MHz) δ 6.81 (d, $J = 9.5\text{ Hz}$, 1H), 6.31 (d, $J = 9.5\text{ Hz}$, 1H), 3.03 (d, $J = 13.5\text{ Hz}$, 1H), 2.74 (m, 1H), 2.67 (septet, $J = 7.0\text{ Hz}$, 1H), 2.35 (m, 3H), 2.17 (m, 1H), 1.96 (s, 3H), 1.71 (m, 1H), 1.59 (m, 1H), 1.22 (s, 3H), 1.13 (m, 6H), 1.09 (s, 3H); ^{13}C NMR (125 MHz) δ 207.4 (s), 186.2 (s), 179.3 (s), 158.0 (s), 157.7 (d), 140.9 (s), 136.0 (s), 128.2 (d), 52.0 (t), 45.6 (t), 45.1 (s), 40.0 (t), 38.4 (t), 29.9 (q), 25.7 (q), 24.7 (d), 23.9 (t), 20.8 (q), 20.7 (q), 13.8 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 299.2010, $[\text{M}+\text{H}]^+$ calculated = 299.2011; IR (film) λ_{max} 2963, 1738, 1693, 1658, 1627, 1379 cm^{-1} .

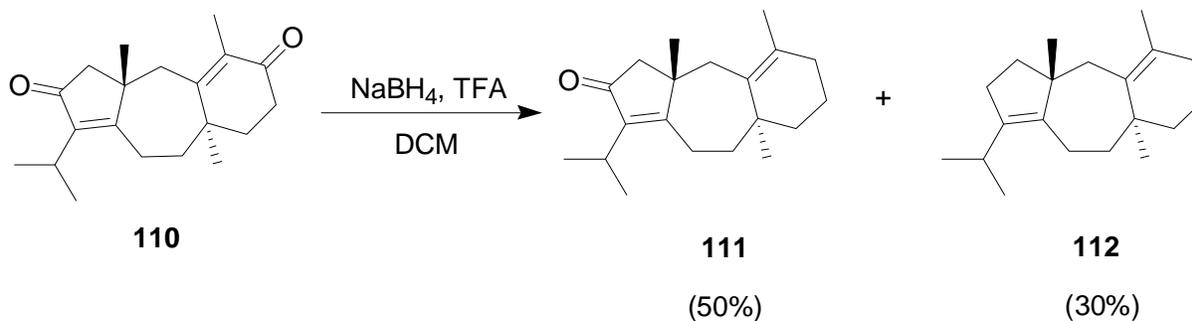


Dienone 109 from dione 97: To a solution of **97** (100 mg, 0.336 mmol) in freshly distilled DCM (10 mL) was added 10% TFA in DCM solution (5 mL), followed by NaBH₄ (64 mg, 1.7 mmol). The resulting mixture was stirred for 0.5 h. Water (5 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 64 mg (67%) of **109** as a light yellow oil (hexane/EtOAc, 4:1, R_f **109** = 0.55): No clean NMR spectrum due to the presence of some inseparable impurity. HRMS: [M+H]⁺_{observed} = 285.2222, [M+H]⁺_{calculated} = 285.2218; IR (film) λ_{max} 2963, 1658, 1462, 1151 cm⁻¹.



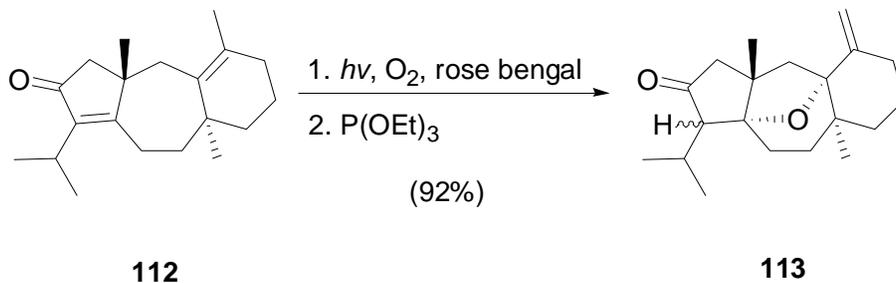
Enone 110 from dione 97: To a dry 20-mL round-bottomed flask was added **97** (100 mg, 0.336 mmol) under nitrogen atmosphere, followed by addition of anhydrous EtOAc (5 mL), and 5% of Pd/C (10 mg, 10% in weight). Nitrogen in the round-bottomed flask was removed by bubbling H₂ under the reaction medium until the reaction flask was filled with H₂. A balloon

filled with H₂ was connected to the round-bottomed flask and the system was sealed with Teflon tape. The resulting mixture was stirred under H₂ for 2 h. At which time the H₂ balloon was disconnected and the residue H₂ gas was removed by bubbling N₂ into the reaction mixture. The mixture was filtrated through a short pad of silica gel to remove the catalyst. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 4:1), gave 100 mg (99%) of **110** as a white solid (hexane/EtOAc, 2:1, R_f **110** = 0.40): mp = 147.0–147.2 °C; ¹H (400 MHz) δ 2.87 (d, *J* = 13.2 Hz, 1H), 2.52–2.79 (m, 4H), 2.39 (d, *J* = 18.0 Hz, 1H), 2.30 (d, *J* = 18.8 Hz, 1H), 2.21 (m, 2H), 2.04 (m, 1H), 1.85 (s, 3H), 1.79 (m, 1H), 1.58 (m, 2H), 1.17 (m, 9H), 1.13 (s, 3H); ¹³C NMR (100 MHz) δ 207.3 (s), 198.5 (s), 179.5 (s), 160.6 (s), 140.6 (s), 135.3 (s), 52.0 (t), 44.5 (s), 41.0 (t), 40.1 (t), 34.9 (t), 34.4 (t), 26.6 (q), 25.5 (q), 24.7 (d), 22.5 (t), 20.9 (q), 20.8 (q), 13.7 (q) ppm; HRMS: [M+H]⁺ observed = 301.2167, [M+H]⁺ calculated = 301.2168; IR (film) λ_{max} 3376, 2959, 1697, 1460, 1379, 1118 cm⁻¹.



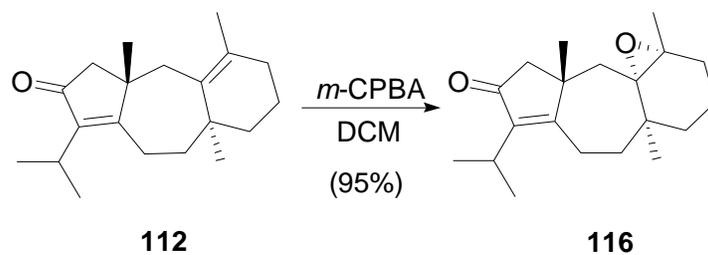
Enone 111 and diene 112 from dienone 110: To a solution of **110** (153 mg, 0.510 mmol) in fresh distilled DCM (15 mL) was added 10% TFA in DCM solution (10 mL), followed by NaBH₄ (97 mg, 2.6 mmol). The resulting mixture was stirred for 0.5 h at rt. Water (5 mL) was

added to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 44 mg (30%) of **112** as a light yellow oil (hexane/EtOAc, 4:1, R_f **112** = 0.90): ^1H (400 MHz) δ 2.67 (m, 3H), 1.70–2.33 (m, 9H), 1.67 (s, 3H), 1.35 (m, 2H), 1.15 (m, 6H), 1.10 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz) δ 208.6 (s), 182.5 (s), 139.7 (s), 132.9 (s), 131.9 (s), 52.0 (t), 44.9 (s), 41.7 (t), 38.3 (s), 37.9 (t), 37.2 (t), 32.3 (t), 28.4 (q), 25.7 (q), 24.6 (d), 22.9 (t), 21.8 (q), 20.9 (q), 19.3 (t) ppm; HRMS: $[\text{M}]^+$ observed = 286.2295, $[\text{M}]^+$ calculated = 286.2297; IR (film) λ_{max} 2933, 1464, 1372 cm^{-1} . Further elution gave 73 mg (50%) of **111** as a light yellow oil (hexane/EtOAc, 4:1, R_f **111** = 0.55): ^1H (400 MHz) δ 2.58–2.74 (m, 3H), 2.30 (d, J = 18.4 Hz, 1H), 2.20 (d, J = 18.0 Hz, 1H), 2.12 (m, 1H), 1.95 (m, 3H), 1.68–1.84 (m, 3H), 1.67 (s, 3H), 1.25–1.44 (m, 3H), 1.15 (m, 6H), 1.10 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz) δ 208.6 (s), 182.5 (s), 139.7 (s), 132.9 (s), 131.9 (s), 52.0 (t), 44.9 (s), 41.7 (t), 38.3 (s), 37.9 (t), 37.2 (t), 32.3 (t), 28.4 (q), 25.7 (q), 24.6 (d), 22.9 (t), 21.8 (q), 20.9 (q), 19.3 (t) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 287.2376, $[\text{M}+\text{H}]^+$ calculated = 287.2375.



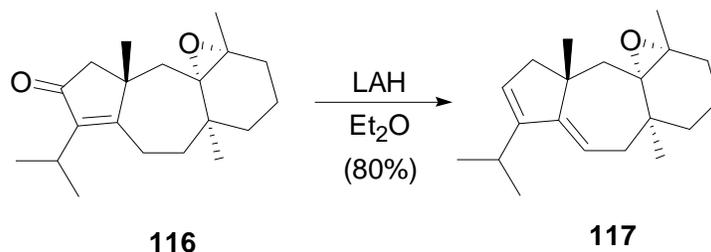
Furan 113 from alkene 112: A solution of **112** (10 mg, 0.034 mmol) and rose bengal (2.0 mg) in 5 mL of a solution of methanol:dichloromethane (1:9) was irradiated at -5 $^\circ\text{C}$ with a 500-W

tungsten lamp while oxygen was bubbled through the reaction mixture. After 40 min, the reaction mixture was treated with triethyl phosphite (0.3 mL) at rt for 1 h with vigorous stirring. After concentration, standard ethereal workup provided a crude residue which was purified by column chromatography (elution with pet ether: EtOAc, 10:1) to gave 9.9 mg (92%) of furan **113** (hexane: EtOAc, 4:1, R_f **113** = 0.45) as a colorless oil: ^1H (400 MHz) δ 4.76 (s, 1H), 4.66 (s, 1H), 2.93 (d, J = 17.6 Hz, 1H), 2.61–2.74 (m, 2H), 2.08–2.41 (m, 6H), 1.72–1.80 (m, 1H), 1.58–1.69 (m, 4H), 1.25–1.40 (m, 2H), 1.20 (m, 6H), 1.12 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz) δ 217.0 (s), 148.7 (s), 103.1 (t), 90.9 (s), 86.6 (s), 59.2 (d), 54.6 (t), 46.6 (t), 44.9 (q), 36.2 (s), 35.8 (t), 32.8 (t), 31.4 (t), 25.7 (d), 24.4 (t), 21.9 (q), 21.2 (t), 19.9 (q), 18.8 (q), 18.1 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 303.2316, $[\text{M}+\text{H}]^+$ calculated = 303.2324; IR (film) λ_{max} 2933, 1740, 1075, 895 cm^{-1} .



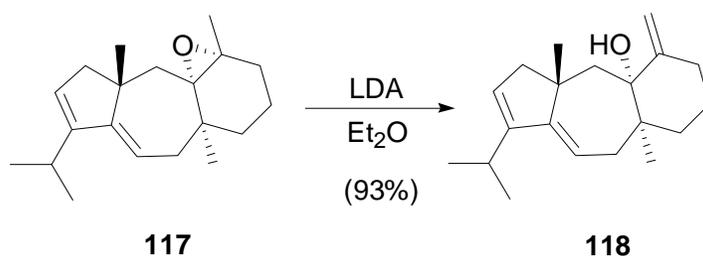
Epoxide 116 from alkene 113: To a solution of diene **113** (35 mg, 0.12 mmol) in freshly distilled DCM (4 mL) under nitrogen atmosphere was added *m*-CPBA (77%, 33 mg, 0.15 mmol, 1.2 equivalents). The resulting mixture was stirred at rt for 1 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 5:1), afforded 35.0 mg (95%) of **116** as a white foam (hexane/EtOAc, 2:1, R_f **116** = 0.49): ^1H (400 MHz) δ 2.87 (m, 1H), 2.73

(septet, $J = 7.2$ Hz, 1H), 2.42 (m, 1H), 2.22 (d, $J = 8.8$ Hz, 2H), 1.90–2.12 (m, 3H), 1.64–1.83 (m, 3H), 1.39–1.52 (m, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.20–1.25 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz) δ 207.3 (s), 179.4 (s), 141.2 (s), 68.6 (s), 65.3 (s), 53.3 (t), 42.8 (s), 42.2 (t), 37.7 (s), 36.8 (t), 36.7 (t), 31.4 (t), 25.9 (q), 24.8 (d), 24.2 (t), 23.4 (q), 23.0 (q), 20.4 (q), 20.3 (q), 16.6 (q) ppm; HRMS: $[\text{M}]^+$ observed = 302.2243, $[\text{M}]^+$ calculated = 302.2246; IR (film) λ_{max} 3006, 2918, 1717, 1364, 1224 cm^{-1} .



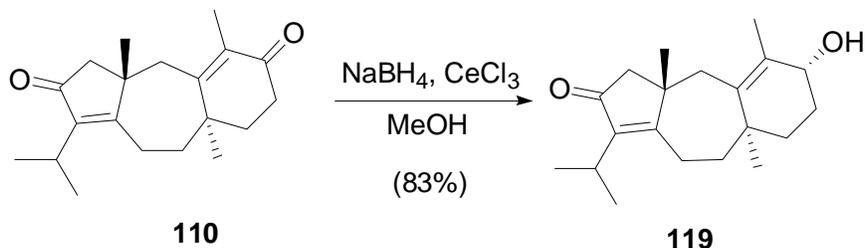
Diene 117 from enone 116: To a solution of **116** (60 mg, 0.20 mmol) in freshly distilled Et_2O (10 mL) at 0°C under nitrogen atmosphere was added LAH (7.6 mg, 0.20 mmol, 1.0 equivalent). The resulting reaction mixture was stirred for 1 h at rt. Water (4 mL) was slowly added to quench the reaction, followed by standard ethereal workup. Concentration of the filtered organic phase afforded yellow oil. Silica gel was added to the bottle and the resulting mixture was allowed to sit on the bench overnight. Column chromatography (elution with pet ether/ EtOAc , 15:1) afforded 45.5 mg (80%) of **117** (hexane/ EtOAc , 8:1, R_f **117** = 0.50) as a colorless oil: ^1H (500 MHz) δ 5.60 (s, 1H), 5.45 (m, 1H), 2.90 (d, $J = 15.0$ Hz, 1H), 2.41 (m, 1H), 2.14–2.33 (m, 3H), 1.70–1.98 (m, 4H), 0.80–1.62 (m, 4H), 1.39 (s, 3H), 1.18 (s, 3H), 1.07–1.13 (m, 6H), 1.03

(s, 3H); ^{13}C NMR 154.5 (s), 149.5 (s), 125.6 (d), 113.6 (d), 70.4 (s), 65.8 (s), 49.6 (t), 43.5 (s), 39.2 (t), 37.9 (s), 37.2 (t), 34.8 (t), 30.1 (t), 25.7 (d), 24.0 (q), 23.7 (q), 23.3 (q), 22.3 (q), 22.3 (q), 16.7 (t) ppm; HRMS: $[\text{M}]^+$ observed = 286.2297, $[\text{M}]^+$ calculated = 286.2297; IR (film) λ_{max} 3247, 2952, 1660, 1359, 1010 cm^{-1} .

