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Total Synthesis of 4'-ester Resveratrol Analogs and a 8, 9-amido
Geldanamycin Analog and toward the
Total Synthesis of (-)-Englerin A

Yong Wang

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

Total Synthesis of 4'-ester Resveratrol Analogs and 8, 9-amido Geldanamycin Analog
and toward the Total Synthesis of (-)-Englerin A

Yong Wang

Department of Chemistry and Biochemistry, BYU
Doctor of Philosophy

The phytoalexin resveratrol and its 4'-ester analogs have been prepared with a decarbonylative Heck reaction. The deprotecting step has been modified and improved to increase yield and avoid chromatography. A set of resveratrol analogs and resveratrol have been tested with melanoma and pancreatic cell assays.

The 8, 9-amido Geldanamycin analog has been synthesized with a convergent route, involving 28 simplified steps in its longest linear sequence. Synthetic methodologies, such as Andrus auxiliary controlled asymmetric anti-glycolate Aldol and selective p-Quinone formation, were employed.

The total synthesis of Englerin A starts from (R)-carvone, passed through the modified Farvoskii ring-contraction and ring closing metathesis to get the ring skeleton. Other routes involving isopropyl group installation before closure of the seven-member ring failed. Although there are still problems to build the isopropyl moiety and the bridged ether, several reasonable alternative routes to address the problems have been designed.

Key words: Resveratrol, Geldanamycin, Englerin A, total synthesis, analog.

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List of abbreviations and acronyms

Ac	Acetyl
acac	Acetylacetonate
Alloc	Allyloxycarbonate
AIBN	Azobis(isobutyronitrile)
Bn	Benzyl
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
CAN	Ammonium cerium (IV) nitrate
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DPPA	Diphenylphosphoryl azide
EDCI	1-(3-Dimethylaminopropyl)3-ethylcarbodiimide hydrochloride
Fig.	Figure
HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HMPA	Hexamethylphosphorotriamide
Hsp	Heat shock protein
HWE	Horner-Wadsworth-Emmons

IBX	2-Iodoxybenzoic acid
iPr	isopropyl
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
mCPBA	<i>meta</i> -Chloroperoxybenzoic acid
MOM	Methoxymethyl
Ms	Methanesulfonyl
NaHMDS	Sodium hexamethyldisilazide
NBS	N-Bromosuccinimide
NEM	N-Ethylmorpholine
NMO	N-Methylmorpholine oxide
NMP	N-Methylpyrrolidinone
pyr.	Pyridine
PPTS	Pyridinium <i>p</i> -Toluenesulfonate
RCM	Ring closing metathesis
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMS	Trimethylsilyl
xyl	xylene

Chapter 1. Total synthesis of 4'-ester-Resveratrol analogs

1.1 Introduction

1.1.1 Discovery

Resveratrol (3,4',5-trihydroxystilbene) **1** is a naturally occurring *phytoalexin* which was first found in 1940 as an off-white solid from roots of *hellebore lily* (*Veratrum grandiflorum* O. Loes).¹ Since 1940, it has also been found in more than seventy plants such as grapes, blueberries, cranberries, mulberries, peanuts, corn lilies, jackfruit, etc. Resveratrol is in high abundance in food products such as grapes, peanuts, soybeans, soy milk and cereals containing soy.^{2,3} The richest natural source of resveratrol is the root of *polygonum cuspidatum*, and its extract is the commercial source of most of the marketed resveratrol-containing supplements in the U.S. The methods to induce plants to produce higher levels of phytoalexin resveratrol are stress from injury, ultraviolet irradiation, and fungal infection as a defense mechanism.

1.1.2 Biological activity of resveratrol

Grapes, one of the sources of resveratrol, are the main ingredient of Darakchasava (fermented juice of red grapes). They are also mainly used in ayurvedic medicine as a cardi tonic.⁴ The dried root and stem of *polygonum cuspidatum* are found in traditional Chinese and Japanese medicine.⁵ In addition, resveratrol found in

the skin of grapes was originally studied to be a causative agent of the “French paradox” in which French population with a high calorie diet showed a low incidence of heart related diseases.⁶

Dysregulation of multiple genes, not just a single gene, causes most diseases. And it was recently reported that drugs targeted to a specific gene failed to cure a disease.⁷ However, resveratrol can regulate multiple cellular targets and so may be proved to be suitable for prevention and treatment of many diseases. Increasing evidence has demonstrated that resveratrol demonstrates a promising biological activity against inflammation, atherosclerosis, and carcinogenesis. Its specific properties include antioxidant, radical scavenging activity,⁸ cyclooxygenase inhibition, lipid modification,⁹ platelet aggregation inhibition and vasodilation,¹⁰ inhibition of tumor initiation, promotion, and progression,¹¹ neuroprotection,¹² and antiviral activity.¹³

Resveratrol was recently reported to significantly extend lifetime in yeast, *C. elegans*, fruit flies, and mice (by 30-50%) through activation of sirtuin-1 (SIRT-1, 2), an NAD⁺ dependent histone deacetylase whose activity correlates with cellular longevity.¹⁴ The activation of SIRT-1 was also supported by another research study which showed that resveratrol-fed mice demonstrated enhanced treadmill endurance compared with controls.¹⁵

1.1.3 Synthesis of 4'-ester and fluoro Resveratrol analogs

While resveratrol has positive impacts on diseases and health, it is quickly metabolized in the liver and excreted when taken orally,¹⁶ and isolation of the pure form of resveratrol is not efficient.^{11, 17} To study the structure-activity relationships and improve therapeutic activity, various resveratrol analogs are necessary to be designed and synthesized.

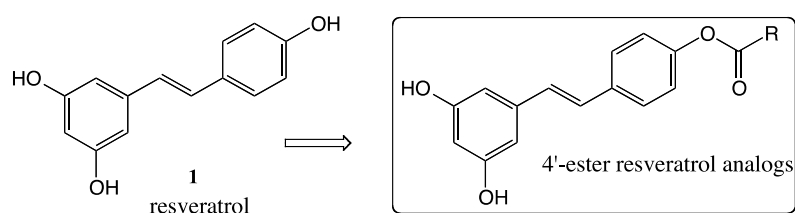
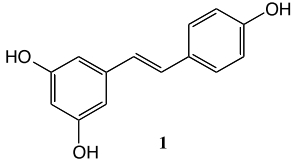
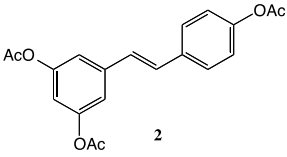
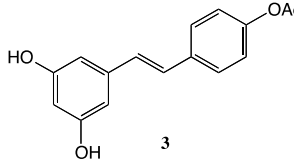
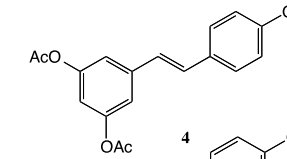
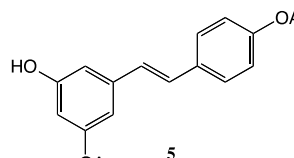
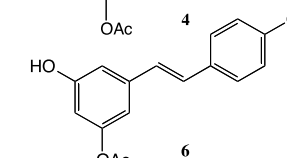


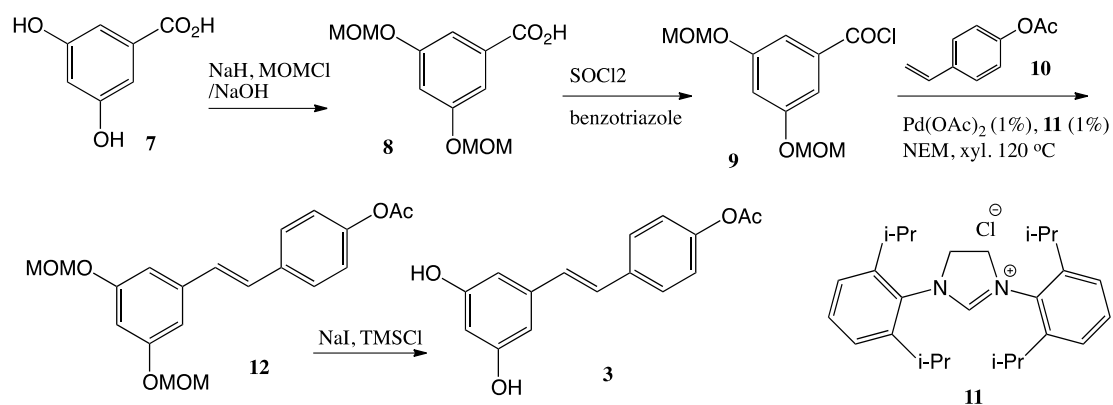
Figure 1.1 4'-ester analogs of resveratrol

To determine anti-cancer potential related to resveratrol, our group synthesized a series of analogs¹⁸ to test on human leukemia HL-60 cells (**Table 1.1**). Only the 4'-acetoxy analog **3** showed improved anti-cancer activity at 17 μM , while fluoro analogs were found to be toxic to the cell lines. And longevity studies showed that the analog **3** possesses enhanced metabolic stability with comparable activity to resveratrol by significantly extending the lifespan of yeast.¹⁹

Table 1.1 Bioactivity of the acetate analogs with Leukemia HL-60 cells

Resveratrol and analogs	ED ₅₀ (μM)	ED ₅₀ (μM)	Analog
 1	23	27	 2
 3	17	33	 4
 5	30	24	 6

Our group developed systematic and selective synthesis of acetate and fluoro analogs¹⁸ of resveratrol using decarbonylative Heck couplings²⁰ starting from cheap resorcylic acid (**Fig. 1.2** and **1.3**). For the synthesis of 4'-acetoxystilben-3,5-diol, MOM protecting group was used.

**Figure 1.2** Synthesis of 4'-acetate resveratrol analogs with decarbonylative Heck reaction.

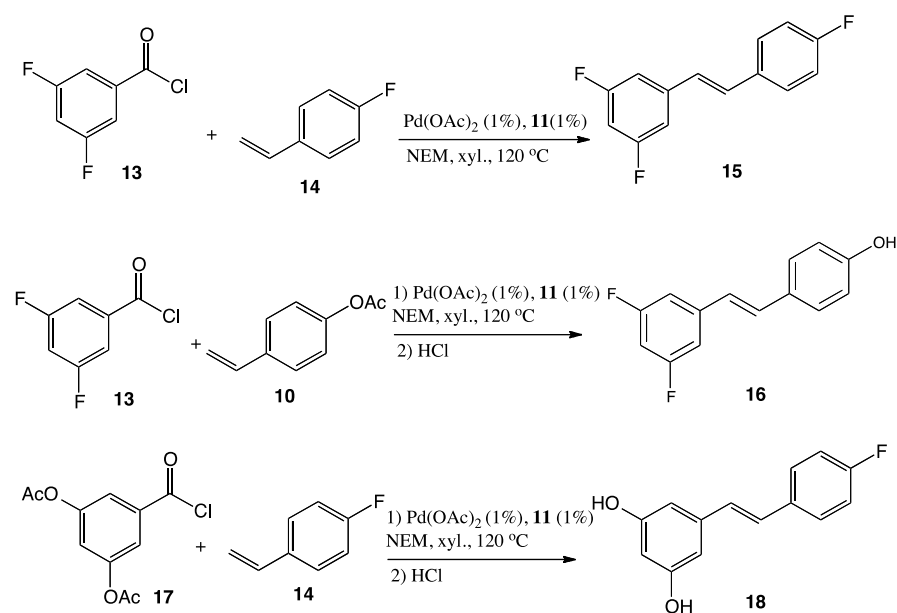


Figure 1.3 Synthesis of fluoro analogs of resveratrol using decarbonylative Heck reaction.

The analog **3** synthesized with the route above is found to be very stable and remains a white solid without decomposition (18 months), while resveratrol, either in synthetic form or from natural sources (Sigma-Aldrich), turns yellow and then brown upon storage at room temperature or -20 °C, forming multiple by-products as identified by NMR. While high purity of the analog **3** can be synthesized with the route in **Fig. 1.2**, the last deprotection step has a problem upon the scale-up. The quenching reagent, Na₂S₂O₃ reacted with excess TMSI formed in situ to give sulfur which decomposed the product in column chromatography, resulting in low yield at large scale reaction (> 2 gram). Another quenching agent, HF/pyr. did not give any product after the reaction was quenched.

1.2 Results and discussions

1.2.1 Modification and improvement of the original reported synthetic route (MOM approach)

The improved synthesis²¹ also started from inexpensive resorcylic acid **7** (Fig. 1.4) which was converted to the bis-MOM protected acid **8** using potassium carbonate and MOMCl (3 equiv). A strong base, sodium hydride, was employed in the original route.¹⁸ The new route used potassium carbonate as the base and gave slightly lower yield (88% vs 91%), but the reaction was more practical and economic due to easy work-up and cheap K₂CO₃. The MOM-ester intermediate was hydrolyzed with aqueous NaOH followed by dilute HCl to give the neutral product **8**. Benzotriazole and thionyl chloride were employed to access acid chloride **9**, which was used in the Heck coupling step without purification. In the Heck reaction, palladium acetate (1%)

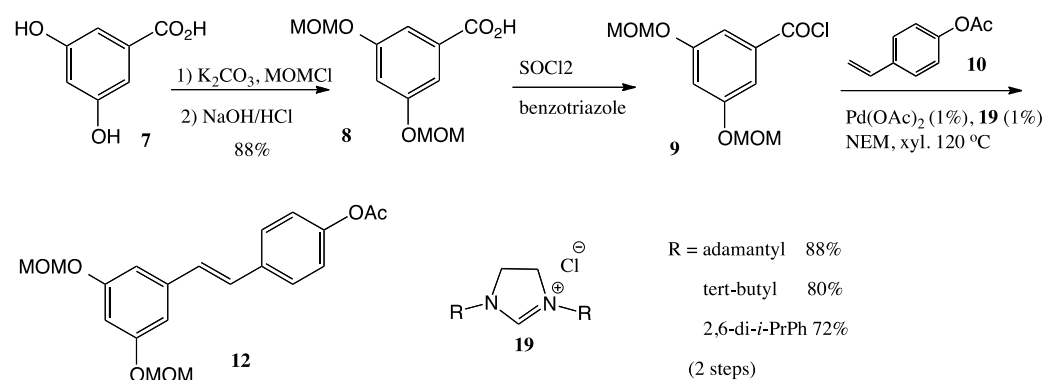


Figure 1.4 Modification of the previous route.

and N-heterocyclic carbene (NHC) ligand **19** were used with N-ethyl morpholine as base in xylenes under 120 °C. The ratio of acid chloride **9** to acetoxystyrene was 1:1.25. The previous yield of the Heck coupling using N, N-diisopropylphenyl-NHC was 72%. The bulky commercially available N, N-bis-adamantyl-NHC ligand and N, N-bis-t-butyl-NHC ligand gave 88% and 80% yield respectively over the two steps (**Fig. 1.4**). Sterically hindered NHC ligands have been reported to improve palladium catalyzed coupling reactions.²²

With the coupling product **12** in hand, selective MOM removal methods have been tried (**Fig. 1.5**). Hot SiO₂.NaHSO₄ gave mono-MOM intermediate at 3 equiv. in 5 hrs, but the intermediate decomposed and no product was formed after 2 more equiv. of SiO₂.NaHSO₄ were added (**Fig. 1.5**, rxn 1). The same result was seen with MgBr₂.OEt₂^{23b} (**Fig. 1.5**, rxn 2). Reactions (3) and (4) gave very little product while compound **12** was consumed over time. Reaction (5) with cyclopentanone catalyzed by HCl (solution in THF) gave no product, and increasing HCl to 2 equiv. decomposed the starting material **12**. Other acid conditions in reaction (6), (7) and (8) gave no product and reaction solutions turned to yellow or brown.

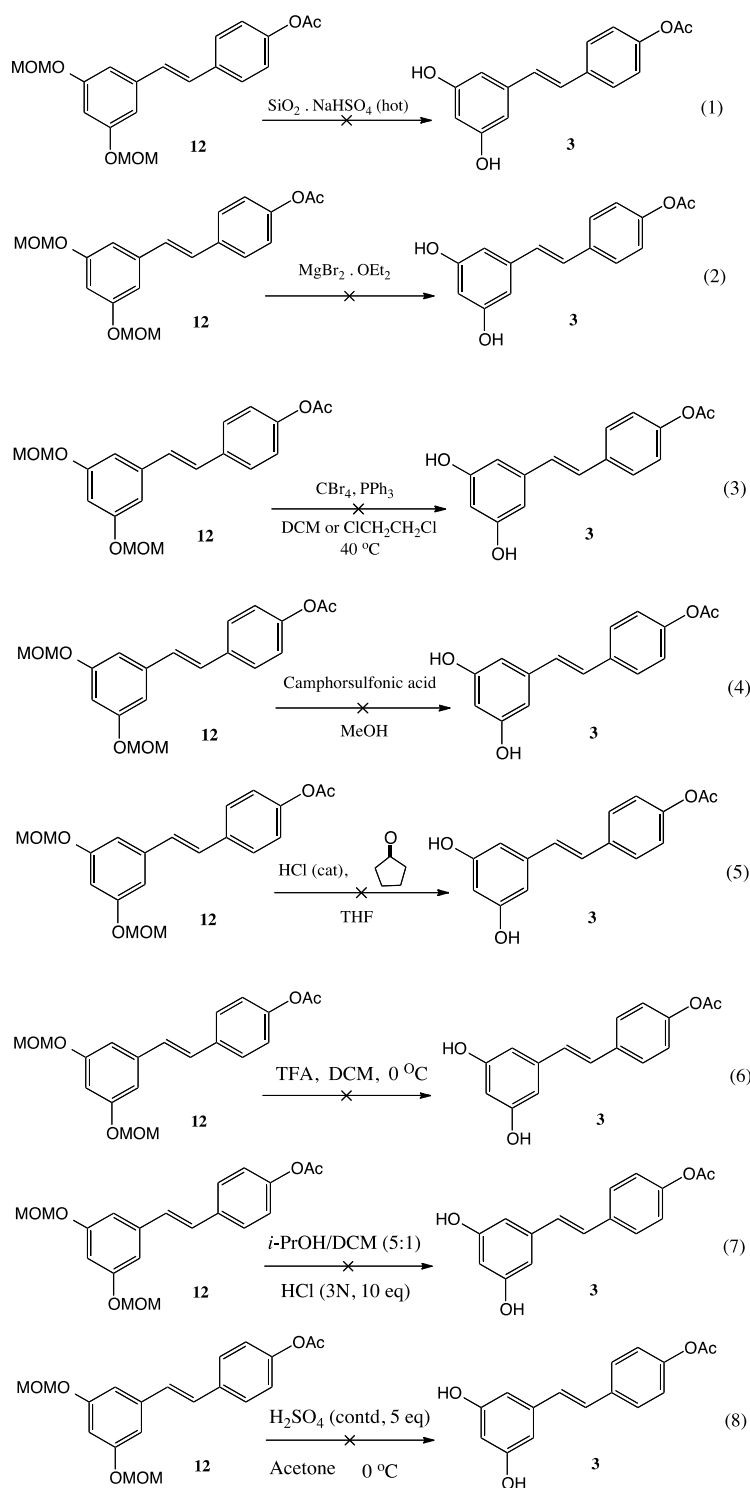


Figure 1.5 Failed selective MOM deprotecting reactions.

Inspired by reaction (5), increasing the equivalents of HCl and diluting the reaction solution might selectively deprotect two MOM groups and keep the ester

group untouched. Solvents, concentration, temperature and equivalent of HCl were screened to get the optimized reaction condition. Row 6 (**Table 1.2**) gave the best yield of the product **3**. A 6 gram scale reaction under HCl in ether gave a yield of approximately 70%.

Table 1.2 Optimization of HCl selective deprotection of bis-MOM.

equiv. of HCl	solvent	concentration (M)	T (°C)	Rxn yield (%)
4 M in dioxane, 2 eq	EtOH/THF(5:1)	0.015	23	<20
1.25 M in MeOH, 2 eq	MeOH/THF(5:1)	0.015	60	<10
6 M in H ₂ O, 2 eq	THF/H ₂ O/AcOH(10:1:1)	0.04	60	no product
4 M in dioxane, 25 eq	Et ₂ O	0.05	0 to 23	~40
25 eq [*]	Et ₂ O	0.05	0 to 23	~40
2 M in Et ₂ O, 25 eq	Et ₂ O	0.05	0 to 23	72

* HCl was generated in situ with the reaction of acetyl chloride (25 eq) and methanol (30 eq).

More 4'-ester analogs have been synthesized from the intermediate **12** (**Fig 1.6**). Hydrolysis of **12** under aqueous base and the following neutralization gave 4'-phenol intermediate which was then esterified with different acid chlorides to form product **20**. HCl in Et₂O approach was employed to selectively deprotect bis-MOM to produce a series of analogs **21**. Only the adipate dimer ester **21e** was obtained in lower yield, 45%. All the others, 4'-*n*-butyrate, 4'-*i*-butyrate, 4'-*n*-hexanoate, and

4'-palmitoate products were produced in moderate to good yield (73-82%).

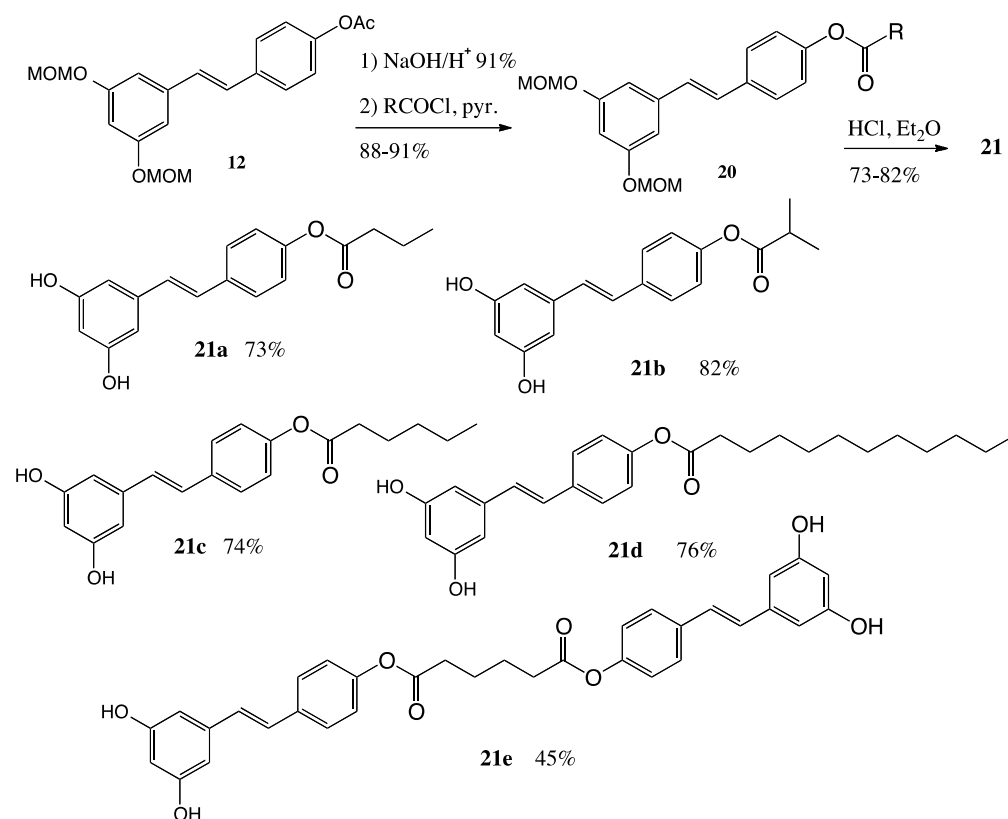


Figure 1.6 Synthesis of additional 4'-ester resveratrol analogs.

While the MOM deprotecting step in the new route worked well with reliable yield of the new analogs, the MOM selective removal required absolute anhydrous solvent, and the reaction produced increasing amount of by-product if run at more than 10 gram scale. Another disadvantage is that the acid chloride intermediate **9** is liquid and had to be used freshly for the decarbonylative Heck coupling. Therefore, a more practical synthetic route without column chromatography needs to be developed for increasing demand of the 4'-ester resveratrol analogs.

THP and TBS protecting groups were used to get the acid chlorides **22** and **24** successfully, but in the Heck coupling step, very little product **23** was obtained, and

product **25** was almost impossible to be separated from the excessive 4-acetoxystyrene. The intermediates **22** and **24** are liquid which proved to be unstable upon storage.

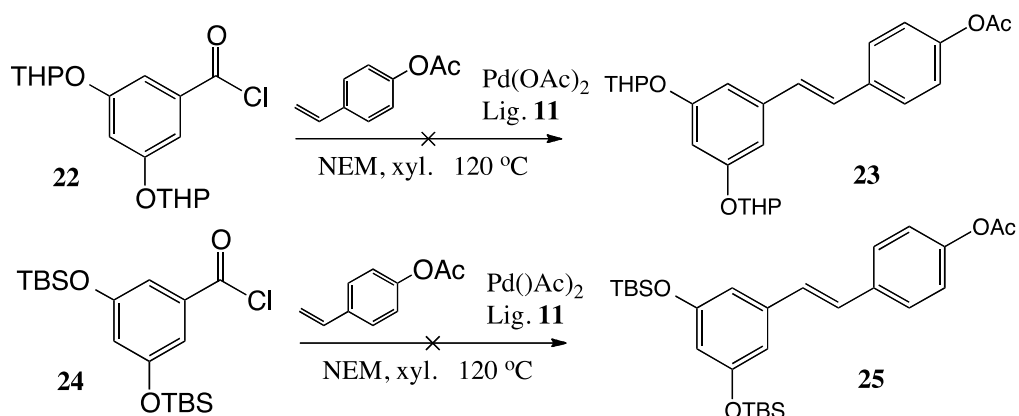


Figure 1.7 Failed Heck coupling steps with THP and TBS protecting groups.

1.2.2 Modification and improvement of the original reported synthetic route (Benzyl approach)

Benzyl protecting group was then tried due to its larger molecular weight and potentially more selective removal than MOM. According to the known procedure,²³ the intermediate **26** was synthesized as a white solid. The Heck coupling with compound **26** gave good yield of **27** in shorter time (70%, 3hrs) (**Fig. 1.8**).

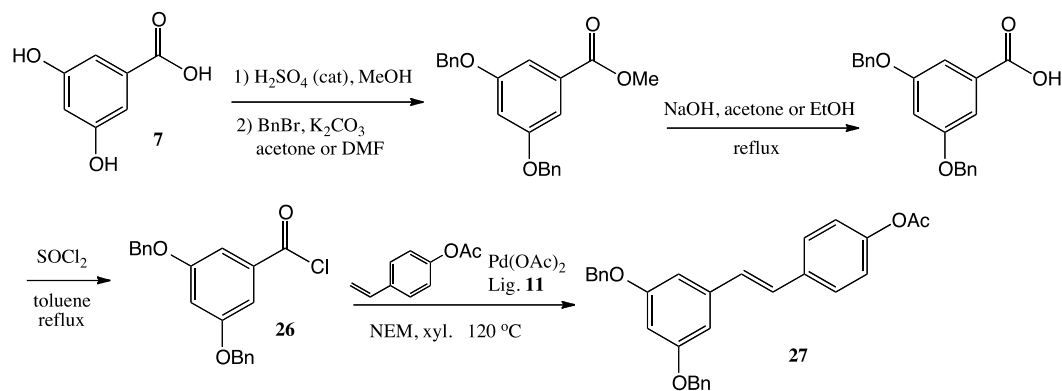


Figure 1.8 The practical synthesis of Heck coupling product **27**.

With the white pure intermediate **27** in hand, several benzyl group deprotection methods have been tried (**Fig 1.9**). Lewis acid BBr_3 did selectively remove bis-Bn at low temperature, but an unknown by-product was equally large and close in Rf on TLC. Catalytic amount of $\text{Pd}(\text{OH})_2$ and 1,4-cyclohexa-diene in EtOH were also employed to remove the bis-Bn, but no product was observed after 2 days. AlCl_3 and PhNMe_2 was also tried at room temperature, but after 5 hours, multiple spots including the product and the starting

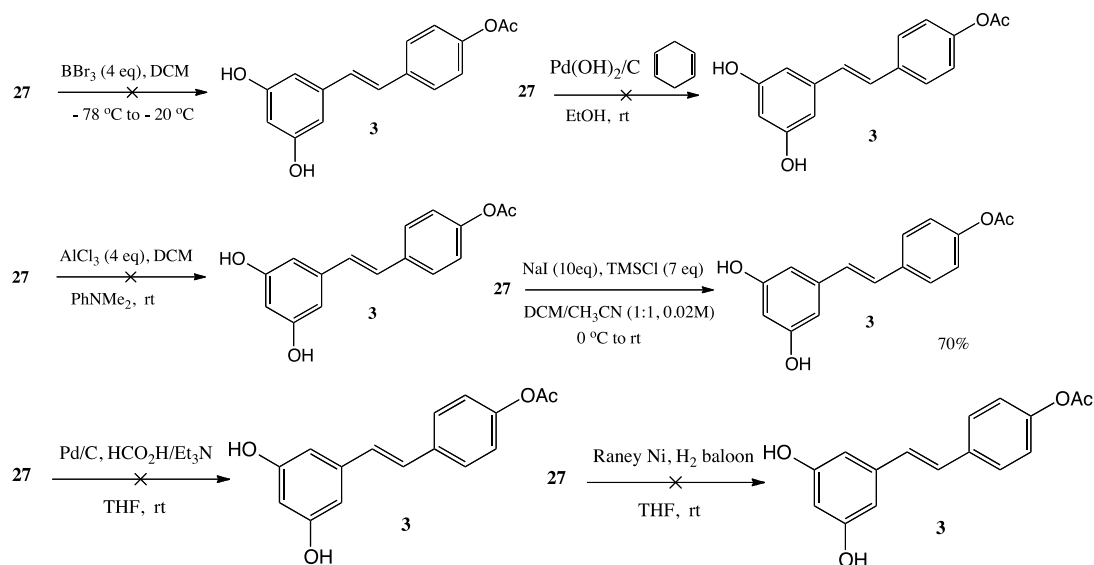


Figure 1.9 Selective removal of bis-Bn group with different methods.

material were observed on TLC plate. Pd/C with formic acid and triethylamine and Raney Ni/H₂ also failed to produce any product. The original approach to deprotect bis-MOM was also employed to deprotect bis-Bn, and fortunately, the product was obtained in good yield when 10 eq. of NaI and 7 eq. of TMSCl were used. However, large-scale reaction (> 10 gram) with this approach was also problematic for the same argument as deprotection of bis-MOM. So a new practical method suitable for the large-scale selective deprotection (>10 gram) still remained to be found.

After careful review of the reactions in **Fig 1.9**, metal catalytic methods was excluded due to poor reactivity and price, but more equivalent of weaker Lewis acids in dilute solvent might be the ideal solution to address the problem in the NaI/TMSCl approach. Fuji's conditions²⁴ (boron trifluoride etherate and dimethyl sulfide) ultimately proved to be an excellent method for the deprotection. From **Table 1.3**, both BF₃.OEt₂/Me₂S and BF₃.OEt₂/dodecyl methyl sulfide gave excellent yields. For large-scale reaction, Me₂S has a bad odor, but it is cheaper, while dodecyl methyl sulfide is odorless and expensive, so recycling is necessary for practical use. A 50-gram scale debenylation has been run without problem. A short large diameter column or large cup was used to separate nonpolar by-products, the crude product was concentrated and recrystallized twice to give off-white product in around 70% yield.

Table 1.3 Selective debenzylation from **27** to **3** with BF₃.OEt₂ in DCM.

yield (%)	eq. of BF ₃ .OEt ₂	additives	eq. of additive	concentration (M)
68	8	Me ₂ S	12	0.05
71	12	Me ₂ S	18	0.05
91	12	Me ₂ S	18	0.05
87	12	dodecyl methyl sulfide	15	0.05
<50	12	dodecanthiol	15	0.05

1.3. Evaluation of resveratrol and its analogs in malignant melanoma and pancreatic cell lines

A set of resveratrol analogs including the 5 newly synthesized analogs (re-numbered here) and 5 previously made analogs (re-numbered here) and resveratrol (**Fig. 1.10**) was selected for a broad structure-activity profile in melanoma cancer cell inhibition investigations.

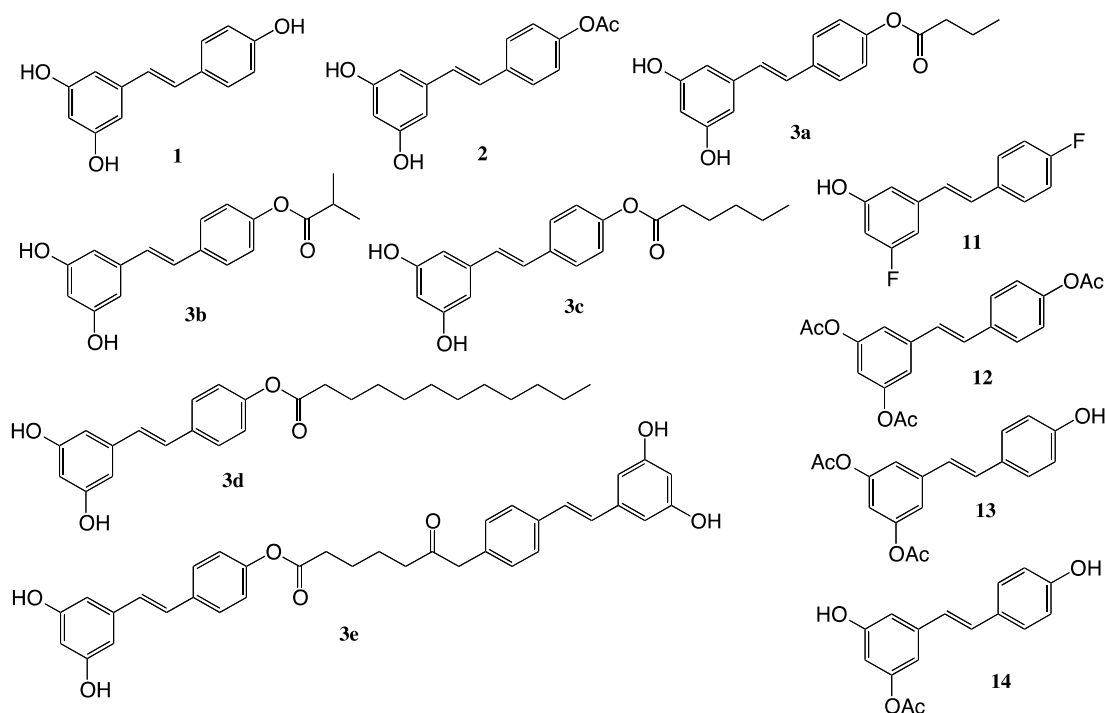


Figure 1.10. Resveratrol and its analogs for evaluation for cancer cell inhibition

Cell assays were performed to access in vivo potential. DM 443 and DM738, were selected for this study because of their chemoresistance properties to melphalan (LPAM) and temozolomide (TMZ) respectively.²⁵ DM443 and DM738 were plated and then resveratrol and its analogs were added and cells were incubated for 24, 48, or 72 hours. Cell viability was then quantified with a colorimetric assay. Cell lines were treated with resveratrol and its 10 analogs at 10, 25, and 50 μ M and evaluated at multiple time points. As comparing efficacies at the 50 μ M dose, analogs **3a**, **3b**, **3c**, and **11** were shown to be significantly more cytotoxic than resveratrol at all time points in both cell lines (all p 's < 0.025), analog **3d** did not show any effect at any time point in either cell line ($0.34 < p < 0.83$), and analogs **2**, **3e**, **12**, **13** and **14** had varying efficacies between these two groups (**Fig. 1.11**). Analog **2** was shown to be

equally effective as natural resveratrol at every time point and dose in both cell lines.

