Title: Total Synthesis of Diterpenoid (+)-Harringtonolide

Authors: Haijun Zhang; Lin Hu, Ph.D.; Zhiqiang Ma, Ph.D.; Ruining Li, Ph.D.; Zhen Zhang; Cheng Tao; Bin Cheng, Ph.D.; Yun Li, Ph.D.; Huifei Wang, Ph.D.; Hongbin Zhai, Ph.D.

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Total Synthesis of Diterpenoid (+)-Harringtonolide

Hai-Jun Zhang,[+[a]] Lin Hu,[+[b]] Zhiqiang Ma,[[b]] Ruining Li,[[b]] Zhen Zhang,[[a]] Cheng Tao,[[a]] Bin Cheng,[[a]] Yun Li,[[a]] Huifei Wang,[[c]] and Hongbin Zhai*[a,b,c]

Dedicated to the memories of Profs. Nanjun Sun and Puzhu Cong

Abstract: Described herein is the first asymmetric total synthesis of (+)-haringtonolide, a natural diterpenoid with an unusual tropone imbedded in a cage-like framework. The key transformations include an intramolecular Diels-Alder reaction and a rhodium-complex-catalyzed intramolecular [3+2] cycloaddition to install the tetracyclic core as well as a highly efficient tropone formation.

(+)-Harringtonolide (**1**, Figure 1), a structurally unique diterpenoid, was first isolated from the seeds of *Cephalataxus harringtonia* by Buta and co-workers in 1978,[1a] and subsequently from the bark of the Chinese species *Cephalotaxus hainanensis* by Sun *et al.* in 1979, yet under the name of hainanolide.[1b] Hainanolidol (**2**), the structural congener of hainanolide was also isolated.[1b] X-ray crystallographic analysis[1] of **1** and its brominated derivative[2] unambiguously confirmed its structure. The cage-like diterpenoid **1** contains an unusual tropone ring, a compact *cis*-fused tricyclic ring system carrying seven contiguous stereogenic centers, a bridged lactone, and a tetrahydrofuran ring. (+)-Harringtonolide was shown to inhibit the growth of tobacco and beans and to be antineoplastically and antivirally active; in addition, it was found to have potent cytotoxic activities with IC_{50} = 43 nM for KB tumor cells and to cause necrosis under certain conditions.[2] In contrast, diterpenoid **2** was biologically inactive,[2,3] suggesting that the THF ring in **1** might have played a decisive role for its biological activity. The chemical relationship between the two natural products was investigated, as exemplified by a biomimetic transformation of alcohol **2** into **1** through an oxidation process promoted by lead tetraacetate, though the yield was not given in the literature.[4]

Owing to their intriguing architecture and outstanding biological activities, harringtonolide and its derivatives have attracted considerable attention from the synthetic community. Many synthetic efforts have been devoted to harringtonolide since its isolation.[5-8] In 1998, Mander's group demonstrated a groundbreaking total synthesis of (±)-hainanolidol, which constituted a formal synthesis of (±)-harringtonolide.[6g] Their elegant strategy utilized arene cyclopropanation and the subsequent ring expansion for the construction of the tropone moiety, though the formation of THF ring of the natural product at an early stage proved to be unfavorable.[6d-6f] More recently, Tang *et al*. reported an efficient total synthesis of (±)-harringtonolide through an intramolecular oxidopyrylium-based [5+2] cycloaddition to assemble the tetracyclic carbon skeleton.[9] Nevertheless, the asymmetric synthesis of this molecule has not been accomplished to date. As part of our long-term efforts on streamlining efficient synthetic strategies for complex natural products, we present herein the first enantioselective total synthesis of (+)-harringtonolide (**1**).

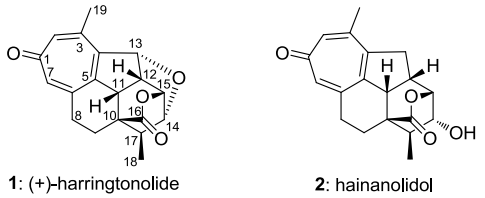

Figure 1. Cephalotaxus Norditerpenes **1** and **2**.