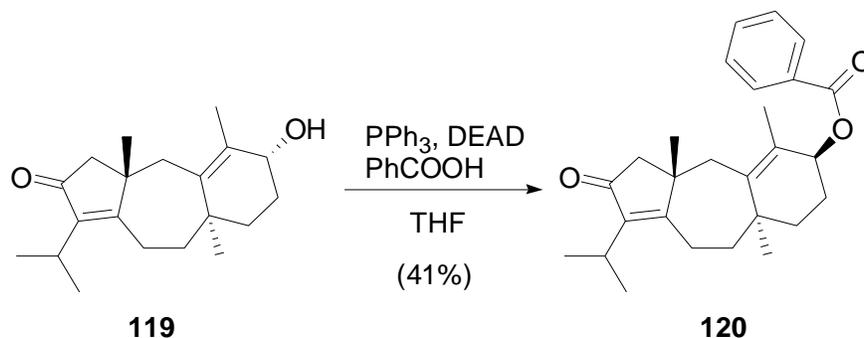


Alcohol 118 from epoxide 117: To a solution of diisopropylamine (0.70 mL, 5.0 mmol) in freshly distilled Et₂O (10 mL) at 0 °C was added *n*-butyllithium (2 mL, 5 mmol). The resulting mixture was stirred at rt for 10 min. Compound **117** (8.0 mg, 0.028 mmol) was transferred into a sealed tube, and 2 mL of the above LDA solution was added. The reaction vessel was closed and it was heated to 50 °C and kept at this temperature for 36 h. Water (2 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 15:1) afforded 7.4 mg (93%) of **118** (hexane/EtOAc, 8:1, R_f **118** = 0.81) as a colorless oil: ^1H (500 MHz) δ 5.74 (t, J = 7.0 Hz, 1H), 5.70 (s, 1H), 5.02 (s, 1H), 4.69 (s, 1H), 3.01 (s, 1H), 2.61 (d, J = 17.0 Hz, 1H), 2.44 (septet, J = 7.0 Hz, 1H), 2.36 (m, 2H), 2.27 (m, 1H), 2.12 (dd, J_1 = 3.0 Hz, J_2 = 16.5 Hz, 1H), 2.03 (dt, J_1 = 12.5 Hz, J_2 = 5 Hz, 1H), 1.83 (m, 2H), 1.40–1.62 (m, 3H), 1.44 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.11 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz) δ 157.5 (s), 153.6 (s), 148.6 (s), 128.3 (d), 125.8 (d), 107.1 (t),

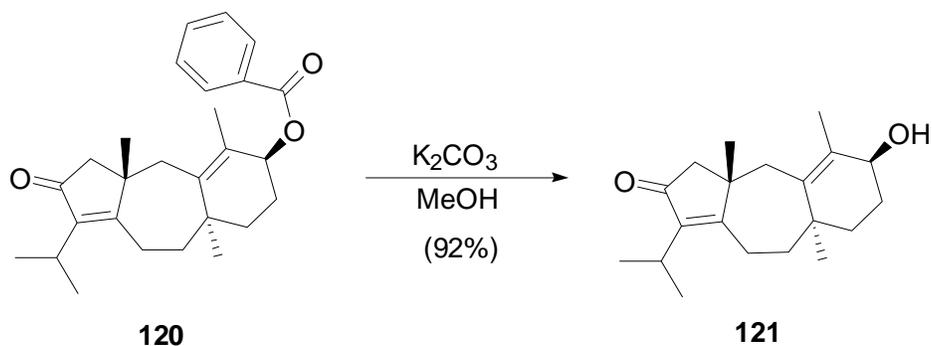
79.2 (s), 50.5 (t), 45.4 (t), 44.4 (s), 41.7 (t), 39.0 (t), 34.7 (t), 30.6 (q), 28.4 (q), 25.9 (d), 23.6 (t), 22.2 (q), 21.7 (q), 21.3 (q) ppm; HRMS: $[M]^+$ observed = 286.2300, $[M]^+$ calculated = 286.2297; IR (film) λ_{\max} 3556, 2923, 1466, 1115 cm^{-1} .



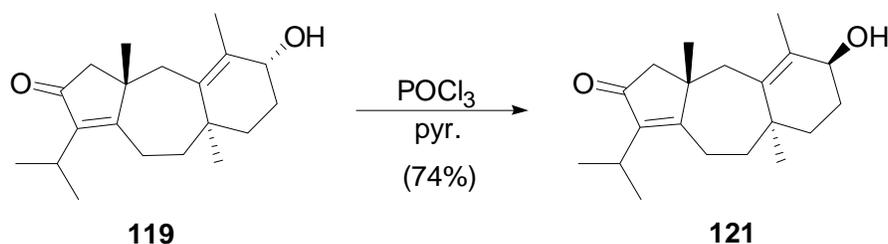
Alcohol 119 from diketone 110: Diketone **110** (23.2 mg, 0.0734 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (27 mg, 0.073 mmol) were dissolved in methanol (2 mL). NaBH_4 (3.3 mg, 0.088 mmol) was added in one portion. The resulting mixture was stirred at rt for 1 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 4:1), afforded 19 mg (83%) of **119** (hexane/EtOAc, 2:1, R_f **119** = 0.31) as a colorless oil: mp = 92.0–92.9 $^\circ\text{C}$; ^1H (400 MHz) δ 4.16 (t, J = 6.8 Hz, 1H), 2.67 (m, 3H), 2.32 (d, J = 18.4 Hz, 1H), 2.22 (d, J = 18.0 Hz, 1H), 2.11 (m, 1H), 1.98 (m, 2H), 1.81 (s, 3H), 1.68–1.80 (m, 4H), 1.38 (m, 2H), 1.16 (d, J = 1.6 Hz, 3H), 1.14 (d, J = 1.2 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz) δ 208.3 (s), 181.5 (s), 140.1 (s), 136.9 (s), 134.5 (s), 70.6 (d), 52.1 (t), 44.7 (s), 41.2 (t), 38.7 (t), 38.5 (s), 35.3 (t), 29.7 (t), 28.5 (q), 25.5 (q), 24.6 (d), 23.1 (t), 20.8 (q), 17.0 (q) ppm; HRMS: $[M]^+$ observed = 302.2251, $[M+H]^+$ calculated = 302.2246; IR (film) λ_{\max} 3448, 2929, 1694, 1458, 1015 cm^{-1} .



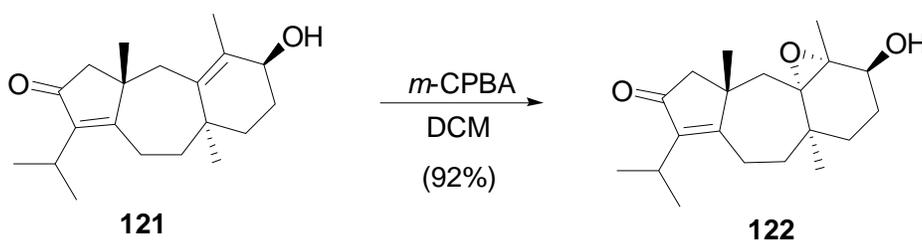
Benzoate 120 from alcohol 119: Allylic alcohol **119** (71 mg, 0.22 mmol) was dissolved in THF (7 mL). Triphenylphosphine (441 mg, 1.68 mmol, 8 equiv), DEAD (0.30 mL, 1.68 mmol, 8 equiv) and benzoic acid (206 mg, 1.68 mmol, 8 equiv) was added. The reaction mixture was allowed to stir overnight. Standard ethereal workup, followed by column chromatography purification (elution with pet ether/EtOAc, 10:1), afforded 39 mg (41%) of **120** (hexane/EtOAc, 2:1, R_f **120** = 0.75): ^1H (400 MHz) δ 8.03 (m, 2H), 7.58 (m, 1H), 7.46 (t, $J = 8.0$ Hz, 2H), 5.41 (d, $J = 3.6$ Hz, 1H), 2.73 (m, 3H), 2.36 (d, $J = 14.4$ Hz, 1H), 2.25 (d, $J = 18.0$ Hz, 1H), 1.96–2.18 (m, 5H), 1.79 (s, 3H), 1.77 (m, 1H), 1.45 (m, 1H), 1.26 (m, 1H), 1.19 (m, 9H), 1.04 (s, 3H); ^{13}C NMR (100 MHz) δ 208.1 (s), 181.6 (s), 166.5 (s), 141.3 (s), 139.9 (s), 133.1 (d), 131.1 (s), 130.0 (s), 129.7 (d), 128.7 (d), 73.1 (d), 52.0 (t), 44.7 (s), 41.4 (t), 39.0 (s), 37.8 (t), 32.2 (t), 27.2 (q), 25.7 (t), 25.6 (q), 24.6 (s), 22.8 (t), 20.9 (q), 20.9 (q), 20.0 (q) ppm; HRMS: $[\text{M}]^+$ observed = 407.2572, $[\text{M}+\text{H}]^+$ calculated = 407.2586; IR (film) λ_{max} 2958, 1790, 1259 cm^{-1} .



Alcohol 121 from benzoate 120: To a solution of **120** (39 mg, 0.091 mmol) in methanol (5 mL) was added K_2CO_3 (126 mg, 0.912 mmol, 10 equiv). The resulting mixture was heated to 40 °C and stirred for 4 days. The solvent was removed followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 4:1) afforded 26.7 mg (92%) of **121** (hexane/EtOAc, 2:1, R_f **121** = 0.30): ^1H (400 MHz) δ 3.92 (bs, 1H), 2.66 (m, 2H), 2.32 (d, J = 18.0 Hz, 1H), 2.21 (d, J = 18.4 Hz, 1H), 2.00 (m, 3H), 1.85 (s, 3H), 1.17–1.82 (m, 6H), 1.14 (m, 9H), 0.97 (s, 3H); ^{13}C NMR (100 MHz) δ 208.4 (s), 182.0 (s), 139.8 (s), 138.1 (s), 133.7 (s), 69.9 (d), 52.0 (t), 44.7 (s), 41.3 (t), 39.1 (s), 37.8 (t), 31.7 (t), 28.4 (t), 27.1 (q), 25.6 (q), 24.6 (d), 22.9 (t), 20.9 (q), 20.0 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 303.2325, $[\text{M}+\text{H}]^+$ calculated = 303.2324; IR (film) λ_{max} 3421, 2958, 1694, 1459 cm^{-1} .

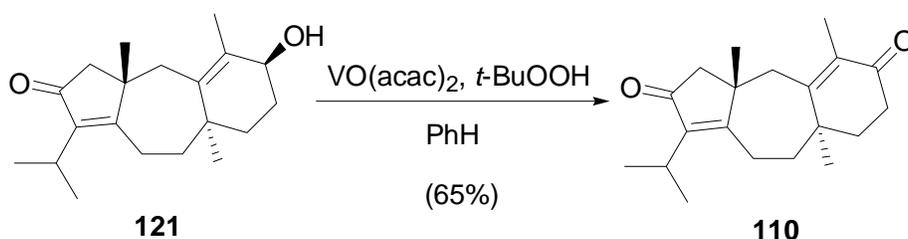


Alcohol 121 from alcohol 119: To a solution of **119** (36 mg, 0.11 mmol) in anhydrous pyridine (2 mL) at 0 °C was added POCl₃ (53 μL, 0.57 mmol, 5 equiv). After stirring at 0 °C for 5 minutes, water (5 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography purification (elution with pet ether/EtOAc, 4:1) afforded 27 mg (92%) of **121** (hexane/EtOAc, 2:1, R_f **121** = 0.30). which was identical to that prepared using the Mitsunobu procedure.

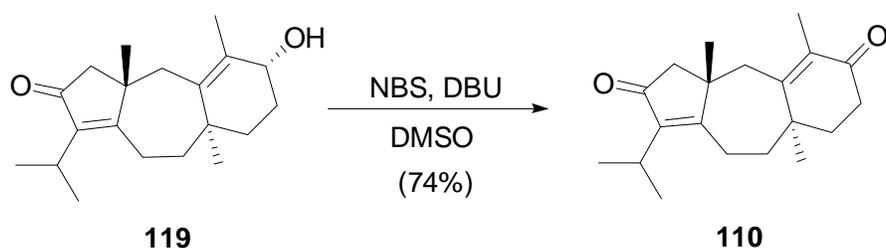


Epoxide 122 from alkene 121: To a solution of diene **121** (28 mg, 0.093 mmol) in freshly distilled DCM (5 mL) under nitrogen atmosphere was added *m*-CPBA (77%, 36 mg, 0.16 mmol, 1.7 equiv). The resulting mixture was stirred at rt for 1 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 4:1), afforded 27 mg (92%) of **122** as a white foam (hexane: EtOAc, 2:1, R_f **122** = 0.25): ¹H (400 MHz) δ 3.97 (t, *J* = 4.4 Hz, 1H), 2.83 (m, 1H), 2.72 (septet, *J* = 6.8 Hz, 1H), 2.42 (m, 1H), 2.26 (d, *J* = 18.0 Hz, 1H), 2.17 (d, *J* = 18.0

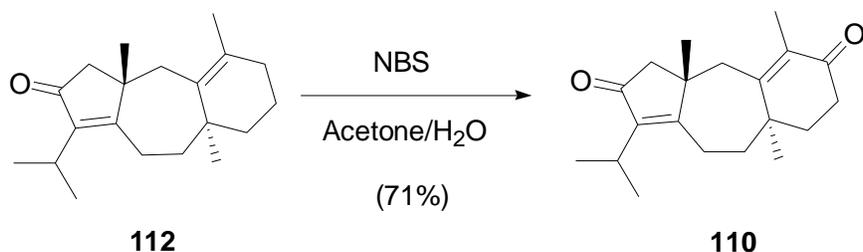
Hz, 1H), 1.98 (m, 1H), 1.88 (m, 1H), 1.66 (m, 2H), 1.51 (s, 3H), 1.39–1.50 (m, 2H), 1.32 (s, 3H), 1.16 (d, $J = 7.2$ Hz, 6H), 1.07 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz) δ 207.5 (s), 180.1 (s), 140.6 (s), 71.0 (d), 69.5 (s), 66.8 (s), 53.1 (t), 42.8 (s), 41.8 (t), 38.2 (t), 37.8 (s), 30.8 (t), 26.3 (t), 26.1 (q), 24.7 (d), 23.9 (q), 23.7 (t), 20.6 (q), 20.5 (q), 19.7 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 319.2272, $[\text{M}+\text{H}]^+$ calculated = 319.2273; IR (film) λ_{max} 3451, 2957, 1695, 1460, 1379 cm^{-1} .