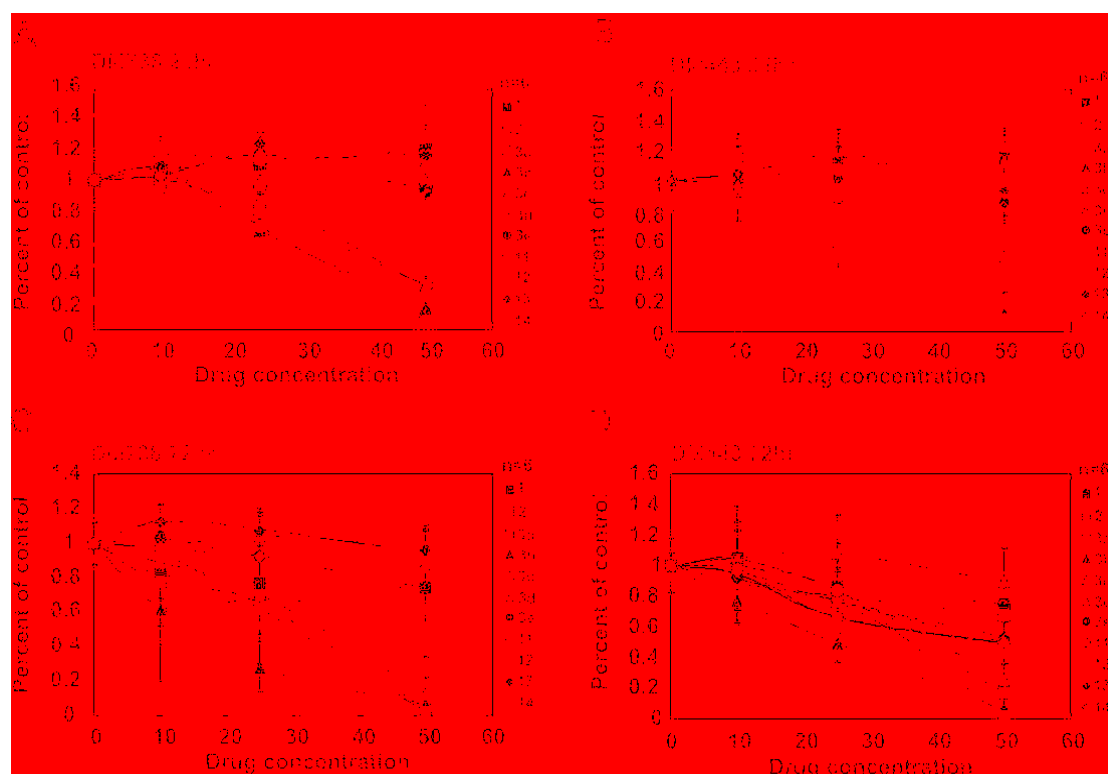


Figure 1.11. DM443 and DM738 treated with resveratrol and its analogs for 24 hrs (A and B) and 72 hrs (C and D) respectively. Data are expressed as mean +/- SEM, n = 6.

Normal human dermal fibroblast (NHDF) cells were treated with resveratrol and its analogs for 72 hours at 50 μ M to evaluate selective cytotoxicity to malignant cells. It was found that analogs **2** and **3e** relatively spared NHDF cells compared to their cytotoxic effect in melanoma cell lines (both p 's < 0.0001) (**Fig. 1.12**).

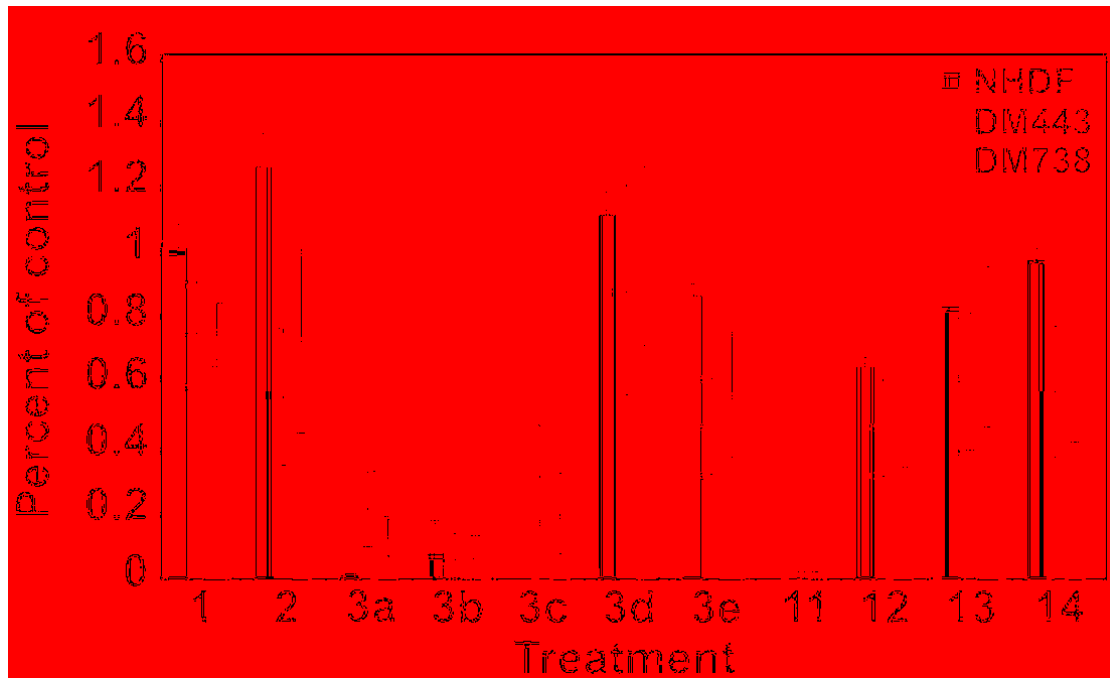


Figure 1.12. Cell lines DM443, DM738 and NHDF were treated with resveratrol and its analogs at 50 μ M for 72 hrs. Data are expressed as mean \pm SEM; n = 6.

Resveratrol and its analogs also have cytotoxic effect to pancreatic cells (Panc-1) (**Fig. 1.13**). A malignant line of pancreatic cells was treated with resveratrol, analog **2** or analog **12** at 50 μ M for 72 hrs. Gemcitabine, a standard treatment of advanced pancreatic cancer,²⁶ was also added at 0, 1, or 10 μ g/ml as control. Resveratrol and both analogs showed significant cytotoxicity to both vehicle alone ($p < 0.0001$) and to treatment with gemcitabine alone at all doses (p 's < 0.0001). It was also found that the addition of gemcitabine did not enhance the cytotoxic response of resveratrol or its analogs.

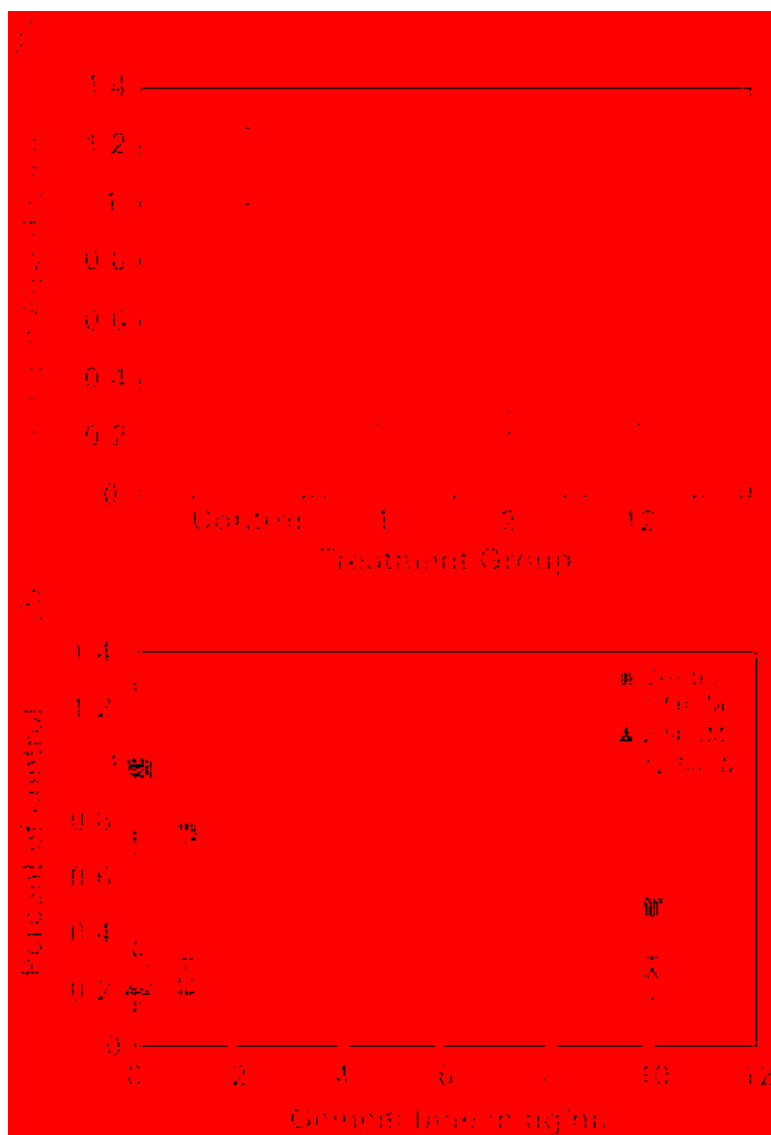


Figure 1.13. (A) Panc-1 treated with resveratrol or analog for 72 hrs. (B) Panc-1 treated with resveratrol and its analogs +/- gemcitabine, or gemcitabine alone for 72 hrs. Data are expressed as mean +/- SEM, n = 6.

1.4. Conclusion

Various 4'-ester resveratrol analogs have been produced using a decarbonylative Heck coupling. The yield of the Heck coupling step has been increased with bulkier ligands. The deprotecting step has been modified and improved

to increase yield and avoid chromatography. A structure-activity profile has been produced from melanoma and pancreatic cell assays.

1.5. References

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Chapter 2. Design and Synthesis of 8,9-amido-Geldanamycin Analog

2.1. Introduction

2.1.1. Isolation and Bioactivity

Geldanamycin **28**, an anti-tumor Hsp90 inhibitor, was isolated from *Streptomyces hygroscopicus* var. *geldmus* var. *nova* (UC5208) by researchers at Upjohn in 1970.¹ It was determined in structure by Rinehart and his coworkers shortly thereafter,² and as a member of anasamycin,³ Geldanamycin is the first member containing a benzoquinone moiety, but other previously discovered members (e.g. rifamycin,⁴ streptovaricins,⁵ tolypomycins⁶) have naphthoquinone nuclei. After Geldanamycin, other benzoquinone anasamycin antibiotics **29** (macbecin I⁷, herbimycin⁸) were discovered (**Fig. 2.1**).

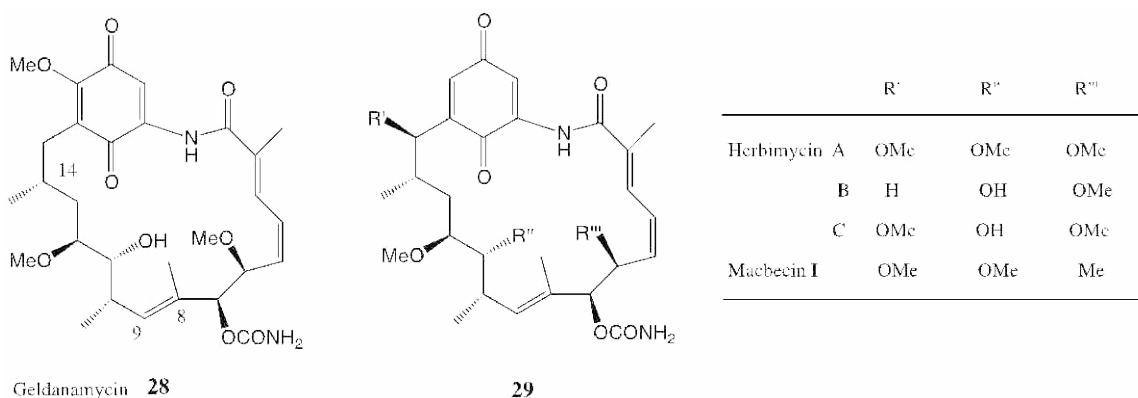


Figure 2.1 Benzoquinone anasamycins.

Geldanamycin was found to have moderate activity in vitro against protozoa, bacteria, and fungi (MIC: 2-100 μ M), and extreme activity against KB cells ($< 0.01 \mu$ M) and

L1210 ($< 0.002 \mu\text{M}$). In vivo, Geldanamycin demonstrated oral activity against the parasite *Syphacia oblevata* at 0.5 mg/mouse/day for 4 days.¹ Geldanamycin, along with herbimycin A and macbecin I, possess various activities including antibacteria and anticancer.⁹ An analog, 17-allylamino-geldanamycin that is a semi-synthetic compound, is currently in phase-III clinical trials.¹⁰

Geldanamycin demonstrated a unique profile against the NCI 60 cell-line panel with an average ED_{50} of 180 nM.¹¹ It also binds to Hsp90, an abundant cytosolic heat shock chaperone protein that regulates cell signaling.¹² Subsequent studies showed that Geldanamycin selectively reduces the stability of several oncogenic tyrosine kinase, such as v-Src, Bcr/Abl, and HER2, by disturbing their association with Hsp90.¹³ While Hsp90 exists abundantly in both tumor and normal cells, nearly all Hsp90 in cancer cells exists in multi-chaperone complexes.¹⁴ Conversely, Hsp90 in normal cells mostly exists in free, uncomplexed form. The complex form of Hsp90 is tightly bound by Geldanamycin with high affinity (12nM), but the free form of Hsp90 in normal cells is bound by Geldanamycin much less tightly (affinity 2-6 μM).

2.1.2. Design of Geldanamycin Diamide Analog

The crystal structures of Hsp90-geldanamycin complex demonstrate that geldanamycin adopts a “C-clamp” shaped conformation, but it is higher in energy (+14.9 kcal/mol) than its free and unbound solution conformation (**Fig. 2.2**).¹⁵ Geldanamycin analogs that favor the *s-cis* “C-clamp” conformation should demonstrate improved selectivity and activity for binding complex Hsp90. An amido moiety as a trisubstituted

alkene mimic provides a rigid *s-trans* conformer which might not impact the other amido conformation but offer a critical disconnection point for the synthesis (**Scheme 2.1**). Synthesis of this alkene region located between five stereocenters in Geldanamycin

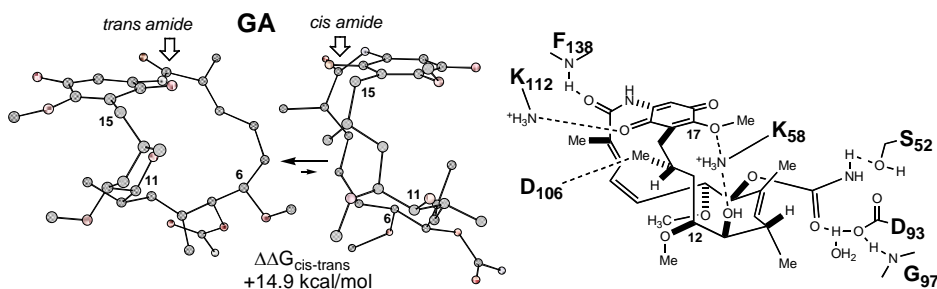
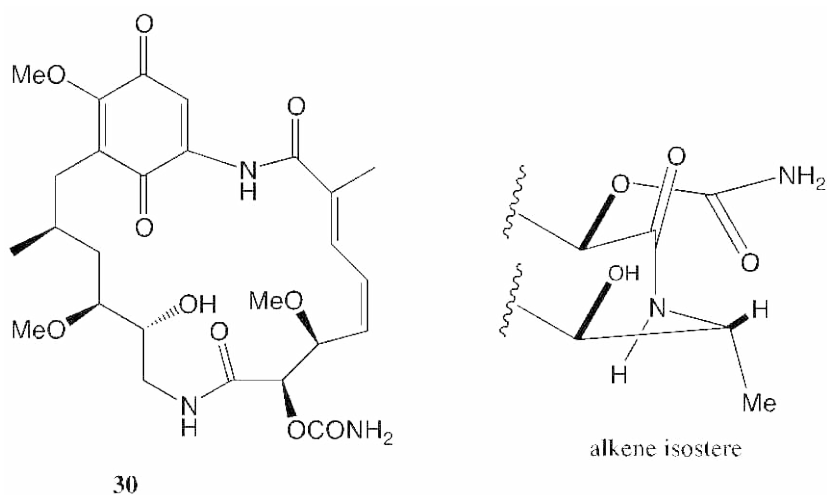


Figure 2.2 Structure of Geldanamycin-Hsp90 binding complex.

has proven to be problematic.¹⁶ The amido analog **30** was designed with the amide located at the 8,9-position with its carbonyl oxygen approximating the C8-methyl group in Geldanamycin. The C14 methyl group was inverted to the *S*-stereochemistry while the natural *R*-C14 methyl group seems to adopt a pseudo axial position. The design was based on B3LYP/6-31G*¹⁷ calculations which show that the analog **30** was more able to adopt the bound conformation than Geldanamycin. The bound conformer of **30** was +6.3 kcal/mol higher in energy and that of Geldanamycin was +14 kcal/mol higher than its unbound form. In addition, the analog is more polar than Geldanamycin that suffers from poor bioavailability due to low water solubility.¹⁸



Scheme 2.1 C8, 9-amide Geldanamycin analog and its amide mimic conformation.

2.1.3. Synthesis of Geldanamycin

The first and only total synthesis of Geldanamycin was finished by the Andrus group with a 41-step linear route starting from 1, 2, 4-trimethoxybenzene **31** (**Fig. 2.3**).¹⁶ The key steps are a chiral dioxanone auxiliary (**32**) controlled asymmetric anti-glycolate aldol reaction¹⁹ to construct the C11,12 stereochemistry, and a chiral norephedrine auxiliary (**33**) controlled syn-aldol²⁰ to set C6,7 stereochemistry. Then the macrolactam ring was closed by amide coupling reagent BOP-Cl. Finally *p*-quinone Geldanamycin **28** was formed as minor product with nitric acid.²¹

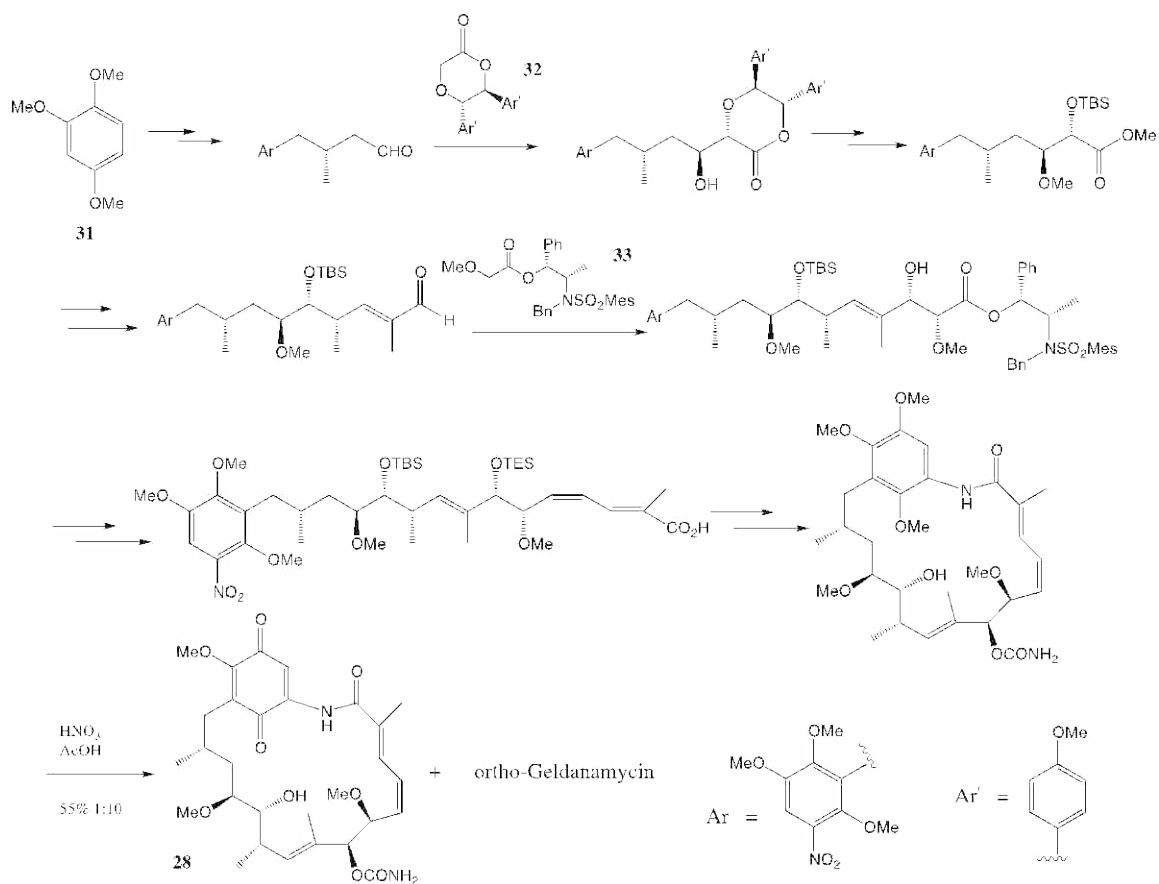


Figure 2.3 Total synthesis of Geldanamycin.

The major drawback of the total synthesis was the poor selectivity of the last step. It has been improved with selective *p*-quinone formation using a 1,4-di-MOM protected model substrate **29** (Fig. 2.4).²² The first step used TMSI formed in situ to remove MOM and TBS protecting groups, then Rapoport conditions²³ oxidized the resulting hydroquinone intermediate to the *p*-quinone of Geldanamycin in high yield.

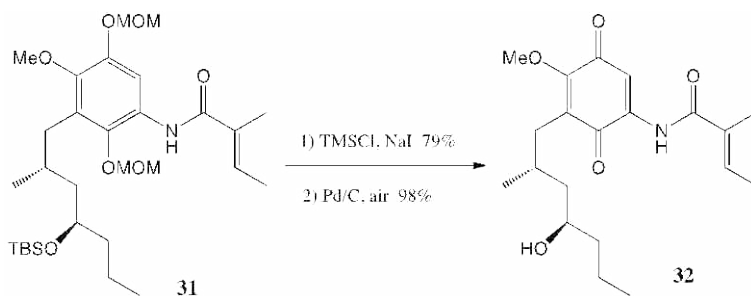


Figure 2.4 Model study of the selective *p*-quinone formation.

2.2 Results and Discussions

2.2.1. Retro-synthesis of 8,9-amido-Geldanamycin Analog

With the developed selective *para*-quinone formation method, the target analog **30** was designed from di-MOM precursor **33**. The bis-amide structure in **33** could be constructed with intra and inter amide formation from **34** and **35** (Fig. 2.5).

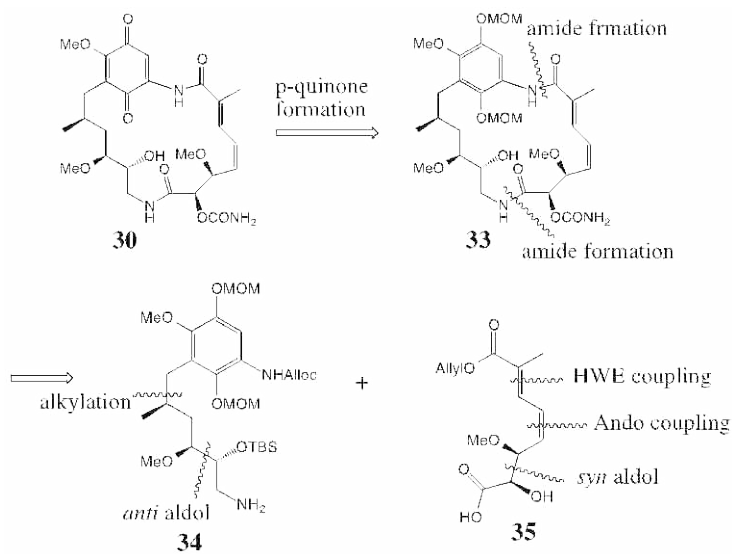


Figure 2.5 Retro-synthesis of 8, 9-amido-geldanamycin analog.

2.2.2 Synthesis of the left hand piece of the 8, 9-amido-geldanamycin analog

It took 10 steps to get the *anti*-glycolate aldol substrate **39** from methoxy hydroquinone **36** according to our previously published and improved procedure (**Fig 2.6**).²² The nitration step unavoidably removed 1 MOM group. Reinstallation of MOM was improved with K_2CO_3 /acetone. The yield of Evans auxiliary removal was improved to 90% by adding a few drops of water.

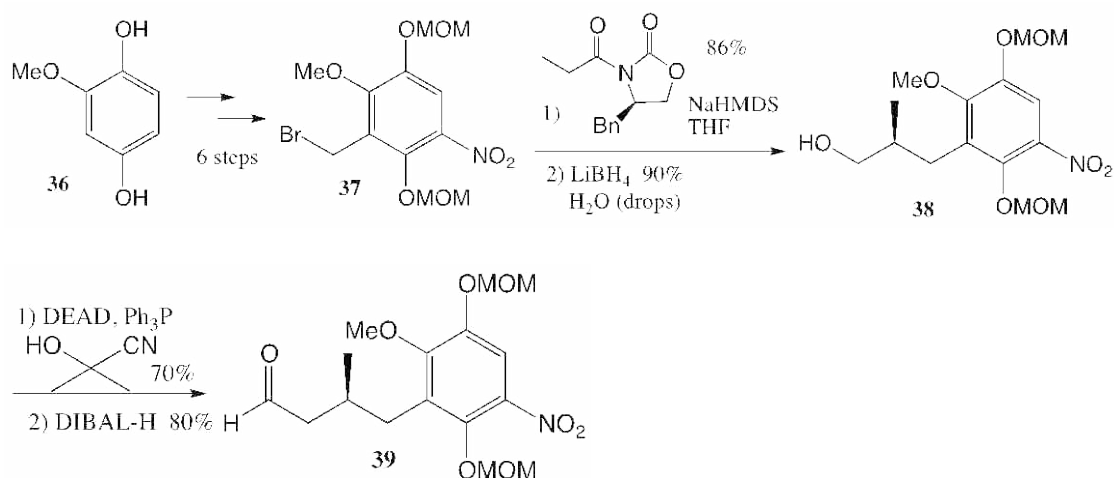


Figure 2.6 Synthesis of the *anti*-aldol aldehyde substrate.

Andrus auxiliary **32** reacted with the aldehyde **39** to generate the *anti*-glycolate adduct **40** in 62% yield and 9:1 selectivity.¹⁹ The secondary alcohol **40** was converted to methoxy group in **41**. The auxiliary removal utilized NaOMe catalyzed lactone-ester exchange followed by oxidative removal of benzyl ether with CAN to give the secondary alcohol which was protected with TBS (**Fig. 2.7**).

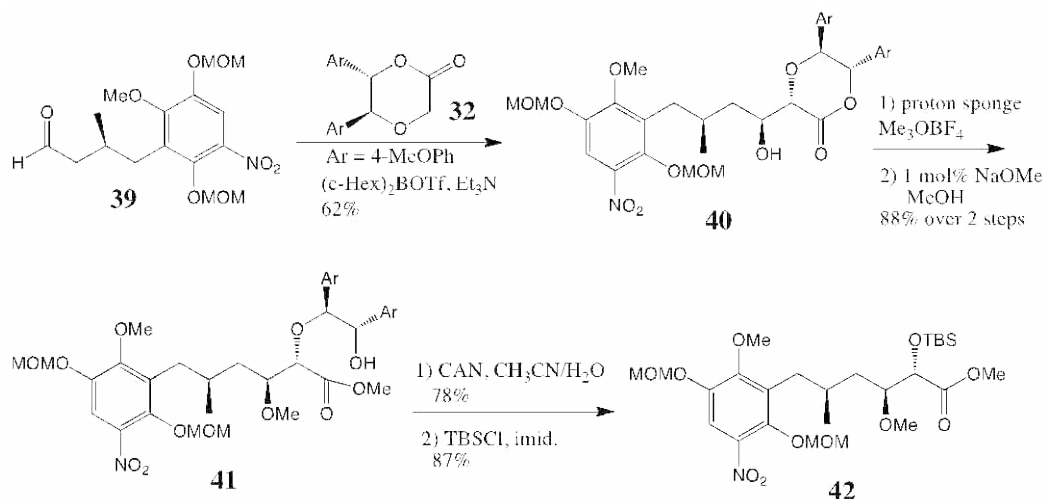


Figure 2.7 Application of the *anti*-glycolate aldol reaction.

The nitro group in **42** was reduced to the aniline that was then protected with Alloc group. The ester in **43** was selectively reduced to the aldehyde **44**, but reductive amination gave the dimer **45** as the only product. Converting to benzyl amine and then deprotecting benzyl group did give the primary alkyl amine, but Alloc group was either removed or reduced at the same time (**Fig. 2.8**).

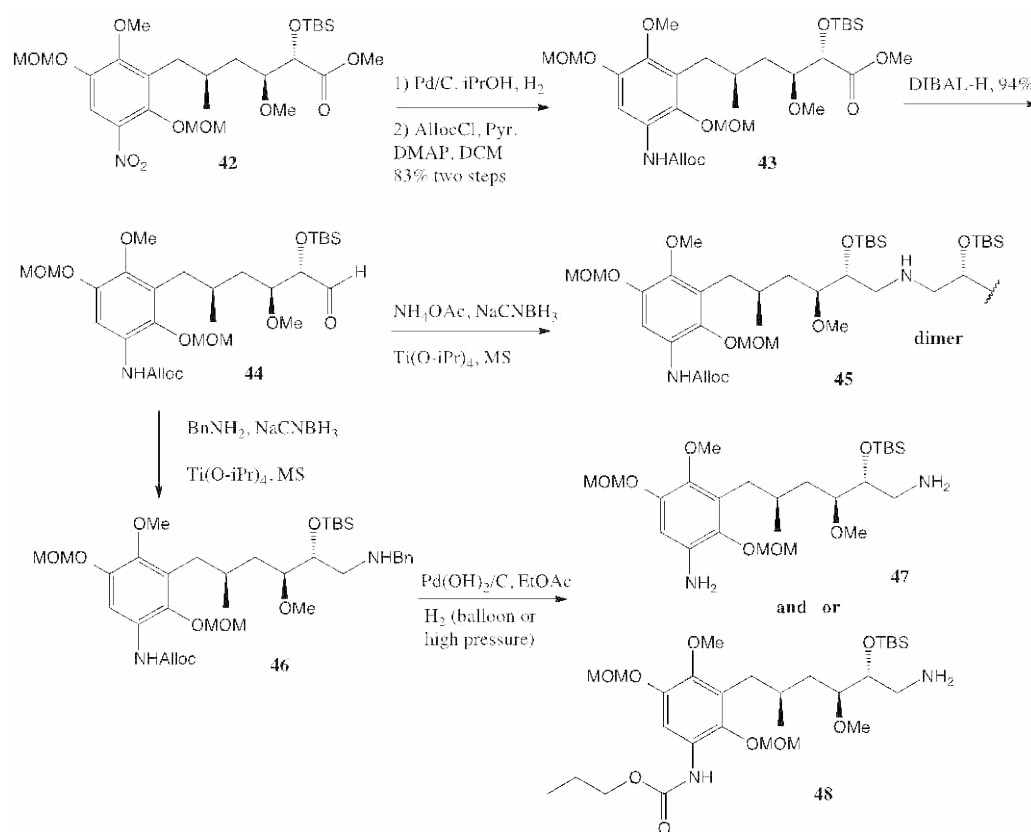


Figure 2.8 Attempts to synthesize the left hand piece--primary amine.

Alternatively we chose functional group conversion to get the primary amine (**Fig 2.9**). The ester **43** was reduced to the primary alcohol **49**, then Mitsunobu reaction conditions with **49** gave the azide that was hydrolyzed to produce the left hand piece **50**.

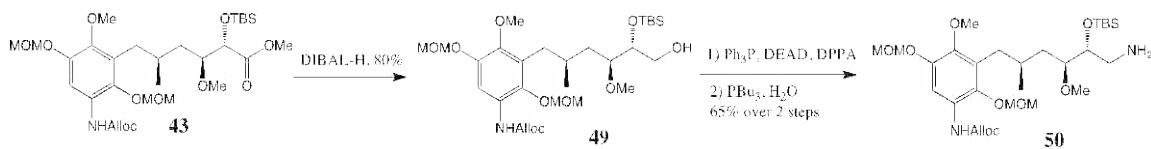


Figure 2.9 Completion of the left hand piece of the Geldanamycin analog.

2.2.3. Synthetic completion of the Geldanamycin analog

The acid **51** had been synthesized previously by Jing Liu in our lab.²⁴ I contributed the one-step norephedrine auxiliary removal to directly give the aldehyde. The primary amine **50** coupled with **51** through amide bond formation under HATU and DIPEA at 0 °C to generate the protected **52**. Removal of Alloc and Allyl groups produced the intermediate²⁵ which formed the macrolactam **53** using HATU and DIPEA in dilute DCM. Then Kocovsky's procedure²⁶ was employed to form the carbamate that produced urethane **54** with K₂CO₃. Deprotection of TBS and MOM groups with TMSI gave the dihydroquinone, which was oxidized to the desired *p*-quinone **30**—the final product.