The retrosynthetic analysis is outlined in Scheme 1. We envisioned that the construction of the tropone, the lactone, and the ether ring moieties in harringtonolide **1** could be achieved by a sequence of late-stage functionalization from oxapentacyclic derivative **3**. In a key synthetic step, intermediate **3** could be constructed through an intramolecular [3+2] cycloaddition of intermediate **4** generated *in situ* from the diazo intermediate **5** catalyzed by Rh(II).[10] Compound **5** with correct configuration of the stereochemical centers and all associated functional groups may be obtained from compound **6** with the *cis*-fused 6-6 rings, which in turn could be derived from ester **7** through an intramolecular Diels-Alder reaction followed by deconjugation. Finally, ester **7** could be disconnected into the known compound **8**.[11]

[a] H. J. Zhang, Z. Zhang, C. Tao, Dr. B. Cheng, Dr. Y. Li, Prof. Dr. H. Zhai
The State Key Laboratory of Applied Organic Chemistry,
College of Chemistry and Chemical Engineering, Lanzhou University,
222 Tianshui South Road, Lanzhou 730000, China
E-mail: zhaihb@pkusz.edu.cn
[b] Dr. L. Hu, Dr. Z. Ma, Dr. R. Li, Prof. Dr. H. Zhai
LiKey Laboratory of Synthetic Chemistry of Natural Substances,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032, China
[c] Dr. H. Wang, Prof. Dr. H. Zhai
Guangdong Provincial Key Laboratory of Nano-Micro Materials Research,
Key Laboratory of Chemical Genomics, Shenzhen Graduate School of Peking University
Shenzhen 518055, China
[+] These authors contributed equally.

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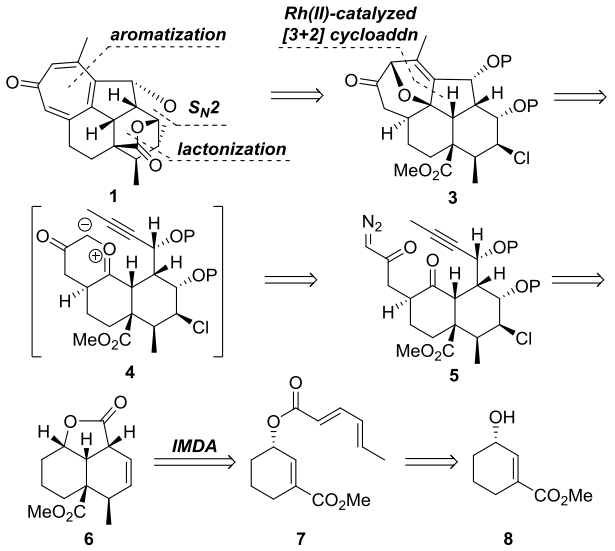
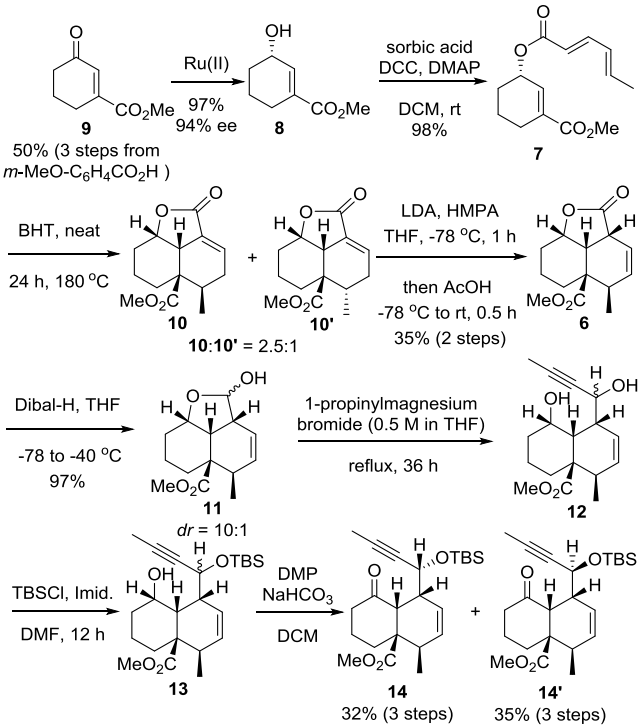