Dienone 110 from alcohol 121: To a solution of **121** (6.0 mg, 0.020 mmol) in anhydrous benzene (1 mL) was added $\text{VO}(\text{acac})_2$ (1.0 mg, 2.8 μmol) and $t\text{-BuOOH}$ (2.0 μL , 0.024 mmol, 1.2 equiv). The resulting mixture was heated to 50 $^\circ\text{C}$ and stirred at this temperature for 3 days. Water (2 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography purification (elution with pet ether/EtOAc, 4:1) gave 3.9 mg as a white solid (65%) of **110** (hexane/EtOAc, 2:1, R_f **110** = 0.40) which was identical to that previously characterized.

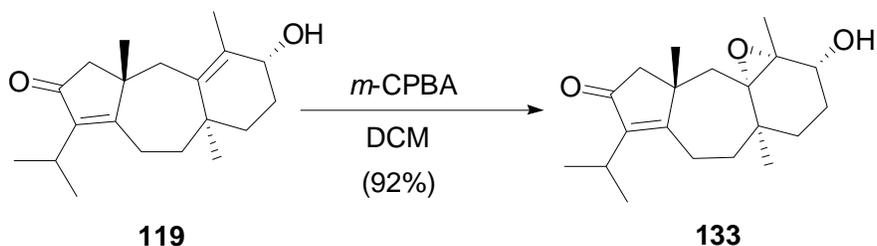


Dienone 110 from alcohol 119: To a solution of **119** (15 mg, 0.050 mmol) in anhydrous DMSO (1 mL) at 10 °C was added *N*-bromosuccinimide (14 mg, 0.079 mmol, 1.6 equiv). The resulting reaction mixture was stirred for 10 minutes. DBU (15 μ L, 0.16 mmol, 2.0 equiv) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (15 mL) was used to extract the DMSO solution. The ethereal extracts were combined and concentrated. Column chromatography (elution with pet ether/EtOAc, 4:1) gave 11 mg (74%) of **110** (hexane/EtOAc, 2:1, R_f **110** = 0.40) as a white solid which was identical to that previously characterized.

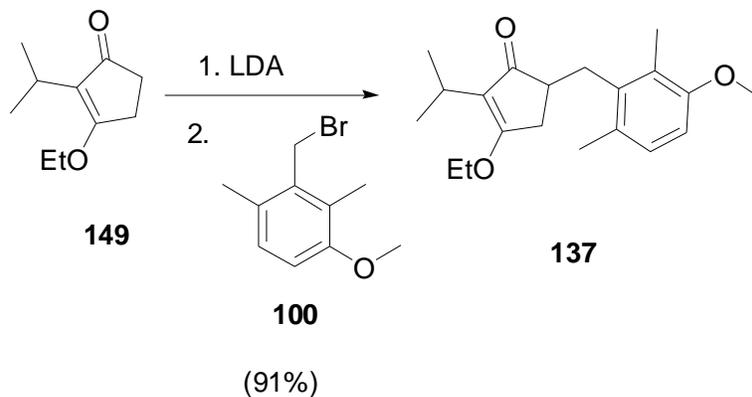


Dienone 110 from enone 112: To a solution of **112** (10 mg, 0.035 mmol) in acetone (2 mL) and H₂O (1 mL) was added *N*-bromosuccinimide (8.1 mg, 0.046 mmol, 1.3 equiv) in one portion. The resulting mixture was stirred at rt for 5 minutes and was quenched with water (2 mL). Acetone was removed under vacuum using a rotary evaporator, followed by standard ethereal

workup. Column chromatographic purification (elution with pet ether/EtOAc, 4:1) gave 7.4 mg (71%) of **110** (hexane/EtOAc, 2:1, R_f **110** = 0.40) as a white solid which was identical to that previously characterized.

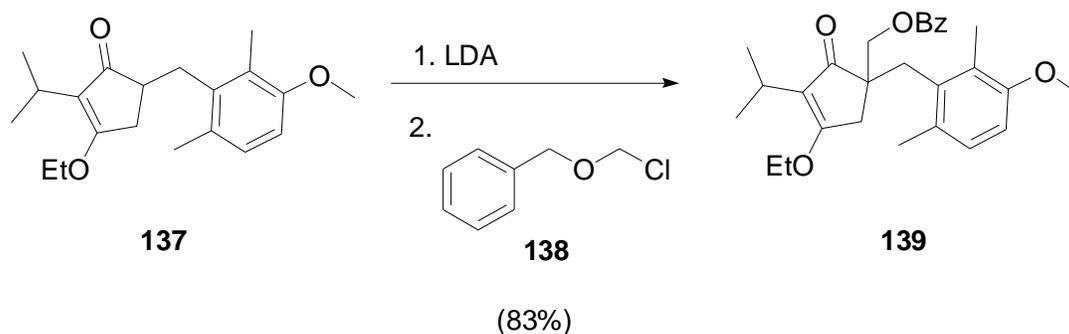


Epoxide 133 from alcohol 119: To a solution of **119** (80 mg, 0.27 mmol) in freshly distilled DCM (4.0 mL) under nitrogen atmosphere was added m -CPBA (77%, 71 mg, 0.32 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 1 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 1:1), afforded 77 mg (92%) of **133** as a white foam (hexane/EtOAc, 1:2, R_f **133** = 0.23): ^1H (400 MHz) δ 3.84 (t, J = 4.8 Hz, 1H), 2.91 (m, 1H), 2.72 (septet, J = 7.2 Hz, 1H), 2.47 (dt, J_1 = 4.8 Hz, J_2 = 17.2 Hz, 1H), 2.28 (d, J = 18.0 Hz, 1H), 2.21 (d, J = 18.4 Hz, 1H), 2.10 (m, 2H), 1.78 (m, 2H), 1.54 (s, 3H), 1.40–1.53 (m, 4H), 1.32 (s, 3H), 1.17 (d, J = 7.2 Hz, 6H), 0.99 (s, 3H); ^{13}C NMR (100 MHz) δ 206.9 (s), 178.2 (s), 142.0 (s), 72.0 (s), 70.1 (d), 68.2 (s), 53.5 (t), 42.7 (s), 42.2 (t), 37.3 (s), 35.2 (t), 33.7 (t), 26.7 (t), 25.6 (q), 24.9 (d), 24.6 (t), 22.7 (q), 20.3 (q), 20.1 (q), 19.4 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 319.2272, $[\text{M}+\text{H}]^+$ calculated = 319.2273; IR (film) λ_{max} 3482, 2958, 1697, 1016 cm^{-1} .



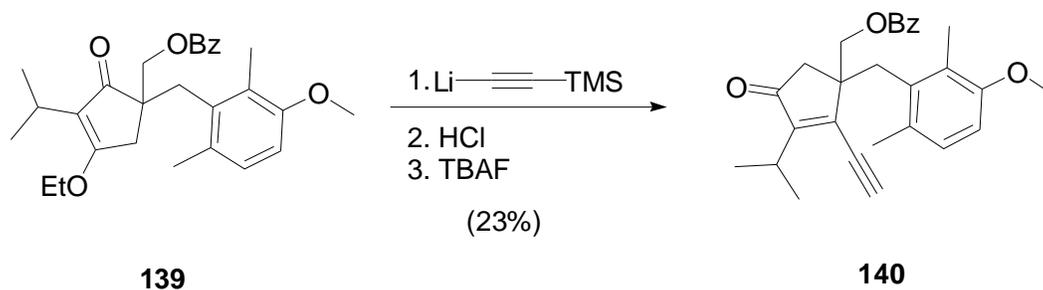
Adduct 137 from enone 149 and bromide 100: To a solution of diisopropylamine (2.39 mL, 17 mmol) in THF (14 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (6.30 mL, 16 mmol) over a 5-minute period. The resulting mixture was stirred at rt for 10 minutes then low to $-78\text{ }^{\circ}\text{C}$. A solution of **71** (2.39 g, 14.2 mmol) and HMPA (2.75 g, 14.2 mmol) in THF (4 mL) was cannulated over a 5-minute period. The resulting solution was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ then the reaction temperature was raised to $-63\text{ }^{\circ}\text{C}$. A solution of **100** (3.92 g, 17.1 mmol) in THF (4 mL) was cannulated into the above solution over a 2-minute period. The resulting mixture was stirred overnight. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 4.07 g (91%) of **137** as light yellow oil (hexane/EtOAc, 4:1, R_f **137** = 0.45): ^1H (400 MHz) δ 6.99 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 3.28 (dd, $J_1 = 3.6$ Hz, $J_2 = 13.2$ Hz, 1H), 2.60–2.84 (m, 3H), 2.54 (dd, $J_1 = 6.4$ Hz, $J_2 = 17.6$ Hz, 1H), 2.31 (s, 3H), 2.25 (m, 1H), 2.24 (s, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.15 (m, 6H); ^{13}C NMR (100 MHz) δ 206.1 (s), 182.5 (s), 156.4 (s), 138.4 (s), 128.6 (s), 128.3 (d), 125.4 (s), 124.5 (s), 108.3 (d), 65.2 (t), 55.7 (q), 44.9 (d), 31.2 (t), 30.5 (t), 23.1 (d), 20.5 (q), 20.4 (q),

15.5 (q), 12.8 (q) ppm; HRMS: $[M+H]^+$ observed = 317.2114, $[M+H]^+$ calculated = 317.2117; IR (film) λ_{\max} 2979, 1622, 1258 cm^{-1} .



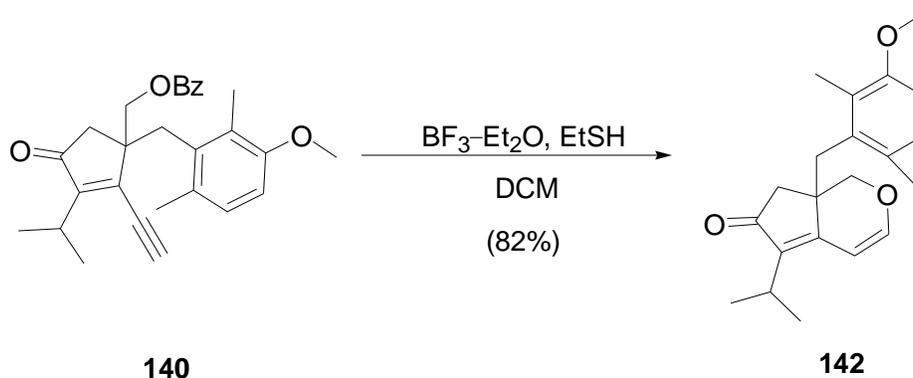
Adduct 139 from enone 137: To a solution of diisopropylamine (0.61 mL, 4.3 mmol) in THF (4 mL) at -78 °C was added *n*-butyllithium (1.8 mL, 4.6 mmol) over a 5-minute period. The resulting mixture was stirred at rt for 10 minutes then cooled to -78 °C. A solution of **137** (1.1 g, 3.5 mmol) and HMPA (0.69 g, 3.5 mmol) in THF (2 mL) was cannulated over a 2-minute period. The resulting solution was stirred for 1 h at -78 °C then the reaction temperature was raised to -63 °C. Chloro-methoxy methylbenzene (1.1 mL, 10.5 mmol) was added slowly. The resulting mixture was stirred overnight. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 1.3 g (83%) of **139** as light yellow oil (hexane/EtOAc, 4:1, R_f **139** = 0.49): ^1H (400 MHz) δ 7.31 (m, 5H), 6.92 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 4.52 (m, 2H), 3.97 (m, 1H), 3.83 (m, 1H), 3.77 (s, 3H), 3.55 (s, 2H), 3.24 (d, J = 14.0 Hz, 1H), 2.84 (d, J = 14.8 Hz, 1H), 2.71 (septet, J = 7.2 Hz, 1H), 2.57 (d, J = 17.2 Hz, 1H), 2.15 (s, 3H), 2.12 (d, 1H), 2.07 (s, 3H), 1.10 (m, 6H); ^{13}C NMR (100 MHz) δ 207.0 (s), 183.7 (s), 156.2 (s), 138.7 (s), 137.0 (s), 130.1 (s), 128.5 (d), 127.9 (d), 127.7 (d),

127.6 (d), 126.8 (s), 124.4 (s), 108.7 (d), 76.1 (t), 73.6 (t), 65.0 (t), 55.8 (q), 51.8 (s), 32.1 (t), 31.9 (t), 23.0 (d), 20.8 (q), 20.3 (q), 20.2 (q), 15.1 (q), 13.1 (q) ppm; HRMS: $[M+H]^+$ observed = 437.2697, $[M+H]^+$ calculated = 437.2692; IR (film) λ_{\max} 2961, 1622, 1257, 1104 cm^{-1} .



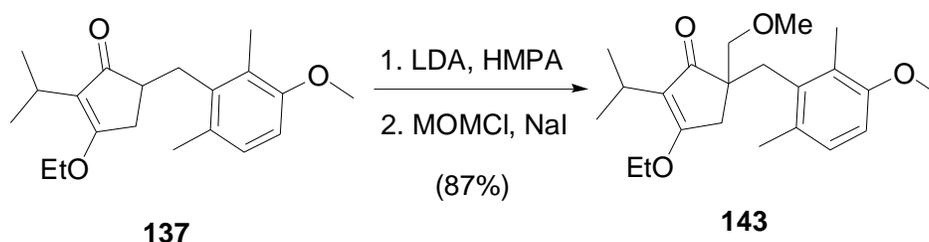
Enynone 140 from enone 139: To a solution of trimethylsilylacetylene (0.44 mL, 3.1 mmol) in THF (1.0 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (1.1 mL, 2.8 mmol). The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 minutes, and then warmed to $0\text{ }^{\circ}\text{C}$ over a 10-minute period. This solution was cannulated into **139** (105 mg, 0.240 mmol) in THF (2.0 mL) solution at $-78\text{ }^{\circ}\text{C}$. The resulting reaction mixture was slowly warmed to rt and was stirred at rt for 1 h. Water (2 mL) was added to quench the reaction followed by HCl (3 mL, 3 M). The resulting mixture was stirred at rt for 1 h, followed by standard ethereal workup. The crude sample was dissolved in THF (2 mL), followed by the addition of TBAF monohydrate (122 mg, 0.437 mmol). After stirring at rt for 10 minutes, the mixture was treated with standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) afforded 23 mg (23%) of **140** as a light yellow oil (hexane/EtOAc, 4:1, R_f **140** = 0.55): ^1H (400 MHz) δ 7.21–7.36 (m, 5H), 6.91 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 4.54 (s, 2H), 3.98 (s, 1H), 3.75 (s, 3H), 3.60 (s, 2H), 3.21 (d, J = 14.4 Hz, 1H), 2.87 (m, 2H), 2.38 (d, J = 18.4 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.02 (d,

$J = 18.8$ Hz, 1H), 1.12–1.20 (m, 6H); ^{13}C NMR (125 MHz) δ 208.0 (s), 156.4 (s), 154.9 (s), 152.1 (s), 138.4 (s), 136.1 (s), 128.5 (d), 128.3 (d), 127.7 (d), 127.5 (d), 126.6 (s), 108.9 (d), 95.8 (s), 78.3 (s), 75.7 (t), 73.5 (t), 55.7 (q), 49.9 (s), 41.9 (t), 32.9 (t), 25.9 (d), 21.1 (q), 20.1 (q), 21.0 (q), 13.5 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 417.2425, $[\text{M}+\text{H}]^+$ calculated = 417.2430; IR (film) λ_{max} 2957, 1699, 1459, 1257, 1103 cm^{-1} .