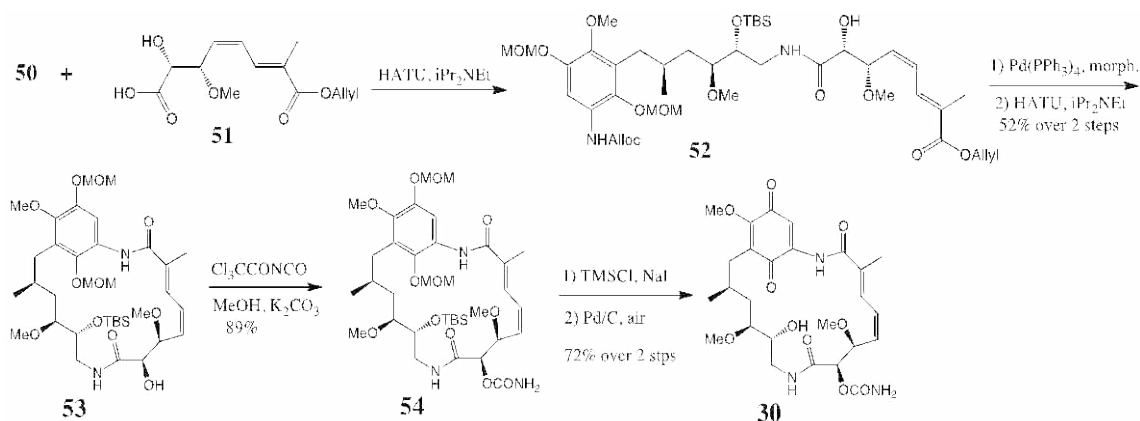


Figure 2.10. Completion of 8,9-amido Geldanamycin analog.

2.3. Conclusion

In summary, the 8,9-amido Geldanamycin analog has been synthesized with a convergent route, involving 28 simplified steps in its longest linear sequence. Synthetic methodologies, such as Andrus auxiliary controlled asymmetric *anti*-glycolate Aldol and

selective *p*-quinone formation, were employed. The convergent route can be applied to synthesis of more polar analogs of the challenging anticancer agent. Unfortunately, preliminary bioactivity assessment of this analog demonstrated 100 times less potent than the Geldanamycin natural product in SKBR3 cells. The assays have been extensively used to query the activity of new Hsp90 inhibitors. Due to very few analogs to compare, it remains difficult to determine which factors contribute to lowered activity in this case.

2.4. References

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Chapter 3. Towards the total synthesis of (-)-englerin A

3.1. Introduction

3.1.1. Isolation and bioactivity

Englerin A was isolated as a white solid from the bark of *Phyllanthus engeri*, a plant in east Africa (**Fig. 1**).¹ It was demonstrated to be a selective and potent inhibitor of six renal cell lines in the NCI 60-cell panel (GI_{50} = 1-87nM). Renal cell carcinoma (RCC) is a type of kidney cancer that originates in the small tubes which act as a filter to remove waste products in blood. RCC is attributed to about 58,000 new cases and 13,000 deaths in US in 2009, ranking among the 10 leading cancer types in the US.² Approved drugs such as bevacizumab, sunitinib, and sorafenib have been a benefit to patients with metastatic renal cancer, but they require long-term administration for disease control, and have serious side effects.³

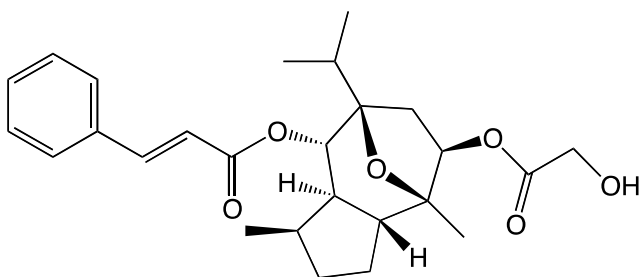


Figure 3.1. Structure of englerin A

Englerin A showed 1000-fold selectivity for the renal cancer cell lines, and

according to the NCI COMPARE analysis, englerin A seems to operate by a new and unknown mechanism. A preliminary mouse toxicity studies showed englerin A is extremely well tolerated.¹ More importantly, englerin A showed overall better activity compared to Paclitaxel (Taxol[®]), with 5 of 8 cell lines having much lower GI₅₀ values than Taxol (**Table 3.1**).¹

Renal cell line	Englarin A	Taxol
786-0	<0.01	0.034
A498	<0.01	0.10
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

Table 3.1. Renal Cancer Cell Growth Inhibition Data (Mean GI₅₀ in μM) for Englerin A, compared to average values for Taxol.

3.1.2 Review of total synthesis of englerin A

Due to its outstanding biological activity and its unique, drug-like⁴ architecture, englerin A has become an attractive target for the synthetic organic chemistry community.⁵

Christmann contributed to the first total synthesis of englerin A and identified its absolute configuration.^{5a} Retrosynthetic removal of cinnamate side chain in (+)-englerin A leads to the protected glycolate ester **1** that may be accessible with a transannular epoxide-opening from **2**. The epoxide precursor **2** could be synthesized by kinetically controlled acylation followed by diastereoselective oxidation from **3**. Allylation of aldehyde **5** with the allylmetal compound **4** can form a new alkene that would react with another terminal alkene under ring closing metathesis condition. The starting material trans, cis-nepetalactone **6** would lead to **5** with an oxidative rearrangement (**Fig. 3.2**).

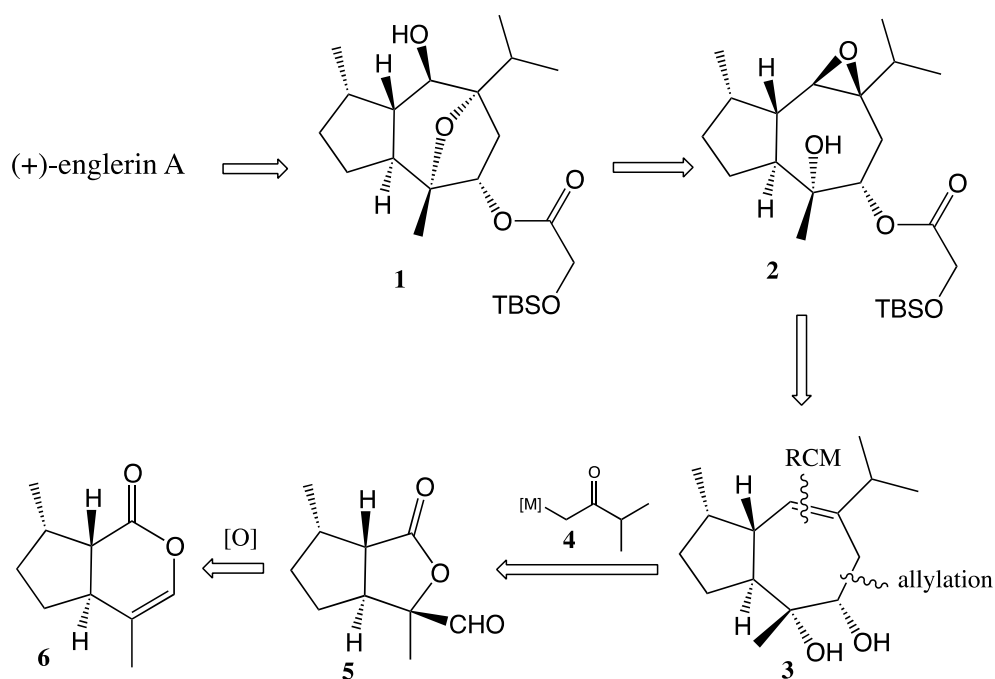


Figure 3.2. Retrosynthetic analysis of (+)-englerin A.

Ma's group is the first group to use organometallic chemistry to construct the core structure of englerin A.^{5b} Intermediate **7** can lead to englerin A through reduction and ester formation, and it would be given through functional group manipulations from **8**. A

recently developed gold catalyzed cyclization of enynes provided an attractive approach (**Fig. 3.3**)⁶ to form **8** from **9**. The commercially available (R)-citronellal as a chiral building block could serve as the starting material to synthesize **9** through functional group conversion (**Fig. 3.4**).

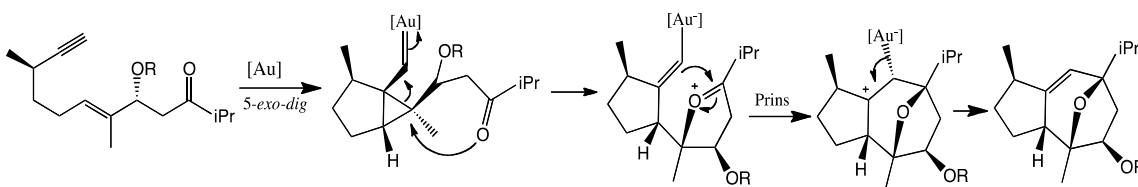


Figure 3.3. Mechanism of Gold catalyzed cyclization of enyne ketone.

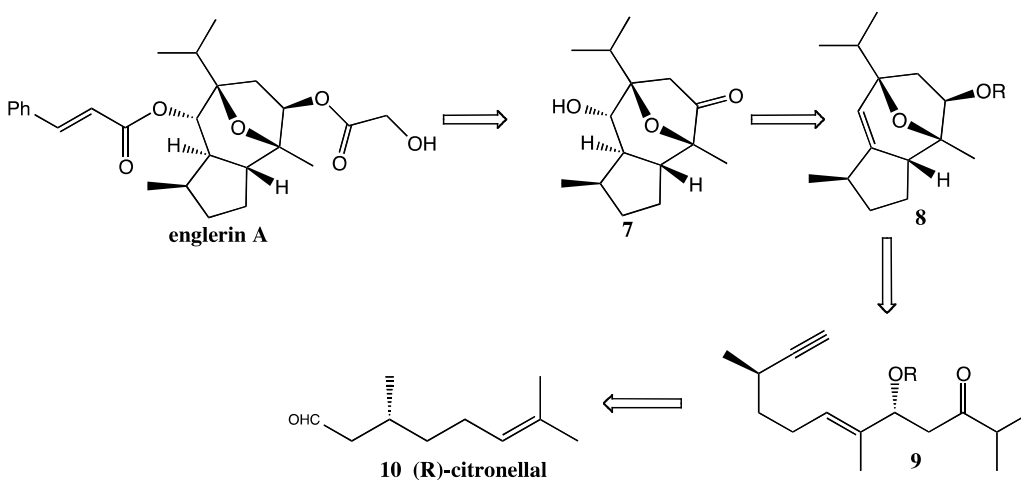


Figure 3.4. Ma's retro-synthesis of englerin A.

Echavarren used the similar gold catalyzed [2+2+2] approach to construct the core structure of englerin A and finish the total synthesis^{5c} almost at the same time as Ma. The intermediate **11** was cyclized to form the key intermediate **12** under a gold complex (**Fig. 3.5**).

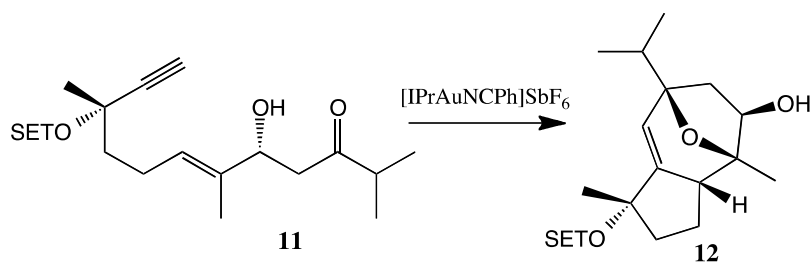


Figure 3.5. Molawi's key step in the total synthesis of englerin A.

Nicolaou developed a [5+2] approach to build the englerin A core structure.^{5d} In his retrosynthesis (**Fig 3.6**), he used an aldol reaction with **13** at a later stage, and **13** was produced by a [5+2] cyclization from ethyl acrylate and the oxopyrillium **14**. The precursor of **14** was given by ring expansion (Achmatowicz rearrangement⁷) from furan **15** upon exposure to mCPBA. Gold-catalyzed ring closure and coupling reaction led to the known compound **17**.

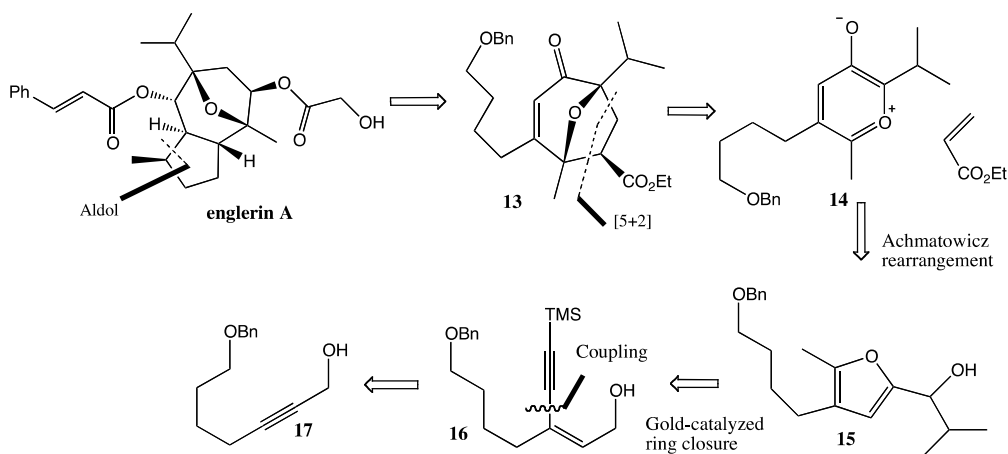


Figure 3.6. Nicolaou's retro-synthesis of englerin A.

Chain's group at the University of Hawaii used only 6 steps from known compounds **18** and **19** to finish the total synthesis of englerin A.^{5e} The key reactions

involved Michael addition and Samarium-mediated reductive reaction sequence (**Fig. 3.7**). The key intermediate **20** was closed concisely and went to the final product in 4 steps.

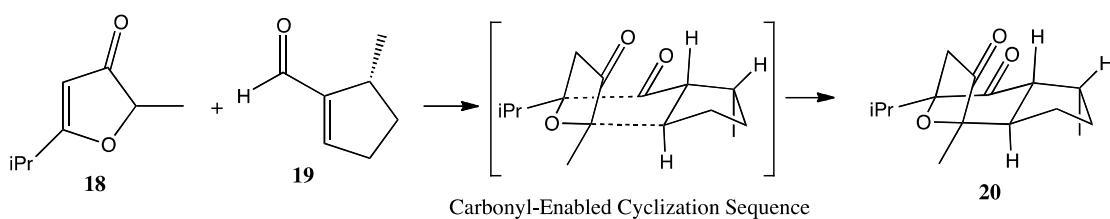


Figure 3.7. A carbonyl-enabled cyclization sequence to form the core structure of englerin A.

Theodorakis used a Rh-catalyzed [4+3] strategy to form the oxo-7-member ring skeleton.^{5f} Englerin A can be derived from diol **21** with esterification, hydrogenation, stereocenter reversion, and regioselective, stereoselective hydroboration of the right double bond in **22**. The cyclopentene moiety in **22** could be built from an intramolecular aldol condensation of **23** which can be prepared from **24**. The oxo-tricyclic compound **24** could be formed with the Davies Rh-catalyzed ring formation⁸ from **25** and **26** (**Fig. 3.8**).

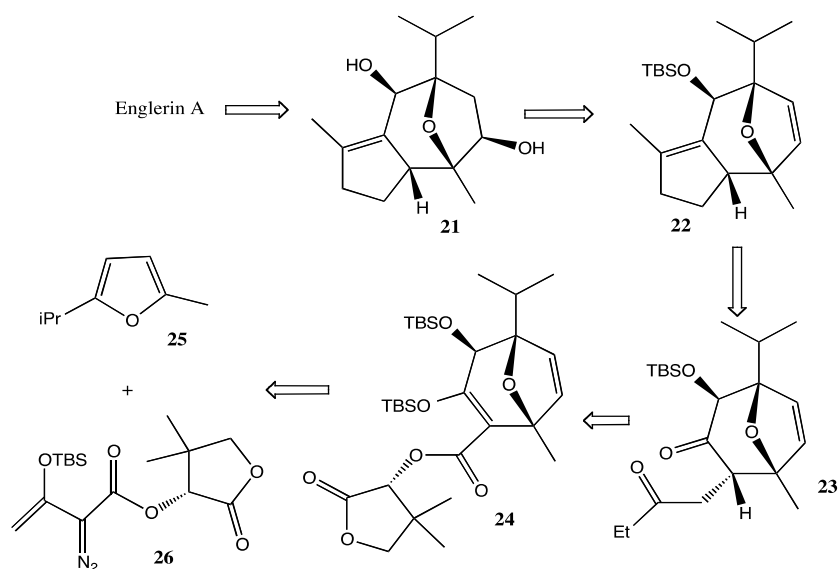


Figure 3.8. Theodorakis' retro-synthesis of englerin A.

3.2. Results and discussions

3.2.1 Original retro-synthetic analysis

Our original retro-synthetic analysis chose (R)-citronellal as the starting material (**Fig. 3.9**). Apparently, sequential esterification of **27** can lead to englerin A after asymmetric dihydroxylation of the double bond in **28** that can be given from α -hydroxyl ketone **29** by chelate controlled allylation followed by ring closing metathesis. The cyclopentane ring in **29** could be built asymmetrically with the recently developed organocatalyzed cyclizations of π -allylpalladium complexes⁹ after its precursor **30** is synthesized from R-citronellal by several standard steps.

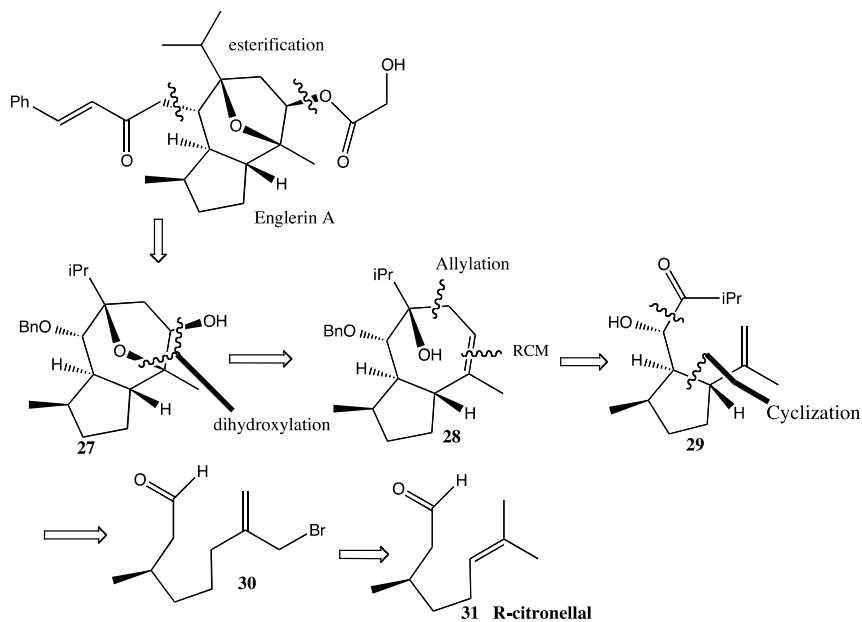


Figure 3.9. Original retro-synthetic analysis of englerin A.

3.2.2. Synthesis of the five-member ring

The absolute structure of englerin A was not known when we started the total synthesis in 2009, so we began with the wrong starting material—(*S*)-citronellal. Standard protection of the aldehyde and oxidation with SeO_2 converted (*S*)-citronellal to allyl alcohol **32**. Functional group conversion and the deprotection gave the substrate **33** for the organocatalyzed cyclization (**Fig. 3.10**).

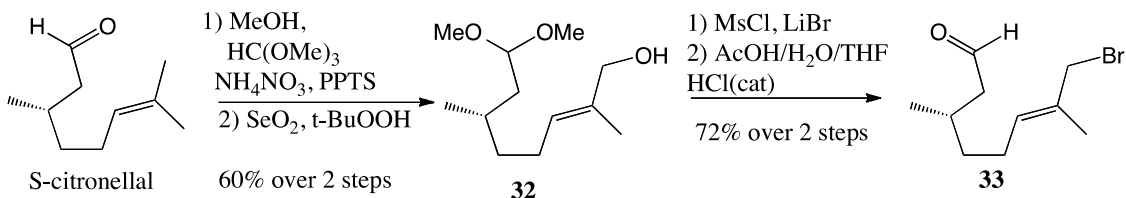


Figure 3.10. Synthesis of the substrate for cyclization.

With the bromide aldehyde **33** in hand, we screened reaction conditions to try to improve the selectivity. We expected the reaction underwent through intermediate **34** and gave the desired product **35** (**Fig. 3.11**).

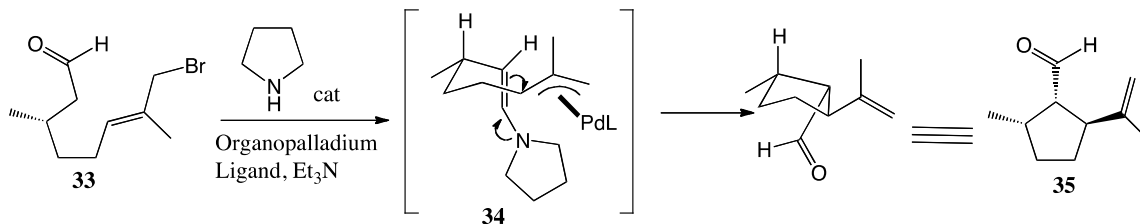
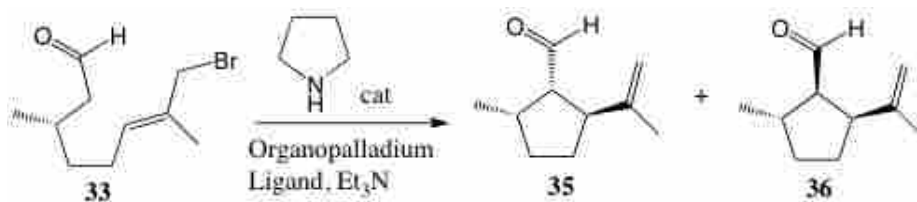
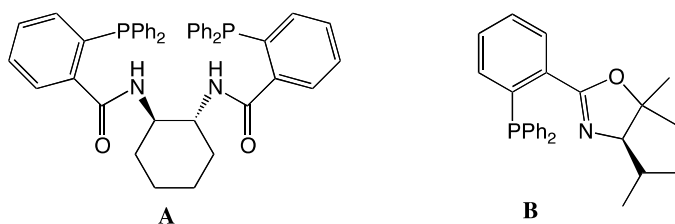


Figure 3.11. Mechanism of the organocatalyzed cyclization.

Two ligands and two palladium complexes were screened at different temperatures and solvents (**Table 3.2**). The best result was 70% yield and 4.5:1 dr. The structure of the desired product **35** was confirmed by making the compound with another route (**Fig. 3.12**).



Organopalladium	Ligand	Solvent	Temperature(°C)	yield	ratio(35:36)
(PdCl ₂ η ³ allyl) ₂	A	THF	0	70	4.5:1
(PdCl ₂ η ³ allyl) ₂	A	THF	-20	72	3.5:1
(PdCl ₂ η ³ allyl) ₂	B	THF	-20	70	4:1
(PdCl ₂ η ³ allyl) ₂	B	THF	-40	N/A	2:1
(PdCl ₂ η ³ allyl) ₂	B	DMSO	60	NA	1.5:1
Pd ₂ (dba) ₃	B	THF	-40	decomposed over 4 d	
(PdCl ₂ η ³ allyl) ₂	B	THF/DMSO	RT	NA	1:1.5*



* L-proline as cat.

Table 3.2. Organocatalyzed cyclization of π -Allylpalladium complexes.

Disappointed at the moderate selectivity of the cyclization under expensive ligands and palladium complexes, we found another route to synthesize aldehyde **35** (Fig. 3.12). The intermediate **38** was synthesized through a few steps from *S*-carvone, an inexpensive commercially available chiral source.¹⁰ **38** gave the different Favorskii ring-contraction product under reflux condition with the ester stereocenter reversed. Without further

purification, the crude product went to alcohol **39** after deprotection of THP group. Barton-McCombie protocol¹¹ was then employed to produce ester **40** that was converted to aldehyde **35** through reduction and selective oxidation sequence. The structure of **35** was confirmed by comparison of ¹HNMR to literature.¹²

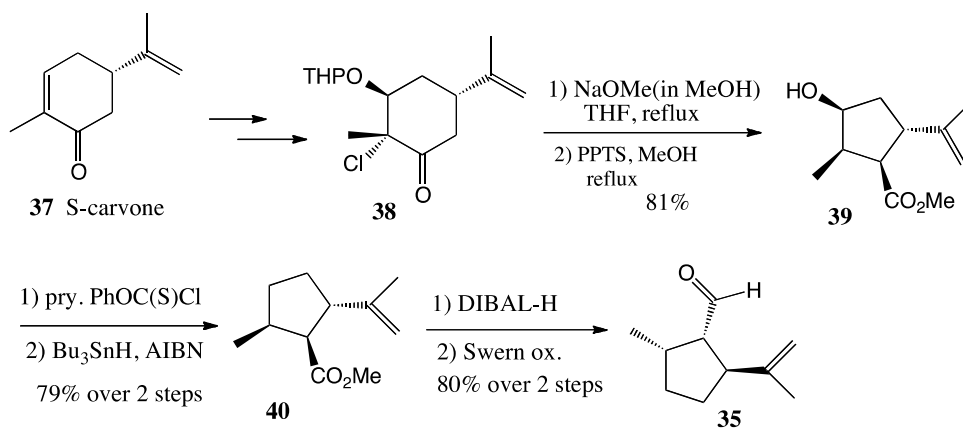


Figure 3.12. Another route to synthesize aldehyde **35**.

3.2.3. Attempts to prepare the α -hydroxyl isopropyl ketone moiety

With the aldehyde **35** in hand, the next task was to build the α -hydroxyl isopropyl ketone moiety. The dithiane approach was tried first (**Fig. 3.13**). The dithiane **41** failed to attack the aldehyde under strong base condition due to steric hindrance. The dithiane **43** successfully reacted with the aldehyde **35** to give the adduct **44**¹³ which was protected with a TES group to form **45**. Unfortunately many attempts to remove dithiane to make the aldehyde **46** failed. We think the terminal alkene at another side acted as a weak nucleophile which disturbed the breaking of the second C-S bond. Alkylation of **45** with strong base also failed to move further to the targeted hydroxyl ketone.

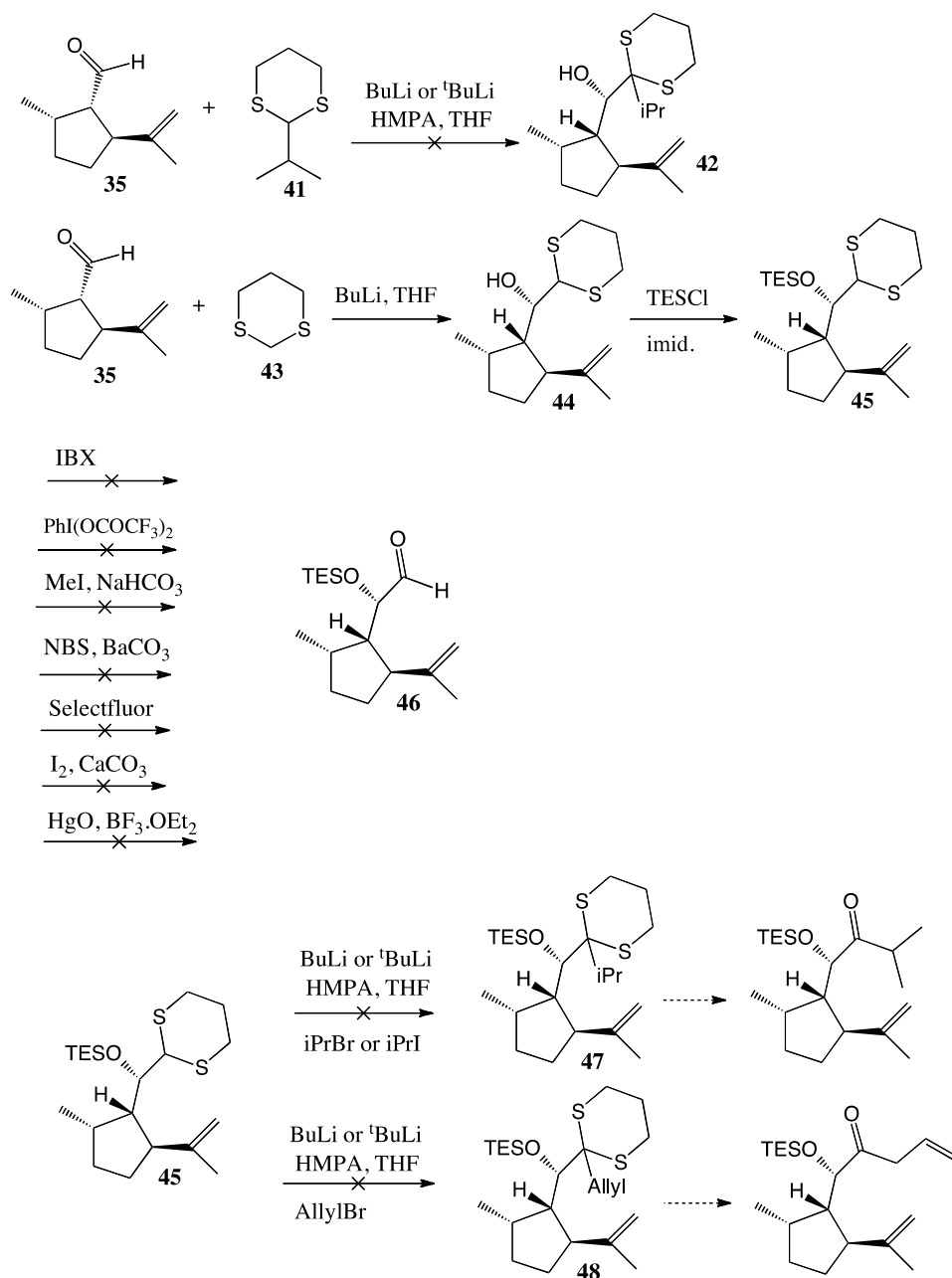


Figure 3.13. Attempts to make α -hydroxy isopropyl ketone moiety with dithiane approach.

More methods were tried to make α -hydroxy isopropyl ketone moiety (**Fig. 3.14**). Aldehyde **49** was prepared from (*R*)-carvone through the modified Favorskii ring-contraction explained above. Cyanohydrin **50** was formed from aldehyde **49** with good yield and selectivity. Here the nucleophilic addition follows Felkin-Anh model that will

be tested if necessary later. The secondary alcohol in **50** was then protected to give intermediate **53**, but it failed to give the desired isopropyl ketone **52**. In ^{13}C NMR, there was a characteristic peak pointing to **51**. Another attempt was to oxidize **51** to **52**. Unfortunately, aldehyde **54** didn't undergo Grignard addition, but was reduced to the primary alcohol **55** through hydride transfer.

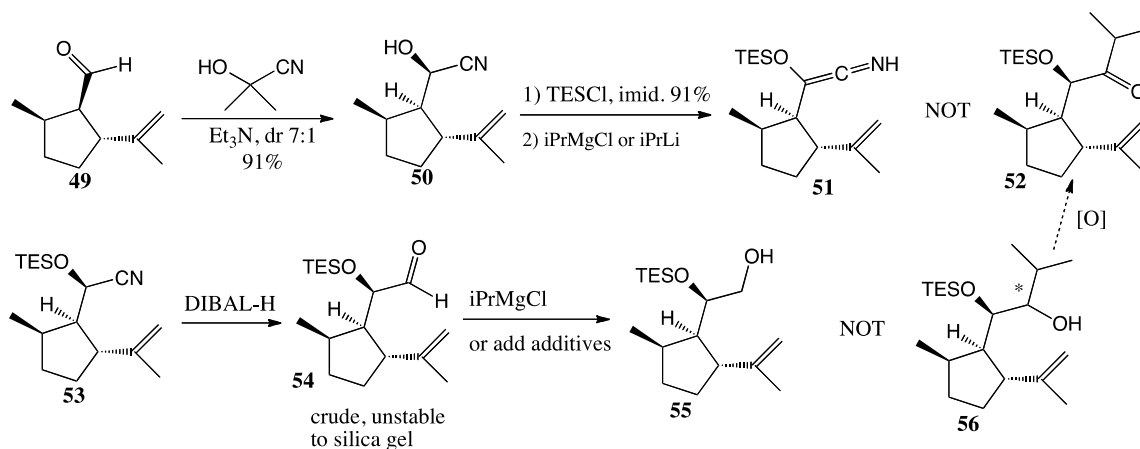


Figure 3.14. Attempts to make α -hydroxyl isopropyl ketone moiety with acetonitrile approach.

More direct routes to make α -hydroxyl isopropyl ketone were also tried (**Fig. 3.15**). Aldehyde **49** reacted with the masked acyl cyanide reagent **57** failed to form ester **58**,¹⁴ but no cyanohydrin product was detected because the aldehyde site is so hindered that only small nucleophiles like nitrile can attack it. The nitrile **59** was employed to introduce the isopropyl group directly with the aldehyde **49**,¹⁵ but no desired product was detected and unknown by-products were given due to the same argument of steric hindrance.

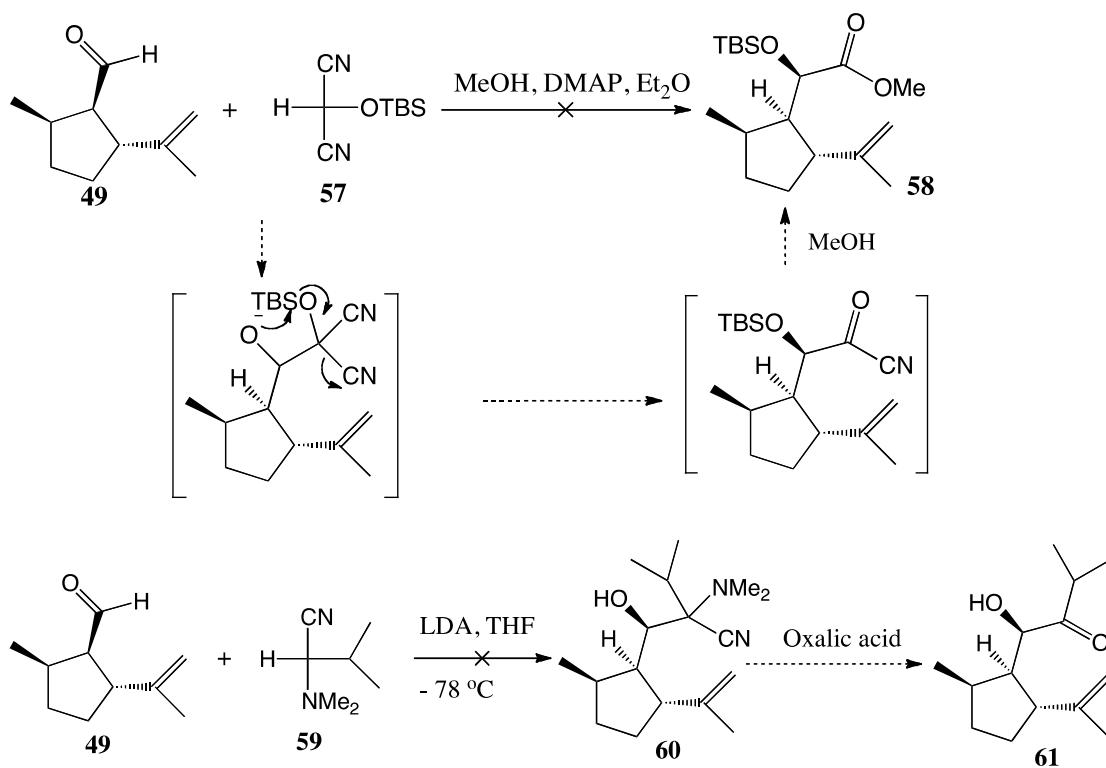


Figure 3.15. Attempts to make α -hydroxyl isopropyl ketone moiety with masked acyl cyanide reagents.