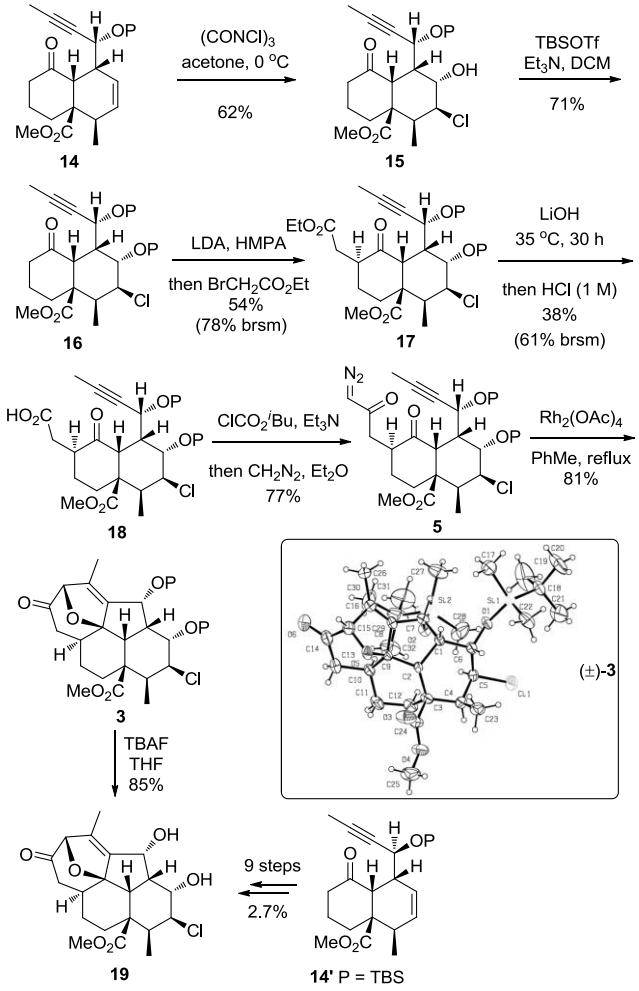
Scheme 1. Retrosynthetic Analysis of (+)-Harringtonolide (**1**).

As delineated in Scheme 2, our synthesis began with enone **9**, accessible from 3-methoxybenzoic acid in three steps (see the Supporting Information). Asymmetric reduction of enone **9** was achieved via a hydride transfer hydrogenation catalyzed by RuCl(p-cymene)[(*S*,*S*)-Ts-DPEN], providing the corresponding allylic alcohol **8** in up to 94% ee and 97% yield.[11] Condensation of alcohol **8** and sorbic acid afforded ester **7**. To our delight, the key intramolecular Diels-Alder reaction and the subsequent spontaneous C=C bond shift proceeded smoothly at 180 °C in the presence of the polymerization inhibitor BHT to afford a diastereomeric mixture of **10** and **10'** in a 2.5:1 ratio.[12] However, the major *endo* compound **10** in the mixture cannot be separated via either column chromatography or recrystallization at this stage. Thus, lactone **6** was obtained by treatment of the diastereomers with LDA and HMPA at -78 °C followed by quenching with AcOH.[13] Selective partial reduction of the lactone moiety in **6** with Dibal-H afforded a mixture of hemiacetals **11** in 97% yield. The chemoselectivity for this step presumably arose from the sterically hindered environment of the methoxycarbonyl functionality. After extensive screening of the nucleophilic reagents, it was found that treatment of the above mixture with 1-propynylmagnesium bromide in refluxing THF furnished propargyl alcohols **12** as a 1:1 diastereomeric mixture. Efforts on optimizing the diastereomeric ratio proved unsuccessful. The propargyl hydroxyl of the crude diols was then protected selectively and the two epimers, **14** and **14'**, was readily separated after oxidation of the unprotected hydroxyl group. The configuration of the propargyl alcohol in **14** was in agreement with that of the natural product via the X-ray crystallographic analyses of several advanced intermediates (in the racemic form, see the Supporting Information for details). Although it was difficult to convert **14'** into **14** in this case, the former (**14'**) may be transformed into intermediate **19** in a similar way.



Scheme 2. Synthesis of Intermediates **14** and **14'**.