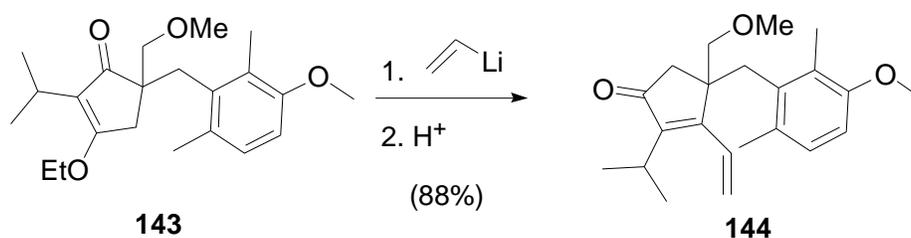
Dihydropyran 142 from enynone 140: To a solution of **140** (11 mg, 0.026 mmol) and ethanethiol (3.8 μL , 0.051 mmol) in freshly distilled DCM (2 mL) at 0 $^{\circ}\text{C}$ was added BF_3 -etherate (6.7 μL , 0.051 mmol). The reaction mixture was heated to 50 $^{\circ}\text{C}$ and refluxed for 10 h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), gave 6.8 mg (82 %) of **142** as a light yellow oil (hexane/EtOAc, 4:1, R_f **142** = 0.51): ^1H (400 MHz) δ 6.96 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 5.5$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 6.00 (d, $J = 6.0$ Hz, 1H), 4.43 (d, $J = 11.0$ Hz, 1H), 3.82 (d, $J = 11.0$ Hz, 1H), 3.78 (d, 3H), 3.06 (d, $J = 14.5$ Hz, 1H), 2.89 (d, $J = 14.0$ Hz, 1H), 2.74 (heptet, $J = 7.0$ Hz, 1H), 2.28 (d, $J = 17.5$ Hz, 1H), 2.18 (s, 3H), 2.11 (m, 4H), 1.16 (m, 6H); ^{13}C NMR (125 MHz) δ 204.7 (s), 184.1 (s), 162.2 (s),

156.4 (s), 150.9 (d), 137.3 (s), 135.6 (s), 129.6 (s), 128.5 (d), 108.8 (d), 99.7 (d), 76.0 (t), 55.6 (q), 21.2 (q), 20.8 (q), 42.8 (t), 41.0 (s), 33.9 (t), 24.9 (d), 21.2 (q), 20.8 (q), 14.0 (q); HRMS: $[M+H]^+$ observed = 327.1960, $[M+H]^+$ calculated = 327.1960.



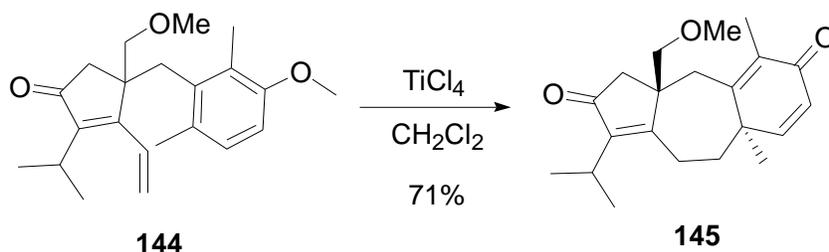
Alkylation product 143 from enone 137: To a solution of diisopropylamine (1.6 mL, 12 mmol) in THF (10 mL) at $-78\text{ }^\circ\text{C}$ was added *n*-butyllithium (4.9 mL, 12 mmol) over a 5-minute period. The resulting mixture was stirred at rt for 10 minutes then low to $-78\text{ }^\circ\text{C}$. A solution of **137** (3.0 g, 9.5 mmol) and HMPA (1.9 g, 9.5 mmol) in THF (6 mL) was cannulated into the LDA solution over a 2-minute period. The resulting solution was stirred for 1 h at $-78\text{ }^\circ\text{C}$ then the reaction mixture was raised to $-63\text{ }^\circ\text{C}$. MOMCl (2.2 mL, 30 mmol) was added slowly followed by NaI (143 mg, 0.95 mmol). The resulting mixture was stirred overnight. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 3.0 g (87%) of **143** as light yellow oil (hexane/EtOAc, 4:1, R_f **143** = 0.49): ^1H (400 MHz) δ 6.92 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 4.00 (m, 1H), 3.83 (m, 1H), 3.77 (s, 3H), 3.43 (s, 2H), 3.34 (s, 3H), 3.21 (d, J = 14.4 Hz, 1H), 2.80 (d, J = 14.4 Hz, 1H), 2.70 (septet, J = 7.2 Hz, 1H), 2.52 (d, J = 17.6 Hz, 1H), 2.20–2.30 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 1.96–2.14 (m, 1H), 1.04–1.16 (m, 9H); ^{13}C NMR (100 MHz) δ 206.9 (s), 183.5 (s), 156.2 (s), 136.9 (s), 130.0 (s), 127.9 (d), 126.8

(s), 124.4 (s), 108.7 (d), 78.4 (t), 64.9 (t), 59.5 (q), 55.8 (q), 51.8 (s), 32.1 (t), 31.8 (t), 23.0 (d), 20.7 (q), 20.3 (q), 20.2 (q), 15.0 (q), 13.1 (q) ppm; HRMS: $[M+H]^+$ observed = 360.2302, $[M]^+$ calculated = 360.2301; IR (film) λ_{\max} 2959, 1621, 1257, 1104 cm^{-1} .

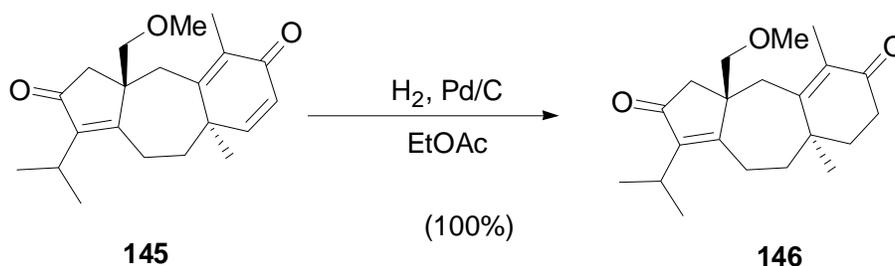


Dienone 144 from enone 143: To a solution of vinyl bromide (3.2 mL, 45 mmol) in freshly distilled Et_2O (30 mL) at -78°C , *t*-butyllithium (54 mL, 1.7 M, 91 mmol) was added over a 15-min period. After stirring 2.5 h at rt, the vinyllithium mixture was cannulated into **143** (1.50 g, 4.2 mmol) dissolved in Et_2O (30 mL) solution. The resulting mixture was warmed to rt and stirred for an additional 8 h. HCl (1.0 M, 20 mL) was added dropwise at 0°C and the resulting mixture was stirred for 30 minutes. Standard ethereal workup, followed by column chromatography (elution with pet ether/ EtOAc , 8:1), gave 1.3 g (88%) of **144** as a light yellow oil (hexane/ EtOAc , 2:1, R_f **144** = 0.70): ^1H (400 MHz) δ 6.93 (d, $J = 8.4$ Hz, 1H), 6.52–6.67 (m, 2H), 5.63 (d, $J = 2.0$ Hz, 1H), 5.59 (s, 1H), 3.77 (s, 3H), 3.51 (d, $J = 8.8$ Hz, 1), 3.47 (d, $J = 8.8$ Hz, 1H), 3.34 (s, 3H), 3.13 (d, $J = 14.8$ Hz, 1H), 2.89 (m, 2H), 2.23 (d, $J = 18.8$ Hz, 1H), 2.14 (s, 3H), 2.06 (m, 4H), 1.19 (d, $J = 6.4$ Hz, 3H), 1.15 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz) δ 207.9 (s), 167.8 (s), 156.4 (s), 146.6 (s), 136.8 (s), 130.5 (d), 130.0 (s), 128.3 (d), 126.5 (s), 122.5 (t), 108.8 (d), 78.8 (t), 59.5 (q), 55.7 (q), 49.5 (s), 43.7 (t), 33.6 (t), 26.0 (d), 21.0 (q), 20.6 (q),

20.2 (q), 13.5 (q) ppm; HRMS: $[M+Na]^+$ observed = 365.2152, $[M+H]^+$ calculated = 365.2093; IR (film) λ_{\max} 2958, 1694, 1257, 1106 cm^{-1} .

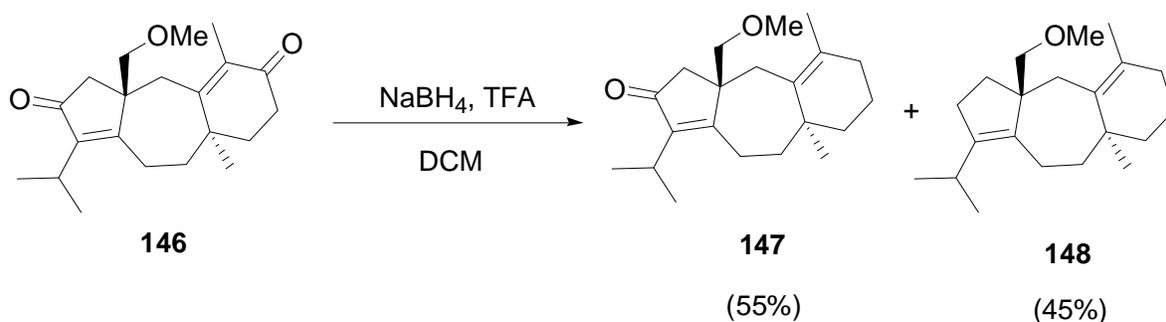


Cyclialkylation product 145 from dienone 144: To a solution of **144** (200 mg, 0.56 mmol) in freshly distilled DCM (2 mL) at -78 °C was added TiCl_4 (0.10 mL, 0.91 mmol). The resulting mixture was stirred under -78 °C for 1 h, and stirred for an additional 0.5 h at -63 °C. Water (3 mL) was added dropwise to quench the reaction, followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 4:1) afforded 115 mg (61%) of **145** as a white solid (hexane/EtOAc, 2:1, R_f **145** = 0.35): ^1H (400 MHz) δ 6.80 (d, J = 9.6 Hz, 1H), 6.30 (d, J = 9.6 Hz, 1H), 3.32 (d, J = 9.2 Hz, 1H), 3.19 (d, J = 12.8 Hz, 1H), 3.18 (s, 3H), 2.99 (d, J = 9.2 Hz, 1H), 2.73 (m, 3H), 2.30 (d, J = 13.2 Hz, 1H), 2.0-2.20 (m, 4H), 1.97 (s, 3H), 1.23 (s, 3H), 1.14 (m, 6H); ^{13}C NMR (100 MHz) δ 207.0 (s), 186.0 (s), 173.9 (s), 157.6 (d), 156.9 (s), 143.7 (s), 136.3 (s), 127.9 (d), 75.6 (t), 59.2 (q), 49.3 (s), 47.8 (t), 45.4 (s), 38.4 (t), 37.2 (t), 29.4 (q), 24.9 (d), 24.4 (t), 20.6 (q), 12.6 (q) ppm; HRMS: $[M+H]^+$ observed = 329.2110, $[M+H]^+$ calculated = 329.2117.



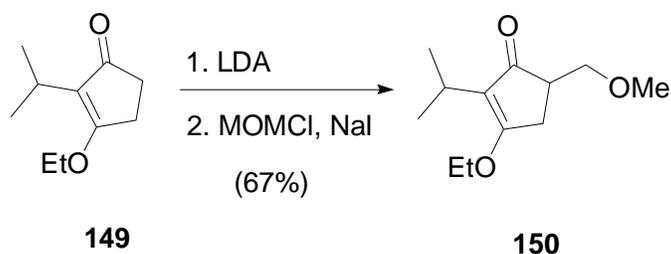
Enone 146 from dienone 145: To a dry 20-mL round-bottom flask was added **145** (19 mg, 0.058 mmol) under nitrogen atmosphere, followed by the addition of anhydrous EtOAc (2 mL), and 5% of Pd/C (3 mg, 16% in weight). Nitrogen in the reaction vessel was removed by bubbling H₂ into the reaction medium until the flask was filled with H₂. A balloon filled with H₂ was connected to the round-bottom flask and the system was sealed with Teflon tape. The resulting mixture was stirred under H₂ for 1 h. At which time the H₂ balloon was disconnected and the residue H₂ gas was removed by saturating the reaction mixture with N₂. The mixture was filtrated through a short pad of silica gel to remove the catalyst. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 3:1), gave 19 mg (100%) of **146** (hexane/EtOAc, 2:1, R_f **146** = 0.36) as a white solid: mp = 147.5–147.8 °C; ¹H (500 MHz) δ 3.34 (d, *J* = 9.0 Hz, 1H), 3.20 (s, 3H), 3.09 (d, *J* = 8.5 Hz, 1H), 2.99 (d, *J* = 13.5 Hz, 1H), 2.54–2.80 (m, 5H), 2.16–2.24 (m, 2H), 2.09 (d, *J* = 18.0 Hz, 1H), 1.97 (dd, *J*₁ = 10.5 Hz, *J*₂ = 13.5 Hz, 1H), 1.86 (s, 3H), 1.82 (m, 1H), 1.44–1.70 (m, 2H) 1.15–1.20 (m, 9H); ¹³C NMR (125 MHz) δ 207.3 (s), 198.5 (s), 174.6 (s), 159.8 (s), 143.3 (s), 135.9 (s), 75.8 (t), 59.3 (q), 49.0 (s), 47.7 (t), 41.0 (t), 40.1 (s), 37.4 (t), 35.1 (t), 34.4 (t), 26.9 (q), 24.9 (d), 23.0 (t), 20.9 (q), 20.8 (q),

12.9 (q) ppm; HRMS: $[M+H]^+$ observed = 331.2281, $[M+H]^+$ calculated = 331.2273; IR (film) λ_{\max} 2877, 1699, 1110 cm^{-1} .