However the protected α -hydroxyl ester or Weinreb amide could be synthesized starting from aldehyde **54** through carboxylic acid in a few steps (**Fig. 3.16**). TES group was removed when **54** was oxidized to the acid **62**. After formation of ester **63** and Weinreb amide **64**, TES group was put on again to give **65** and **66** respectively. Unfortunately, the desired isopropyl ketone **67** failed to form under *i*PrMgCl or *i*PrLi. Starting material was recovered under *i*PrMgCl, and it was decomposed under *i*PrLi even at -78°C .

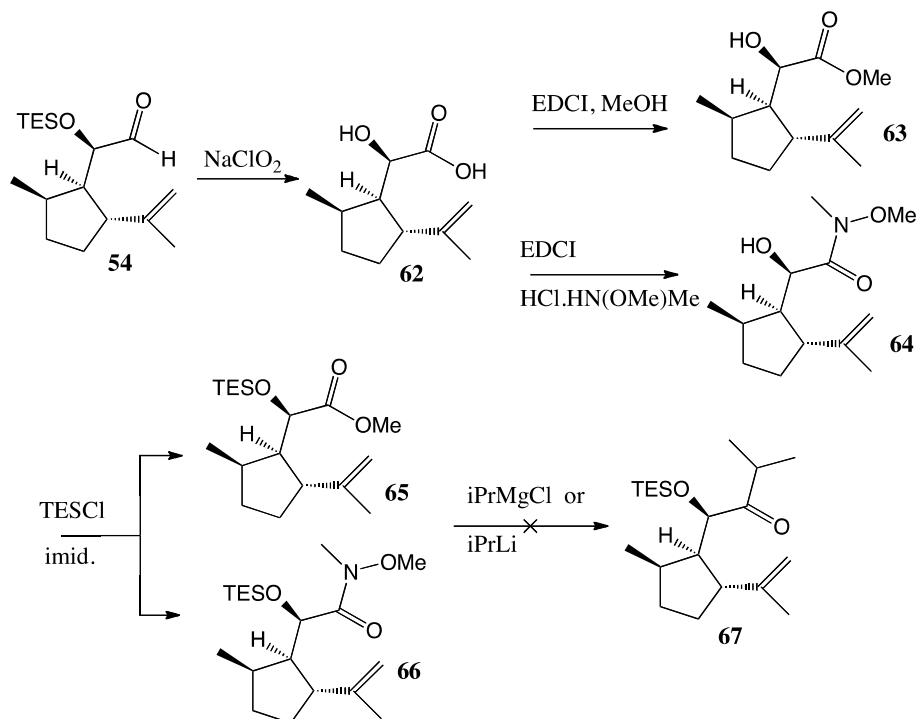


Figure 3.16. Attempts to make α -hydroxyl isopropyl ketone moiety through ester or Weinreb amide.

So far the α -hydroxyl isopropyl ketone moiety failed to be constructed due to either large steric hindrance of the aldehyde or poor reactivity of precursors. Then we decided to put on the isopropyl group first with a coupling reaction and then form the diol moiety at a late stage (**Fig. 3.17**). The olefination of aldehyde **49** could provide a dibromoolefin that could undergo selective coupling to put on isopropyl group to form **70**. One more allyl coupling and RCM reaction could produce the diene **69** intermediate which could give **68** under dihydroxylation conditions. The two tertiary alcohols in **68** could then selectively form the bridged ether in the englerin A skeleton. After differentiation of the two secondary alcohols and esterification, englerin A will be finally synthesized.

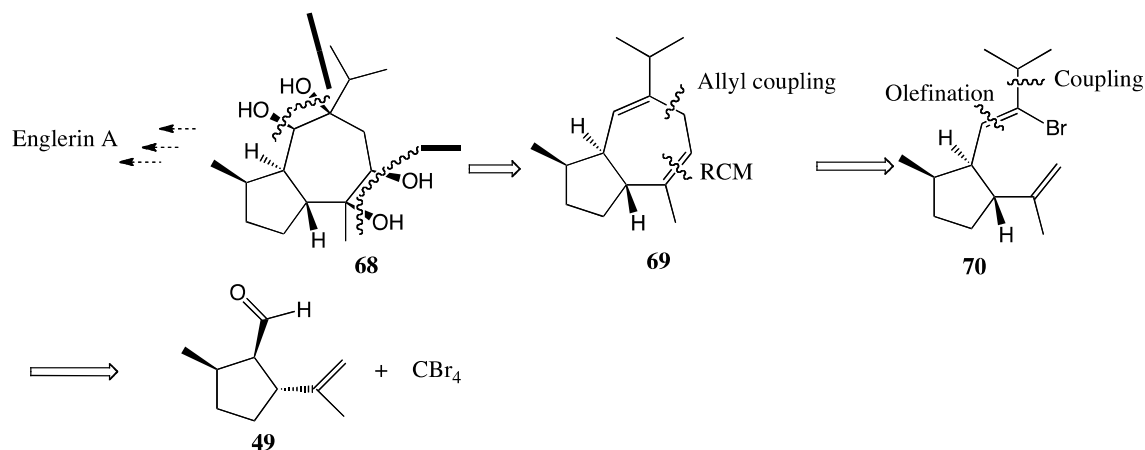


Figure 3.17 Partial retro-synthetic analysis of new route to englerin A.

With the new idea in mind, Dibromoolefin **71** was successfully prepared from **49** with good yield.¹⁶ However, the first stereoselective coupling failed to give the desired product **72** (**Fig. 3.18**). Another approach to put on the isopropyl group used Z-selective HWE reaction¹⁷ that didn't give the desired intermediate **74**, instead the aldehyde stereocenter was racemized through proton transfer because of the large steric hindrance at the aldehyde site.

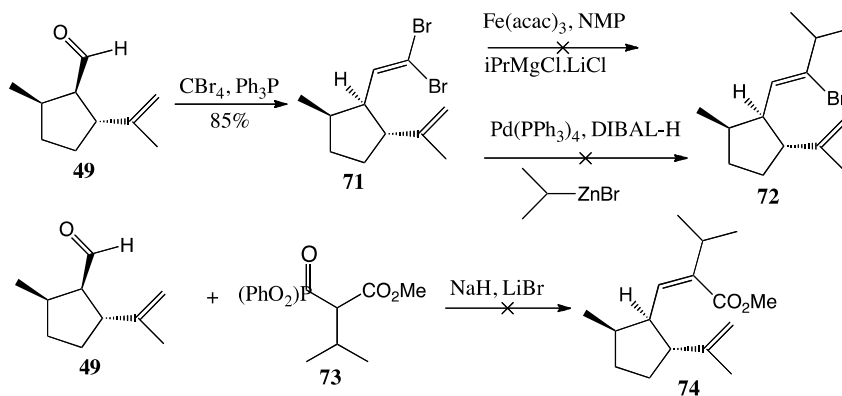


Figure 3.18. Attempts to build the isopropyl moiety with *E*-selective coupling.

The isopropyl group was successfully built in a few steps from the alcohol **75** that is the substrate of aldehyde **49** (Fig. 3.19). Mitsunobu reaction¹⁸ converted the primary alcohol **75** to the nitrile **76** which failed to undergo decyanization to form **77** directly. An indirect method worked through reduction, Grignard addition and oxidation.

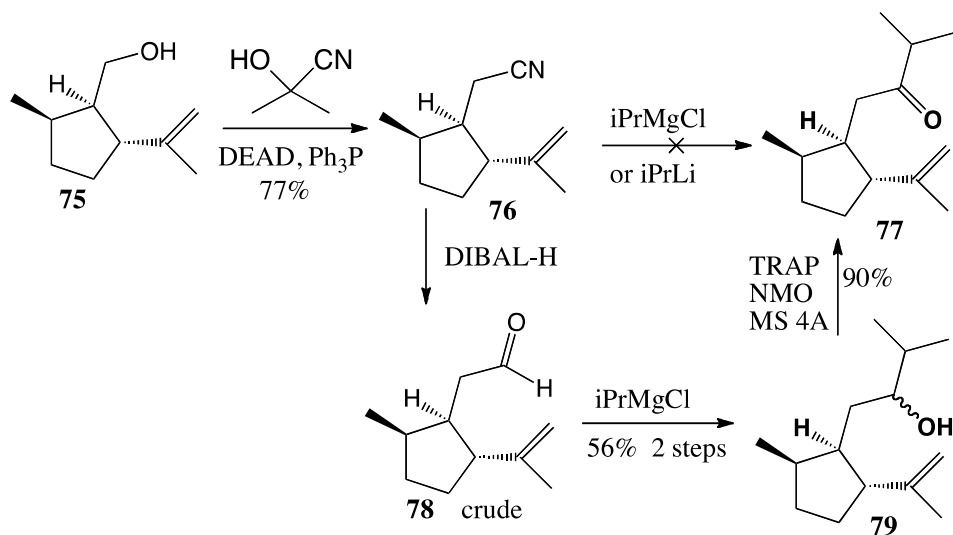


Figure 3.19. Successful synthesis of isopropyl ketone without α -hydroxyl group

Before the intermediate **77** moves on to attach the allyl group, the α -hydroxyl group should be installed. Oxo nucleophiles such as mCPBA, Davis oxiridine,¹⁹ and nitrosobenzene²⁰ and different bases were tried. Unfortunately, they all failed to form the desired product **80** (Fig. 3.20).

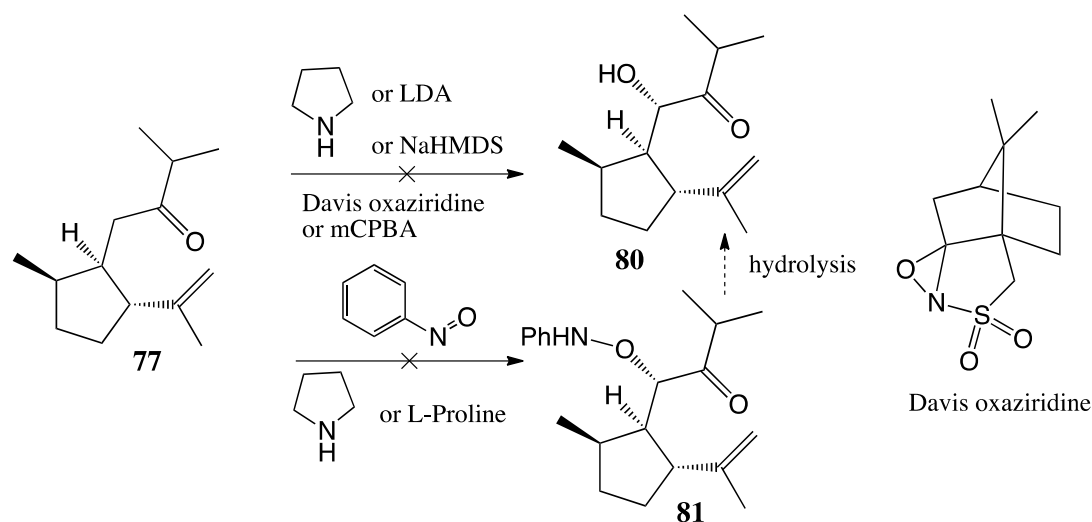


Figure 3.20. Attempts to make the α -hydroxyl isopropyl ketone through α -hydroxylation.

We also tried different protecting groups for the cyanohydrin **50**. MOM group failed to put on, but instead went back to aldehyde **49**. However, EOE group attached to the cyanohydrin, but the protected intermediate had the same problems as TES in later steps (**Fig. 3.21**).

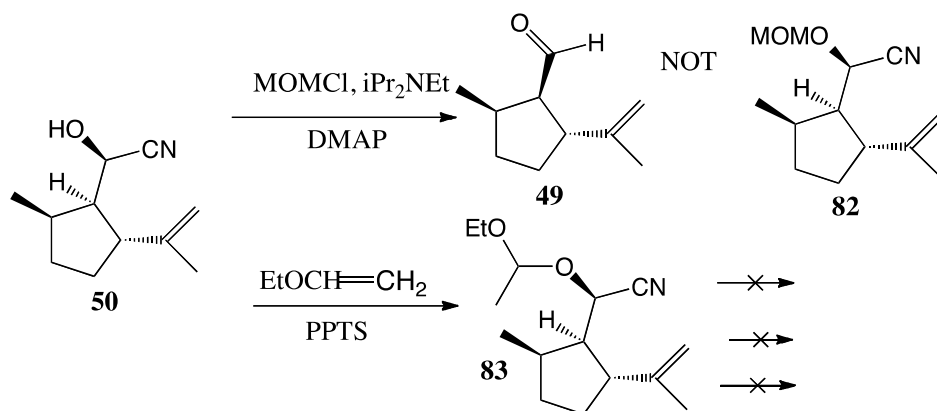


Figure 3.21. Protection of cyanohydrin with different groups

We had tried many methods to put on the α -hydroxyl isopropyl ketone moiety, but they all failed. So we thought we could close the 7-member ring first and then construct the moiety at late stages because many times reactivity of the ring and carbon chain is different.

3.2.4 Retro-synthetic analysis of new routes

We decided to close the 7-member ring first and then attach the isopropyl and esters group to the ring and link the ether bridge. So we designed new retro-synthesis (**Fig 3.22**).

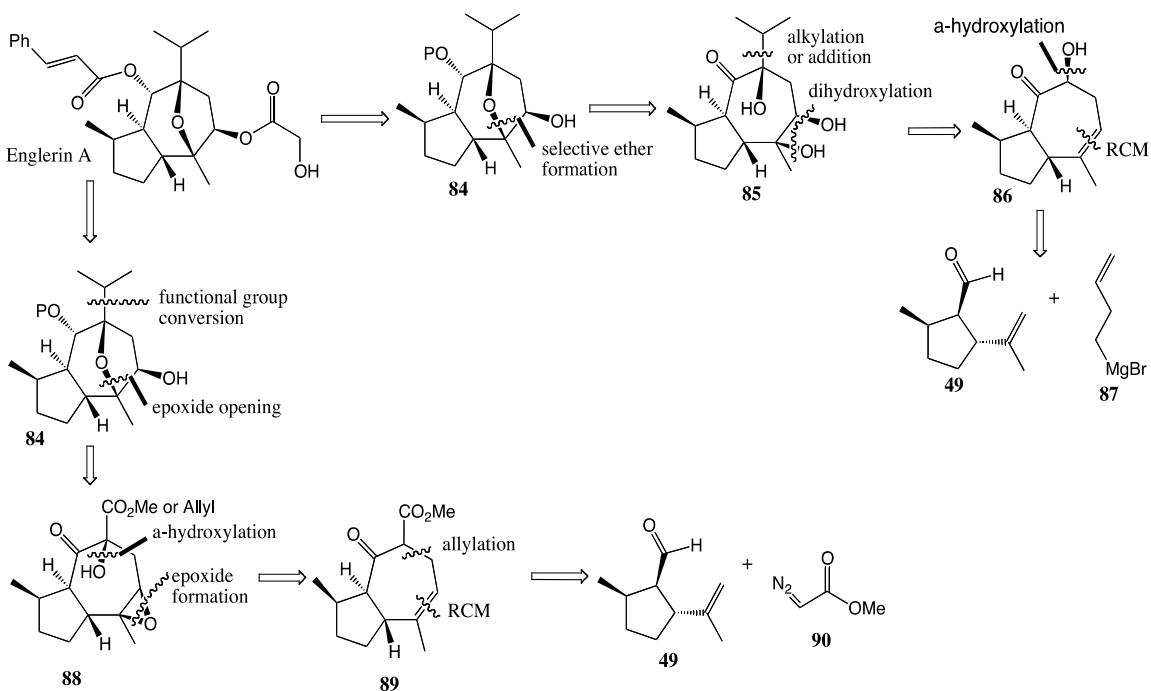


Figure 3.22. Retrosynthetic analysis of new synthetic routes of englerin A

The new routes above started from aldehyde **49** which we successfully made before from R-carvone (**Fig. 3.22**), and they both involved ring closing metathesis reaction at early stages. The isopropyl group was constructed from functional group manipulation and alkylation or Grignard addition. The ether bridge could be built by epoxide opening or selective ether formation between the two quaternary carbons. The intermediates diol and epoxide both point up based on a molecular model we built, but the absolute configuration should be identified after we finish the total synthesis or link the ether bridge.

3.2.5. Attempts to attach the isopropyl moiety to the seven-member ring

We carried out the top route first because it involved less steps. Aldehyde **49** was treated with Grignard and oxidation to give ketone **90** at high yield, and then RCM²¹ and α -hydroxylation²² reaction to produce alcohol **92**. However, **92** didn't get alkylated to form **93**, and strong bases such as NaHMDS and NaH only made dehydration occur to give conjugated diene ketone product. Then we switched to stereoselective Grignard addition to di-ketone **94** that was prepared from **92** by oxidation. Unfortunately, the enol product **95** was formed exclusively (**Fig. 3.23**).

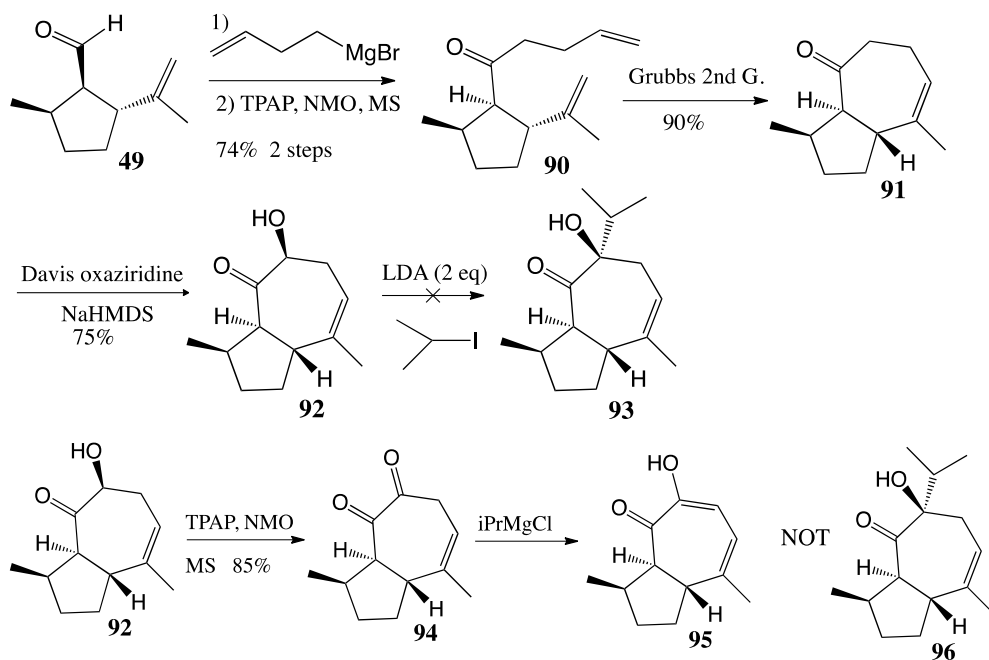


Figure 3.23. New approach to construct isopropyl moiety after ring closing

Since the double bond disabled the alkylation and Grignard addition, we chose to convert it to a diol and protect the diol before the α -hydroxylation (**Fig. 3.24**). Following the standard dihydroxylation,²³ the desired product **97** was not given because the semi-ketal **98** might form according to a similar reaction published recently.⁵ⁱ

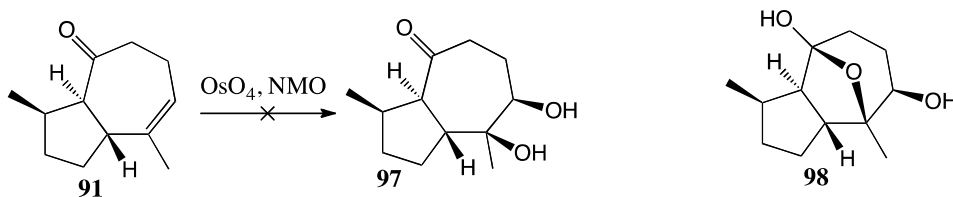


Figure 3.24. Attempt to synthesize the diol and protect it.

In order not to get the possible semi-ketal **98** we can protect the secondary alcohol that was prepared from the Grignard reaction, and then make the diol, but that involves

more steps and the stereoselective Grignard addition to the di-ketone might give low yield, so we abandoned the route and chose the bottom route in **Fig. 3.21**.

3.2.6. Alternative routes to make the isopropyl moiety

Alternatively we chose to get isopropyl from isopropene. Aldol reaction of **91** and acetone gave the tertiary alcohol **99** that underwent Burgess dehydration¹² to produce **100**, the substrate for α -hydroxylation. The tertiary alcohol **101** was prepared with the Davis oxiridine at moderate yield, but the following epoxidation has poor yield and stereoselectivity, and the desired intermediate **102** failed to give epoxide opening product using CSA (**Fig 3.25**). Although other Lewis acids like BF_3OEt_2 might catalyze the epoxide opening reaction and only a few steps were left for completion of total synthesis of englerin A, intermediate **101** was depleted, and some intermediate had been left for the alternative route.

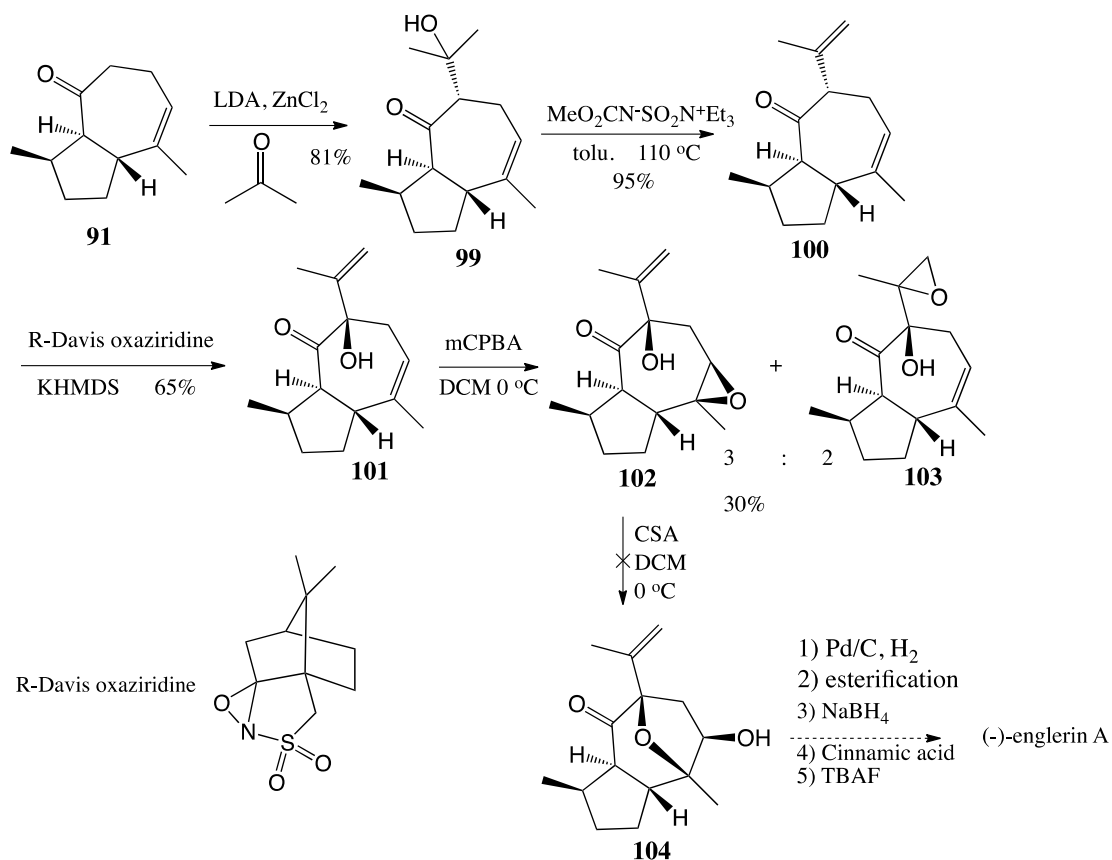


Figure 3.25. Alternative route to make isopropyl moiety

Then we chose ester as the precursor of the isopropyl group (**Fig 3.26**). Aldehyde **49** reacted with methyl diazoacetate assisted by SnCl_2 to afford β -ketoester.¹² Allylation and ring closing metathesis were then used to produce intermediate **107**. Substrate **107** underwent asymmetric α -hydroxylation over R-Davis oxaziridine to form the tertiary alcohol **108** which was converted to epoxide **109** with mCPBA. Unfortunately the following epoxide opening was non-repeatable. The methyl group in the ester was removed in the reaction and gave an unknown product.

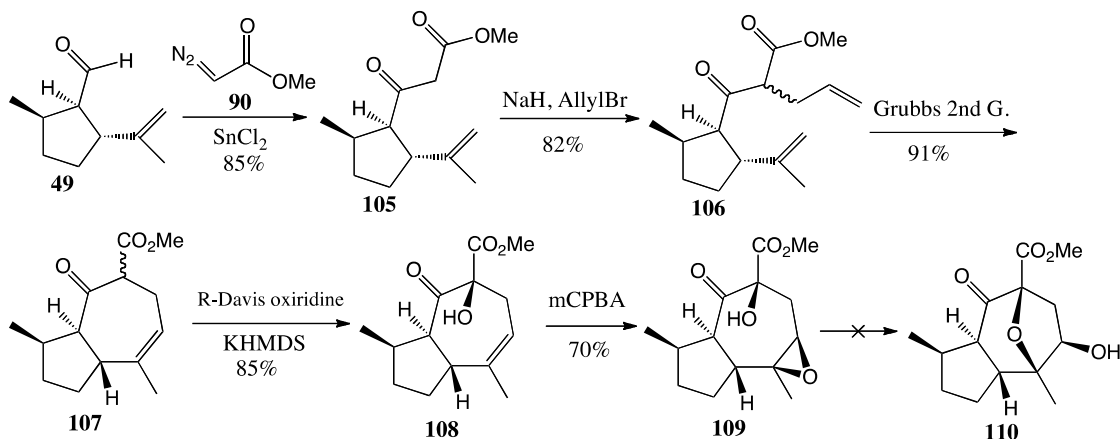


Figure 3.26. An approach to choose methyl ester as a precursor of isopropyl group

Bulkier esters should be difficult to attack, so *tert*-butyl ester substitute was chosen as the precursor of the isopropyl group (**Fig. 3.27**). Starting from **111** made from R-carvone through modified Farvoskii ring-contraction, the β -ketoester **112** was formed with an aldol reaction. Unfortunately the following allylation product **113** was extremely difficult to separate, so even if impure intermediate **113** did lead to the correct product **114** in the next step, **114** was impure even after flash chromatography.

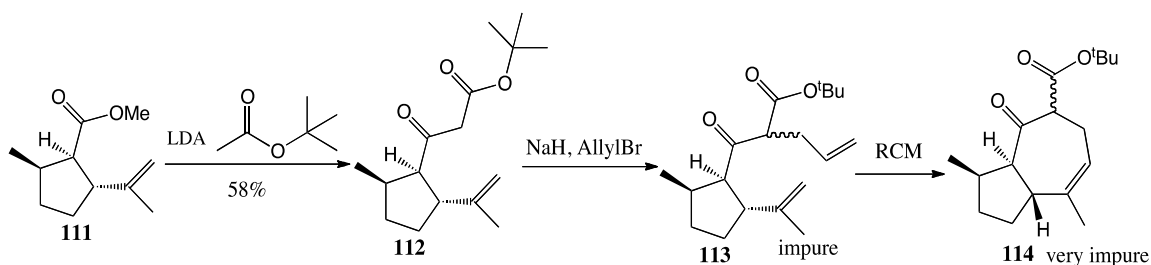


Figure 3.27. An approach to choose *tert*-butyl ester as a precursor of isopropyl group

Weinreb amide could also be a precursor for the isopropyl group, and hopefully be more stable than esters in the epoxide opening reaction, so we chose Weinreb amide as a

strategy to build the isopropyl moiety (**Fig. 3.28**). Starting also from ester **111**, the Claisen reaction gave the β -amide ketone **115**. The allylation product **116** was successfully separated and led to the ring closure intermediate **117**. **117** gave the tertiary alcohol **118** with α -hydroxylation. Unfortunately, after formation of epoxide **119** the product **120** with the bridged ether failed to form.

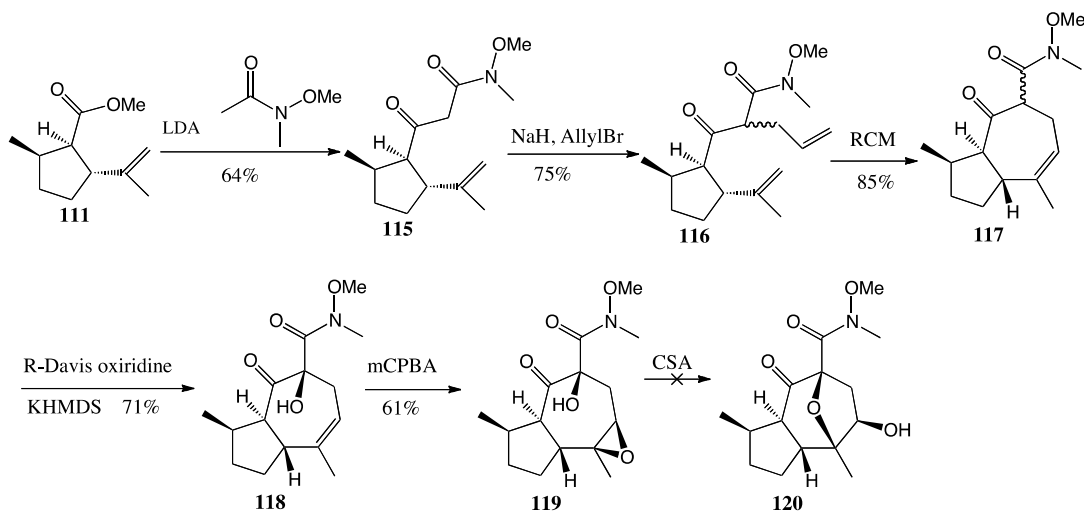


Figure 3.28. An approach to choose Weinreb amide as a precursor of isopropyl group

So the ether bridge formation might not tolerate the ester or ketone functional groups on the same ring. Changing the ester or ketone or both to other groups before formation of the ether bridge was another option to move forward to the total synthesis. Starting from the tertiary alcohol **108** (**Fig. 3.29**), the MOM protected intermediate **121** was selectively reduced to **122** which, without protection, was then converted to the tertiary alcohol **123** with a little bit of ketone by-product that was not further reduced. Then the secondary alcohol in **123** was oxidized back to ketone **124** with the tertiary alcohol intact. The double bond in **124** was oxidized again with mCPBA to form the epoxide **125** in which the MOM protecting group was removed and epoxide opened to give the secondary alcohol **126** at the same time. Under esterification with the protected glycolic

acid **127**, ester **128** was produced to be ready for dehydration. Unfortunately, it decomposed at the high temperature of Burgess dehydration conditions. Another dehydration method such as $\text{Et}_3\text{N}/\text{MsCl}$ also failed. Harsh conditions involving high temperature have not been tried.

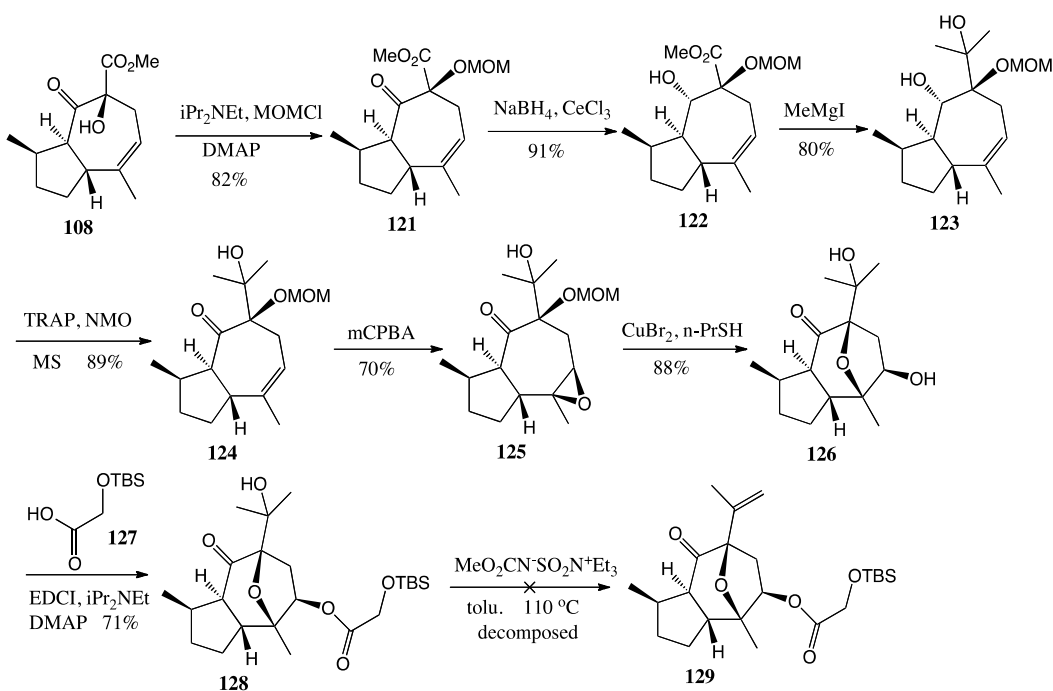


Figure 3.29. Alternative route to move forwards to englerin A and attach the isopropyl group

The ether bridge or the glycolate ester is unstable at high temperature, so Burgess dehydration needed to occur before the formation of the ether bridge. The tertiary alcohol **124** was successfully converted to terminal alkene **130** after dehydration, but the following selective epoxide formation gave **131** at low yield. Originally we hoped **131**, like **125**, could undergo cascade reaction to give **132**, but only deprotection of MOM happened to give **102** (**Fig. 3.30**).