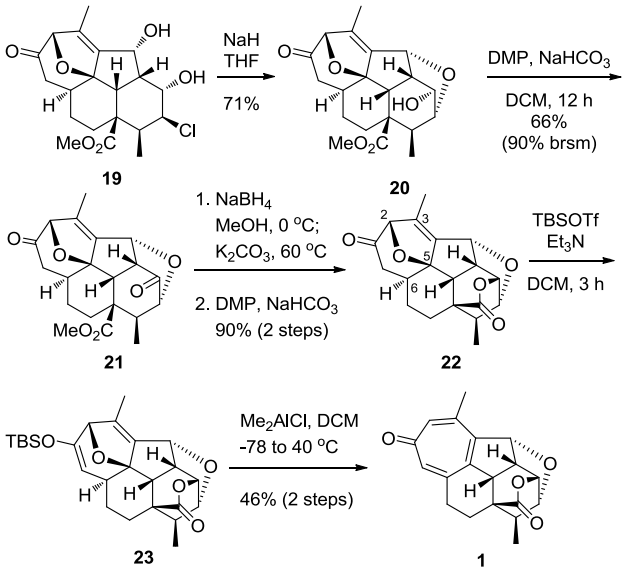
Next, bicycle **14** was employed to investigate the intramolecular [3+2] cycloaddition (i.e., **5** → **3**, Scheme 3). Preliminary studies[14,15] suggested that the carbon-carbon double bond in **14** should be converted prior to the cycloaddition into a chlorohydrin moiety, which could be used to construct the lactone and THF rings present in the target molecule at a late stage. Thus, compound **14** was treated with $(CONCl)_3$ (trichloroisocyanuric acid)[16] to afford chlorohydrin **15** stereoselectively and regioselectively. The Cl^+ species generated *in situ* was attacked by carbon-carbon double bond from the convex face of the *cis*-fused 6-6 rings, and the reactive intermediate thus formed with a three-membered ring was subsequently opened up by nuceophilic attack of water at the less hindered side from the α-face.



Scheme 3. Construction of Oxapentacycle **19** from Compound **14**.

Protection of the hydroxyl group in **15** by TBS led to **16**. The side chain in acyldiazo **5** was constructed through a reaction sequence including alkylation of **16**, saponification of ester **17**, and activation of acid **18** followed by reaction with freshly prepared CH_2N_2.[10] It is worth mentioning that only about half of **17** underwent the saponification to yield acid **18** and the reaction conditions should be controlled rigorously, or isomerization of the *cis*-fused 6-6 rings would occur and the amount of byproducts would increase substantially.[17] As the stereogenic centers in acyldiazo **5** were in agreement with the natural product, the following key intramolecular [3+2] cycloaddition was carried out to assemble the tetracyclic carbon backbone of the natural product. According to the procedure reported by Schmalz,[10] the $Rh_2(OAc)_4$–catalyzed [3+2] cycloaddition took place smoothly in refluxing toluene, furnishing oxapentacycle **3** in 81% yield. The structure was partially confirmed by an X-ray crystallographic analysis of (±)-**3**. Desilylation of **3** with TBAF generated diol **19**. Similar to bicycle **14,** epimer **14**' was also utilized to construct oxapentacycle **19** (see the Supporting Information for more details).

With compound **19** secured, the remaining tasks for the total synthesis of **1** were to install the THF ring, the lactone, and the tropone moiety (Scheme 4). Diol **19** was subjected to a NaH-mediated S_N2 reaction, furnishing the desired cyclic ether **20** as the major product.[18] In order to close the lactone ring, the configuration of the remaining hydroxyl in **20** had to be inverted. Mitsunobu reaction was fruitless with the recovery of the starting material, possibly .due to the steric hindrance present in the molecule; thus, a redox protocol was employed instead. Compound **20** was oxidized to dione **21**, reduction of which followed by lactonization was realized in one-pot fashion. Oxidation of the remaining hydroxyl led to compound **22**, possessing the desired skeleton of the natural product.



Scheme 4. Completion of the Total Synthesis of (+)-Harringtonolide (**1**).

The endgame for the total synthesis of (+)-harringtonolide (**1**) was the formation of the tropone unit. According to the literature procedure,[10c] cleavage of the C5-O bond, elimination of the proton at C6 (adjacent to the tertiary carbenium at C5), and dehydration involving the hydroxyl group at C2 would generate the tropone moiety. In our case, treatment of **22** with Me_2AlCl led to a diene compound.[19] We speculated that preferential elimination of C6-H (adjacent to the tertiary carbenium at C5) would eventually favor the tropone formation. Therefore, the carbonyl group within the seven-membered ring had better be converted into an enol ether in order to further activate the C6-H bond. Based upon the above analysis, exposure of **22** to TBSOTf and Et_3N furnished silyl enol ether **23**, which was used directly in the next step without further purification. Gratifyingly, the tropone unit was smoothly constructed and the natural product (+)-harringtonolide (**1**) was obtained as the major product upon treatment of crude **23** with Me_2AlCl.[20] The spectroscopic data (HRMS; ^1H & ^{13}C NMR) were fully consistent with those reported for the natural product.[1,9]

In summary, we have developed a novel and concise strategy for the enantioselective total synthesis of (+)-harringtonolide (**1**) in 20 steps from the known alcohol **8**.[11] The key transformations include an asymmetric transfer

hydrogenation, an intramolecular Diels-Alder reaction, selective functionalization of the olefin in the presence of an acetylenic group, a rhodium-complex-catalyzed intramolecular [3+2] cycloaddition, and formation of the tropone via a silyl enol ether.