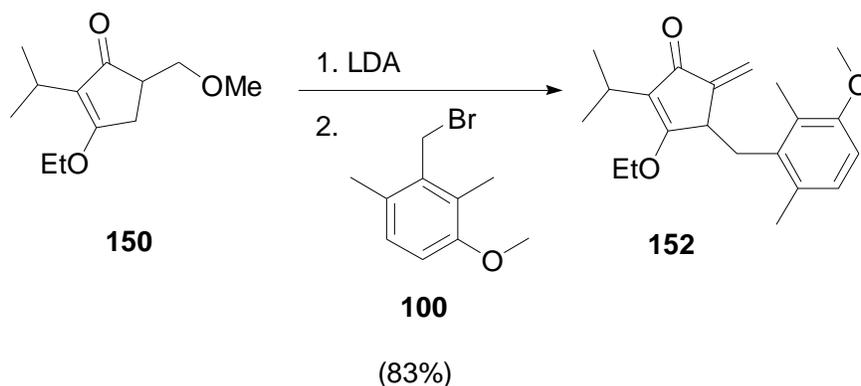
Enone 147 and diene 148 from 146: To a solution of **146** (19 mg, 0.058 mmol) in freshly distilled DCM (5 mL) was added 10% TFA in DCM solution (3 mL), followed by NaBH₄ (20 mg, 0.54 mmol). The resulting mixture was stirred for 0.5 h. Water (1 mL) was added to quench the reaction, followed by standard ethereal workup. Column chromatography (elution with pet ether: EtOAc, 10:1) gave 8.0 mg (45%) **148** as a light yellow oil (hexane: EtOAc, 8:1, R_f **155** = 0.92): ¹H (400 MHz) δ 3.25 (s, 3H), 3.20 (d, J = 8.8 Hz, 1H), 2.92 (d, J = 8.8 Hz, 1H), 2.65 (m, 2H), 2.01–2.24 (m, 5H), 1.67–1.99 (m, 3H), 1.66 (s, 3H), 1.19–1.65 (m, 7H), 0.98 (d, J = 6.4 Hz, 3H), 0.97 (s, 3H), 0.93 ((d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz) δ 140.2 (s), 140.0 (s), 133.6 (s), 130.7 (s), 76.0 (t), 58.9 (q), 55.4 (s), 43.0 (t), 38.3 (s), 37.7 (t), 36.5 (t), 34.7 (t), 32.5 (t), 28.8 (q), 28.3 (t), 26.6 (d), 21.9 (q), 21.5 (q), 21.1 (t), 20.4 (q), 19.5 (t) ppm; HRMS: $[M]^+$ observed = 302.2602, $[M]^+$ calculated = 302.2610; IR (film) λ_{\max} 3601, 2956, 1716, 1365, 1225, 1115 cm^{-1} . Further elution gave 10 mg (55%) of **147** as a light yellow oil (hexane/EtOAc, 8:1, R_f **147** = 0.33): ¹H (400 MHz) δ 3.40 (d, J = 8.8 Hz, 1H), 3.24 (d, 1H), 3.22 (s, 3H), 2.65–2.80 (m, 4H), 2.04–2.18 (m, 2H), 1.89–2.02 (m, 3H), 1.60–1.86 (m, 6H), 1.21–1.40 (m, 3H), 1.16 (m, 6H),

0.97 (s, 3H); ^{13}C NMR (100 MHz) δ 212.0 (s), 181.7 (s), 142.6 (s), 132.9 (s), 131.7 (s), 75.8 (d), 59.4 (q), 50.0 (s), 47.2 (t), 41.3 (t), 38.3 (s), 37.6 (t), 35.0 (t), 32.3 (t), 28.4 (q), 24.8 (d), 23.8 (t), 21.0 (q), 20.6 (q), 19.1 (t) ppm; HRMS: $[\text{M}]^+$ observed = 316.2401, $[\text{M}]^+$ calculated = 316.2402; IR (film) λ_{max} 2926, 1696, 1109 cm^{-1} . (Note: the ratio of the two products can be controlled by the reaction time and the amount of NaBH_4 used.)



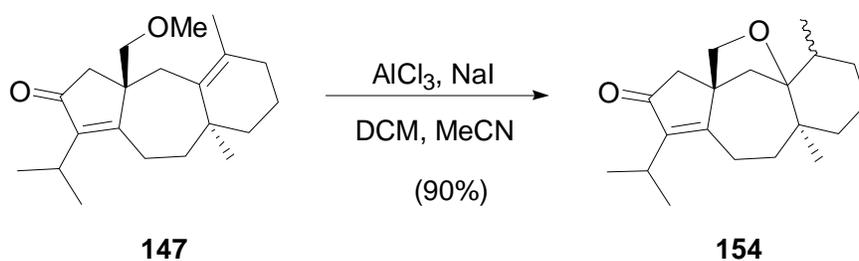
Alkylation adduct 150 from enone 149: To a solution of diisopropylamine (1.0 mL, 7.1 mmol) in THF (7 mL) at $-78\text{ }^\circ\text{C}$ was added *n*-butyllithium (3.1 mL, 7.7 mmol) over a 5-minute period. The resulting mixture was stirred at rt for 10 minutes then cooled to $-78\text{ }^\circ\text{C}$. A solution of **149** (1.0 g, 6.0 mmol) and HMPA (1.2 g, 6.0 mmol) in THF (2 mL) was cannulated over a 2-minute period. The resulting solution was stirred for 1 h at $-78\text{ }^\circ\text{C}$ then warmed to $-63\text{ }^\circ\text{C}$. MOMCl (1.4 mL, 18 mmol) was added slowly followed by NaI (89 mg, 0.60 mmol). The resulting mixture was allowed to stir overnight at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 1:1), afforded 850 mg (67%) of **150** as light yellow oil (hexane/EtOAc, 1:2, R_f **150** = 0.42): ^1H (400 MHz) δ 4.19 (q, $J = 7.2$ Hz, 2H), 3.67 (dd, $J_1 = 4.0$ Hz, $J_2 = 9.2$ Hz, 1H), 3.46 (dd, $J_1 = 9.2$ Hz, $J_2 = 7.6$ Hz, 1H), 3.32 (s, 3H),

2.55–2.80 (m, 4H), 1.39 (t, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 1.6$ Hz, 1H), 1.09 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (125 MHz) δ 204.0 (s), 183.6 (s), 125.4 (s), 73.0 (t), 65.3 (t), 59.2 (q), 45.7 (d), 29.3 (t), 23.0 (d), 20.4 (q), 20.4 (q), 15.5 (q) ppm; HRMS: $[\text{M}+\text{Na}]^+$ observed = 235.1304, $[\text{M}+\text{Na}]^+$ calculated = 235.1310; IR (film) λ_{max} 2985, 1770, 1758, 1246, 1050 cm^{-1} .



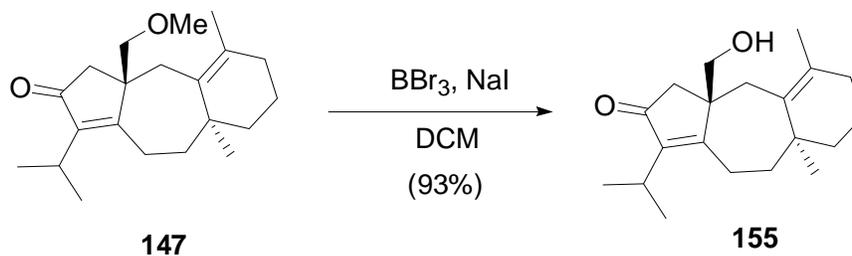
Enone 152 from enone 150: To a solution of diisopropylamine (0.65 mL, 4.6 mmol) in THF (4 mL) at -78 °C was added *n*-butyllithium (2.0 mL, 5.0 mmol) over a 2-minute period. The resulting mixture was stirred at rt for 10 minutes then low to -78 °C. A solution of **150** (825 mg, 3.89 mmol) and HMPA (750 mg, 3.89 mmol) in THF (1 mL) was cannulated over a 5-minute period. The resulting solution was stirred for 1 h at -78 °C then careful warmed to -63 °C. A solution of **100** (1.3 g, 5.7 mmol) in THF (1 mL) was cannulated over a 2-minute period. The resulting mixture was allowed to slowly warm to rt and was then stirred at rt overnight. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 1.059 g (83%) of **152** (hexane/EtOAc, 4:1, R_f **152** = 0.46) as white solid: mp = 69.1–69.4 °C; ^1H (400 MHz) δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 5.82 (s, 1H), 4.59 (s,

1H), 3.89 (m, 2H), 3.82 (s, 3H), 3.59 (dd, $J_1 = 7.8$ Hz, $J_2 = 7.8$ Hz, 1H), 3.06 (dd, $J_1 = 7.8$ Hz, $J_2 = 14.4$ Hz, 1H), 2.90 (septet, $J = 7.2$ Hz, 1H), 2.83 (dd, $J_1 = 8.8$ Hz, $J_2 = 14.0$ Hz, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.21 (d, $J = 2.8$ Hz, 3H), 1.19 (d, $J = 2.8$ Hz, 3H); ^{13}C NMR (125 MHz) δ 192.8 (s), 183.1 (s), 156.3 (s), 144.9 (s), 136.9 (s), 129.2 (s), 129.0 (s), 128.2 (d), 125.6 (s), 114.2 (t), 108.9 (d), 66.3 (t), 55.8 (q), 40.2 (d), 35.3 (t), 23.5 (d), 20.6 (q), 20.5 (q), 20.4 (q), 15.7 (q), 12.6 (q) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 329.2110, $[\text{M}+\text{H}]^+$ calculated = 329.2117; IR (film) λ_{max} 2962, 1686, 1606, 1340, 1103 cm^{-1} .

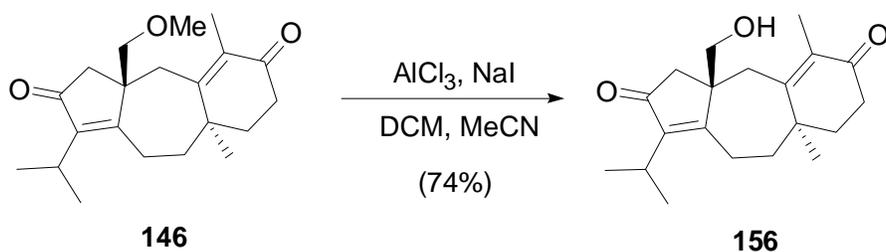


Furan 154 from enone 147: To a solution of **147** (34 mg, 0.11 mmol) in anhydrous DCM (1 mL) and CH_3CN (2 mL) was added AlCl_3 (423 mg, 3.18 mmol) and NaI (477 mg, 3.18 mmol). The resulting mixture was stirred overnight at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 29 mg (90%) of **154** (hexane/EtOAc, 4:1, R_f **154** = 0.42) as a white foam: ^1H (500 MHz) δ 3.88 (s, 2H), 2.88 (m, 1H), 2.73 (septet, $J = 7.0$ Hz, 1H), 2.60 (m, 1H), 2.46 (d, $J = 18.0$ Hz, 1H), 2.37 (d, $J = 18.0$ Hz, 1H), 2.19 (d, $J = 13.0$ Hz, 1H), 1.93 (d, $J = 13.0$ Hz, 1H), 1.72–1.86 (m, 3H), 1.09 (m, 6H), 0.92 (s, 3H), 0.86 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz) δ 206.1 (s), 176.4 (s), 140.0 (s), 89.7 (s),

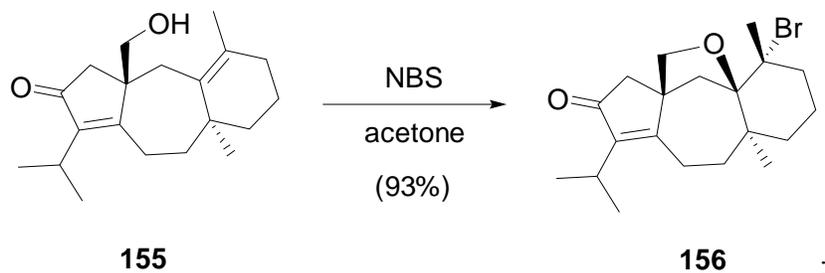
78.3 (t), 50.5 (q), 45.7 (t), 39.4 (q), 37.8 (t), 36.8 (t), 35.2 (t), 33.1 (d), 30.6 (t), 23.8 (d), 23.5 (t), 20.5 (q), 20.3 (d), 19.2 (q), 19.1 (q), 15.3 (q) ppm; HRMS: $[M+H]^+$ observed = 303.2308, $[M+H]^+$ calculated = 303.2324; IR (film) λ_{\max} 2929, 1694, 1379 cm^{-1} .



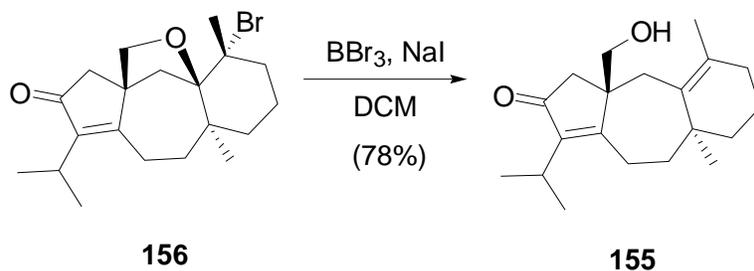
Alcohol 155 from ether 147: To a solution of **147** (48 mg, 0.15 mmol) in freshly distilled DCM (3 mL) was added NaI (23 mg, 0.15 mmol) and BBr_3 (0.75 mL, 1.0 M, 0.75 mmol). The resulting solution was stirred for 8 h at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 3:1), afforded 41 mg (90%) of **155** as colorless oil (hexane/EtOAc, 2:1, R_f **155** = 0.25): ^1H (400 MHz) δ 3.65 (q, J = 10.8 Hz, 2H), 2.63–2.81 (m, 3H), 2.51 (d, J = 18.0 Hz, 1H), 1.89–2.16 (m, 5H), 1.67–1.87 (m, 3H), 1.66 (s, 3H), 1.23–1.45 (m, 3H), 1.19 (d, 3H), 1.17 (d, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz) δ 208.0 (s), 176.3 (s), 144.0 (s), 132.4 (s), 132.2 (s), 66.4 (t), 50.4 (q), 47.5 (t), 41.4 (t), 38.4 (q), 37.3 (t), 35.3 (t), 32.3 (t), 28.3 (q), 24.9 (d), 23.2 (t), 21.5 (q), 21.1 (q), 21.0 (q), 19.1 (t) ppm; HRMS: $[M]^+$ observed = 302.2247, $[M]^+$ calculated = 302.2246; IR (film) λ_{\max} 3448, 2930, 1694, 1465, 1259, 1107 cm^{-1} .



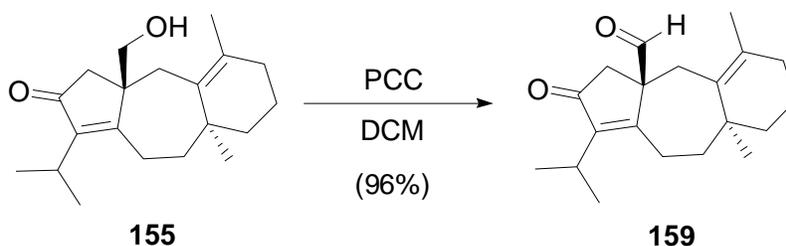
Alcohol 156 from dienone 146: To a solution of **146** (10 mg, 0.030 mmol) in anhydrous DCM (1 mL) and CH₃CN (2 mL) was added AlCl₃ (141 mg, 1.06 mmol) and NaI (159 mg, 1.06 mmol). The resulting mixture was stirred overnight at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 7.1 mg (74%) of **156** as a colorless oil (hexane/EtOAc, 1:1, R_f **156** = 0.48): ¹H (400 MHz) δ 3.66 (d, *J* = 10.8 Hz, 1H), 3.55 (d, *J* = 10.4 Hz, 1H), 2.94 (d, *J* = 13.2 Hz, 1H), 2.78 (m, 2H), 2.61 (m, 3H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.21 (dt, *J*₁ = 6.0 Hz, *J*₂ = 13.6 Hz, 1H), 2.12 (d, *J* = 18.0 Hz, 1H), 2.02 (m, 1H), 1.84 (s, 3H), 1.81 (m, 1H), 1.63 (m, 2H), 1.19 (m, 9H); ¹³C NMR (100 MHz) δ 207.3 (s), 198.4 (s), 173.8 (s), 159.8 (s), 144.5 (s), 135.6 (s), 65.6 (t), 50.2 (s), 47.4 (t), 40.8 (t), 40.2 (s), 37.4 (t), 34.9 (t), 34.3 (t), 26.6 (q), 25.0 (d), 22.7 (t), 21.0 (q), 21.0 (q), 13.5 (q) ppm; HRMS: [M]⁺_{observed} = 316.2026, [M]⁺_{calculated} = 316.2038; IR (film) λ_{max} 3475, 2933, 1697, 1122 cm⁻¹.