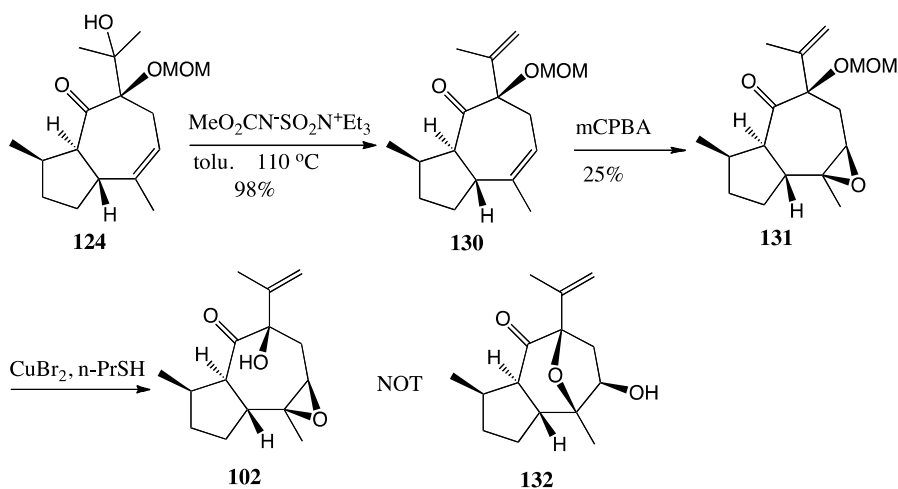


Figure 3.30. An approach to link the ether bridge after Burgess dehydration

A different protecting group for the tertiary alcohol in **108** had been tried. Acetate **133** formed with high yield, then the selective reduction converted the ketone to the secondary alcohol **134**. Without protection of the alcohol, the ester would undergo Grignard addition to give tertiary dimethyl alcohol, at the same time the acetyl protecting group would be removed to get the other tertiary alcohol **136**, however the diene **135** formed because methyl magnesium iodide as a base deprotonated the allyl proton and gave the conjugated double bond by removing acetate leaving group (**Fig. 3.31**). The original plan was to get **126** in less steps by oxidation of the secondary alcohol and the double bond followed by epoxide opening.

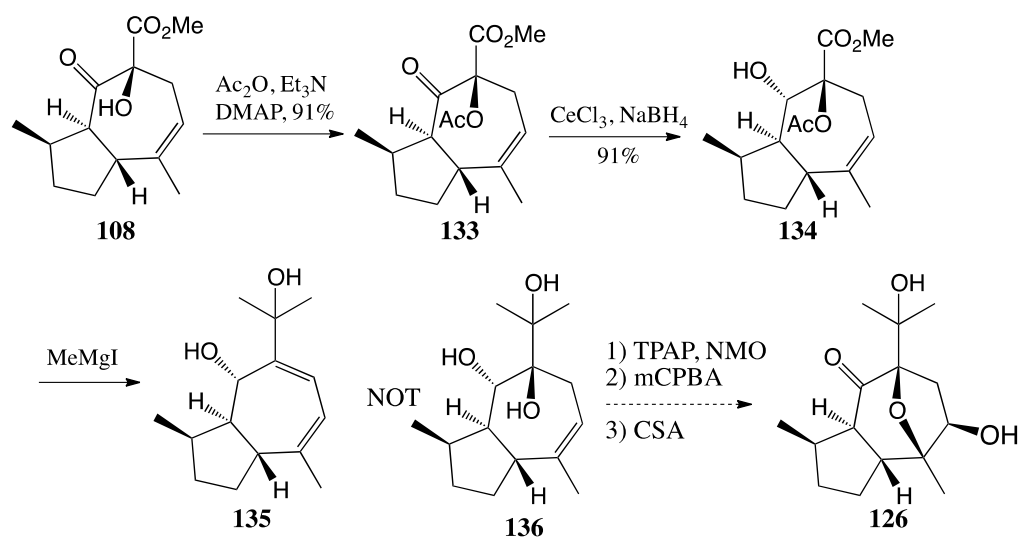


Figure 3.31. Acetyl protecting group approach towards the ether bridge intermediate

3.3. More alternative routes towards total synthesis of englerin A

3.3.1. Option 1

A similar compound in the literature¹² showed the ether bridge could tolerate the Burgess dehydration condition in spite of around 50% yield. So selective protection of the second alcohol in **126** and then Burgess dehydration might form the terminal alkene **137** at moderate yield. Hydrogenation of **137** and the following stereoselective reduction with NaBH₄ would produce the secondary alcohol that could furnish **138** under esterification. The following deprotection, esterification and deprotection again from **138** would complete the total synthesis. If **137** decomposes or gives **138** at very low yield under the dehydration, reduction of the ketone on the 7-member ring might be necessary,

then selective dehydration would then occur to form **140** that would change to **139** after hydrogenation and esterification (**Fig. 3.32**).

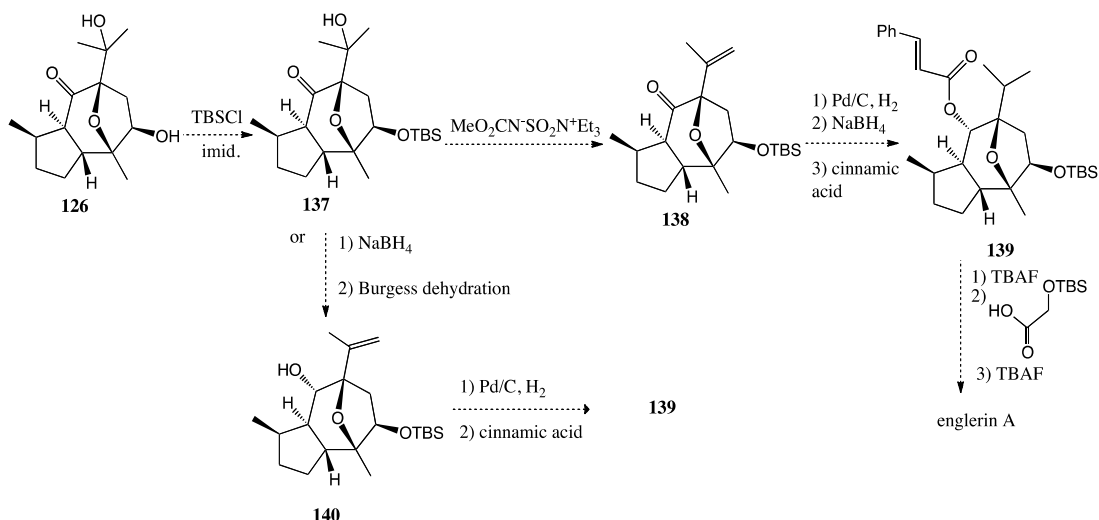


Figure 3.32. Alternative route to finish the total synthesis of englerin A

3.3.2. Option 2

In case the selective Burgess dehydration in **Fig. 3.32** might not work, another option will be chosen to reduce the ketone and protect it at an early stage (**Fig. 3.33**). The stereocenter of the secondary alcohol in **122** remains unknown now, but its advanced ^1H NMR data is being analyzed. We can convert it with Mitsunobu reaction if it is not the desired stereocenter. After we get the alcohol with correct stereocenter, it will be protected with benzyl group to form intermediate **141**. The next three steps will be reliable because similar reactions have been run from **122** through **126**. After protection of the secondary alcohol in **143**, the Burgess dehydration might work to produce intermediate **144**. The same intermediate **139** as in option 1 would be given in two steps.

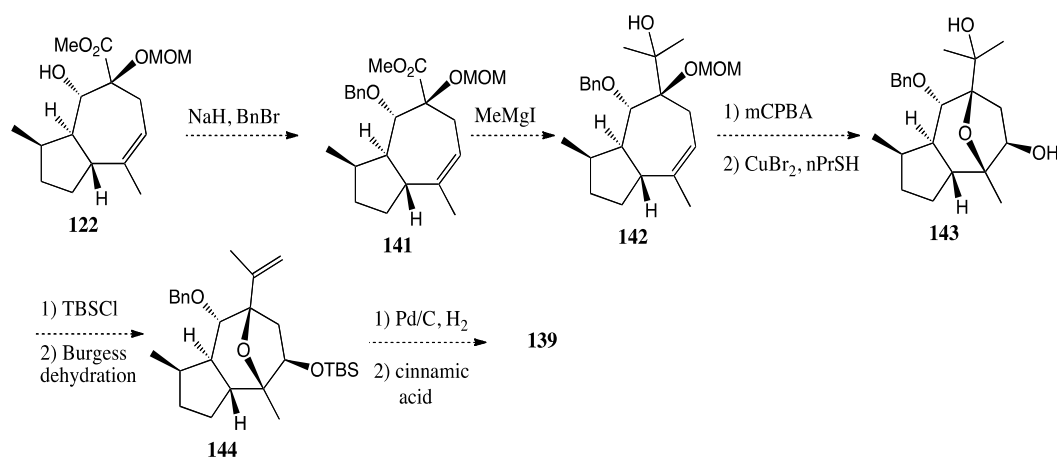


Figure 3.33. Early protection of the secondary alcohol as an approach to complete the total synthesis of englerin A

3.3.3. Option 3

The Burgess dehydration might fail even after protection of the secondary alcohol with benzyl group, so another precursor of the isopropyl group should be designed. Methyl ketone can serve as the precursor because it can transfer to terminal isopropene after Wittig reaction or Tebbe olefination. The methyl ketone **145** would be given by adding 1 equivalent MeMgI to **141**. The subsequent epoxidation and cascade reaction would furnish the secondary alcohol **146** that would be esterified and olefinated to produce the isopropene **147**. After three standard steps from **147**, englerin A will be finally synthesized (**Fig. 3.34**).

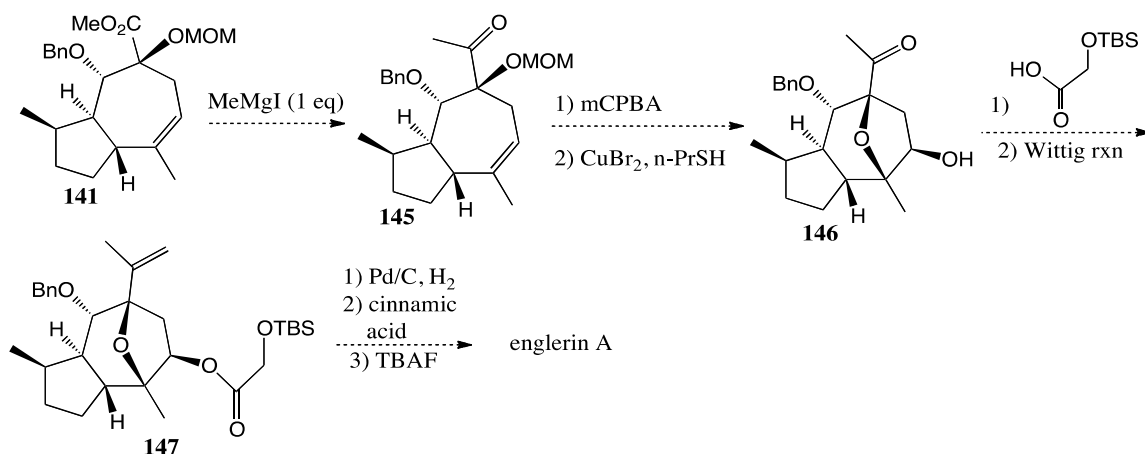


Figure 3.34. Methyl ketone as a precursor of isopropyl group to finish the total synthesis of englerin A

3.3.4. Option 4

In **Fig. 3.25**, reaction from **109** to **110** didn't work reliably. The reason might be that ketone group didn't tolerate the reaction due to its enol form under the acidic conditions. Option 4 would address that problem by reducing and protecting it before epoxide opening reaction (**Fig. 3.35**). Starting from **141**, after epoxide formation, the cascade deprotection/epoxide opening might happen assisted by the methyl ester. Then the secondary alcohol should be protected before Grignard addition and Burgess dehydration to give the same intermediate **144** in **Figure 3.33**. After hydrogenation/deprotection, cinnamic moiety would be constructed to produce **139**. Then englerin A will be given by following a few more steps in **Fig. 3.32**.

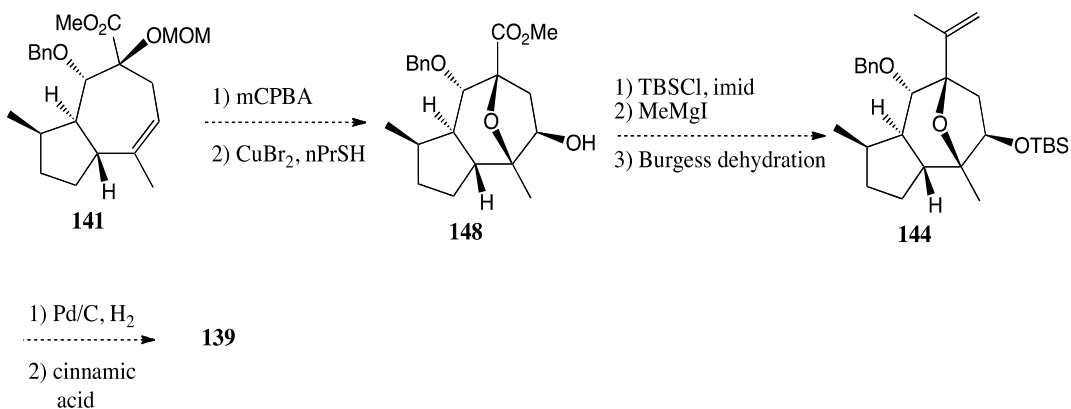


Figure 3.35. Approach to address the problem of ketone disturbing epoxide opening

3.3.5. Reliability of the alternative routes to the total synthesis

All the options above are trying to address problems that occurred in the previous routes. The key problem is to install the isopropyl group on the 7-member ring. From previous analysis, the 7-member ring should be closed before conversion of functional groups to the isopropyl group. So, after the ring closing, two routes that involve Burgess dehydration have been designed. They address the tolerance of functional groups to high temperature, and convert possible sensitive groups to stable functional groups to high temperature before the dehydration. The last alternative route chooses methyl ketone as a precursor because Wittig or Tebbe olefination is milder and ketone can be selectively olefinated over ester. Another feature of the routes is that benzyl group removal and hydrogenation of the isopropene can occur in the same step.

3.4 Conclusion and future work

In summary, englerin A showed attractive bioactivity against renal cancer. So far, six successful routes to synthesize it have been published.⁵ More groups including Dr. Andrus' group in Brigham Young University are still striving for the completion of the total synthesis and methodologies of the core structure. Our synthetic route has passed through the modified Farvoskii ring-contraction and ring closing metathesis to get the confused ring skeleton. The key problem that remains is still the isopropyl installation, but three alternative routes have been designed to address the problem. I am confident that one of the routes will solve the problem and lead to the final product—englerin A.

In the near future, I will finish the total synthesis by following the alternative routes, then englerin A analogs and mimics will be designed and synthesized in our group.

3.5. References

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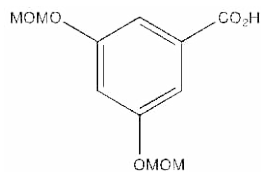
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Chapter 4. Experimental details and data

4.1. General method and materials

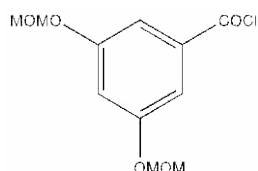
Air and moisture sensitive reagents were introduced via an oven-dry syringe or cannula. Toluene, xylene, pyridine, ethyl acetate, and N-methyl morpholine were distilled from CaH₂. DMF was dried by storage over 4Å molecular sieves. Reagents were purchased from commercial sources. Flash chromatography was carried out using 60-230 mesh silica gel. Radical chromatography was performed using 1, 2, and 4 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F₂₅₄, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV₂₅₄. All ¹H NMR spectra were obtained with 300 spectrometers using TMS (0.00ppm), Chloroform (7.26 ppm), or acetone-d₆ (2.05 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), and bs (broad singlet). ¹³C NMR were obtained with 75 MHz spectrometer using TMS (0.0 ppm), Chloroform (77.2 ppm), or acetone-d₆ (30.6 ppm) as the internal standard. Mass spectra data (HRMS, EI) were obtained from the department mass spectrometry facility. Optical rotations were obtained on a Perkin Elmer 241 polarimeter using the sodium D line at ambient temperature. Low temperature was maintained using an immersion cooler with a cooling probe placed in an acetone bath.

4.2 Synthesis of 4'-ester analogs of Resveratrol



Preparation of 3,5-bis(methoxymethoxy)benzoic acid (8)

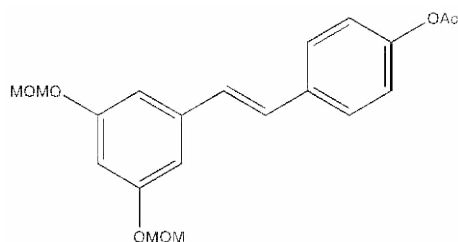
A flame dried 100 mL round bottom flask was charged with 3,5-dihydroxybenzoic acid **4** (308 mg, 2.0 mmol) and acetone (40 mL), then anhydrous potassium carbonate (5.52 g, 40 mmol) was then added. After stirring at rt for 10 min under N₂, MOMCl (1.5 mL, 6.0 mmol/mL in AcOMe) was added slowly so that the inner temperature did not exceed 50 °C. After 4 hr, potassium carbonate was filtered and rinsed with AcOEt. The combined filtrate was concentrated to give an oil which was dissolved in 5 mL methanol. 2N NaOH (3 mL, 6 mmol) was added and the mixture was stirred overnight. The mixture was concentrated and dissolved in 10 mL water. The aqueous solution was washed with benzene and acidified with 10% aqueous HCl at 0 °C. The white solid precipitate was filtered and washed with water and dried to give 426mg (88%) of white product **5**. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.44 (d, 2H), 6.98 (t, *J*=4 Hz, 1H), 5.21 (s, 4H), 3.50 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.9, 158.4, 131.4, 111.5, 110.7, 94.7, 56.4; mp = 129-130 °C; HRMS (EI⁺) found 242.0796 M⁺, calcd 242.0790 for C₁₁H₁₄O₆.



Preparation of 3,5-bis(methoxymethoxy)benzoic chloride (9).

A stock solution was prepared by dissolving benzotriazole (1.49 g, 12.5 mmol), thionyl chloride (0.91 mL, 0.0125 mmol) in 8.0 mL DCM. The reaction was carried out by adding the stock

solution intermittently into a stirred solution of 3,5-bis(methoxymethoxy)benzoic acid **5** (2.42 g, 10 mmol) in 200 mL DCM. Before the addition was complete, benzotriazole hydrochloride started precipitating out as a white solid. The mixture was stirred for another 10 min. After filtration, the filtrate was stirred with MgSO₄·7H₂O (5g) to destroy the excess thionyl chloride. The white solid was filtered and the filtrate concentrated to give 2.5 g (97%) crude product **6**, which was used for the next step without further purification. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.44 (d, 2H), 7.04 (t, *J*=4 Hz, 1H), 5.20 (s, 4H), 3.49 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.1, 158.5, 135.3, 112.6, 111.9, 94.7, 56.4; HRMS (EI⁺) found 260.0465 M⁺, calcd 260.0452 for C₁₁H₁₃O₅Cl.

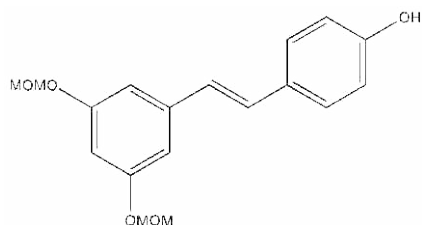


Preparation of 3,5-bis(methoxymethoxy)-4'-acetoxy stilbene (**12**).

A 50 mL round bottom flask was charged with p-xylene (20 mL), Pd(OAc)₂ (22.5 mg, 0.1 mmol), 1,3-bis-(1-adamantyl)imidazolium tetrafluoroborate (42.6 mg, 0.1 mmol) **8**, 3,5-bis(methoxymethoxy)benzoic chloride **6** (2.42 g, 10 mmol), 4-acetoxystyrene **7** (2.02 g, 12.5 mmol), and *N*-ethyl morpholine (1.58 mL, 12.5 mmol). A condenser column was attached and the flask and column were degassed three times with Ar. The mixture was heated at 115-120 °C for 3.5 h under an Ar atmosphere. The solution was cooled to rt and then poured on a silica gel column. Eluting solvent: 5-10% EtOAc/Hex. Flash chromatography gave product **9** (3.15 g, 88%) as a white solid. Data are: ¹H NMR (CDCl₃, 300 MHz) δ 7.48 (d, *J*=6 Hz, 2H), 7.08-6.93 (m, 4H), 6.86 (d, 2H), 6.66 (t, 1H), 5.19 (s, 4H), 3.50 (s, 6H), 2.30 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ

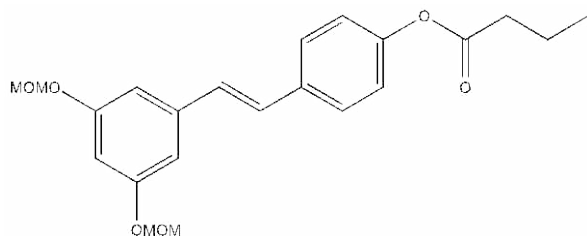
169.5, 158.7, 150.3, 139.5, 135.0, 128.7, 128.5, 127.6, 121.9, 108.0, 104.5, 94.6, 56.2, 21.2;

HRMS (EI⁺) found 358.1409 M⁺, calcd 358.1416 for C₂₀H₂₂O₆.



Preparation of (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol (after compound 12)

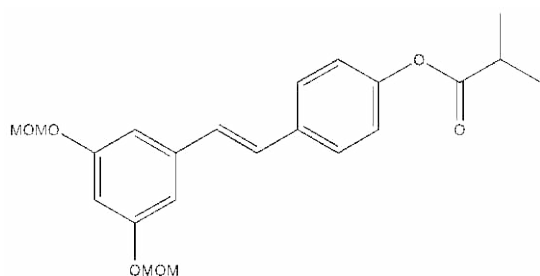
To 3,5-bis(methoxymethoxy)-4'-acetoxy stilbene (1.79 g, 5.0 mmol) was added 5% KOH in EtOH (100 mL) at rt. After stirring for 10 to 15 min, the solution was concentrated, then neutralized with HCl (2N). EtOAc was added to extract the aqueous solution for 3 times. The combined organic layers were dried with anhydrous Na₂SO₄. Chromatography gave slight yellow solid product (1.5 g, 95%). Data are: ¹H NMR (CDCl₃, 500 MHz) δ 7.378 (d, *J*=6 Hz, 2H), 7.00 (d, *J*=5 Hz, 1H), 6.86 (d, *J*=3 Hz, 1H), 6.84 (s, 1H), 6.82 (d, *J*=5 Hz, 2H), 6.63 (t, *J*=6 Hz, 1H), 5.20 (s, 4H), 3.51 (s, 6H); ¹³C NMR (CDCl₃, 500 MHz) δ 158.6, 155.6, 140.1, 130.2, 129.1, 128.3, 126.4, 115.8, 107.8, 104.2, 94.6, 56.3;



Preparation of (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol butyrate (20a)

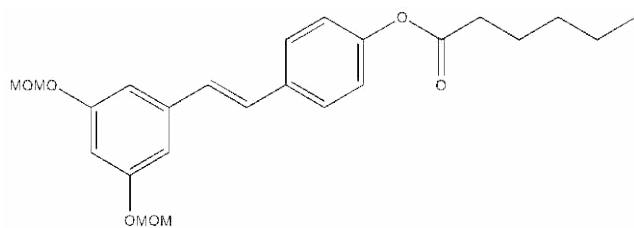
Flame dried 250 mL round bottom flask was added (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol (1.26 g, 4.0mmol), and dry CH₂Cl₂ (100 mL). Et₃N (0.56 mL, 4.0 mmol) was then added slowly.

After stirring for 5 min under N₂, butyryl chloride (0.42 mL, 4.0 mmol) was added dropwise into the flask. After 15 to 20 min, reaction solution was concentrated. The remaining residue was dissolved in benzene, washed with H₂O, and then 5% NaHCO₃. The organic layer was concentrated. The crude product was purified via flash chromatography and gave the product (1.41 g, 91%) as a white solid. Data are: ¹H NMR (CDCl₃, 500 MHz) δ 7.50 (d, *J*=4 Hz, 2H), 7.08 (d, *J*=5 Hz, 2H), 7.07 (d, *J*=5 Hz, 1H), 6.98 (d, *J*=3 Hz, 1H), 6.87 (d, *J*=4 Hz, 2H), 6.67 (t, *J*=5 Hz, 1H), 5.20 (s, 4H), 3.50 (s, 6H), 2.55 (t, *J*=7 Hz, 2H), 1.80 (m, 2H), 1.055 (t, *J*=7 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 172.3, 158.7, 150.4, 139.6, 134.9, 128.7, 128.6, 127.7, 122.0, 108.0, 104.5, 94.6, 56.3, 36.4, 18.6, 13.8; HRMS (EI⁺) found 358.1409 M⁺, calcd 358.1416 for C₂₀H₂₂O₆.



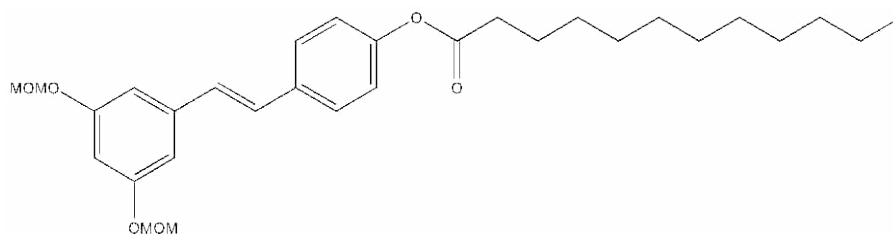
Preparation of (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol isobutyrate (20b)

Same procedure to make **20a**. White solid. Yield: 90%. Data are: ¹H NMR (CDCl₃, 500 MHz) δ 7.50 (d, *J*=4 Hz, 2H), 7.08 (s, 2H), 7.05 (d, *J*=5 Hz, 1H), 6.98 (d, *J*=5 Hz, 1H), 6.86 (d, *J*=4 Hz, 2H), 6.66 (t, *J*=6 Hz, 1H), 5.20 (s, 4H), 3.50 (s, 6H), 2.81 (m, 1H), 1.32 (d, *J*=7 Hz, 6H); ¹³C NMR (CDCl₃, 500 MHz) δ 175.8, 158.7, 150.6, 139.6, 135.0, 128.7, 128.6, 127.7, 122.0, 108.0, 104.6, 94.7, 56.3, 34.4, 19.2; HRMS (EI⁺) found 387.18313 [M+H]⁺, calcd 387.18022 for C₂₂H₂₇O₆.



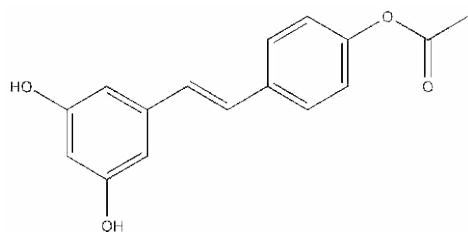
Preparation of (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol hexanoate (20c)

Same procedure to make **20a**. White solid. Yield: 90%. Data are: ^1H NMR (CDCl_3 , 500 MHz) δ 7.50 (d, $J=3$ Hz, 2H), 7.08 (d, $J=6$ Hz, 2H), 7.07 (d, $J=4$ Hz, 1H), 6.98 (d, $J=2$ Hz, 1H), 6.88 (d, $J=4$ Hz, 2H), 6.68 (t, $J=5$ Hz, 1H), 5.20 (s, 4H), 3.50 (s, 6H), 2.56 (t, $J=6$ Hz, 2H), 1.77 (m, 2H), 1.40 (m, 4H), 0.95 (t, $J=7$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 172.4, 158.6, 150.4, 139.5, 134.9, 128.6, 128.5, 127.6, 121.0, 107.9, 104.5, 94.6, 56.2, 34.5, 31.4, 24.8, 22.5, 14.1; HRMS (EI^+) found 437.19426 $[\text{M}+\text{Na}]^+$, calcd 437.19346 for $\text{C}_{24}\text{H}_{30}\text{O}_6$.



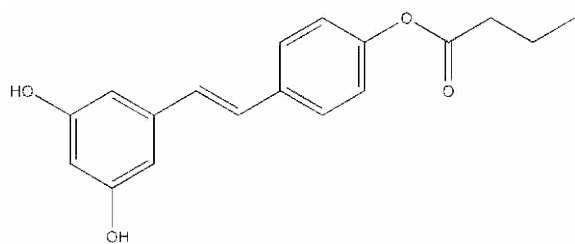
Preparation of (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol palmitate (20d)

Same procedure to make **20a**. White solid. Yield: 88%. Data are: ^1H NMR (CDCl_3 , 500 MHz) δ 7.50 (q, $J=5$ Hz, 2H), 7.07 (d, $J=3$ Hz, 2H), 7.06 (d, $J=4$ Hz, 1H), 6.94 (d, $J=4$ Hz, 1H), 6.86 (d, $J=5$ Hz, 2H), 6.66 (t, $J=5$ Hz, 1H), 5.19 (s, 4H), 3.50 (s, 6H), 2.56 (t, $J=6$ Hz, 2H), 1.75 (m, 2H), 1.35 (m, 2H), 1.35-1.26 (m, 22H), 0.88 (t, $J=6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 172.5, 158.7, 150.4, 139.6, 135.0, 128.7, 128.6, 127.7, 122.0, 108.0, 104.6, 94.7, 56.3, 34.6, 32.1, 29.91, 29.88, 29.82, 29.68, 29.59, 29.48, 29.33, 25.16, 22.92, 14.36;



Preparation of (E)-4-(3,5-dihydroxystyryl)phenol acetate (3)

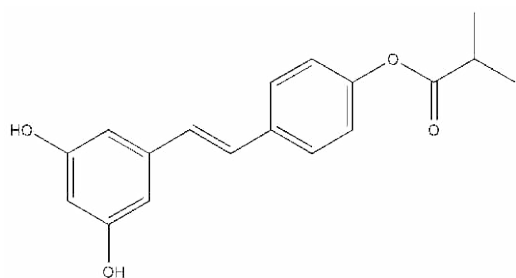
To a flame dried 500 mL round bottomed flask was charged (E)-4-(3,5-bis(methoxymethoxy)styryl)phenol acetate (716 mg, 2 mmol) and 200 mL anhydrous ether, then HCl (1.0M in ether, 50 mL) was added dropwise under Ar. The septum was sealed with parafilm. After 30 to 35 hr of stirring, the reaction was quenched with saturated NaHCO₃ until pH 7 was obtained. The two layers were separated and the aqueous layer was then extracted with ether twice. The combined ether layers were washed with brine, then dried with anhydrous Na₂SO₄. Concentration and chromatography gave the product (389 mg, 72%) as a white solid.



Preparation of (E)-4-(3,5-dihydroxystyryl)phenol butyrate (21a)

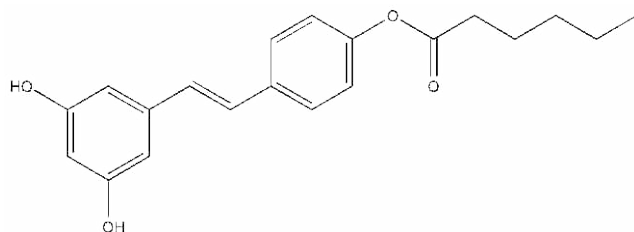
Same procedure to make **3**. White solid. Yield: 73%. Data are: ¹H NMR (Acetone-d₆, 500 MHz) δ 8.27 (s, 2H), 7.61 (q, *J* = 4 Hz, 2H), 7.12 (d, *J* = 5 Hz, 1H), 7.10 (q, *J* = 3 Hz, 2H), 7.10 (d, *J* = 3 Hz, 1H), 6.59 (d, *J* = 5 Hz, 2H), 6.31 (t, *J* = 5 Hz, 1H), 2.56 (t, *J* = 7 Hz, 2H), 1.73 (m, 2H), 1.02 (t, *J* = 7 Hz, 3H); ¹³C NMR (Acetone-d₆, 500 MHz) δ 172.7, 160.1, 151.8, 140.8, 136.4, 130.3, 128.6, 123.4, 106.45, 106.36, 103.7, 36.9, 19.4, 14.3; HRMS (EI⁺) found 299.12681 [M+H]⁺, calcd

299.12779 for C₁₈H₁₉O₄.



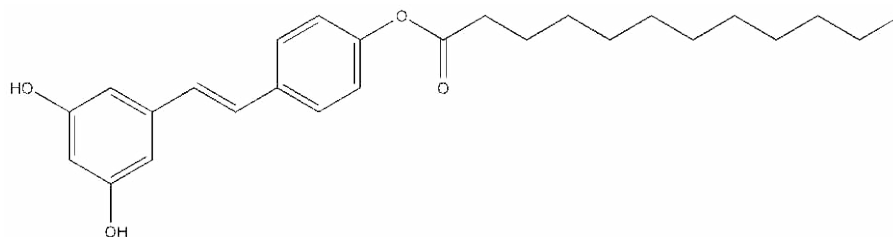
Preparation of (E)-4-(3,5-dihydroxystyryl)phenol isobutyrate (21b)

Same procedure to make **3**. White solid. Yield: 82%. ¹H NMR (Acetone-d₆, 500 MHz) δ 8.31 (s, 2H), 7.60 (q, *J*=4 Hz, 2H), 7.12 (d, *J*=5 Hz, 1H), 7.11 (q, *J*=4 Hz, 2H), 7.06 (d, *J*=4 Hz, 1H), 6.58 (d, *J*=3 Hz, 2H), 6.31 (t, *J*=3 Hz, 1H), 2.87-2.79 (m, 1H), 1.26 (m, 6H); ¹³C NMR (Acetone-d₆, 500 MHz) δ 176.1, 160.0, 151.8, 140.7, 136.3, 130.3, 128.6, 123.2, 106.4, 106.3, 103.6, 35.1, 19.6; HRMS (EI⁺) found 321.11241 [M+Na]⁺, calcd 321.10973 for C₂₀H₂₂O₆Na.



Preparation of (E)-4-(3,5-dihydroxystyryl)phenol hexanoate (21c)

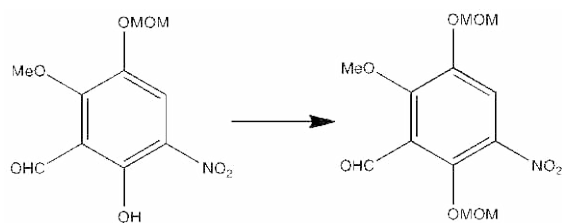
Same procedure to make **3**. White solid. Yield: 74%. ¹H NMR (Acetone-d₆, 500 MHz) δ 8.27 (s, 2H), 7.60 (m, 2H), 7.12 (m, 1H), 7.11 (q, *J*=4 Hz, 2H), 7.06 (m, 1H), 6.58 (d, *J*=4 Hz, 2H), 6.31 (t, *J*=5 Hz, 1H), 2.86 (d, *J*=6 Hz, 1H), 2.58 (m, 2H), 1.72 (m, 2H), 1.39 (m, 3H), 0.92 (t, *J*=6 Hz, 3H); ¹³C NMR (Acetone-d₆, 500 MHz) δ 172.9, 160.1, 151.8, 140.8, 136.3, 130.3, 128.67, 128.63, 123.3, 106.4, 103.6, 35.0, 32.4, 25.7, 23.5, 14.7; HRMS (EI⁺) found 327.15896 [M+H]⁺, calcd 327.15909 for C₂₀H₂₃O₄.