Acknowledgements

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Keywords: diterpenoid • natural product • asymmetric total synthesis • intramolecular [3+2] cycloaddition • tropone

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[14] We attempted to construct the lactone and THF rings in a one-step fashion in the presence of $Yb(OTf)_3$ after the carbon-carbon bond was converted into epoxypropane stereochemically according to the literature,[7e] but a γ-lactone rather than a δ-lactone was constructed on the tetracyclic carbon skeleton (**A**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre (tracking number: 1456997). See the Supporting Information for more details.

[15] We attempted to construct the THF ring on the tetracyclic carbon skeleton after the formation of the tropone moiety. However, a four-membered cyclic ether ring was obtained (**B**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre (tracking number: 1457121). See the Supporting Information for more details.

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[17] In order to identify the stereochemical structure of the by-product in the saponification step, a [3+2] cycloaddition product was obtained (**C**). The X-ray structural data was deposited at the Cambridge Crystallographic Data Centre (tracking number: 1457120). See the Supporting Information for more details.

[18] The epoxypropane compound **D** was obtained as a by-product in 14% yield. See the Supporting Information for more details.

[19] The structure of the by-product was considered to be **E**. See the Supporting Information for more details.

[20] The mechanism for the formation of the tropone was proposed in the Supporting Information.

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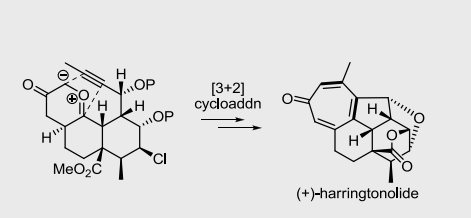

The first asymmetric total synthesis of diterpenoid (+)-haringtonolide has been accomplished. The key features include an asymmetric transfer hydrogenation, an intramolecular Diels-Alder reaction, chemoselective functionalization of the olefin in the presence of an acetylenic group, a rhodium-complex-catalyzed intramolecular [3+2] cycloaddition, and efficient formation of the tropone.

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Total Synthesis of Diterpenoid (+)-Harringtonolide

Supporting Information

Total Synthesis of Diterpenoid (+)-Harringtonolide

Hai-Jun Zhang,[+] *Lin Hu,*[+] *Zhiqiang Ma, Ruining Li, Zhen Zhang, Cheng Tao, Bin Cheng, Yun Li, Huifei Wang, and Hongbin Zhai*[*]

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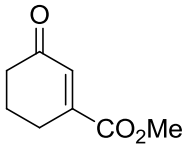
General Information

All reactions involving air or moisture sensitive reagents or intermediates were performed under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2), diisopropylamine (*i*-Pr_2NH), and triethylamine (Et_3N) were freshly distilled from calcium hydride. Toluene and THF were freshly distilled in the presence of the sodium/benzophenone couple. All reagents were reagent grade and used without purification unless otherwise noted. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 ^oC unless otherwise noted. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$. Chemical shifts are referenced to the deuterated solvent ($CDCl_3$, δ = 7.27 ppm and 77.0 ppm for ^1H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ)

relative to tetramethylsilane (TMS, δ = 0.00 ppm). Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br), and coupling constants (J) are reported in Hz. ^{1}H spectra were recorded on a Brucker Avance 400 III spectrometer (400 MHz). ^{13}C NMR spectra were recorded on Brucker Avance 400 III spectrometer at 100 MHz. HPLC was recorded on a Waters 600/2996 spectrometer using CHIRALCEL OJ-H, Column No OJHOCE-EAO30. Optical rotations were recorded on a RUDOLPH A21202-T digital polarimeter at ambient temperature. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer. Melting point was recorded on a SGW®X-4A melting point apparatus. X-ray diffraction was recorded on a Supernova apparatus.

Experimental Procedures and Characterization Data for (+)-Harringtonolide



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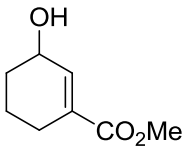
To a 1 L three-necked flask equipped with a stirrer, an ammonia (g) outlet and a cold-finger condenser was added *m*-Anisic acid (70 g, 0.46 mol) and H_2O (90 mL). Ammonia (800 mL) was collected through the condenser containing N_2 (l). Lithium wire (9.6 g, 1.4 mol) was added in small pieces over a period of 30 min and the reaction stirred vigorously for 4 h. The stirring was stopped and the solution was allowed to warm to room temperature overnight. Then KOH (aq, 1.0 M, 580 mL) was added and stirring was restarted. The solution was heated for 3 h at 60 ^{o}C and then cooled to about 10 ^{o}C. Concentrated HCl (72 mL) was added at 0 ^{o}C until the pH = 2. The aqueous solution was extracted with DCM:^{i}PrOH = 3:1. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was used for the next step without further purification.