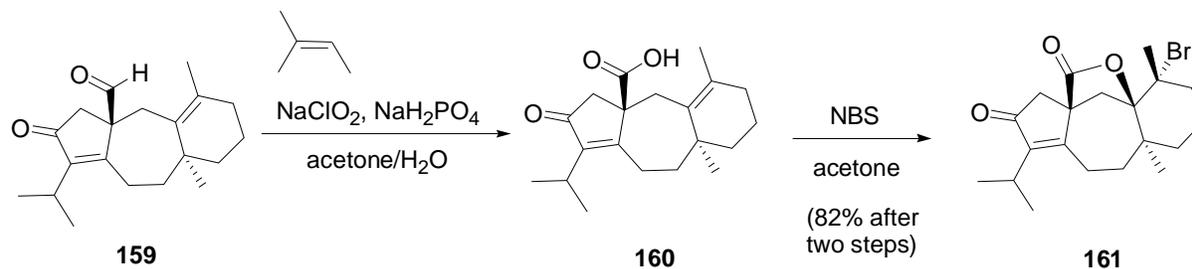
Furan 156 from alcohol 155: To a solution of **155** (8.0 mg, 0.027 mmol) in anhydrous acetone (1 mL) was added NBS (9.4 mg, 0.053 mmol). The resulting solution was stirred for 30 minutes under rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 9.4 mg (93%) of **156** as colorless oil (hexane/EtOAc, 2:1, R_f **156** = 0.85). No NMR spectrum was obtained due to the presence of an inseparable impurity.



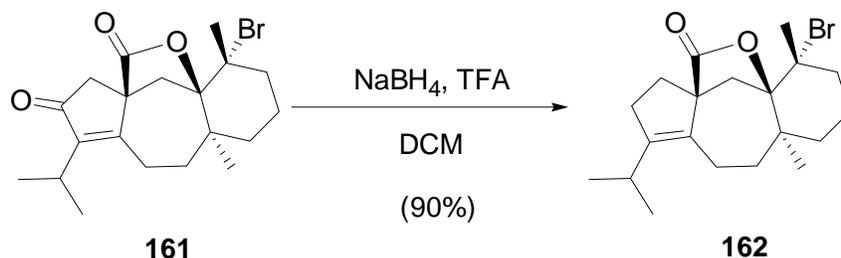
Alcohol 156 from furan 155: To a solution of **155** (21 mg, 0.055 mmol) in freshly distilled DCM (4 mL) was added NaI (68 mg, 0.45 mmol) and BBr₃ (2.3 mL, 1.0 M, 2.3 mmol). The resulting solution was stirred for 36 h at rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 3:1), afforded 13 mg (78%) of **156** (hexane/EtOAc, 2:1, R_f **156** = 0.25) as a colorless oil which was identical to that previously characterized.



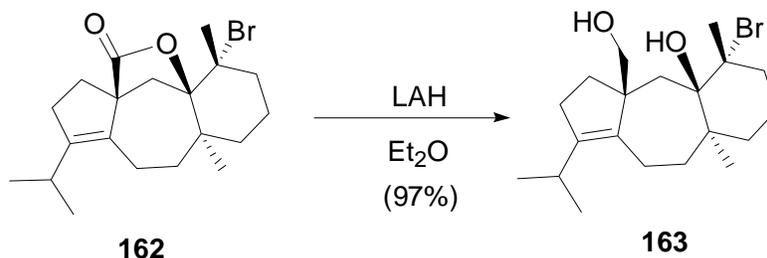
Aldehyde 159 from alcohol 155: To a solution of **155** (19 mg, 0.063 mmol) in freshly distilled DCM (5 mL) was added PCC (27 mg, 0.13 mmol). The resulting mixture was stirred for 6 h under rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 18 mg (96%) of **159** as light yellow oil (hexane/EtOAc, 2:1, R_f **159** = 0.81): ^1H (500 MHz) δ 9.73 (s, 1H), 3.11 (d, $J = 14.0$ Hz, 1H), 2.88 (d, $J = 18.5$ Hz, 1H), 2.78 (m, 2H), 2.32 (m, 1H), 2.19 (d, $J = 14.5$ Hz, 1H), 2.07 (m, 2H), 1.96 (m, 1H), 1.66–1.83 (m, 3H), 1.63 (s, 3H), 1.61 (m, 1H), 1.45 (m, 1H), 1.36 (m, 1H), 1.16 (m, 6H), 1.02 (s, 3H); ^{13}C NMR (125 MHz) δ 205.6 (s), 201.8 (d), 173.1 (s), 144.3 (s), 132.7 (s), 130.8 (s), 59.1 (s), 43.2 (t), 40.9 (t), 38.3 (s), 37.1 (t), 35.2 (t), 32.2 (t), 27.8 (q), 24.9 (d), 24.8 (t), 21.4 (q), 20.8 (q), 20.6 (q), 19.1 (t) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 301.2169, $[\text{M}+\text{H}]^+$ calculated = 301.2168; IR (film) λ_{max} 2984, 1746, 1246, 1049 cm^{-1} .



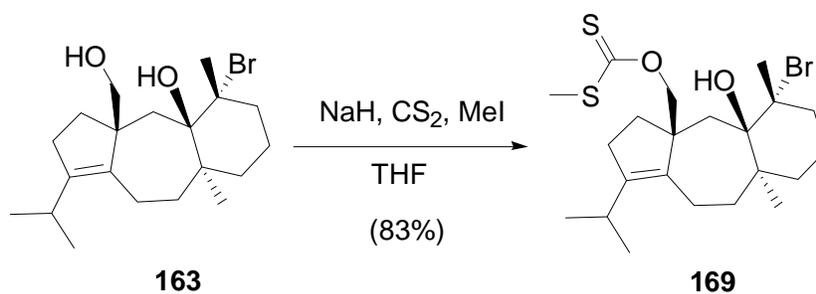
Lactone 161 from aldehyde 159: To a solution of **159** (57 mg, 0.19 mmol) in anhydrous acetone (10 mL) was added 2-methyl-2-butene (0.45 mL, 4.2 mmol) followed by the oxidation solution (2.8 mL, 92.5 mg NaClO₂ and 91.5 mg NaH₂PO₄ in 5 mL H₂O solution). The resulting mixture was stirred for 10 minutes under rt. Standard ethereal workup provided a crude residue which was dissolved in anhydrous acetone (5 mL) followed by the addition of NBS (34 mg, 0.19 mmol). The mixture was stirred for 30 minutes under rt followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) afforded 61 mg (82%) of **161** (hexane/EtOAc, 2:1, R_f **161** = 0.81) as a white foam: ¹H (500 MHz) δ 2.95 (dd, J₁ = 5.0 Hz, J₂ = 18.5 Hz, 1H), 2.88 (d, J = 18.0 Hz, 1H), 2.74 (septet, J = 7.5 Hz, 1H), 2.67 (d, J = 14.5 Hz, 1H), 2.63 (dd, J₁ = 2.0 Hz, J₂ = 14.0 Hz, 1H), 2.53 (d, J = 14.5 Hz, 1H), 2.28 (d, J = 17.5 Hz, 1H), 2.15 (m, 1H), 2.02 (m, 2H), 1.83 (s, 3H), 1.64 (m, 1H), 1.55 (s, 3H), 1.25–1.38 (m, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz) δ 205.2 (s), 178.0 (s), 168.2 (s), 145.1 (s), 89.4 (s), 67.4 (s), 53.1 (s), 46.2 (t), 42.3 (s), 41.3 (t), 38.3 (t), 37.2 (t), 36.4 (t), 30.5 (q), 25.5 (d), 24.4 (t), 23.8 (q), 20.1 (q), 20.0 (q), 18.9 (t) ppm; HRMS: [M+H]⁺_{observed} = 395.1227, [M+H]⁺_{calculated} = 395.1222; IR (film) λ_{max} 2935, 1772, 1705, 1233, 1173 cm⁻¹.



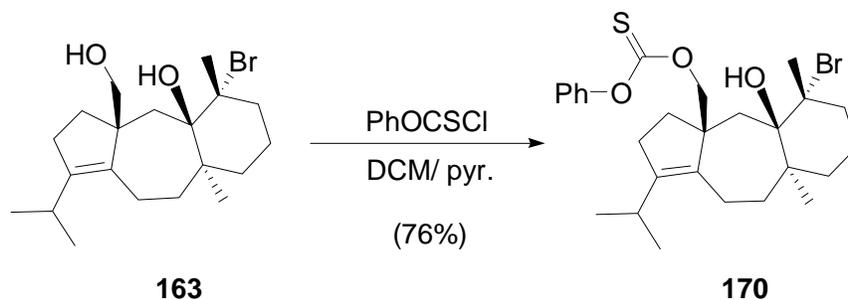
Lactone 162 from enone 161: To a solution of **161** (100 mg, 0.254 mmol) in freshly distilled DCM (15 mL) was added 10% TFA in DCM solution (10 mL), followed by NaBH_4 (49 mg, 1.3 mmol). The resulting mixture was stirred at rt for 2.5 h. Water (5 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 10:1) gave 87 mg (90%) of **162** as a white solid (hexane/EtOAc, 4:1, R_f **162** = 0.75): ^1H (500 MHz) δ 2.71 (m, 1H), 2.63 (septet, $J = 7.0$ Hz, 1H), 2.51 (m, 2H), 2.32 (m, 2H), 2.09 (m, 1H), 1.99 (m, 2H), 1.81 (s, 3H), 1.55–1.76 (m, 3H), 1.49 (s, 3H), 1.26 (m, 1H), 1.11 (m, 2H), 0.99 (m, 6H); ^{13}C NMR (125 MHz) δ 181.7 (s), 145.0 (s), 133.6 (s), 89.0 (s), 68.6 (s), 59.2 (s), 42.3 (s), 41.4 (t), 39.9 (t), 38.4 (t), 36.6 (t), 33.7 (t), 30.6 (q), 30.2 (t), 27.5 (d), 23.9 (q), 21.3 (t), 21.2 (q), 21.1 (q), 19.0 (t) ppm; HRMS: $[\text{M}+\text{H}]^+$ observed = 381.1439, $[\text{M}+\text{H}]^+$ calculated = 381.1429; IR (film) λ_{max} 2924, 1777, 1462, 1170 cm^{-1} .



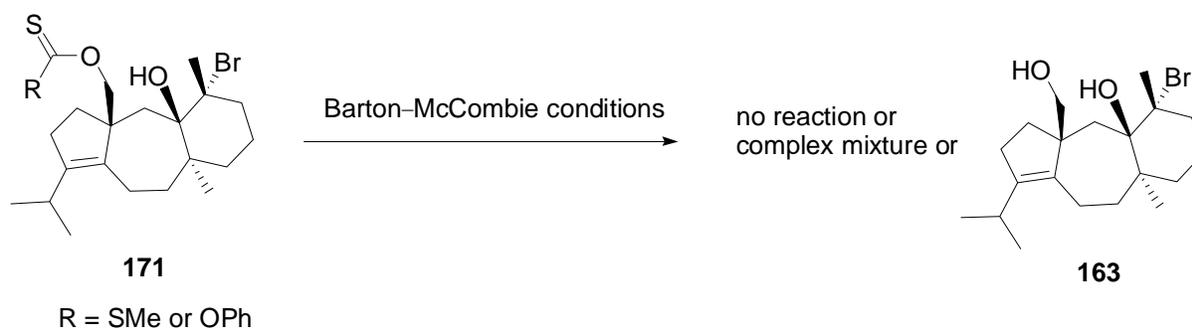
Diol 163 from lactone 162: To a solution of **162** (20 mg, 0.053 mmol) in freshly distilled Et₂O (3 mL) at 0 °C under nitrogen atmosphere was added LAH (2.60 mg, 0.063 mmol, 1.2 equiv). The resulting reaction mixture was stirred for 1 h at rt. Water (3 mL) was slowly added to quench the reaction, followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 4:1) afforded 16 mg (77%) of **163** as a colorless oil (hexane/EtOAc, 1:2, R_f **163** = 0.50): ¹H (400 MHz) δ 3.81 (d, J = 12.0 Hz, 1H), 3.18 (dd, J_1 = 10.0 Hz, J_2 = 10.8 Hz, 1H), 2.95 (bs, 1H), 2.64 (septet, J = 7.2 Hz, 1H), 2.45 (m, 1H), 2.32 (m, 1H), 1.28 (m, 2H), 2.00 (m, 2H), 1.82 (m, 4H), 1.63 (s, 1H), 1.51 (m, 2H), 1.37 (s, 3H), 1.20–1.36 (m, 2H), 1.05 (s, 3H), 0.97 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H); ¹³C NMR (125 MHz) δ 143.5 (s), 135.4 (s), 70.5 (s), 66.4 (t), 64.5 (s), 56.8 (s), 37.5 (s), 36.8 (t), 36.5 (t), 36.4 (t), 35.4 (t), 30.0 (t), 27.6 (t), 27.2 (d), 22.7 (q), 22.7 (t), 21.4 (q), 21.1 (q), 21.0 (q), 17.1 (t) ppm; HRMS: $[M-Br]^+$ observed = 305.2477, $[M-Br]^+$ calculated = 305.2481; IR (film) λ_{max} 2925, 1460, 1044 cm⁻¹.



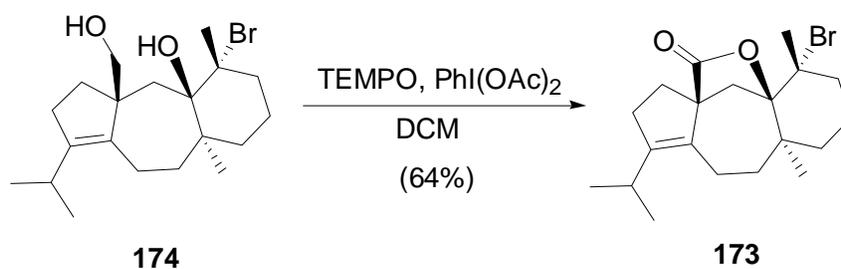
Xanthate 169 from alcohol 163: To a solution of **163** (4.5 mg, 0.012 mmol) in THF (0.5 mL) was added NaH (1.0 mg, 0.025 mmol), followed by the addition of CS₂ (1.5 μL, 0.025 mmol). The resulting mixture was stirred at rt for 10 minutes then MeI (1.6 μL, 0.025 mmol) was added to the mixture and the resulting mixture was stirred for an additional 30 minutes. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), afforded 4.6 mg (83%) of **169** as a colorless oil (hexane/EtOAc, 4:1, R_f **169** = 0.88): ¹H (500 MHz) δ 4.69 (s, 2H), 2.71 (septet, J = 6.5 Hz, 1H), 2.53 (s, 3H), 2.46–2.52 (m, 1H), 2.18–2.28 (m, 3H), 1.82–2.23 (m, 5H), 1.71 (m, 1H), 1.32–1.63 (m, 4H), 1.31 (s, 3H); 1.25 (m, 1H), 1.03 (s, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.87 (m, 1H); ¹³C NMR (125 MHz) δ 215.7 (s), 143.7 (s), 135.6 (s), 78.7 (t), 69.0 (s), 62.2 (s), 55.1 (s), 37.8 (s), 37.7 (t), 36.6 (t), 36.5 (t), 35.9 (t), 30.0 (t), 28.1 (t), 27.1 (d), 23.5 (q), 22.5 (q), 22.0 (t), 21.2 (q), 21.2 (q), 19.0 (q), 17.0 (t) ppm; HRMS: $[M-HBr+K]^+$ observed = 433.1631, $[M-HBr+K]^+$ calculated = 433.1637; IR (film) λ_{max} 2954, 2923, 2851, 1459, 1224, 1062 cm⁻¹.