Preparation of (E)-4-(3,5-dihydroxystyryl)phenol palmitate (21d)

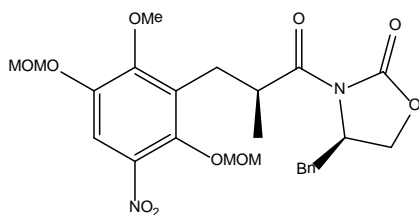
Same procedure to make **3**. White solid. Yield: 76%. ^1H NMR (Acetone- d_6 , 500 MHz) δ 8.31 (s, 2H), 7.60 (m, 2H), 7.12 (d, $J=4$ Hz, 1H), 7.11 (m, 2H), 7.06 (d, $J=3$ Hz, 1H), 6.59 (m, 2H), 6.32 (t, $J=4$ Hz, 1H), 2.90 (t, $J=7$ Hz, 2H), 2.59 (t, $J=6$ Hz, 2H), 1.73 (m, 2H), 1.44 (m, 2H), 1.41-1.30 (m, 20H), 0.88 (t, $J=6$ Hz, 3H); ^{13}C NMR (Acetone- d_6 , 500 MHz) δ 172.0, 159.1, 150.9, 139.8, 135.4, 129.4, 127.7, 122.4, 105.4, 102.6, 34.1, 32.2, 29.92, 29.89, 29.82, 29.73, 29.67, 29.60, 29.51, 29.36, 29.25, 29.20, 29.05, 28.89, 25.1, 22.8, 13.9; HRMS (EI^+) found 467.31305 $[\text{M}+\text{H}]^+$, calcd 467.31559 for $\text{C}_{30}\text{H}_{43}\text{O}_4$.

4.3. Synthesis and evaluation of 8,9-amido analogs of Geldanamycin



The phenol was dissolved in dry acetone (0.01 M), and then dry power K_2CO_3 (10 eq) was added all the once at room temperature. Cooled the reaction mixture to 0 °C after stirring for 15 minutes, then MOMCl (3.0 eq) was added slowly so that the needle can be seen clearly in the fume. Remove ice bath after the addition of MOMCl. The mixture was stirred for 2.5-3 hrs. Filter out the solid and wash it with EtOAc, then concentrate the solution to give the residue that was purified by

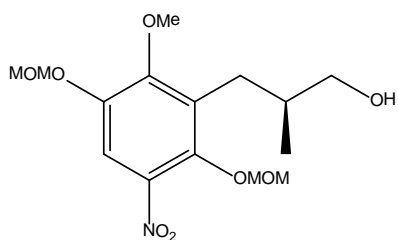
chromatography. Yield: 90%. The NMR data was identical to lit. (Org. Lett. 5, 3859).



(R)-4-benzyl-3-((S)-3-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-2-methylpropanoyl)oxazolidin-2-one

To a flame dried 50-mL round bottom flask was added (4R)-4-benzyl-3-propionyl-oxazolidin-2-one (0.678 g, 2.91 mmol) and 10 mL of THF. The stirring solution was then cooled to $-78\text{ }^{\circ}\text{C}$ under a Ar atmosphere. Then NaHMDS (3.20 mL, 1.0 M THF) was added dropwise. The solution was then allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 15 min. Then 3-bromomethyl-2-methoxy-1,4-bis-methoxymethoxy-5-nitro-benzene **37** (1.075 g, 3.199 mmol) was added along the inner wall as a solution in THF (6 mL). Stirring continued for an additional 2.5 hrs before being quenched by the addition of a saturated NH_4Cl solution (5 mL). Upon warming to ambient temperature the solution was diluted with 20 mL of Et_2O and 10 mL of a saturated NH_4Cl solution. The organic layer was then removed and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were then dried over MgSO_4 , filtered, and concentrated. The crude reaction materials were the purified via flash chromatography (20% EtOAc /hexanes) to provide 1.18 g (83%) of the desired compound as a $>20:1$ mixture of diastereomers and as a light yellow, sticky foam. Data are: TLC $R_f = 0.18$ (30% EtOAc /hexanes); $[\alpha]_D^{22} - 2.50^{\circ}$ (c 3.5, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) 7.62 (s, 1H), 7.32-7.18 (m, 5H), 5.20 (s, 2H), 5.01 (s, 2H), 4.66-4.63 (m, 1H), 4.16-4.08 (m, 3H) 3.99 (s, 3H), 3.55 (s, 3H), 3.49 (s, 3H), 3.35 (dd, $J = 13.0$ Hz, 3.0 Hz, 1H), 3.13 (dd, $J = 13.0$

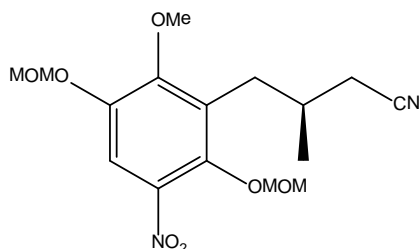
Hz, 7.0 Hz, 1H), 3.05 (dd, $J = 13.5$ Hz, 8.0 Hz, 1H), 2.69 (dd, $J = 14.0$ Hz, 10.0 Hz, 1H) 1.18 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 176.8, 171.3, 153.5, 153.1, 146.1, 145.8, 139.6, 135.8, 129.4, 127.4, 111.7, 101.9, 95.6, 66.2, 61.3, 60.5, 58.0, 56.7, 55.6, 52.7, 37.6, 28.6, 21.2, 17.5, 14.3; HRMS (FAB+) found 541.17873 $[\text{M}+\text{Na}]^+$, calcd 541.17927 for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_{10}\text{Na}$.



(S)-3-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-2-methylpropan-1-ol (38)

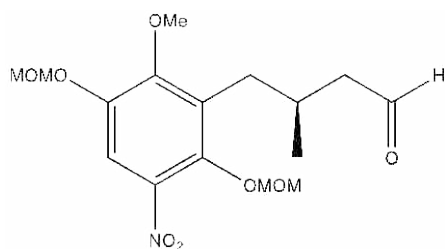
A 50 mL flame dried conical flask containing the previous oxazolidin-2-one (0.175 g, 0.338 mmol) and 6.75 mL Et_2O and 2 drops of water was cooled to 0 °C under a nitrogen atmosphere. Then with stirring LiBH_4 (0.015 g, 0.676 mmol) was added in one portion. The reaction stirred at 0 °C for 0.5 h at which time it was quenched by the addition of 10 mL of a saturated NH_4Cl solution and allowed to stir for an additional 20 min. The solution was then allowed to warm to ambient temperature at which point the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were then washed with a saturated NaCl solution and then dried over MgSO_4 . The mixture was then filtered and the solvent removed in vacuo. Purification via radial chromatography (2 mm plate, gradient 30-40% EtOAc /hexanes) afforded 0.114 g (98%) of the title compound as a thick golden oil. Data are: TLC $R_f = 0.2$ (40% EtOAc /hex); $[\alpha]_D^{22} + 1.2^\circ$ (c 3.5, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) 7.62 (s, 1H), 5.23 (s, 2H), 5.04 (s, 2H), 3.95 (s, 3H), 3.59 (s, 3H), 3.52 (s, 3H), 3.40 (m, 2H), 2.78 (dd, $J = 12.5$ Hz, 8.0 Hz, 1H), 2.69 (dd, $J = 13.5$ Hz, 6.5 Hz, 1H), 1.96 (bs, 1H), 1.02 (d, 6.5, $J=7.0$, 2H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 152.7, 145.9, 145.3,

139.1, 129.3, 118.7, 111.2, 101.6, 95.1, 60.9, 57.6, 56.3, 31.0, 30.7, 23.8, 19.3; HRMS (FAB+) found 368.38273 $[M+Na]^+$, calcd 368.38293 for $C_{15}H_{23}NO_8Na$.



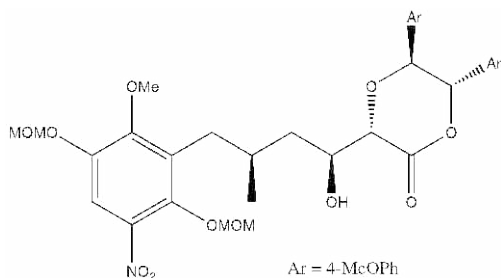
(S)-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-3-methylbutanenitrile

To a 500 mL round bottom flask containing the previous primary alcohol **38** (2.035 g, 5.90 mmol) was added 20 mL of THF. The solution was then cooled to 0 °C under a nitrogen atmosphere. Then with stirring Ph_3P (3.09 g, 11.8 mmol) was added followed by the dropwise addition of DEAD (1.86 mL, 11.8 mmol) over 10 min. The thick light yellow mixture was stirred for at least 10 min or until the stir bar was stuck at which time acetone cyanohydrin (1.08 mL, 11.8 mmol) was added as a THF (6.5 mL) solution. The mixture was allowed to stir at ambient temperature for overnight. Then the entire reaction mixture was filtered directly over a silica plug eluting with 200 mL of 50% EtOAc/hexanes. The resulting filtrate was then concentrated and the crude oil purified by flash chromatography (5:1:4, CH_2Cl_2 :Et₂O:hexanes) to give 2.046 g (98%) of the desired compound. Data are: TLC $R_f = 0.3$ (30% EtOAc/hexanes); $[\alpha]_D^{22} + 26.0^\circ$ (c 2.8, $CHCl_3$); 1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 5.20 (s, 2H), 4.98 (s, 2H), 4.05 (m, 2H), 3.93 (s, 3H), 3.54 (s, 3H), 3.49 (s, 3H), 2.81 (dd, $J = 7.0$ Hz, 1H), 2.69 (dd, $J = 7.0$ Hz, 1H), 2.27 (m, 1H), 0.98 (d, $J = 7.0$ Hz, 3H); HRMS (FAB+) found 377.13190 $[M + Na^+]$, calcd 377.13192 for $C_{16}H_{22}O_7N_2Na$.



(S)-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-3-methylbutanal (39)

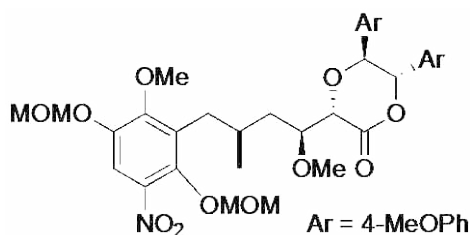
To a 100 mL round bottom flask containing the previous nitrile (0.20 g, 0.565 mmol) was added 7.0 mL of toluene. Then with stirring the solution was cooled to $-78\text{ }^{\circ}\text{C}$ under an Ar atmosphere. Then DIBAL-H (1.13 mL, 1.0 M toluene) was added slowly along inner wall over 10 min. The red/orange solution was then allowed to slowly warm from $-78\text{ }^{\circ}\text{C}$ to $-20\text{ }^{\circ}\text{C}$ over 1 h. The solution was then quenched by the sequential addition of 0.3 mL of acetone, 0.3 mL of EtOAc and 0.4 mL of pH 7 phosphate buffer. The solution was then warmed to ambient temperature where it stirred vigorously for 0.5 h. Then anhydrous powdered Na_2SO_4 was added and the solution stirred for 20 min. The entire reaction mixture was then filtered through a bed of silica gel over anhydrous Na_2SO_4 and washed with 50% EtOAc/hexanes. After generous washing the filtrate was concentrated and then purified using radial chromatography (2 mm plate, 30% EtOAc/hexanes) to afford 0.159 g (79%) of the desired compound as a viscous golden oil. Data are: TLC $R_f = 0.28$ (30% EtOAc/hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ 9.67 (app t, $J = 2.0$, 1H), 7.59 (s, 1H), 5.20 (s, 2H), 4.98 (ABq, 2H), 3.91 (s, 3H), 3.52 (s, 3H), 3.49 (s, 3H), 2.69 (d, $J = 7.5$ Hz, 2H), 2.43-2.24 (m, 2H), 0.96 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 202.6, 153.1, 146.2, 145.7, 139.6, 130.5, 111.3, 101.9, 95.5, 61.2, 57.9, 56.7, 50.4, 31.8, 29.0, 20.4; HRMS (FAB+) found 380.1355 [$\text{M} + \text{Na}^+$], calcd 380.1322 for $\text{C}_{16}\text{H}_{23}\text{NO}_8\text{Na}$.



(3*S*,5*S*,6*S*)-3-((1*S*,3*S*)-1-hydroxy-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-3-methylbutyl)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-one (40**)**

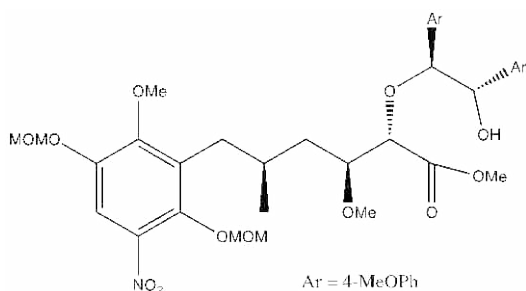
A flame dried flask was charge with *S,S*-dioxanone **32** (0.93 g, 2.97 mmol) and 80 mL CH₂Cl₂. The solution was cooled to -78 °C under nitrogen atmosphere. Et₃N (1.03 mL, 7.43 mmol) was added dropwisely, followed by *c*-hex₂BOTf (6 mL, 1M in hexanes) over 0.5 h. The resulting mixture was stirred at -78 °C for 3 h, at which time aldehyde **39** (1.2 g, 3.56 mmol) was added in 3 mL CH₂Cl₂ dropwisely over 10 min. The reaction was stirred for another 3 h at -78 °C and then quenched with pH 7 buffer (10 mL), MeOH (10 mL) and 30% aqueous H₂O₂ (3 mL). The mixture was warmed to ambient temperature and NaHCO₃ aqueous solution was added. The layers were separated and aqueous layer was extracted 3 times with CH₂Cl₂. The organic layers were combined and dried over Na₂SO₄, filtered and concentrated. Chromatograph (30-40% EtOAc/hexanes) provided the desired product **8a** (1.26 g, 63%) and an isomer (0.16 g, 8%). Data are: TLC R_f = 0.2 (30% EtOAc/hexanes); [α]_D₂₃ = -64.0° (c 1.5, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (s, 1H), 6.98-6.93 (m, 4H), 6.75-6.72 (m, 4H), 5.36 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 5.00 (q, *J* = 6.0 Hz, 2H), 4.96 (s, 1H), 4.53 (d, *J* = 4.5 Hz, 1H), 4.30 (m, 1H), 3.90 (s, 3H), 3.73 (s, 6H), 3.49 (s, 3H), 3.48 (s, 3H), 2.82 (d, *J* = 5.5 Hz, 1H), 2.53 (m, 2H), 2.04 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 0.91 (d, *J* = 6.0Hz, 3H); ¹³C NMR (CDCl₃, 164 500MHz) δ 170.2, 160.4, 160.2, 153.5, 146.6, 145.7, 140.0, 132.0, 129.3, 129.0, 128.4, 127.1, 114.2, 111.4, 101.9, 95.9, 85.7, 78.3, 77.0, 72.4, 61.6, 58.3, 57.0, 55.7, 41.3, 31.6, 30.9, 21.0; HRMS (FAB+) found 694.2440 [M+Na]⁺, calcd

694.2470 for C₃₄H₄₁NO₁₃Na.



(3*S*,5*S*,6*S*)-3-((1*S*,3*S*)-1-methoxy-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-3-methylbutyl)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-one

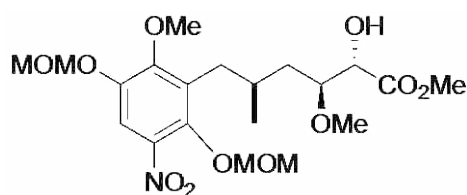
A flame dried 100 mL flask was charged with the aldol product **40** (1.7 g, 2.53 mmol) and 40 mL CH₂Cl₂. The solution was cooled to 0 °C before proton sponge (1.09 g, 5.06 mmol) was added, followed by Me₃OBF₄ (0.75 g, 5.06 mmol). The resulting mixture was warmed to ambient temperature and stirred for 5 h, at which time another portion of proton sponge (0.54 g, 2.53 mmol) and Me₃OBF₄ (0.37 g, 2.53 mmol) was added. The reaction was stirred for overnight, at which time it was filtered through a silicon plug eluting with Et₂O and concentrated. Chromatograph (20-30% EtOAc/hexanes) provided the title compound (1.73 g, 100%). Data are: TLC R_f = 0.5 (30% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 7.59 (s, 1H), 7.23 (t, *J* = 9.0 Hz, 4H), 6.84 (q, *J* = 8.5 Hz, 4H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.21 (s, 2H), 4.97 (s, 2H), 4.53 (d, *J* = 1.0 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 6H), 3.54 (m, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 2.63 (m, 1H), 2.35 (m, 1H), 1.85 (m, 1H), 1.36 (m, 1H), 0.84 (m, 1H), 0.71 (d, *J* = 6.5 Hz); HRMS (FAB⁺) found 708.25651[M+Na]⁺, calcd 708.26266 for C₃₅H₄₃NO₁₃Na.



(2S,3S,5S)-Methyl 2-((1S,2S)-2-hydroxy-1,2-bis(4-methoxyphenyl)ethoxy)-3-

methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (41)

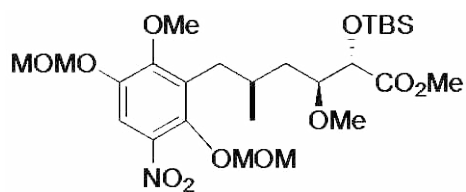
A solution of the protected aldol product above (1.73 g, 2.53 mmol) in 20 mL dry THF and 20 mL dry MeOH was cooled to 0 °C. A freshly prepared NaOMe (0.25 mL, 0.1 M in MeOH) was added. The resulting mixture was stirred at 0 °C for 3 h, at which time it was quenched with NH₄Cl solution. The mixture was extracted 5 times with Et₂O. The combined organic layer was dried over Na₂SO₄, filtered and concentrated. Chromatograph (30% EtOAc/hexanes) provided desired product **41** (1.60 g, 88%). Data are: TLC R_f = 0.4 (50% EtOAc/hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 7.60 (s, 1H), 6.93 (apparent q, *J* = 8.5 Hz, 4H), 6.69 (t, *J* = 9.0 Hz, 4H), 5.22 (s, 2H), 4.98 (q, *J* = 6.0 Hz, 2H), 4.71 (d, *J* = 9.0 Hz, 1H), 4.29 (d, *J* = 8.5 Hz, 1H), 4.19 (d, *J* = 4.0 Hz, 1H), 3.93 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.57 (m, 1H), 3.53 (s, 3H), 3.51 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 2.75 (m, 1H), 2.54 (m, 1H), 2.01 (m, 1H), 1.75 (m, 1H), 1.57 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.2, 159.4, 159.1, 153.2, 146.3, 145.6, 139.8, 131.6, 129.6, 129.4, 128.6, 113.4, 113.4, 111.1, 101.8, 95.6, 90.1, 81.5, 79.1, 78.6, 61.2, 58.0, 57.9, 56.7, 55.3, 51.9, 38.3, 32.1, 30.7, 20.8.



(2*S*,3*S*,5*S*)-Methyl 2-hydroxy-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)

-5-nitrophenyl)-5-methylhexanoate

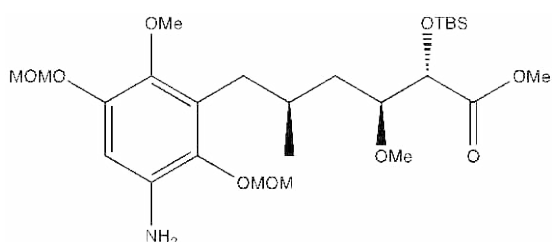
To a stirred solution of the methyl ester **41** (1.36 g, 1.89 mmol) in 25 mL CH₃CN and 2.7 mL H₂O was added ceric ammonium nitrate (2.59 g, 4.72 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min, at which time the reaction was diluted with H₂O and Et₂O. The two layers were separated and aqueous layer was extracted 5 times with Et₂O. The Et₂O layers were combined, dried, filtered, concentrated, and chromatographed (30% EtOAc/hexanes) to provide the title compound (0.68 g, 78%). Data are: TLC R_f = 0.3 (50% EtOAc/hexanes); Yield: 88%. ¹H NMR (CDCl₃, 500 MHz) δ 7.59 (s, 1H), 5.22 (s, 2H), 4.99 (apparent q, *J* = 6.5 Hz, 2H), 4.36 (m, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.55 (s, 3H), 3.60-3.57 (m, 1H), 3.52 (s, 3H), 3.43 (s, 3H), 2.94 (d, *J* = 6.0 Hz, 1H), 2.74-2.71 (m, 1H), 2.58-2.54 (m, 1H), 1.98 (m, 1H), 1.61 (m, 1H), 1.36 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 173.2, 153.2, 146.3, 145.7, 139.8, 131.5, 111.1, 101.8, 95.6, 81.6, 71.9, 61.2, 58.1, 58.0, 56.7, 52.6, 37.2, 32.3, 30.6, 20.5; HRMS (+TOF MS) found 484.17776 [M+Na]⁺, calcd 484.17893 for C₂₀H₃₁NO₁₁Na.



(2*S*,3*S*,5*S*)-Methyl 2-(tert-butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (42**)**

A flame dried 25 mL flask was charge with the previous α -hydroxy ester (0.33 g, 0.72 mmol), 5 mL DMF, and imidazole (0.25 g, 3.61 mmol). The resulting solution was cooled to 0 °C before TBSCl (0.22 g, 1.44 mmol) was added in portions. The reaction was stirred for overnight, at which

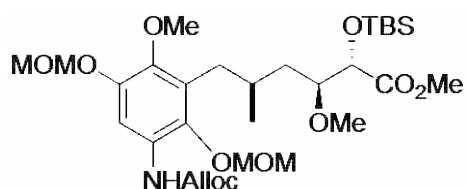
time it was quenched with NH_4Cl and diluted with Et_2O . The two layers were separated and aqueous layer was extracted 3 times with ether. Ether layers were combined, dried, filtered, concentrated, and chromatographed (10% EtOAc /hexanes) to give desired title product (0.36 g, 88%). Data are: TLC $R_f = 0.7$ (30% EtOAc /hexanes); Yield: 88%. ^1H NMR (CDCl_3 , 500 MHz) δ 7.57 (s, 1H), 5.20 (s, 2H), 4.96 (q, $J = 6.5$ Hz, 2H), 4.31 (d, $J = 3.5$ Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.53-3.48 (m, 1H), 3.38 (s, 3H), 2.72- 2.46 (m, 2H), 1.94 (m, 1H), 1.58-1.53 (m, 1H), 1.48-1.43 (m, 1H), 0.87 (s, 9H), 0.84 (d, $J = 6.0$ Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.8, 153.2, 146.2, 145.7, 139.7, 131.8, 111.0, 101.7, 95.5, 82.3, 73.5, 61.1, 58.0, 57.9, 56.6, 52.0, 38.4, 32.1, 30.6, 25.8, 20.6, 18.4, -5.0, -5.1.



(2S,3S,5S)-methyl 6-(3-amino-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-2-(tert-butyl dimethylsilyloxy)-3-methoxy-5-methylhexanoate

To a stirred solution of the prepared methyl ester **42** (0.112 g, 0.19 mmol) in 9 mL *i*-PrOH was added Pd/C (43mg, 10 wt%), the solution was degassed three times, then a big H_2 balloon was charged. After overnight, the suspension was filtered with a celite plug eluting with MeOH. Concentration and chromatography gave 90 mg desired product. Yield: 93%. ^1H NMR (CDCl_3 , 500 MHz) δ 6.45 (s, 1H), 5.12 (s, 2H), 4.90 (m, 2H), 4.31 (d, $J = 3.5\text{Hz}$, 1H), 3.81 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.56 (s, 3H), 3.55-3.52 (m, 1H), 3.40 (s, 3H), 2.66-2.30 (m, 2H), 1.95 (m, 1H), 1.57-1.53 (m, 1H), 1.47-1.42 (m, 1H), 0.89 (s, 9H), 0.82 (d, $J = 6.5$ Hz, 3H), 0.04 (s, 6H); ^{13}C

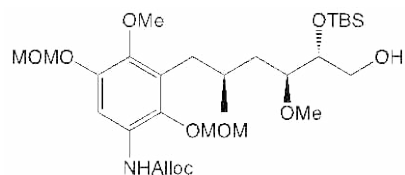
NMR (CDCl₃, 125 MHz) δ 172.9, 147.5, 140.5, 138.9, 136.1, 129.3, 102.6, 99.8, 95.6, 82.4, 73.8, 61.0, 58.1, 57.5, 56.3, 51.9, 38.9, 32.1, 30.7, 25.8, 20.5, 18.4, -5.0, -5.1; HRMS (+TOF MS) found 568.29062 [M+Na]⁺, calcd 568.29123 for C₂₆H₄₇NO₉SiNa.



(2S,3S,5S)-methyl-6-(3-(allyloxycarbonylamino)-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-2-(tert-butyldimethylsilyloxy)-3-methoxy-5-methylhexanoate
(43)

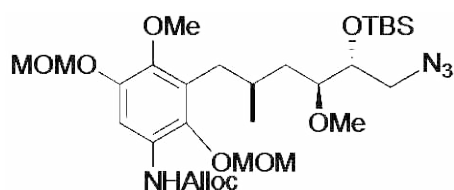
The previously prepared aniline (273 mg, 0.5 mmol) and 10 mL dry CH₂Cl₂ were added to flame dried 50 mL flask. At 0 ° C pyridine (0.12 mL, 1.5 mmol) was added dropwisely, followed by AllocCl (0.16 mL, 1.5 mmol) and DMAP (0.022g). After stirring at 0 ° C for 2 hrs and 3 hrs at rt, reaction solution was neutralized with dilute HCl. The solution was extracted with EtOAc three times, then combined organic layers was dried, concentrated. Final chromatography give the title compound 280 mg (yield: 89%). Data are: TLC R_f = 0.4 (20% EtOAc/hexanes); [α]_D²³ -14.4° (c 3.6, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.81 (bd, 1H), 5.96-5.91 (m, 1H), 5.32 (d, *J* = 17.0Hz, 1H), 5.21 (d, *J* = 10.5Hz, 1H), 5.18 (s, 2H), 4.90 (s, 2H), 4.64 (d, *J* = 4.0Hz, 2H), 4.31 (d, *J* = 3.5Hz, 1H), 3.79 (s, 2H), 3.69 (s, 3H), 3.59 (s, 3H), 3.50 (s, 3H), 3.53-3.49 (m, 1H), 3.45 (s, 3H), 2.65-2.61 (m, 1H), 2.33-2.29 (m, 1H), 1.91 (m, 1H), 1.55-1.52 (m, 1H), 1.46-1.41 (m, 1H), 0.88 (s, 9H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.8, 153.5, 147.0, 144.2, 141.1, 132.8, 128.7, 127.7, 117.7, 106.3, 100.7, 95.6, 82.3, 73.6, 65.7, 60.9, 58.0, 57.5, 56.6, 51.9, 38.4, 32.1, 30.7, 25.8, 20.6, 18.4, -5.0, -5.1; HRMS (+TOF MS) found 652.31602 [M+Na]⁺,

calcd 652.31236 for $C_{30}H_{51}NO_{11}SiNa$.



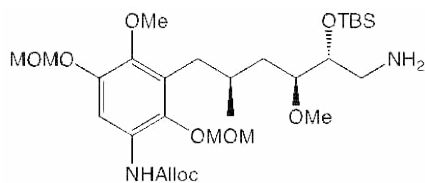
Allyl 3-((2S,4S,5R)-5-(tert-butyldimethylsilyloxy)-6-hydroxy-4-methoxy-2-methylhexyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (49)

The solution of the ester **43** from above (629 mg, 1.0 mmol) in 15 mL dry CH_2Cl_2 was cooled to $-78^\circ C$, then DIBAL-H (2.0 ml, 1.5 M in CH_2Cl_2) was added dropwise. The reaction solution was warmed slowly over 1 hr to rt. Sat. Na/K tartrate aqueous solution was added and resulting solution was stirred for 30 min. Et_2O was used to extract the solution three times, and combined ether layers were washed with brine, dried and concentrated. Chromotography gave the desired alcohol **14** 601 mg (yield: 80%). Date: TLC $R_f = 0.3$ (40% EtOAc/hexanes); 1H NMR ($CDCl_3$, 500 MHz) δ 7.80 (bs, 1H), 5.97-5.92 (m, 1H), 5.33 (d, $J = 17.5Hz$, 1H), 5.22 (d, $J = 10.5Hz$, 1H), 5.18 (s, 2H), 4.90 (s, 2H), 4.64 (d, $J = 5.0Hz$, 2H), 3.79 (s, 2H), 3.66-3.61 (m, 2H), 3.59 (s, 3H), 3.55-3.53 (m, 1H), 3.50 (s, 3H), 3.40 (s, 3H), 3.26 (bs, 1H), 2.66-2.63 (m, 1H), 2.38-2.33 (m, 1H), 1.96 (m, 1H), 1.44 (t, $J = 6.5Hz$, 2H), 0.88 (s, 9H), 0.84 (d, $J = 7.0 Hz$, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5, 147.1, 144.0, 141.1, 132.8, 128.8, 127.8, 117.8, 106.3, 100.8, 95.6, 82.0, 74.4, 65.7, 64.0, 60.9, 58.8, 57.5, 56.6, 39.5, 32.3, 30.8, 26.0, 21.2, 18.2, -4.4, -4.5; HRMS (+TOF MS) found 619.36283 $[M+NH_4]^+$, calcd 619.36205 for $C_{29}H_{55}N_2O_{10}Si$.



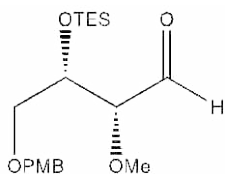
Allyl 3-((2S,4S,5R)-6-azido-5-(tert-butyldimethylsilyloxy)-4-methoxy-2-methylhexyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate

To a 25 mL flame dried round bottom flask was added the primary alcohol **49** (205 mg, 0.34 mmol) and 1.2 mL THF. The solution was cooled to 0 ° C and with stirring triphenylphosphine (178 mg, 0.68 mmol) was added followed by dropwise addition of DEAD (0.11 ml, 0.68 mmol). During the addition of DEAD, the stir bar stopped intermittently due to the viscosity of the solution. The stir bar was kept running for 10 min. DPPA (0.15 ml, 0.68 mmol) in 0.4 mL THF was added dropwise while the stir bar was maintained in motion. After 24 hrs, the clear solution was filtered with silica gel and eluted with 30 mL ether. Removal of the solvents followed by concentration gave the crude product which was then purified with flash chromatography. The pure product (190 mg, 89% yield). Data: R_f : 0.5 (40% EtOAc/Hex.); $[\alpha]_{D_{23}} = -7.6^\circ$ (c 3.6, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.79 (bs, 1H), 5.99-5.94 (m, 1H), 5.35 (d, $J = 17.0$ Hz, 1H), 5.23 (d, $J = 9.5$ Hz, 1H), 5.20 (s, 2H), 4.92 (s, 2H), 4.66 (d, $J = 5.5$ Hz, 2H), 3.81 (s, 2H), 3.74-3.71 (m, 2H), 3.61 (s, 3H), 3.53 (s, 3H), 3.44 (s, 3H), 3.34-3.25 (m, 2H), 2.68-2.64 (m, 1H), 2.39-2.34 (m, 1H), 1.96 (m, 1H), 1.41 (t, $J = 8.5$ Hz, 2H), 0.92 (s, 9H), 0.85 (d, $J = 6.5$ Hz, 3H), 0.12 (d, $J = 3.0$ Hz, 3H), 0.09 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.6, 147.2, 144.2, 141.1, 132.9, 128.6, 127.9, 117.9, 106.6, 100.8, 95.7, 81.9, 74.4, 65.8, 61.0, 59.0, 57.6, 56.8, 53.9, 39.6, 32.3, 31.0, 26.0, 20.9, 18.3, -4.4, -4.5; HRMS (+TOF MS) found 644.36836 [M+NH₄]⁺, calcd 644.36853 for C₂₉H₅₄N₅O₉Si.



Allyl 3-((2S,4S,5R)-6-amino-5-(tert-butyldimethylsilyloxy)-4-methoxy-2-methylhexyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (50)

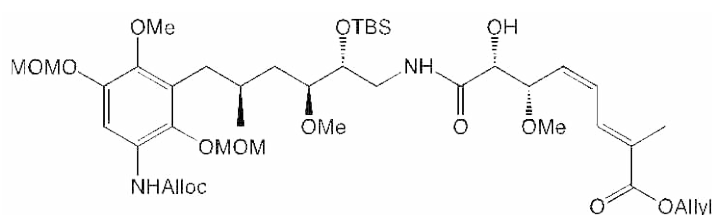
To a flame dried 25 mL round bottom flask was added the azide from above (63 mg, 0.1 mmol) and 2 mL benzene followed by dropwise addition of *n*-Bu₃P (0.05 ml, 0.2 mmol). After 1 hr of stirring at rt, 0.13 mL H₂O was added. After 30 hrs, the solution was concentrated. Flash chromatography gave the primary amine 44 mg (73% yield). Data: *R_f* = 0.3 (MeOH/CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.79 (bs, 1H), 5.99-5.94 (m, 1H), 5.33 (d, *J* = 17.0Hz, 1H), 5.23 (d, *J* = 10.5Hz, 1H), 5.19 (s, 2H), 4.91 (s, 2H), 4.65 (d, *J* = 5.5Hz, 2H), 3.80 (s, 2H), 3.63 (bs, 2H), 3.60 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H), 3.27 (bs, 2H), 2.85 (bs, 2H), 2.68-2.62 (m, 1H), 2.38-2.33 (m, 1H), 1.94 (m, 1H), 1.42 (m, 2H), 0.90 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.08-0.04 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.6, 147.1, 144.2, 141.1, 132.9, 128.7, 127.8, 117.8, 106.6, 100.8, 95.7, 82.7, 74.4, 65.8, 60.9, 58.7, 57.6, 56.6, 39.4, 32.4, 31.0, 26.1, 20.9, 18.3, -4.2, -4.4 v; HRMS (+TOF MS) found 601.35051 [M+H]⁺, calcd 601.35148 for C₂₉H₅₃N₂O₉Si.



(2R,3S)-2-Methoxy-4-(4-methoxybenzyloxy)-3-(triethylsilyloxy)butanal

A flame dried 250 mL round bottom flask was charged with the TES protected aldol product from above (2.25 g, 2.8 mmol) and 80 mL dry CH₂Cl₂. The resulting solution was cooled to -78 °C

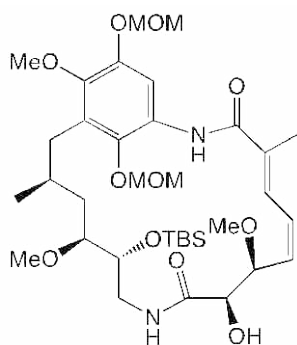
under nitrogen atmosphere. DIBAL-H (4.7 mL, 1.5 M in toluene) was added along the inner wall of the flask over 20 min. The mixture was stirred for 3 h before being quenched with 4 mL MeOH and 12 mL Na/K tartrate aqueous solution at -78 °C. The mixture was allowed to warm to ambient temperature and stirred for another 1.5 h, at which time it was diluted with 80 mL Na/K tartrate salt solution and extracted 4 times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, concentrated, and chromatographed (10% acetone/hexanes) to give the title compound **134** (0.86 g, 87%). Data are: TLC R_f = 0.6 (20% EtOAc/hexanes); [α]_D²³ = +31.7° (c 3.3, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 9.76 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.45 (A of AB q, *J* = 11.5 Hz, 1H), 4.41 (b of AB q, *J* = 11.5 Hz, 1H), 4.20-4.17 (m, 1H), 3.81 (s, 3H), 3.69-3.68 (m, 1H), 3.59-3.56 (m, 1H), 3.48 (s, 3H), 3.45-3.43 (m, 1H), 0.93-0.89 (m, 9H), 0.61-0.56 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 203.6, 159.4, 130.2, 129.6, 113.9, 87.0, 73.2, 72.1, 70.1, 59.6, 55.5, 6.9, 4.9; HRMS (FAB+) found 391.1916 [M+Na]⁺, calcd 391.1917 for C₁₉H₃₂O₅SiNa.