Thionoformate 170 from alcohol 163: To a solution of **163** (4.5 mg, 0.012 mmol) in freshly distilled DCM (0.5 mL) and anhydrous pyridine (0.1 mL) was added *o*-phenyl chlorothionoformate (3.5 μ L, 0.025 mmol). The resulting mixture was stirred for 30 minutes at rt. Standard ethereal workup, followed by column chromatographic purification (elution with pet ether/EtOAc, 10:1), afforded 4.6 mg (76%) of **170** as a colorless oil (hexane/EtOAc, 4:1, R_f **170** = 0.75): ^1H (400 MHz) δ 7.43 (m, 2H), 7.29 (m, 1H), 7.11 (m, 2H), 4.74 (d, J = 8.4 Hz, 1H), 4.48 (d, J = 8.4 Hz, 1H), 2.74 (septet, J = 5.6 Hz, 1H), 2.51 (m, 1H), 2.27 (m, 3H), 2.06 (m, 1H), 1.82–1.99 (m, 4H), 1.77 (m, 1H), 1.67 (m, 1H), 1.40–1.53 (m, 3H), 1.35 9s, 3H), 1.27 (m, 1H), 1.06 (s, 3H), 1.02 (d, J = 5.2 Hz, 3H), 0.99 (d, J = 5.2 Hz, 3H), 0.89 (m, 1H); ^{13}C NMR (125 MHz) δ 195.3 (s), 153.7 (s), 144.0 (s), 135.7 (s), 129.8 (d), 129.7 (d), 126.6 (d), 122.3 (d), 121.2 (d), 78.6 (t), 69.0 (s), 62.1 (s), 54.9 (s), 38.4 (t), 37.8 (s), 36.4 (t), 36.1 (t), 35.1 (t), 29.7 (t), 28.0 (t), 27.1 (d), 23.7 (q), 22.3 (q), 21.9 (t), 21.3 (q), 21.2 (q), 16.9 (t) ppm; HRMS: $[\text{M}-\text{HBr}+\text{Na}]^+$ observed = 463.2298, $[\text{M}-\text{HBr}+\text{Na}]^+$ calculated = 463.2283; IR (film) λ_{max} 2297, 1285, 1196 cm^{-1} .

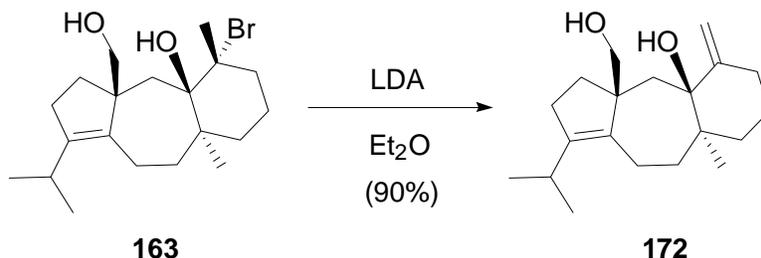


Alcohol 163 from xanthate derivative 171: To a solution of 10 mg **171** in 1 mL solvent (PhH, PhMe or *o*-xylene) at refluxing temperature was added the 3.0 equiv of a hydride source (*n*-Bu₃SnH, Ph₂SiH₂ or TMS₃SiH), then 0.5 equiv of a radical initiator [AIBN or (PhCOO)₂O]. The resulting mixture was refluxed for 30 minutes. TLC was used to monitor the reaction until all the starting material was consumed. Standard ethereal workup, followed by column chromatography gave only alcohol **163** which was identical to that previously characterized.

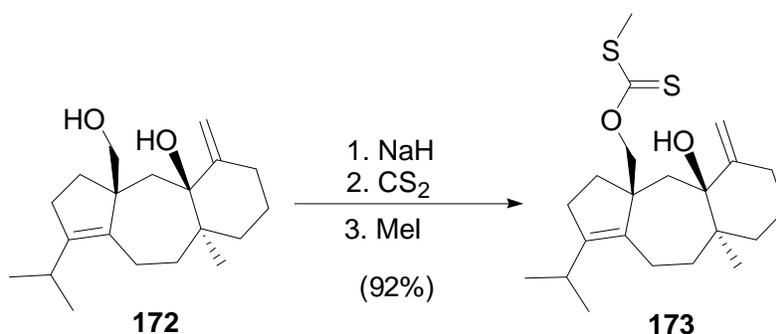


Lactone 173 from alcohol 174: To a solution of **174** (6.0 mg, 0.016 mmol) in freshly distilled DCM (1 mL) was added TEMPO (1.3 mg, 0.008 mmol, 0.5 equiv), phenyl iodine diacetate (10 mg, 0.032 mmol). The resulting solution was stirred for 10 h under rt. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), gave 3.80 mg (64%)

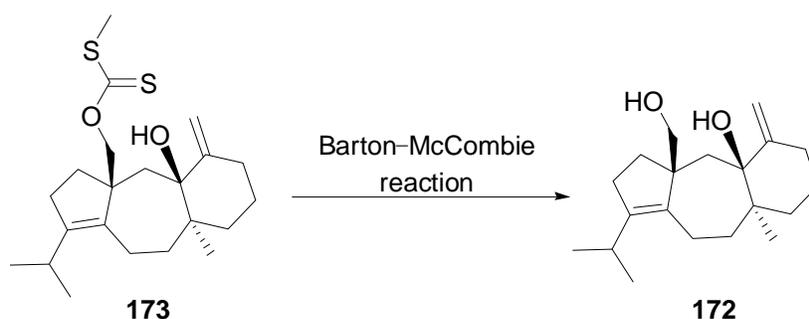
of **173** as a white solid (hexane/EtOAc, 4:1, R_f **173** = 0.60) which was identical to that previously characterized.



Alkene 172 from diol 163: To a solution of diisopropylamine (0.70 mL, 5.0 mmol) in freshly distilled Et₂O (10 mL) at 0 °C was added *n*-butyllithium (2 mL, 5 mmol). The resulting mixture was stirred at rt for 10 minutes. Compound **163** (5.0 mg, 0.013 mmol) was transferred into a sealed tube, 2 mL LDA solution was added. The reaction vessel was sealed and heated to 50 °C and kept at this temperature for 36 h. Water (2 mL) was added to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 8:1) afforded 7.4 mg (93%) of **172** as a colorless oil (hexane/EtOAc, 4:1, R_f **172** = 0.30): ¹H (400 MHz) δ 4.86 (s, 1H), 4.82 (s, 1H), 4.06 (d, J = 11.2 Hz, 1H), 3.36 (d, J = 10.8 Hz, 1H), 2.64 (septet, J = 6.4 Hz, 1H), 2.40–2.57 (m, 4H), 2.00–2.26 (m, 5H), 1.73–1.96 (m, 3H), 1.50–1.60 (m, 2H), 1.02–1.11 (m, 2H), 0.95 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.83 (s, 3H); ¹³C NMR (125 MHz) δ 152.9 (s), 143.2 (s), 135.2 (s), 109.1 (t), 78.5 (q), 68.2 (t), 56.9 (s), 42.6 (t), 42.1 (s), 38.2 (t), 38.1 (t), 32.6 (t), 32.3 (t), 27.6 (t), 27.2 (d), 23.2 (t), 22.9 (t), 21.2 (q), 20.7 (q), 18.2 (q) ppm; HRMS: $[M+Na]^+$ observed = 327.2300, $[M+Na]^+$ calculated = 327.2300; IR (film) λ_{max} 3412, 2931, 1022 cm⁻¹.

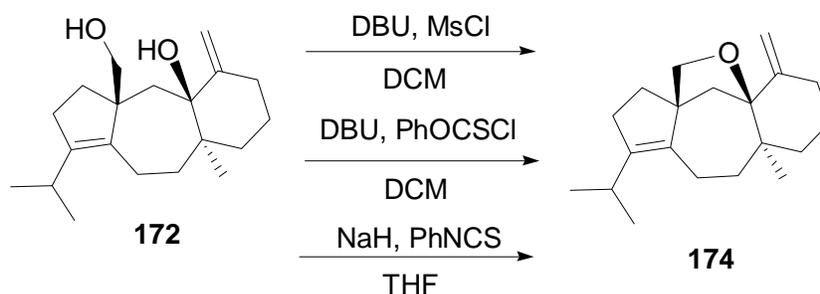


Xanthate 173 from alcohol 172: To a solution of **172** (10 mg, 0.033 mmol) in THF (2 mL) was added NaH (4.0 mg, 0.10 mmol), followed by the addition of CS₂ (6.0 μL, 0.10 mmol). The resulting mixture was stirred for 10 minutes at rt. MeI (6.4 μL, 0.10 mmol) was added to the mixture and the resulting mixture was stirred for an additional 50 minutes. Standard ethereal workup, followed by column chromatographic purification (elution with pet ether/EtOAc, 10:1), afforded 12 mg (92%) of **173** (hexane/EtOAc, 4:1, R_f **173** = 0.88) as a colorless oil. Because of our concern for its stability, xanthate **173** was used in the next step without purification or characterization.

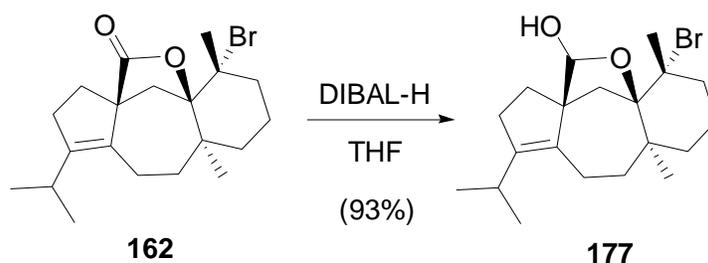


Alcohol 172 from xanthate 173: To a solution of 10 mg **173** in 1 mL solvent (PhH, PhMe or *o*-xylene) at refluxing temperature was added the 3.0 equiv of a hydride source (*n*-Bu₃SnH, Ph₂SiH₂ or TMS₃SiH), then 0.5 equiv of a radical initiator [AIBN or (PhCOO)₂O]. The resulting

mixture was refluxed for 30 minutes. TLC was used to monitor the reaction until all the starting material was consumed. Standard ethereal workup, followed by column chromatography gave only alcohol **172** which was identical to that previously characterized.

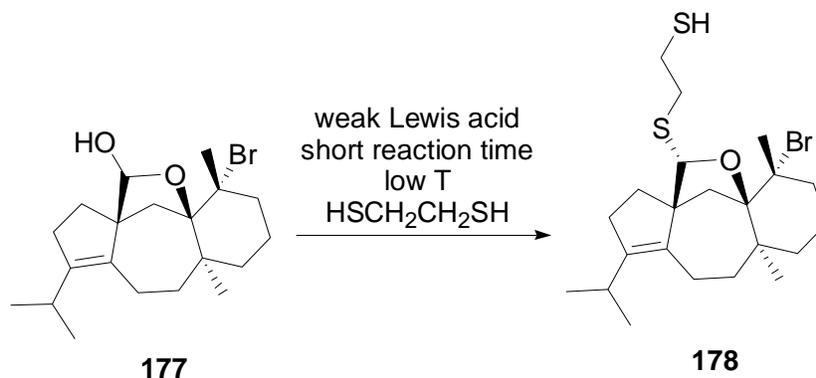


Furan 174 from diol 172: To a solution of **172** (10 mg, 0.033 mmol) in 1mL freshly distilled solvent (DCM or THF) was added 1.5 equiv of reagent (MsCl, PhOCSCl or PhNCS) followed by 1.5 equiv of base. The resulting solution was stirred at rt. TLC analysis was used to monitor the reaction until all diol **172** was consumed. Standard ethereal workup, followed by column chromatography, afford **174** as a colorless oil (hexane/EtOAc, 4:1, R_f **174** = 0.96).

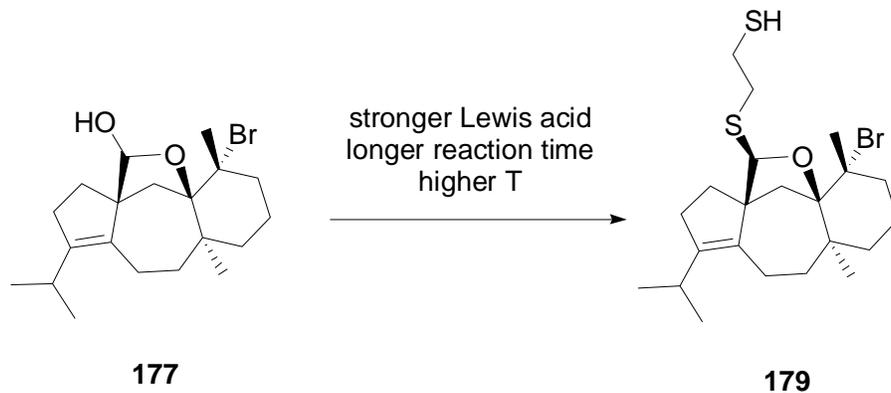


Lactol 177 from lactone 162: To a solution of lactone **162** (20 mg, 0.053 mmol) in freshly distilled THF (5 mL) was added DIBAL-H (0.26 mL, 1.0 M, 0.26 mmol). The resulting solution was stirred for 10 minutes at rt. Water (3 mL) was added to quench the reaction. Standard

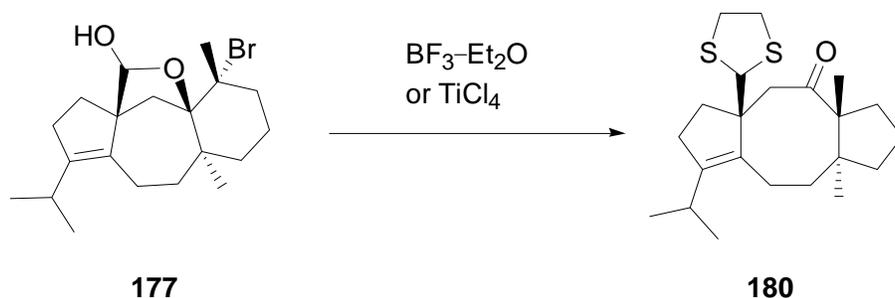
ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 10:1), gave 19 mg (93%) of **177** (hexane/EtOAc, 4:1, R_f **177** = 0.71) as a colorless oil. NMR shows it is a mixture of at least two compounds.



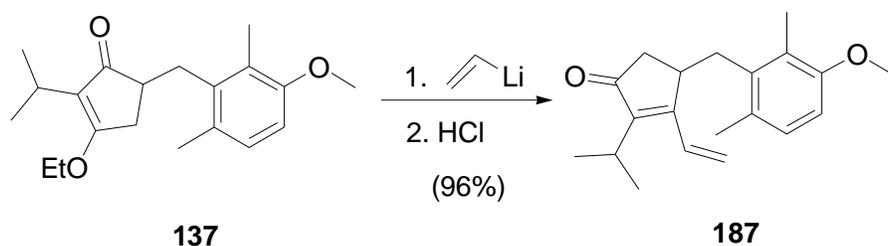
Formation of hemi-thioacetal 178 from lactol 177: Lactol **177** was dissolved in the anhydrous solvent. Ethanedithiol (3 equiv) was added followed by the Lewis acid (2 equiv). The resulting solution was stirred under a nitrogen atmosphere at rt until TLC analysis indicate that all the starting material was consumed. Standard ethereal workup, followed by column chromatography (elution with pet ether: EtOAc, 15:1), afford the pure **178** (hexane/EtOAc, 4:1, R_f **178** = 0.79) as a light yellow oil. The reaction yield ranged from 50–90%. However, compound **178** is not stable in CDCl₃.



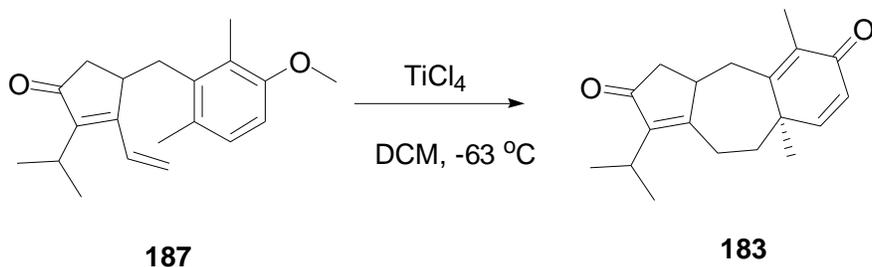
Conversion of lactol **177 to hemi-thioacetal **179**:** Lactol **177** was dissolved in the anhydrous solvent. Ethanedithiol (3 equiv) was added followed by the Lewis acid (2 equiv). The resulting solution was stirred under a nitrogen atmosphere at rt until TLC analysis indicate that all the starting material was consumed. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 15:1), afford the pure hemi-thioacetal **179** as a light yellow oil (hexane/EtOAc, 4:1, R_f **179** = 0.79): ^1H (400 MHz) δ 5.01 (s, 1H), 2.66–2.93 (m, 4H), 2.47 (m, 2H), 1.83–2.28 (m, 8H), 1.82 (s, 3H), 1.38 (s, 3H), 1.26 (s, 3H), 0.99 (d, $J = 7.2$ Hz, 3H), 0.95 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz) δ 144.3 (s), 135.3 (s), 98.7 (d), 92.0 (s), 72.2 (s), 62.1 (s), 42.0 (t), 41.6 (t), 41.1 (t), 40.6 (s), 37.6 (t), 37.6 (t), 34.5 (s), 31.1 (q), 29.9 (t), 29.2 (t), 27.5 (d), 26.3 (t), 23.6 (q), 21.4 (q), 21.4 (t), 21.0 (q), 19.4 (q) ppm; IR (film) λ_{max} 2922, 2553, 1761, 1202 cm^{-1} .



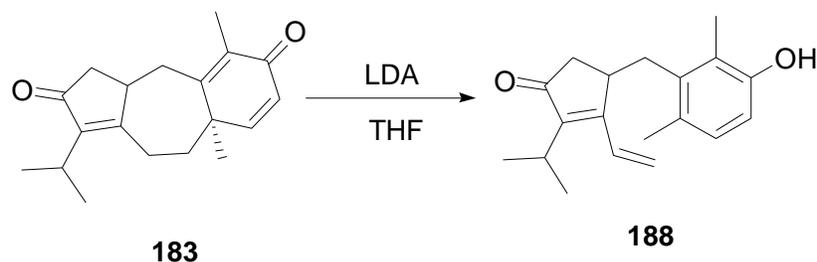
The rearrangement of lactol **177 to thioacetal **180**:** Lactol **177** was dissolved in fresh distilled DCM. Ethanedithiol (3 equiv) was added followed by the Lewis acid (2 equiv). The resulting solution was stirred under nitrogen atmosphere at rt until TLC analysis indicate that all the starting material was consumed. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 15:1), afford thioacetal **180** (hexane/EtOAc, 4:1, R_f **180** = 0.83) as a light yellow oil: ^1H (500 MHz) δ 5.24 (s, 1H), 3.27 (m, 1H), 3.21 (m, 2H), 3.11 (m, 1H), 3.01 (d, J = 12.0 Hz, 1H), 2.85–3.02 (m, 2H), 2.70 (septet, J = 4.2 Hz, 1H), 2.61 (d, J = 12.0 Hz, 1H), 2.17–2.40 (m, 5H), 1.86 (m, 1H), 1.40–1.78 (m, 6H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 216.7 (s), 145.9 (s), 135.5 (s), 62.6 (d), 60.4 (s), 59.6 (s), 49.4 (t), 48.2 (s), 42.0 (t), 39.1 (t), 39.0 (t), 37.7 (t), 35.5 (t), 32.3 (t), 29.3 (t), 27.5 (d), 24.0 (q), 21.9 (q), 21.2 (q), 21.0 (t), 20.9 (q), 18.8 (t) ppm; HRMS: $[\text{M}]^+$ observed = 378.2049, $[\text{M}]^+$ calculated = 378.2051; IR (film) λ_{max} 2958, 1685, 1455 cm^{-1} .



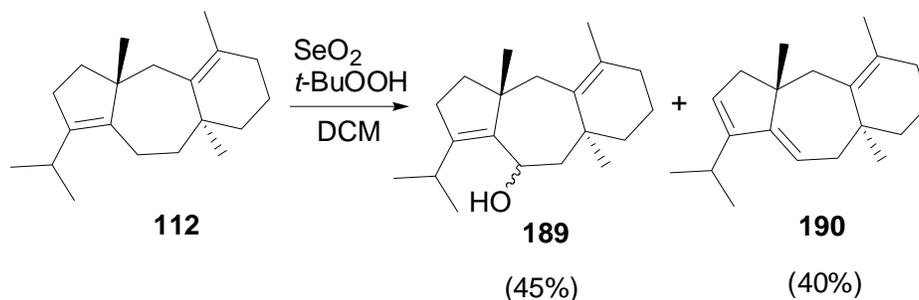
Dienone 187 from enone 137: To a solution of vinyl bromide (5.0 mL, 70 mmol) in freshly distilled Et₂O (50 mL) at -78 °C, *t*-butyllithium (85 mL, 1.7 M, 143 mmol) was added over a 15-minute period. After stirring for 2.5 h at rt, the vinyl lithium solution was cannulated into a solution of **137** (2.88g, 9.11 mmol) in Et₂O (50 mL) at -78 °C. The resulting mixture was warmed to rt and stirred for an additional 8 h. HCl (20.0 mL, 1.0 M) was added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 8:1), gave 2.61 g (96%) of dienone **187** as a light yellow oil (hexane/EtOAc, 4:1, R_f **187** = 0.55): ¹H (400 MHz) δ 6.96 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J*₁ = 11.2 Hz, *J*₂ = 17.6 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.63 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 3.43 (m, 1H), 3.08 (dd, *J*₁ = 6.4 Hz, *J*₂ = 14.0 Hz, 1H), 2.93 (septet, *J* = 7.2 Hz, 1H), 2.57 (dd, *J*₁ = 10.0 Hz, *J*₂ = 14.0 Hz, 1H), 2.28 (m, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 2.08 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 1H); ¹³C NMR (125 MHz) δ 208.3 (s), 166.9 (s), 156.4 (s), 145.0 (s), 138.1 (s), 130.4 (d), 128.4 (s), 128.3 (d), 125.2 (t), 121.5 (t), 108.4 (d), 55.5 (q), 41.1 (t), 36.8 (d), 35.8 (t), 25.3 (d), 20.9 (q), 20.6 (q), 20.5 (q), 12.8 (q) ppm; HRMS: [M+H]⁺ observed = 299.2004, [M+H]⁺ calculated = 299.2011; IR (film) λ_{max} 2960, 1693, 1258, 1102 cm⁻¹.



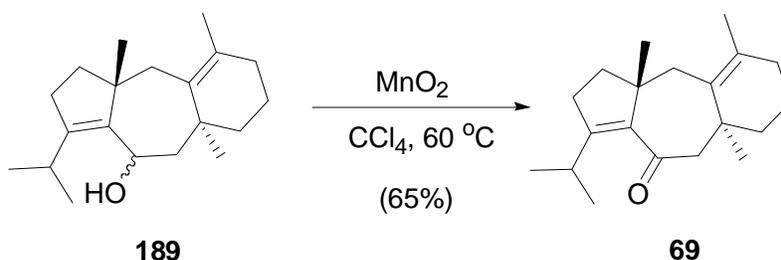
Cyclialkylation product 183 from dienone 187: To a solution of dienone **187** (200 mg, 0.641 mmol) in fresh distilled DCM (2 mL) at $-78\text{ }^\circ\text{C}$ was added TiCl_4 (0.10 mL, 0.91 mmol). The resulting mixture was stirred under $-78\text{ }^\circ\text{C}$ for 1 h, then stirred for an additional 0.5 h at $-63\text{ }^\circ\text{C}$. Water (5 mL) was added dropwise to quench the reaction followed by standard ethereal workup. Column chromatography (elution with pet ether/EtOAc, 4:1) gave 143 mg **187** back together with 30 mg (55%, brsm) of **183** as a light yellow oil (hexane/EtOAc, 2:1, R_f **97** = 0.31): ^1H (500 MHz) δ 6.75 (d, $J = 10.0$ Hz, 1H), 6.32 (d, $J = 10.0$ Hz, 1H), 2.96 (dd, $J_1 = 3.0$ Hz, $J_2 = 12.5$ Hz, 1H), 2.82 (dd, $J_1 = 8.5$ Hz, $J_2 = 13.0$ Hz, 1H), 2.73 (septet, $J = 7.0$ Hz, 1H), 2.61–2.70 (m, 2H), 2.02–2.20 (m, 3H), 1.98 (s, 3H), 1.58–1.70 (m, 2H), 1.24 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz) δ 207.7 (s), 186.2 (s), 174.4 (s), 159.0 (s), 156.5 (d), 143.7 (s), 133.6 (s), 128.5 (d), 44.7 (s), 42.0 (t), 41.9 (d), 37.1 (t), 34.8 (t), 27.6 (q), 25.9 (t), 24.7 (d), 20.9 (q), 20.7 (q), 11.1 (q) ppm; HRMS: $[\text{M}]^+$ observed = 284.1781, $[\text{M}]^+$ calculated = 284.1776; IR (film) λ_{max} 2924, 1698, 1460, 1378 cm^{-1} .



Phenol 188 from tricycle 183: To a solution of diisopropylamine (19 μL , 0.13 mmol) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (51 μL , 0.13 mmol). The resulting mixture was stirred at rt for 10 minutes. A solution of **183** (32 mg, 0.11 mmol) in THF (10 mL) was cannulated over a 5-minute period. The resulting solution was stirred for 1 h at rt. Water (5 mL) was added to quench the reaction. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 4:1), afforded 25 mg (78%) of phenol **188** as a light yellow oil (hexane/EtOAc, 2:1, R_f **188** = 0.54): ^1H (400 MHz) δ 6.88 (m, 2H), 6.60 (d, J = 8.0 Hz, 1H), 5.64 (d, J = 17.6 Hz, 1H), 5.49 (d, J = 10.8 Hz, 1H), 5.25 (3.43 (m, 1H), 3.08 (dd, J_1 = 6.4 Hz, J_2 = 14.4 Hz, 1H), 2.93 (septet, J = 7.8 Hz, 1H), 2.56 (m, 1H), 2.29 (dd, J_1 = 7.2 Hz, J_2 = 18.8 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 2.08 (m, 1H), 1.24 (m, 6H); ^{13}C NMR (125 MHz) δ 207.7 (s), 186.2 (s), 174.4 (s), 159.0 (s), 156.5 (d), 143.7 (s), 133.6 (s), 128.5 (d), 44.7 (s), 42.0 (t), 41.9 (d), 37.1 (t), 34.8 (t), 27.6 (q), 25.9 (t), 24.7 (d), 20.9 (q), 20.7 (q), 11.1 (q) ppm; HRMS: $[\text{M}]^+$ observed = 284.1781, $[\text{M}]^+$ calculated = 284.1776; IR (film) λ_{max} 2924, 1698, 1460, 1378 cm^{-1} .



Alcohol 189 and triene 190 from diene 112: To a solution of SeO_2 (9.1 mg, 0.089 mmol) in freshly distilled DCM (0.50 mL) was added $t\text{-BuOOH}$ (37 μL , 0.36 mmol). The resulting mixture was stirred for 25 minutes at rt. Diene **112** (48 mg, 0.18 mmol) in DCM (0.50 mL) was added dropwise. The resulting mixture was stirred at rt for 8 h, followed by standard ethereal workup. Column chromatography (elution with pet ether/ EtOAc , 10:1) afforded 19 mg (40%) of triene **190** as a light yellow oil (hexane/ EtOAc , 4:1, R_f **190** = 0.95): No clean NMR spectrum due to the presence of some inseparable impurity. Further elution gave 23 mg (45%) of **189** as a light yellow oil (hexane/ EtOAc , 4:1, R_f **189** = 0.39). No clean NMR spectrum due to the presence of some inseparable impurity.



Enone 69 from alcohol 189: To a solution of allylic alcohol **189** (5.2 mg, 0.018 mmol) in CCl_4 (0.5 mL) was added MnO_2 (16 mg, 0.18 mmol). The resulting mixture was heated at $60\text{ }^\circ\text{C}$ for 6

h. Standard ethereal workup, followed by column chromatography (elution with pet ether/EtOAc, 12:1), afforded 3.4 mg (65%) of enone **69** as a light yellow oil (hexane/EtOAc, 4:1, R_f **69** = 0.75): ^1H (400 MHz) δ 3.34 (heptet, $J = 7.2$ Hz, 1H), 2.85 (d, $J = 14.8$ Hz, 1H), 2.57 (d, $J = 14.0$ Hz, 1H), 2.40 (t, $J = 7.2$ Hz, 2H), 2.22 (d, $J = 14.8$ Hz, 1H), 2.16 (d, $J = 14.0$ Hz, 1H), 2.01 (bs, 2H), 1.67 (s, 3H), 1.46–1.75 (m, 6H), 1.08 (s, 3H), 0.98–1.04 (m, 9H); ^{13}C NMR (125 MHz) δ 202.7, 161.7, 142.9, 133.7, 129.0, 58.0, 48.7, 42.0, 40.8, 39.6, 36.1, 33.4, 29.1, 27.9, 25.6, 23.0, 20.9, 20.7, 20.7, 19.1 ppm.

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