(2E,4Z,6S,7R)-allyl 8-((2R,3S,5S)-6-(3-(allyloxycarbonylamino)-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-2-(tert-butyldimethylsilyloxy)-3-methoxy-5-methylhexylamino)-7-hydroxy-6-methoxy-2-methyl-8-oxoocta-2,4-dienoate (52)

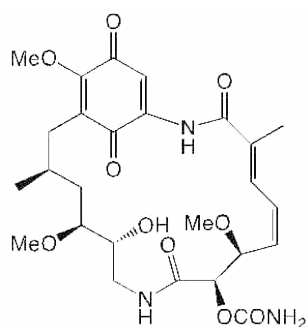
A solution of acid **51** (0.054 g, 0.20 mmol) and amine **50** (0.12 g, 0.20 mmol) in 4 mL CH₂Cl₂ was cooled to 0 ° C. HATU (0.091 g, 0.24 mmol) was added followed by *i*Pr₂NEt (0.077 g, 0.1 mL).

After 3 h, acid **5** (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 2 h, more acid **5** (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 3 h, the reaction mixture was passed through a silica plug eluting with EtOAc. The filtrate was concentrated and purified with radial chromatograph (30% EtOAc/hexanes) to provide amide products **52** (0.143 g, 84%). Data are: TLC R_f = 0.3 (60% EtOAc/hexanes); [α]_D²³ +9.1° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.85 (bs, 1H), 7.80 (bs, 1H), 7.55 (d, *J* = 12.5 Hz, 1/2H), 7.15 (t, *J* = 4.0 Hz, 1/2H), 6.63 (t, *J* = 12.0 Hz, 1H), 5.99-5.93 (m, 1H), 5.70 (t, *J* = 11.0 Hz, 1H), 5.34 (apparent d, *J* = 17.5 Hz, 2H), 5.23 (m, 2H), 5.20 (s, 2H), 4.91 (q, 2H), 4.68-4.64 (m, 8H), 4.10-4.08 (m, 1H), 3.81 (s, 3H), 3.75-3.73 (m, 1H), 3.60 (s, 3H), 3.52 (s, 3H), 3.49-3.24 (m, 6H), 3.40 (s, 3H), 3.30 (s, 3H), 2.67-2.63 (m, 1H), 2.38-2.34 (m, 1H), 2.02 (m, 1H), 1.98 (s, 3H), 1.50-1.38 (m, 2H), 0.90 (s, 9H), 0.02- 0.05 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 171.2, 168.0, 153.6, 147.1, 144.1, 141.2, 133.2, 132.9, 132.6, 132.0, 130.3, 129.5, 128.8, 127.8, 118.2, 117.9, 106.4, 100.8, 95.6, 82.6, 76.7, 73.5, 72.9, 65.7, 61.0, 59.2, 57.6, 57.1, 56.7, 41.8, 39.7, 32.4, 30.9, 29.9, 26.0, 21.1, 18.2, 12.8, 1.2, 0.2, -4.3, -4.6; HRMS (+TOF MS) found 853.45126 [M+H]⁺, calcd 853.45126 for C₄₂H₆₉N₂O₁₄Si.



To a stirred solution of previous amide **52** (85.2 mg, 0.1 mmol) in 2.5 mL dry THF was added morpholine (0.18 mL, 2.0 mmol) and Pd(PPh₃)₄ (46.9 mg, 0.04 mmol). The resulting solution was

stirred 4 h at ambient temperature before being diluted with Et₂O and quenched with 10% NaH₂PO₄. The ether layer was separated and aqueous layer was extracted twice with Et₂O and 8 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatography (50% EtOAc/hexanes) to get crude amino acid product. HRMS (+TOF MS) found 729.39294 [M+H]⁺, calcd 729.39883 for C₃₉H₆₁N₂O₁₂Si. This crude amino acid was dissolved in 100 mL CH₂Cl₂ (0.001M). HATU (66.9 mg, 0.18 mmol), DIPEA (0.08 mL, 0.44 mmol) and DMAP (5.0 mg) were added at ambient temperature. The resulting mixture was stirred for 1 day, at which time the mixture was concentrated and passed through a silica plug eluting with EtOAc. The concentrated crude product was purified with radial chromatograph (50% EtOAc/hexanes) to provide desired product **53** (38 mg, 52%). HRMS (+TOF MS) found 711.38569 [M+H]⁺, calcd 711.38826 for C₃₅H₅₉N₂O₁₁Si.

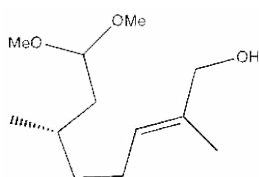


(4E,6Z,8S,9R,13R,14S,16S)-13-hydroxy-8,14,19-trimethoxy-4,16-dimethyl-3,10,20,22-tetraoxo-2,11-diazabicyclo[16.3.1]docosa-1(21),4,6,18-tetraen-9-yl carbamate (30)

A 10 mL round bottom flask was charged with the previous diamide **53** (8.5 mg, 0.012mmol), trichloroacetyl isocyanate (0.014 mL, 0.12 mmol) and 1 mL CH₂Cl₂. The mixture was allowed to stir for 30 min before MeOH (1 mL) and K₂CO₃ (10 mg, 0.07 mmol) was added. The mixture was stirred for 2 h before it was quenched with water and 1 drops of 1 N HCl aqueous solution. The

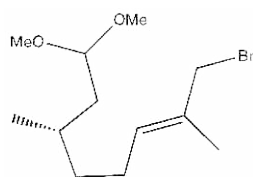
mixture was extracted 5 times with CH₂Cl₂ and 5 times with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by radial chromatograph (50% EtOAc/hexanes) to provide the urethane product 8.0 mg (yield: 89%); Data: TLC R_f = 0.2 (50% EtOAc/Hex.); [α]_D²³ -23.8° (c 0.4, CHCl₃); HRMS (+TOF MS) found 776.37151 [M+Na]⁺, calcd 776.37602 for C₃₆H₅₉N₃O₁₂SiNa. To a stirred solution of the urethane (4.0 mg, 0.006 mmol) in 1 mL CH₂Cl₂ and 1 mL CH₃CN was added NaI (8 mg, 0.06 mmol) and TMSCl (0.07 mL, 0.6 mmol). The resulting mixture was stirred 1 h before being quenched with saturated Na₂S₂O₃ solution. The organic layer was washed 3 times with sat. Na₂S₂O₃ solution. And the combine aqueous layers were extracted 3 times with CH₂Cl₂ and 5 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatography (7% MeOH/CH₂Cl₂) provided deprotected product. This intermediate was dissolved in 2 mL EtOAc. And Pd/C (5 mg, 10 wt%) was added. The mixture was stirred at ambient temperature, open to the air for 45 min. The mixture was then filtered through a celite plug eluting with EtOAc. The crude product was further purified by pipet column (5% MeOH/CH₂Cl₂) to provide desired product **3** (2.3 mg, 72%). Data are: TLC R_f = 0.3 (10% MeOH/CH₂Cl₂); [α]_D²³ +40.0 (c 0.1, CHCl₃); ¹NMR (CDCl₃, 300 MHz) δ 8.91 (s, 1H), 7.79 (d, *J* = 11.0 Hz, 1H), 7.24 (s, 1H), 6.60 (t, *J* = 11.5 Hz, 1H), 5.80 (q, *J* = 4.5 Hz, 1H), 5.43 (d, *J* = 2.5 Hz, 1H), 4.71 (m, 1H), 4.18 (s, 3H), 4.12 (m, 1H), 3.79 (m, 2H), 3.65 (bs, 1H), 3.49 (s, 3H), 3.34 (s, 3H), 3.29 (m, 1H), 3.24 (s, 3H), 2.54-2.50 (m, 1H), 2.40-2.36 (m, 1H), 1.98 (s, 3H), 1.70 (m, 1H), 1.62 (m, 1H), 1.26 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H); HRMS (+TOF MS) found 550.23831 [M+H]⁺, calcd 550.23952 for C₂₆H₃₆N₃O₁₀.

4.4. Towards the total synthesis of englerin A



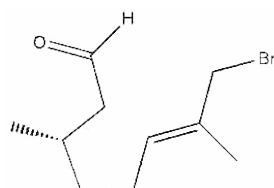
(*S,E*)-8,8-dimethoxy-2,6-dimethyloct-2-en-1-ol (32)

Into a 250-mL flask was introduced 5.5 g (0.05 mol) of SeO_2 , 75 mL of CH_2Cl_2 , and 22 mL (0.2 mol) of 90% tert-butylhydroperoxide. After the mixture had been stirred for 0.5 h at 25 °C (water bath), 11.2 g (0.1 mol) of (*S*)-8,8-dimethoxy-2,6-dimethyloct-2-ene was added over several minutes. The mixture was stirred at 25 °C for 48 hrs. Benzene (50 mL) was added and the DCM was removed on a rotary evaporator. Ether (100 mL) was added and the organic phase was washed four times with 25 mL of 10% KOH and once with brine. To destroy excess tert-butyl hydroperoxide, the solvents were removed, the residue was dissolved in 20 mL of cold acetic acid, and 25 mL (excess) of methyl sulfide was added slowly with stirring and water bath cooling. After 4 hrs at 25-30 °C, the mixture was cooled in an ice bath and neutralized with 20% K_2CO_3 . The aqueous phase was extracted with ether, and the combined organic phases were washed with water and brine, dried over Na_2SO_4 , concentrated, and chromatography to afford the allyl alcohol **32** (yield: 65%). Data: ^1NMR (CDCl_3 , 500 MHz) δ 5.35 (t, $J = 7.5$ Hz, 1H), 4.43 (t, $J = 5.0$ Hz, 1H), 3.94 (s, 2H), 3.27 (s, 3H), 3.26 (s, 3H), 2.11 (bs, 1H), 2.01 (m, 2H), 1.62 (s, 3H), 1.59 (m, 1H), 1.55 (m, 1H), 1.34 (m, 2H), 1.19 (m, 1H), 0.89 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 500 MHz) δ 134.69, 126.09, 103.03, 68.75, 52.54, 52.23, 39.28, 36.88, 28.68, 24.89, 19.65, 13.59.



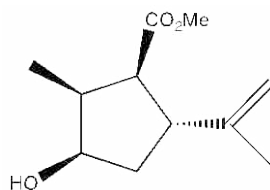
(*S,E*)-1-bromo-8,8-dimethoxy-2,6-dimethyloct-2-ene

A 250 mL flame dried round bottom flask was charged with LiBr (3.14 g, 36.1 mmol) and 100 mL of THF. To this stirring solution was added freshly distilled NEt₃ (1.26 mL, 9.03 mmol). Then a solution of alcohol **32** (780 mg, 3.61 mmol) in 20 mL of THF is added. The mixture was then stirred at ambient temperature until LiBr had completely dissolved. Then the solution was cooled to 0°C and methane sulfonyl chloride (0.59 mL, 7.58 mmol) was added dropwise. The reaction was stirred at 0°C for 1 h at which time it was quenched by the addition of H₂O. The resulting solution was extracted 3 times with Et₂O. The combined Et₂O layers were then washed with a saturated NaHCO₃ solution and then a saturated NaCl solution. The organic phase was then dried over MgSO₄, filtered and the solvent removed in vacuo. The crude mixture was purified by column chromatography to provide 906 mg (90%) of the title compound. Data: ¹NMR (CDCl₃, 500 MHz) δ 5.58 (t, *J* = 7.0 Hz, 1H), 4.45 (t, *J* = 5.0 Hz, 1H), 3.96 (s, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 2.04 (m, 2H), 1.75 (s, 3H), 1.62 (m, 1H), 1.58 (m, 1H), 1.38 (m, 2H), 1.21 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 131.53, 103.04, 52.69, 52.31, 41.84, 39.35, 36.42, 28.74, 25.66, 19.63, 14.59.



(*S,E*)-8-bromo-3,7-dimethyloct-6-enal (33**)**

To a 100 ml flask was added the allyl bromide (3.45 g, 12.37 mmol), THF 11 ml, AcOH 11 ml, and H₂O 11 ml. The mixture was stirred at room temperature, 20 drops of HCl (6.0 M) was added. Stirring continued for 1 h, then quenched the reaction with sat. NaHCO₃ carefully. Ether was used to extract aqueous layer, the combined organic layers were washed with brine and dried over Na₂SO₄. Concentration and chromatography gave the product **33** (2.30 g, 80%). Data: $[\alpha]_D^{23} = -15.8$ (c 7.1, CHCl₃) ¹NMR (CDCl₃, 500 MHz) δ 9.74 (d, $J = 2.0$ Hz, 1H), 5.58 (t, $J = 7.0$ Hz, 1H), 3.97 (s, 2H), 2.40 (m, 1H), 2.47 (m, 1H), 2.08 (m, 3H), 1.76 (s, 3H), 1.42 (m, 1H), 1.31 (m, 1H), 0.98 (d, $J = 6.5$ Hz, 3H).

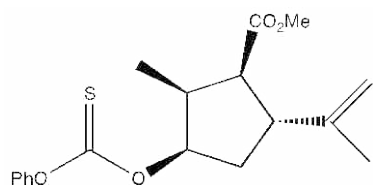


(1S,2S,3R,5R)-methyl 3-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate

Freshly prepared NaOMe solution (80 mL, 1.0M in methanol) was added dropwise to a solution of chloroketone (15.2 g, 53 mmol) in THF (220 mL) at 0 °C. The mixture was stirred at reflux temperature for 12 hrs, then cooled to rt, quenched with sat. NH₄Cl (100 mL). The quenched solution was stirred at rt for 30 min, then extracted with Et₂O (3 X 120 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo, the resulting product methyl ester was used for next step without further purification.

The methyl ester prepared above dissolved in methanol (200 mL), then PPTS (350 mg, 1.4 mmol) was added. The mixture was heated to reflux and stirred for 12 hrs, then was concentrated to about 30 mL, quenched with sat. NaHCO₃ (70 mL), diluted with H₂O (30 mL). The mixture was

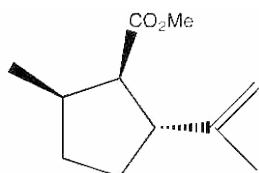
extracted with Et₂O (3 X 100 mL). The combined organic layers were washed with brine, dried over MgSO₄, concentrated. The crude product was separated with chromatography to give the title product (8.5 g, 81% over 2 steps). $[\alpha]_D = -17.3$ (c = 1.50, CHCl₃); ¹H NMR (CDCl₃, 500 MHz), δ 4.75 (d, *J* = 44.0 Hz, 2H), 4.26 (d, *J* = 3.5 Hz, 1H), 3.61 (s, 3H), 3.27-3.22 (m, 1H), 2.84 (t, *J* = 9.5 Hz, 1H), 2.52-2.48 (m, 1H), 2.08-2.02 (m, 1H), 1.86-1.82 (m, 1H), 1.73 (s, 3H), 1.38 (d, *J* = 2.5 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 175.1, 145.5, 111.7, 75.4, 53.4, 51.5, 46.9, 42.7, 39.6, 22.7, 13.8; HRMS (+TOF MS) found 199.1327 [M+H]⁺, calcd 198.1256 for C₁₁H₁₈O₃.



(1S,2S,3R,5R)-methyl 2-methyl-3-((phenoxy-carbonylthio)oxy)-5-(prop-1-en-2-yl)cyclopentanecarboxylate

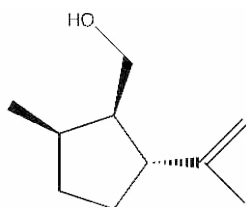
Pyridine (8.6 mL, 107.3 mmol) and phenyl chlorothionoformate (6.5 mL, 46.0 mmol) were added successively to a stirred solution of the secondary alcohol (8.5 g, 43.6 mmol) in DCM (150 mL) at room temperature under Ar atmosphere. After 1 hour, the reaction mixture was quenched by 1.0 M aqueous HCl (200 mL), and then extracted with DCM (3×100 mL). The combined organic layers were washed with Sat. NaHCO₃, dried over Na₂SO₄, concentrated and separated with chromatography to give the titled yellow product (12.2 g, 88%). ¹H NMR (CDCl₃, 500 MHz), δ 7.43-7.40 (m, 2H), 7.30-7.26 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 5.79 (t, *J* = 4.5 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.62 (s, 3H), 3.21-3.16 (m, 1H), 2.92 (t, *J* = 8.5 Hz, 1H), 2.85-2.81 (m, 1H), 2.29-2.24 (m, 1H), 2.21-2.16 (m, 1H) 1.76 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500

MHz) δ 194.6, 174.1, 153.3, 144.3, 129.5, 126.5, 121.9, 111.9, 88.7, 53.9, 51.5, 46.6, 41.5, 36.6, 22.5, 13.9; HRMS (+TOF MS) found 335.1308 [M+H]⁺, calcd 334.1239 for C₁₈H₂₂O₄S.



(1R,2R,5R)-methyl 2-methyl-5-(prop-1-en-2-yl)cyclopentanecarboxylate

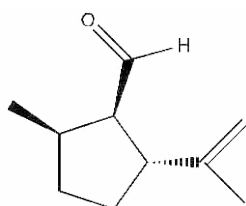
n-Bu₃SnH (12.8 mL) and AIBN (cat.) were added to a stirred solution of the thionocarbonate (12.2 g, 38.4 mmol) in benzene (150 mL) at reflux under an Ar atmosphere. After 30 min the reaction solution was allowed to cool to room temperature, and the solvent was removed in vacuo. The residue was subjected to chromatography to give the product as colorless oil (6.28 g, 90%). Data: $[\alpha]_D^{23} = +14.4$ (c 2.1, CHCl₃) ¹H NMR (CDCl₃, 500 MHz), δ 4.73 (d, *J* = 26.5 Hz, 2H), 3.59 (s, 3H), 2.82-2.77 (m, 1H), 2.62-2.58 (m, 1H), 2.48-2.42 (m, 1H), 2.09-2.03 (m, 1H), 1.91-1.83 (m, 1H), 1.80-1.76 (m, 1H), 1.74 (s, 3H), 1.71 (d, *J* = 7.0 Hz, 1H), 1.23-1.15 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 175.1, 145.5, 110.7, 55.7, 51.0, 49.7, 36.9, 33.8, 29.8, 22.6, 21.2; HRMS (+TOF MS) found 200.1643 [M+H]⁺, calcd 182.1307 for C₁₁H₁₈O₂.



((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methanol

To a 250 mL dry flask was introduced the ester 1.82 g (10 mmol) and DCM 70 mL, the mixture was cooled to -20 °C, then DIBAL-H 22 mL (1.0 M in toluene) was added dropwise.

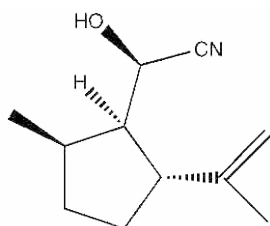
Stirring for 2 hrs and then HCl (1.0 M) 25 mL and sat. Na⁺K⁺ tartrate 30 mL were added sequentially and slowly. The mixture was allowed to warm to rt, and stirred overnight. Organic layer was separated and aqueous layer was extracted with ether twice. The combined organic layers were washed with brine and dried over Na₂SO₄. Concentration and chromatography gave the titled compound 1.36 g (yield 88%). Data: ¹H NMR (CDCl₃, 500 MHz), δ 4.82 (d, *J* = 24.5 Hz, 2H), 3.51 (m, 1H), 3.38 (m, 1H), 2.61 (q, *J* = 7.5 Hz, 1H), 1.94 (m, 1H), 1.85 (m, 2H), 1.82 (s, 3H), 1.73-1.63 (m, 3H), 1.18-1.10 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 147.42, 110.37, 63.98, 51.04, 48.15, 36.30, 33.53, 29.23, 23.68, 21.47; HRMS (+TOF MS) found 155.1416 [M+H]⁺, calcd 154.1358 for C₁₀H₁₈O.



(1*R*,2*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehyde (49)

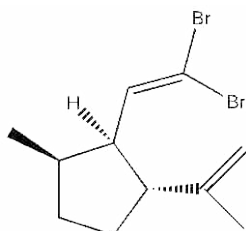
Oxalyl chloride (2.0 ml, 1.3 equiv) was dissolved in 30 ml DCM under argon at -78 °C. To this stirred solution was slowly added a solution of DMSO (2.75 mL, 2.2 equiv) in 3 ml DCM. The reaction mixture was stirred for 15 minutes, then a solution of the primary alcohol above (17.6 mmol) dissolved in 10 ml DCM was added dropwise. The reaction mixture was stirred for 15 minutes, then triethylamine (12.0 ml, 5.0 equiv) was added. The reaction was then allowed to warm to room temperature over 1 h. The reaction was quenched with water and extracted with DCM three times. The organic layers were combined and washed with brine, dried over Na₂SO₄, filtered and concentration vacuo. The crude mixture was purified with flash chromatography to

provide **49** as a colorless oil (2.43 g, 91% yield). ^1H NMR (CDCl_3 , 500 MHz), δ 9.51 (d, $J = 3.5$ Hz, 1H), 4.83 (d, $J = 17.0$ Hz, 2H), 2.87 (q, $J = 9.0$ Hz, 1H), 2.42 (m, 1H), 2.37 (m, 1H), 2.04 (m, 1H), 1.78-1.68 (m, 1H), 1.75 (s, 3H), 1.27 (m, 2H), 1.06 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 204.04, 143.87, 111.55, 60.40, 48.94, 34.46, 34.15, 30.38, 23.01, 20.67.



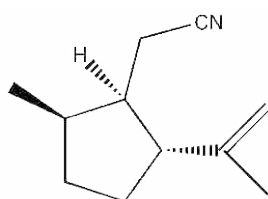
(R)-2-hydroxy-2-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)acetonitrile (50)

To a solution of the aldehyde **49** (61 mg, 0.4 mmol) in DCM (3 ml) at -20 °C acetone cyanohydrin (71 μl , 2 equiv.) and triethylamine (10 μl , 0.2 equiv.) and the solution was stirred at that temperature under nitrogen for 2 hrs. Solvent was removed in vacuo, and the crude product was purified by chromatography to give the product **50** as a colorless oil (91%). Data: ^1H NMR (CDCl_3 , 500 MHz), δ 4.95 (d, $J = 34.5$ Hz, 2H), 4.47 (m, 1H), 2.66 (m, 1H), 2.39 (m, 2H), 2.07 (m, 1H), 2.01 (m, 1H), 1.84 (s, 3H), 1.88-1.78 (m, 1H), 1.70 (m, 1H), 1.25-1.16 (m, 1H), 1.19 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 145.72, 119.91, 112.62, 62.55, 52.15, 49.21, 34.56, 34.25, 30.53, 24.10, 22.70.



(1R,2R,3R)-2-(2,2-dibromovinyl)-1-methyl-3-(prop-1-en-2-yl)cyclopentane (71)

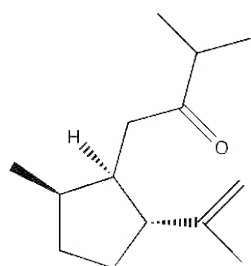
PPh₃ (927 mg, 3.53 mmol) was added to a solution of CBr₄ (586 mg, 1.77 mmol) in CH₂Cl₂ (3.5 mL) at 0 °C. After cooling the reaction mixture to -78 °C, a solution of the aldehyde **49** (152 mg, 1.0 mmol) in CH₂Cl₂ (3.0 ml) was added. The reaction mixture was stirred for 90 minutes at -78 °C, and then diluted with saturated aqueous NH₄Cl solution. The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (3×). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. Purification of the crude product by chromatography afforded the dibromide (252 mg, 85%) as colorless oil. Data: ¹H NMR (CDCl₃, 500 MHz), δ 6.20 (d, *J* = 9.5 Hz, 1H), 4.78 (d, *J* = 55.0 Hz, 2H), 2.71 (q, *J* = 8.5 Hz, 1H), 2.56 (m, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.72-1.64 (m, 1H), 1.70 (s, 3H), 1.21 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 145.82, 140.87, 110.67, 87.35, 53.28, 48.80, 40.53, 33.62, 29.54, 23.43, 20.81.



2-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)acetonitrile (76)

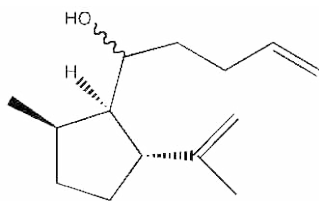
To a 100 mL round bottom flask containing the previous primary alcohol **75** (909 mg, 5.9 mmol) was added 20 mL of THF. The solution was then cooled to 0°C under a nitrogen atmosphere. Then with stirring triphenylphosphine (3.09 g, 11.8 mmol) was added followed by the dropwise addition of DEAD (1.86 mL, 11.8 mmol) over 10 min. The thick light yellow mixture was stirred for at least 10 min at which time acetone cyanohydrin (1.08 mL, 11.8 mmol) was added as a THF (6.5 mL) solution. The mixture was allowed to stir at ambient temperature for 22 h. Then the entire reaction mixture was filtered directly over a silica plug eluting with 200 mL of 50%

EtOAc/hexanes. The resulting filtrate was then concentrated and the crude oil purified by flash chromatography to afford 741 mg of the title compound **76** (yield: 77%). Data: ^1H NMR (CDCl_3 , 500 MHz), δ 4.82 (d, $J = 68.0$ Hz, 2H), 2.64 (m, 1H), 2.14 (dd, 1H), 2.03-1.95 (m, 4H), 1.75-1.71 (m, 1H), 1.74 (s, 3H), 1.65-1.59 (m, 1H), 1.22 (m, 1H), 1.15 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 144.17, 120.05, 112.19, 48.55, 44.90, 39.07, 32.73, 27.86, 23.33, 21.90, 18.87.



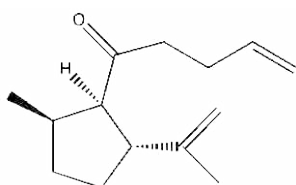
3-methyl-1-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)butan-2-one (77)

Alcohol **79** (210 mg, 1.0 mmol) was dissolved in DCM 20 ml, then N-morpholine oxide (293 mg, 2.5 mmol) and 300 mg 3Å MS was added. The mixture was stirred for 5 minutes, then TRAP (18 mg, 5 mmol %) was added) After 2 hrs of stirring at room temperature, the solution was filtered with celite, eluted with EtOAc. Concentration of the EtOAc solution followed by flash chromatography gave the product **77** (188 mg, 90% yield). Data: ^1H NMR (CDCl_3 , 500 MHz), δ 4.70 (d, $J = 71.5$ Hz, 2H), 2.67 (q, $J = 9.5$ Hz, 1H), 2.55 (m, 1H), 2.32-2.19 (ddd, 2H), 2.15 (m, 1H), 1.93 (m, 1H), 1.73 (m, 1H), 1.67 (s, 3H), 1.59 (m, 1H), 1.16 (m, 1H), 1.06 (d, $J = 7.0$ Hz, 3H), 1.04 (d, $J = 7.0$ Hz, 3H), 1.00 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 214.88, 146.51, 111.28, 48.18, 43.85, 41.33, 41.08, 39.31, 32.75, 31.57, 28.26, 22.96, 21.63, 18.13.



1-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)pent-4-en-1-ol

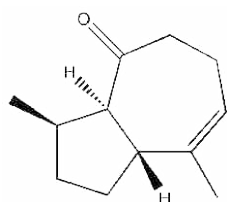
Aldehyde **49** (91 mg, 0.6 mmol) was dissolved in THF 3.0 ml, the solution was cooled to 0 °C, then 3-butenylmagnesium bromide 1.8 ml (0.5 M in THF, 0.9 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C, then HCl 2 ml (1.0 M) was added slowly to quench the reaction. After reaction solution was warmed to room temperature, organic layer was extracted with ether twice. Combined organic layers were washed with brine and dried over Na₂SO₄, after concentration the crude product was purified by chromatography to give the titled compound 102 mg (yield: 82%). Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.81 (m, 1H), 5.01 (d, *J* = 17.5 Hz, 1H), 4.94 (d, *J* = 9.5 Hz, 1H), 4.86 (d, *J* = 24.5 Hz, 2H), 3.67 (m, 1H), 2.53 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.80 (s, 3H), 1.74 (m, 1H), 1.67 (m, 1H), 1.62-1.53 (m, 3H), 1.40 (m, 1H), 1.14-1.05 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 2H); ¹³C NMR (CDCl₃, 500 MHz) δ 148.18, 138.72, 114.18, 109.81, 71.42, 51.96, 50.07, 34.76, 34.07, 32.12, 30.82, 30.62, 24.12, 23.28; HRMS (+TOF MS) found 231.1744 [M+Na]⁺, calcd 208.1851 for C₁₄H₂₄O.



1-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)pent-4-en-1-one (90)

Same procedure as making **77**. Product **90** is colorless oil. Yield: 90%. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.76 (m, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.70 (d, *J* = 21.5 Hz, 2H), 2.94 (q, *J* = 8.5 Hz, 1H), 2.64 (t, *J* = 9.0 Hz, 1H), 2.52-2.46 (m, 1H), 2.40-2.34 (m, 2H),

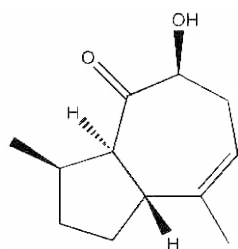
2.30-2.17 (m, 2H), 2.01-1.95 (m, 1H), 1.84-1.71 (m, 2H), 1.64 (s, 3H), 1.16 (m, 1H), 0.97 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 211.33, 145.82, 137.54, 114.81, 112.03, 63.18, 50.04, 42.92, 35.91, 33.64, 30.20, 27.63, 21.85, 20.93; HRMS (+TOF MS) found 207.1761 $[\text{M}+\text{H}]^+$, calcd 206.1688 for $\text{C}_{14}\text{H}_{22}\text{O}$.



(3R,3aR,8aR)-3,8-dimethyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one (91)

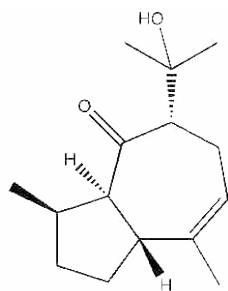
A flask containing **90** (116 mg, 0.564 mmol) was outfitted with a reflux condenser and evacuated and backfilled with Ar three times. Deoxygenated CH_2Cl_2 (37 mL) was added, and the solution was heated to reflux. A solution of Grubbs 2nd-generation catalyst (24 mg, 0.0282 mmol) in deoxygenated CH_2Cl_2 (2.5 mL) was added to the reaction mixture. The light brown reaction mixture was heated at reflux for 2.5 h, at which point a second portion of Grubbs 2nd-generation catalyst (12 mg, 0.0141 mmol) dissolved in CH_2Cl_2 (1 mL) was added. The reaction mixture was heated to reflux for an additional 4 h, and was then cooled to room temperature and evaporated *in vacuo* until ca. 15 mL remained. Pentane (60 mL) was added, and the solution was filtered through a plug of silica gel, eluting with pentane:Et₂O (9:1, 100 mL). The filtrate was evaporated *in vacuo* and purified by column chromatography to afford **91** as clear oil (90%). Data: ^1H NMR (CDCl_3 , 500 MHz), δ 5.51 (t, $J = 6.0$ Hz, 1H), 2.98-2.88 (m, 2H), 2.60-2.51 (m, 1H), 2.51-2.45 (m, 3H), 2.14-2.08 (m, 1H), 1.97-1.91 (m, 1H), 1.42-1.34 (m, 1H), 1.11-1.03 (m, 1H), 0.97 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 212.07, 140.07, 123.34, 60.08, 46.37, 44.68, 34.38, 33.21, 31.67, 24.10, 21.93, 21.08; HRMS (+TOF MS) found 196.1697 $[\text{M}+\text{NH}_4]^+$, calcd 178.1358 for

C₁₂H₁₈O.



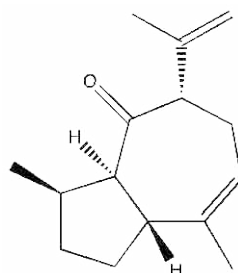
(3*R*,3*aR*,5*S*,8*aR*)-5-hydroxy-3,8-dimethyl-1,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one (92)

To a 25 ml oven dried flask 91 (78 mg, 0.4 mmol) was added followed by addition of THF (4 ml). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, then NaHMDS (0.6 ml, 1.0 M in THF) was added dropwise. The solution was stirred at that temperature for 30 minutes, and then the R-Davis oxiridine (165 mg, 0.72 mmol) in a solution of THF (4 ml) was added dropwise. Stirring continued for 4 hrs at that temperature. Then sat. NH_4Cl was added to quench the reaction. The solution was allowed to warm to room temperature. Organic phase was separated and aqueous phase was extracted with ether twice. The combined organic phases were washed with brine and dried over Na_2SO_4 , and concentrated. Purification by chromatography gave 92 (58 mg, yield 75%) as colorless oil. Data: ^1H NMR (CDCl_3 , 500 MHz), δ 5.51 (t, $J = 6.0$ Hz, 1H), 4.35 (m, 1H), 3.62 (d, $J = 3.0$ Hz, 1H), 3.05 (m, 1H), 2.92 (dd, 1H), 2.69 (bd, $J = 14.0$ Hz, 1H), 2.60 (m, 1H), 2.38 (ddd, 1H), 1.95 (m, 2H), 1.66 (s, 3H), 1.57-1.48 (m, 1H), 1.17-1.08 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 211.20, 141.26, 121.11, 79.27, 57.28, 46.46, 34.66, 33.88, 31.09, 30.05, 23.19, 20.54; HRMS (+TOF MS) found 217.1220 $[\text{M}+\text{Na}]^+$, calcd 194.1307 for C₁₂H₁₈O₂.



(3*R*,3*aR*,5*S*,8*aR*)-5-(2-hydroxypropan-2-yl)-3,8-dimethyl-1,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one (93)

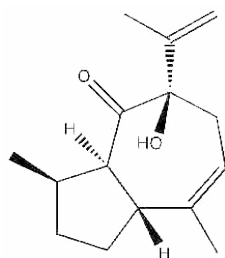
A solution of ketone **91** (125 mg, 0.7 mmol) in THF (6 ml) was added dropwise to freshly prepared LDA (4.7 ml, 2.1 mmol, 0.45 M in THF) at $-45\text{ }^{\circ}\text{C}$. The resulting mixture was stirred for 1 h before ZnCl_2 (0.85 ml, 0.85 mmol, 1.0 M in ether) was added dropwise at $-78\text{ }^{\circ}\text{C}$, followed by addition of acetone (0.6 ml, 8.15 mmol). After 30 minutes, the reaction mixture was quenched by sat. NH_4Cl , diluted with water and extracted by ether. The combined organic layers were washed with brine, dried over Na_2SO_4 . The residue was purified by chromatography to give the alcohol **93** as colorless oil (126 mg, 81%). Data: ^1H NMR (CDCl_3 , 500 MHz), δ 5.48 (bs, 1H), 3.11 (dd, 1H), 2.89 (t, $J = 15.0$ Hz, 2H), 2.60-2.48 (m, 3H), 2.22 (m, 1H), 2.00 (m, 2H), 1.68 (s, 3H), 1.42 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.13 (m, 1H), 1.01 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 216.16, 139.09, 122.21, 71.72, 62.40, 60.87, 47.10, 35.30, 33.64, 32.49, 29.15, 27.35, 24.97, 24.66, 21.07.



(3*R*,3*aR*,5*S*,8*aR*)-3,8-dimethyl-5-(prop-1-en-2-yl)-1,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one

(100)

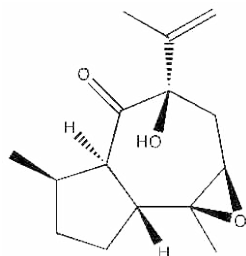
Burgess reagent (89 mg, 0.4 mmol) was added to a stirred solution of alcohol **99** (24 mg, 0.1 mmol) in toluene (10 ml) and the mixture was stirred at 110 °C for 5 minutes. Then the solution was evaporated and the residue was purified by flash chromatography providing alkene **100** (20 mg, 95%) as a colorless oil. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.52 (bs, 1H), 4.89 (d, *J* = 49.0 Hz, 2H), 3.10 (dd, 1H), 3.02 (dd, 2H), 2.63-2.52 (m, 2H), 2.13 (m, 1H), 1.92 (m, 2H), 1.73 (s, 3H), 1.66 (s, 3H), 1.46 (m, 1H), 1.06 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 211.60, 142.65, 140.69, 122.55, 111.75, 62.09, 56.37, 47.20, 34.31, 33.59, 31.40, 26.71, 23.12, 22.66, 20.56.



(3*R*,3*aR*,5*R*,8*aR*)-5-hydroxy-3,8-dimethyl-5-(prop-1-en-2-yl)-1,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one (101)

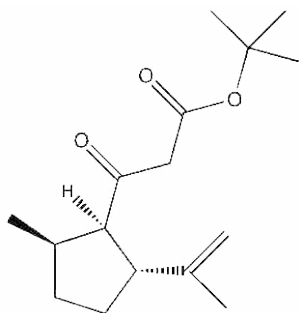
To a 25 ml oven dried flask **100** (78 mg, 0.4 mmol) was added followed by addition of THF (3 ml) and HMPA (1.5 ml). The solution was cooled to – 78 °C, then KHDMS (1.2 ml, 0.5 M in toluene) was added dropwise. The reaction solution was stirred at that temperature for 30 minutes, and then the R-Davis oxiridine (165 mg, 0.72 mmol) in a solution of THF (4 ml) was dropwise added. Stirred for 4 hrs at that temperature, then warm to room temperature over 1 h. The solution was then cooled to 0 °C and quenched with sat. NH₄Cl. Organic phase was separated and aqueous phase was extracted with ether three times. The combined organic phases were washed with brine

and dried over Na₂SO₄, and concentrated. Purification by chromatography gave **101** (61 mg, 65%) as colorless oil. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.50 (t, *J* = 6.5 Hz, 1H), 5.06 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 1H), 2.95-2.85 (m, 3H), 2.65 (m, 1H), 2.50 (dd, 1H), 2.13 (m, 1H), 1.95 (m, 1H), 1.72 (s, 6H), 1.56 (m, 1H), 1.16 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 212.73, 145.48, 142.46, 120.43, 113.52, 83.18, 61.64, 48.46, 38.26, 35.87, 33.16, 31.38, 25.66, 19.74, 19.02.



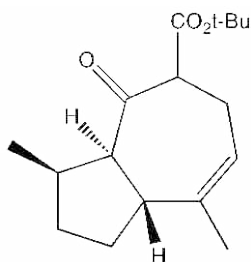
(1aR,3R,4aR,5R,7aR,7bS)-3-hydroxy-5,7b-dimethyl-3-(prop-1-en-2-yl) octahydroazuleno[4,5-b]oxiren-4(1aH)-one (102)

To a stirred solution of **101** (23.4 mg, 0.1 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added *m*-CPBA (95%, 19.6 mg, 0.12 mmol). After 3 h of stirring at 0 °C, the solution was quenched with an saturated aqueous Na₂CO₃ solution (3.0 mL), then diluted with H₂O (10.0 mL). The aqueous phase was extracted twice with CH₂Cl₂. The combined organic phases were washed by brine and dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography to produce **102** (7.5 mg, yield 30%). Data: [α]_D²³ = -9.3 (c 0.4, CHCl₃); ¹H NMR (CDCl₃, 500 MHz), δ 5.04 (d, *J* = 11.0 Hz, 2H), 4.49 (s, 3H), 3.11 (d, *J* = 6.5 Hz, 1H), 2.98-2.90 (, 2H), 2.81 (d, *J* = 15.0 Hz, 1H), 2.53 (dd, 1H), 2.38 (m, 1H), 2.02 (m, 2H), 1.71 (s, 3H), 1.64-1.56 (m, 1H), 1.33 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 212.32, 145.67, 113.54, 80.38, 64.09, 60.38, 58.84, 47.97, 38.43, 35.39, 31.59, 30.68, 24.33, 20.20, 18.61.



***tert*-butyl 3-((1*R*,2*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)-3-oxopropanoate (**112**)**

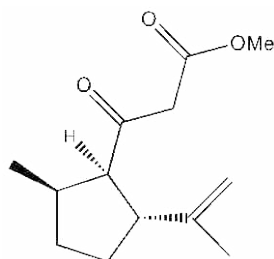
A solution of *tert*-butyl acetate (174 mg, 1.5 mmol) was added to freshly made LDA solution (4 ml, 0.3 M in THF) at $-78\text{ }^{\circ}\text{C}$. Stirring continued for 1 h, then aldehyde **49** (152 mg, 1.0 mmol) was added in a solution of THF (2 ml) dropwise. Then the reaction solution was stirred at $-40\text{ }^{\circ}\text{C}$ for 3 hrs before quenched with ssat. NH_4Cl . Organic layer was separated and aqueous layer was extracted with ether three times. The combined organic layers were washed with brine and dried over Na_2SO_4 . Concentration and chromatography gave **112** (155 mg, 58%) as colorless oil. Data: ^1H NMR (CDCl_3 , 500 MHz), δ 4.82-4.71 (m, 2H), 3.37-3.26 (m, 2H), 3.03-2.99 (m, 1H), 2.79 (t, $J = 9.0$ Hz, 1H), 2.48-2.45 (m, 1H), 2.03-1.99 (m, 1H), 1.87-1.83 (m, 1H), 1.79-1.72 (m, 2H), 1.68 (s, 3H), 1.46 (s, 3H), 1.22-1.18 (m, 2H), 1.02 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 204.5, 166.5, 145.5, 112.6, 81.5, 63.1, 55.8, 51.5, 50.5, 50.0, 35.7, 33.5, 30.1, 28.3, 27.9, 21.5, 20.6.



(3*R*,3*aR*,8*aR*)-*tert*-butyl 3,8-dimethyl-4-oxo-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate

(114)

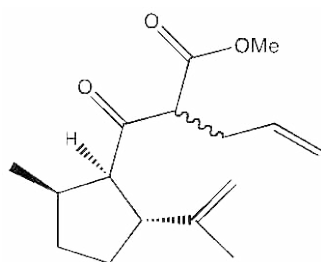
To a 25 ml oven dried flask was added dry THF (5 ml) and then 95% NaH (27.8 mg, 1.1 mmol). After the suspension was cooled to 0 °C, 112 (266 mg, 1.0 mmol) in THF (1 ml) was added dropwise. Stirring continued at 0 °C for 1 h. Then allyl bromide (0.17 ml, 2.0 mmol) was added dropwise. Kept stirring at 0 °C for 30 minutes, then warm to room temperature and stir for 5 hrs. Sat. NH₄Cl was added to quench the reaction, ether was used to extract the aqueous layer twice after the organic layer was separated. The combined organic layers were washed with brine. Concentration and chromatography gave the impure allylation product **113**. The impure intermediate went to RCM reaction following the procedure to make **91**. The titled compound **114** (impure) was given even after chromatography. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.46 (t, *J* = 6.5 Hz, 1H), 3.34-3.31 (m, 1H), 3.12-3.09 (m, 1H), 3.06 (m, 1H), 2.69 (m, 1H), 2.57-2.53 (m, 1H), 2.36-2.31 (m, 1H), 1.95-1.89 (m, 2H), 1.64 (s, 3H), 1.43 (s, 9H), 1.12-1.06 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 206.7, 168.8, 141.8, 121.5, 82.1, 61.7, 58.8, 47.2, 35.0, 33.8, 31.6, 28.2, 26.2, 23.5, 20.6.



methyl 3-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)-3-oxopropanoate (105)

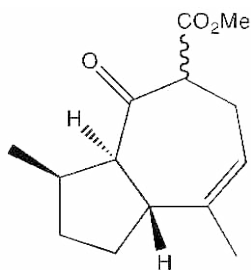
Anhydrous tin (II) chlorides (900 mg, 4.7 mmol) was added, followed by dropwise addition of ethyl diazoacetate (0.8 mL, 7.3 mmol) to the foregoing solution of aldehyde **49** in CH₂Cl₂. Stirring was continued for 2 h, and then the mixture was transferred to a separatory funnel, containing

saturated NaCl (10 mL) and diethyl ether (20 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (20 mL), saturated NaCl solution (20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give β-keto ester **105** (447 mg, 85%). Data: ¹HNMR (CDCl₃, 500 MHz), δ 4.80-4.71 (m, 2H), 3.71 (s, 3H), 3.48-3.38 (m, 2H), 3.03-2.98 (m, 1H), 2.79 (t, *J* = 8.0 Hz, 1H), 2.47-2.44 (m, 1H), 2.32 (m, 1H), 2.04-1.99 (m, 1H), 1.88-1.83 (m, 1H), 1.79-1.73 (m, 1H), 1.69 (d, *J* = 14.0 Hz, 3H), 1.24-1.18 (m, 1H), 1.06-0.96 (m, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 180.5, 167.8, 145.5, 112.6, 89.3, 63.2, 52.1, 51.0, 36.0, 33.5, 30.2, 21.7, 20.7.



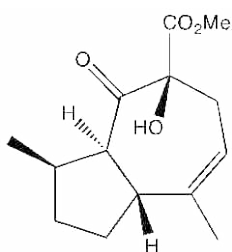
methyl 2-((1R,2R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclopentanecarbonyl)pent-4-enoate (106)

Follow the procedure to make **113** from **112**. Yield: 82%. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.57 (m, 1H), 5.08 (m, 2H), 4.74 (d, 2H), 3.71 (s, 3H), 2.88 (m, 2H), 2.63 (m, 2H), 2.41 (m, 1H), 2.01 (m, 2H), 1.85 (m, 1H), 1.71 (s, 3H), 1.22 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H); HRMS (+TOF MS) found 265.1798 [M+H]⁺, calcd 264.1725 for C₁₆H₂₄O₃.



(3*R*,3*aR*,8*aR*)-methyl 3,8-dimethyl-4-oxo-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate (107)

Follow the procedure to make **91** from **90**. Yield: 91%. Data: $^1\text{H NMR}$ (CDCl_3 , 500 MHz), δ 5.48 (t, 1H), 3.71 (s, 3H), 3.45 (dd 1H), 3.17 (dd, 1H), 3.07 (m, 1H), 2.76 (m, 1H), 2.59 (m, 1H), 2.40 (m, 1H), 1.95 (m, 2H), 1.67 (s, 3H), 1.47 (m, 1H), 1.11 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 500 MHz) δ 206.40, 169.90, 141.91, 121.00, 60.27, 58.57, 52.26, 47.11, 34.80, 33.58, 31.48, 25.94, 23.29, 20.36; HRMS (+TOF MS) found 237.1463 $[\text{M}+\text{H}]^+$, calcd 236.1412 for $\text{C}_{14}\text{H}_{20}\text{O}_3$.

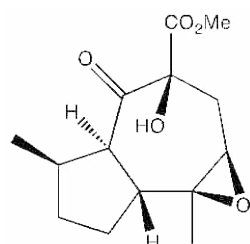


(3*R*,3*aR*,5*S*,8*aR*)-methyl 5-hydroxy-3,8-dimethyl-4-oxo-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate (108)

To a 25 ml oven dried flask **107** (94 mg, 0.4 mmol) was added followed by addition of THF (4 ml). The solution was cooled to -78 $^\circ\text{C}$, then KHDMS (1.2 ml, 0.5 M in toluene) was added dropwise. The reaction solution was stirred at that temperature for 30 minutes, and then the R-Davis oxiridine (165 mg, 0.72 mmol) in a solution of THF (4 ml) was dropwise added. Stirred for 1 h at that temperature, then warm to room temperature over 1 h. The solution was then cooled to 0

°C and quenched with sat. NH₄Cl. Organic phase was separated and aqueous phase was extracted with ether three times. The combined organic phases were washed with brine and dried over Na₂SO₄, and concentrated. Purification by chromatography gave **108** (86 mg, 85%) as colorless oil.

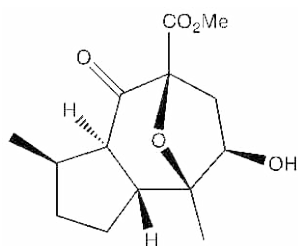
Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.45 (m, 1H), 4.02 (s, 1H), 3.80 (s, 3H), 3.19 (dd, 1H), 3.09 (m, 1H), 2.62 (d, *J* = 7.0 Hz, 2H), 2.48 (m, 1H), 2.03-1.93 (m, 2H), 1.70 (s, 3H), 1.55 (m, 1H), 1.14 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 207.38, 172.71, 142.31, 119.88, 83.14, 57.00, 53.20, 47.67, 35.80, 34.76, 31.97, 31.61, 24.26, 19.92; HRMS (+TOF MS) found 275.1265 [M+Na]⁺, calcd 252.1352 for C₁₄H₂₀O₄.



(1aR,3S,4aR,5R,7aR,7bS)-methyl 3-hydroxy-5,7b-dimethyl-4-oxodecahydroazuleno[4,5-b]oxirene-3-carboxylate (109)

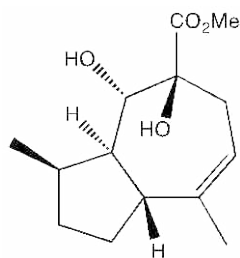
To a stirred solution of **108** (126 mg, 0.5 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C was added *m*-CPBA (95%, 180mg, 1.0 mmol). After 2 h of stirring at 0 °C, the solution was quenched with an saturated aqueous Na₂SO₃, then diluted with H₂O (10.0 mL). The aqueous phase was extracted twice with CH₂Cl₂. The combined organic phases were washed with Na₂CO₃ and brine and dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography to produce **109** (94 mg, yield 70%). Data: ¹H NMR (CDCl₃, 500 MHz), δ 4.43 (s, 1H), 3.79 (s, 3H), 3.04 (m, 2H), 2.87 (m, 2H), 2.36 (dd, 1H), 2.29 (m, 1H), 2.01 (m, 2H), 1.66 (m, 1H),

1.26 (s, 3H), 1.22 (m, 1H), 0.90 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 206.80, 170.98, 80.83, 62.36, 59.24, 57.00, 53.10, 47.17, 36.55, 34.97, 31.96, 29.64, 23.03, 18.90; HRMS (+TOF MS) found 269.1404 $[\text{M}+\text{H}]^+$, calcd 268.1311 for $\text{C}_{14}\text{H}_{20}\text{O}_5$.



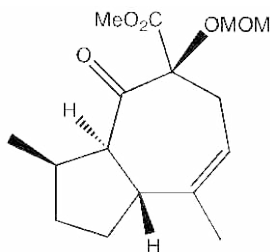
(1R,3aR,4S,5R,7S,8aR)-methyl 5-hydroxy-1,4-dimethyl-8-oxodecahydro-4,7-epoxyazulene-7-carboxylate (110)

To a solution of **109** (27 mg, 0.1 mmol) in DCM (2 ml) was added CSA (2.3 mg, 0.01 mmol) at 0 °C, the mixture was stirred for 30 minutes. Then Et_3N (0.05 ml) was added at 0 °C, and the mixture was warmed to room temperature and stirred for 30 minutes. The solvent was removed in vacuo, and the residue was purified by chromatography to give **110** (8 mg, 30%). The reaction is not reliable, and I didn't repeat successfully after the first time. Data: ^1H NMR (CDCl_3 , 500 MHz), δ 5.13 (d, $J = 10.5$ Hz, 1H), 4.61 (m, 1H), 3.82 (s, 3H), 2.83 (d, $J = 5.0$ Hz, 1H), 2.59 (m, 1H), 2.46 (m, 1H), 2.24 (m, 3H), 2.00 (m, 2H), 1.69 (s, 3H), 1.36 (m, 1H), 1.27 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 175.46, 173.32, 138.93, 124.11, 76.01, 66.82, 52.75, 52.31, 37.14, 36.54, 33.99, 27.67, 19.47, 14.24; HRMS (+TOF MS) found 286.1679 $[\text{M}+\text{NH}_4]^+$, calcd 268.1340 for $\text{C}_{14}\text{H}_{20}\text{O}_5$.



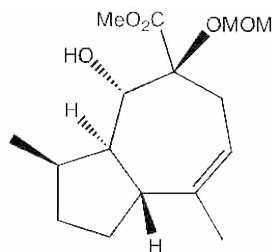
(3*R*,3*aR*,4*S*,5*S*,8*aR*)-methyl 4,5-dihydroxy-3,8-dimethyl-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate

Cerium (III) chloride heptahydrate (295mg, 1.2 mmol) was added to the solution of crude ketone **108** (76 mg, 0.3 mmol) in methanol (8 mL) and the mixture stirred for 30 min at room temperature, before it was cooled to $-78\text{ }^{\circ}\text{C}$ and sodium borohydride (36 mg, 0.9 mmol) was added in portions. Stirring was continued for 3 h at the same temperature. The reaction was quenched by slow addition of water, and most of methanol was removed in vacuo. Diethyl ether (10 mL) and water (10 mL) were added, the layers separated, and the aqueous layer was extracted with diethyl ether ($4 \times 10\text{ mL}$). The combined organic layers were washed with saturated NaCl solution, dried over MgSO_4 , filtered, and concentrated in vacuo to give crude alcohol that was purified by chromatography to give the titled compound (38 mg, 50%) as colorless oil. Data: ^1H NMR (CDCl_3 , 500 MHz), δ 5.56 (bs, 1H), 3.80 (s, 3H), 3.53 (d, $J = 12.0\text{ Hz}$, 1H), 3.02 (m, 1H), 2.93 (s, 1H), 2.44 (m, 2H), 2.08 (m, 2H), 1.99 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.78 (s, 3H), 1.53 (m, 1H), 1.06 (m, 1H), 1.04 (d, $J = 6.5\text{ Hz}$, 3H); ^{13}C NMR (CDCl_3 , 500 MHz) δ 175.70, 143.51, 120.02, 80.19, 77.61, 52.52, 47.02, 43.10, 37.85, 34.39, 32.49, 32.02, 22.30, 18.70.



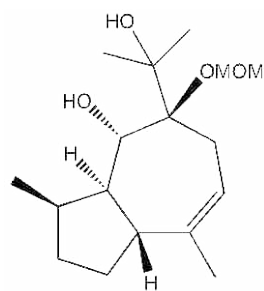
(3R,3aR,5S,8aR)-methyl 5-(methoxymethoxy)-3,8-dimethyl-4-oxo-1,2,3,3a,4,5,6,8a-octahydroazulene-5-carboxylate (121)

To a dry 100 ml flask was introduced 108 (504 mg, 2.0 mmol) and DCM (20 ml). the solution was cooled to 0 °C, and then DIPEA (0.7 ml, 8.0 mmol) was added and stirred for 10 minutes before dropwise addition of MOMCl (0.83 ml, 6.0 M in AcOMe, 10.0 mmol). After there was no fume in the flask, DMAP (37 mg, 0.3 mmol) was added. Then the mixture was allowed to warm to room temperature, and stirred for 12 hrs when additional DIPEA (0.7 ml) and the same MOMCl (0.83 ml) were added at 0 °C. Stirring continued for additional 12 hrs before the third DIPEA (0.7 ml) and the sme MOMCl (0.83 ml) were added at 0 °C. The solution was stirred for 24 hrs at room temperaure before quenched by slow addition of sat. NaHCO₃. Extraction of aqueous layer with ether three times and the combined organic layers were washed with brine, and dried over Na₂SO₄. Filtration and concentration gave the crude product that was purified by chromatography to generate 121 (485 mg, 82%) as slightly yellow oil. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.40 (t, *J* = 6.5 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.39 (s, 3H), 3.34 (m, 1H), 3.05 (m., 1H), 2.77 (m, 1H), 2.55 (m, 2H), 1.96 (m, 2H), 1.69 (s, 3H), 1.46 (m, 1H), 1.11 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 206.24, 171.15, 140.85, 118.84, 94.02, 88.23, 56.35, 55.60, 52.26, 47.34, 34.89, 33.33, 32.04, 31.17, 23.88, 20.73.



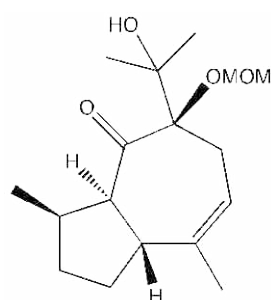
(3*R*,3*aR*,4*S*,5*S*,8*aR*)-methyl 4-hydroxy-5-(methoxymethoxy)-3,8-dimethyl-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate (122**)**

Cerium (III) chloride heptahydrate (295 mg, 1.2 mmol) was added to the solution of ketone **121** (118 mg, 0.4 mmol) in methanol (11 mL) and the mixture stirred for 30 min at room temperature, before it was cooled to $-78\text{ }^{\circ}\text{C}$ and sodium borohydride (32 mg, 0.8 mmol) was added in portions. Stirring was continued for 3 h at the same temperature. The reaction was quenched by slow addition of water, and most of methanol was removed in vacuo. Diethyl ether (10 mL) and water (10 mL) were added, the layers separated, and the aqueous layer was extracted with diethyl ether ($4 \times 10\text{ mL}$). The combined organic layers were washed with saturated NaCl solution, dried over MgSO_4 , filtered, and concentrated in vacuo to give crude alcohol that was purified by chromatography to afford the titled compound **122** (108 mg, 91%) as colorless oil. Data: $[\alpha]_{\text{D}}^{23} = -4.4^{\circ}$ (c 1.6, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 500 MHz), δ 5.60 (bs, 1H), 4.80 (d, $J = 7.5\text{ Hz}$, 1H), 4.56 (d, $J = 7.5\text{ Hz}$, 1H), 3.79 (d, $J = 13.0\text{ Hz}$, 1H), 3.76 (s, 3H), 3.38 (s, 3H), 2.98 (bd, $J = 8.0\text{ Hz}$, 1H), 2.80 (dd, 1H), 2.31 (dd, 1H), 2.04-1.97 (m, 3H), 1.93 (m, 1H), 1.84 (m, 1H), 1.77 (s, 3H), 1.52 (m, 1H), 1.05 (d, $J = 5.5\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 500 MHz) δ 173.45, 143.63, 120.44, 92.71, 81.66, 77.71, 56.41, 51.92, 48.02, 42.92, 37.91, 34.40, 31.94, 30.91, 22.11, 18.71.



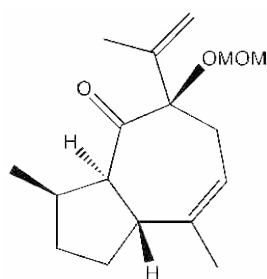
(3*R*,3*aR*,4*S*,5*S*,8*aR*)-5-(2-hydroxypropan-2-yl)-5-(methoxymethoxy)-3,8-dimethyl-1,2,3,3*a*,4,5,6,8*a*-octahydroazulen-4-ol (123**)**

Methylmagnesium iodide (2.2 mL, 1.0 M solution in Et₂O, 2.2 mmol) was added dropwise to a stirred solution of ester **122** (108 mg, 0.36 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 1 h before quenched with saturated NH₄Cl (10 mL), diluted with water (5 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give tertiary alcohol **123** (86 mg, 80%) as colorless oil. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.47 (bs, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 6.5 Hz, 1H), 3.40-3.33 (m, 1H), 3.36 (s, 3H), 2.97 (bd, *J* = 8.0 Hz, 1H), 2.50 (m, 2H), 2.14-2.04 (m, 2H), 1.96-1.87 (m, 2H), 1.81 (m, 1H), 1.71 (s, 3H), 1.46 (m, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.03 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 122.29, 92.13, 78.64, 55.79, 47.00, 43.19, 38.35, 34.58, 32.37, 28.82, 26.50, 25.68, 22.34, 19.20.



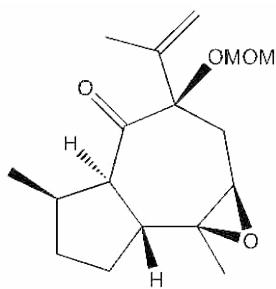
(3*R*,3*aR*,5*R*,8*aR*)-5-(2-hydroxypropan-2-yl)-5-(methoxymethoxy)-3,8-dimethyl-,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one (124)

Follow the procedure to make **77**. Yield: 89%. Product is colorless oil. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.28 (t, *J* = 7.0 Hz, 1H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.84 (d, *J* = 6.5 Hz, 1H), 3.94 (bs, 1H), 3.50 (dd, 1H), 3.41 (s, 3H), 3.00 (m, 1H), 2.66 (m, 1H), 2.55 (m, 1H), 2.26 (dd, 1H), 1.96 (m, 2H), 1.67 (s, 3H), 1.36 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.11 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 215.02, 140.67, 119.69, 82.80, 75.33, 55.38, 47.53, 34.24, 32.97, 31.45, 30.84, 26.45, 24.22, 23.73, 21.10; HRMS (+TOF MS) found 297.2068 [M+H]⁺, calcd 296.1995 for C₁₇H₂₈O₄.



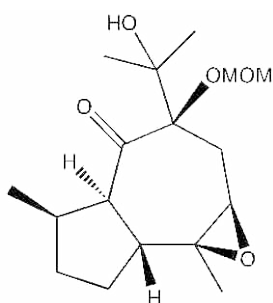
(3*R*,3*aR*,5*R*,8*aR*)-5-(methoxymethoxy)-3,8-dimethyl-5-(prop-1-en-2-yl)-1,3,3*a*,5,6,8*a*-hexahydroazulen-4(2*H*)-one (130)

Follow the procedure to make **100**. Product is colorless oil. Yield: 98%. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.31 (t, *J* = 6.5 Hz, 1H), 5.07 (d, *J* = 6.1 Hz, 2H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.56 (d, *J* = 7.0 Hz, 1H), 3.44 (dd, 1H), 3.39 (s, 3H), 3.00 (m, 1H), 2.87 (dd, 1H), 2.58 (m, 1H), 2.42 (dd, 1H), 1.98 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.46-1.37 (m, 1H), 1.14-1.07 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 208.65, 143.18, 140.57, 119.54, 115.66, 92.57, 89.26, 56.61, 56.07, 47.52, 35.13, 34.20, 33.35, 31.66, 24.20, 21.02, 20.20.



(1aR,3R,4aR,5R,7aR,7bS)-3-(methoxymethoxy)-5,7b-dimethyl-3-(prop-1-en-2-yl)octahydroazuleno[4,5-b]oxiren-4(1aH)-one (131)

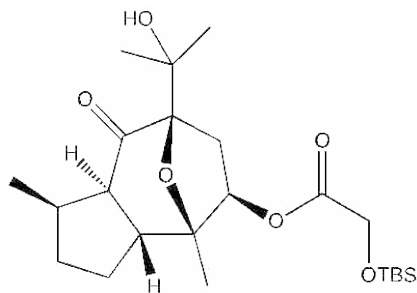
To a stirred solution of **130** (29.4 mg, 0.1 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was added *m*-CPBA (95%, 21.6 mg, 0.12 mmol). After 2 h of stirring at 0 °C, the solution was quenched with saturated aqueous Na₂SO₃, then diluted with H₂O (10.0 mL). The aqueous phase was extracted twice with CH₂Cl₂. The combined organic phases were washed with Na₂CO₃ and brine and dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography to produce **131** (7.8 mg, yield 25%). Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.24 (d, *J* = 21.0 Hz, 2H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 3.42 (s, 3H), 3.23 (dd, 1H), 2.87-2.79 (m, 2H), 2.72 (m, 1H), 2.41 (m, 1H), 2.18 (dd, 1H), 1.97 (m, 2H), 1.74 (s, 3H), 1.68 (m, 1H), 1.18 (s, 3H), 1.17 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 207.63, 142.62, 117.42, 92.35, 86.51, 61.15, 60.33, 56.51, 56.14, 46.82, 36.36, 34.60, 34.36, 28.99, 22.33, 19.45, 19.17.



(1aR,3R,4aR,5R,7aR,7bS)-3-(2-hydroxypropan-2-yl)-3-(methoxymethoxy)-5,7b-

dimethyloctahydroazuleno[4,5-*b*]oxiren-4(1*aH*)-one (125)

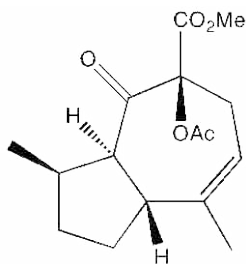
Follow the procedure to make **131** except addition of 2 eq of mCPBA. Product is colorless oil. Data: ¹H NMR (CDCl₃, 500 MHz), δ 4.66 (d, *J* = 7.0 Hz, 1H), 4.56 (d, *J* = 7.5 Hz, 1H), 3.38 (s, 3H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.16 (bs, 1H), 2.13 (dd, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.45 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 211.61, 93.11, 84.86, 77.31, 74.51, 71.74, 57.07, 55.90, 44.93, 35.66, 35.46, 32.50, 27.59, 27.20, 25.85, 21.99.



(1*R*,3*aR*,4*S*,5*R*,7*R*,8*aR*)-7-(2-hydroxypropan-2-yl)-1,4-dimethyl-8-oxodecahydro-4,7-epoxyazulen-5-yl 2-((*tert*-butyldimethylsilyl)oxy)acetate (128)

Acid **127** (14.3 mg, 0.075 mmol, 1.5 eq) was dissolved in DCM (0.5 ml) and was cooled under Ar to 0 °C, then **126** (13.4 mg, 0.05 mmol, 1.0 eq), DIPEA (0.013 ml, 0.075 mmol, 1.5 eq), and DMAP (1 mg) were added sequentially. This suspension was stirred for 5 minutes, then EDCI (14.3 mg, 0.075 mmol, 1.5 eq) was added. The reaction suspension was allowed to warm to room temperature and stirred for 24 hrs. Once the **126** was consumed (TLC), the reaction crude was diluted with water (1 mL) and DCM (2 mL). The layers were mixed and separated, and the aqueous layer was extracted with DCM (3 x 2 mL). The organic layers were combined and were washed sequentially with 3M H₃PO₄ (3 mL), saturated aqueous NaHCO₃ (3 mL), and saturated aqueous NaCl (3 mL). The organic layers were then dried

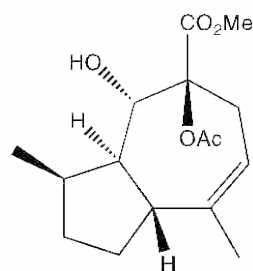
(MgSO₄), filtered, and concentrated. The crude material was purified by column chromatography the product **128** (15.6 mg, 71%) as colorless oil. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.32 (dd, 1H), 4.28 (s, 2H), 4.18 (s, 1H), 2.67 (dd, 1H), 2.57-2.47 (m, 3H), 1.84 (m, 1H), 1.71 (m, 2H), 1.56 (m, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.09 (m, 1H), 0.97 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ¹³C NMR (CDCl₃, 500 MHz) δ 215.84, 170.77, 78.72, 75.77, 75.50, 73.56, 61.85, 55.12, 46.00, 37.82, 34.60, 33.18, 27.87, 27.56, 26.69, 25.69, 22.09, 18.30, -0.02, -5.45.



(3R,3aR,5S,8aR)-methyl 5-acetoxy-3,8-dimethyl-4-oxo-1,2,3,3a,4,5,6,8a-octahydroazulene-5-carboxylate (133)

Into a 25 ml dry flask was introduced **108** (50.0 mg, 0.2 mmol) and DCM (2.0 ml). Et₃N (56 μl, 0.4 mmol) was added followed by Ac₂O (28 μl, 0.3 mmol). Then DMAP (2 mg) was added, and the solution was stirred at room temperature for 6 hrs. Water (2 ml) was used to quench the reaction. Ether was used to extract aqueous layer, and the combined layers were washed with brine and dried over MgSO₄. Concentration and chromatography gave the product **133** (53.5 mg, 91%) as colorless oil. Data: ¹HNMR (CDCl₃, 500 MHz), δ 5.48 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.20-3.10 (m, 3H), 2.53 (m, 2H), 2.13 (s, 3H), 1.94 (m, 2H), 1.69 (s, 3H), 1.57 (m, 1H), 1.14 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 202.96, 169.27, 168.43, 142.44, 119.48, 88.02, 56.33, 52.63, 47.37, 35.14, 33.96, 31.73, 30.90, 23.43, 20.85, 20.17; HRMS (+TOF MS) found

317.1395 [M+Na]⁺, calcd 294.1467 for C₁₆H₂₂O₅.



(3*R*,3*aR*,4*S*,5*S*,8*aR*)-methyl 5-acetoxy-4-hydroxy-3,8-dimethyl-1,2,3,3*a*,4,5,6,8*a*-octahydroazulene-5-carboxylate (134)

Follow the procedure to make **122**. Yield: 91%. Data: ¹H NMR (CDCl₃, 500 MHz), δ 5.63 (m, 1H), 3.82 (d, *J* = 12.5 Hz, 1H), 3.75 (s, 3H), 3.20 (dd, 1H), 3.03 (m, 1H), 2.23 (m, 1H), 2.07 (s, 3H), 2.01 (m, 2H), 1.95 (m, 1H), 1.88 (m, 1H), 1.79 (s, 3H), 1.55 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (CDCl₃, 500 MHz) δ 171.13, 169.48, 143.99, 120.33, 82.26, 52.22, 48.08, 42.86, 37.80, 34.32, 31.92, 31.37, 22.20, 21.00, 18.66; HRMS (+TOF MS) found 297.1714 [M+H]⁺, calcd 296.1624 for C₁₆H₂₄O₅.