To a solution of the crude product in MeOH (400 mL) was added $SOCl_2$ (44 g, 0.37 mol) at 0 ^oC. The solution was allowed to warm to rt and stirred overnight. The solution was concentrated under vacuum and the residue was diluted with EtOAc. The solution was washed with $NaHCO_3$ (aq) and brine sequentially. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was used for the next step without further purification.

To a solution of the crude product in $CHCl_3$ (858 mL) was added DBU (56 g, 0.37 mmol) at 0 ^oC. The solution was stirred at rt for 12 h and then washed with 1.0 M HCl (aq) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.29) to give **9** (35 g, 50% over three steps) as a light yellow oil.

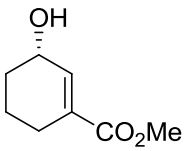
9 ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, J = 2.0 Hz 1H), 3.83 (s, 3H), 2.61 - 2.57 (m, 2H), 2.47 - 2.44 (m, 2H), 2.10 - 2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 167.0, 148.7, 133.1, 52.6, 37.7, 24.8, 22.1; HRMS (ESI) for $C_8H_{10}O_3$ + H (M + H), 155.0703 (Calc), found 155.0705.



(±)-**8**

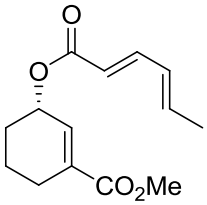
To a solution of **9** (28.4 g, 184 mmol) in MeOH (367 mL) was added $NaBH_4$ (6.99 g, 184 mmol) at 0 ^oC. The mixture was stirred for 10 min before it was quenched with NH_4Cl (aq). The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.22) to give the alcohol (±)-**8** (27.8 g, 98%) as a light yellow oil.

(±)-**8** ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 1.2 Hz, 1H), 4.36 (s, 1H), 3.76 (s, 3H), 2.34 - 2.20 (m, 2H), 1.99 - 1.91 (m, 1H) 1.87 - 1.76 (m, 1H) 1.68 - 1.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 139.7, 132.5, 66.0, 51.8, 31.1, 24.2, 19.1. HRMS (ESI) for $C_8H_{12}O_3$ + Na (M + Na), 179.0679 (Calc), found 179.0676.



8

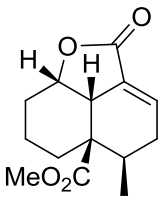
To a solution of **9** (10.2 g, 66.2 mmol) in DCE (200 mL) was added RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (210 mg, 0.331 mmol), NEt_3 (6.70 g, 66.2 mmol) and HCOOH (4.88 g, 106 mmol) sequentially at room temperature and the reaction was monitored by TLC. When the reaction was completed, the solution was washed with $NaHCO_3$ (aq), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give **8** (10.0 g, 97%, *ee* = 94.0%) as a light brown oil. $[\alpha]_D^{18.2}$ = - 46.1 (*c* 1.28, $CHCl_3$).



7

To a solution of alcohol **8** (30.0 g, 192 mmol) in DCM (550 mL) was added sorbic acid (27.6 g, 246 mmol) and DMAP (23.5 g, 192 mmol). After the solution was cooled to 0 ^oC, DCC (50.7 g, 246 mmol) was added. The solution was allowed to warm to rt and stirred overnight at this temperature. The mixture was filtered using a Buchner funnel and washed with DCM three times. The filtrate was washed with $NaHCO_3$ (aq) and 1.0 M HCl (aq) sequentially. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.77) to give **7** (47.1 g, 98%) as a light yellow oil.

7 ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.23 (m, 1H), 6.85 - 6.84 (m, 1H), 6.23 - 6.12 (m, 2H), 5.76 (d, *J* = 15.6 Hz, 1H), 5.49 - 5.46 (m, 1H), 3.75 (s, 3H), 2.40 - 2.22 (m, 2H), 1.98 - 1.90 (m, 1H), 1.86 (d, *J* = 5.2 Hz, 3H), 1.84 - 1.78 (m, 1H), 1.74 - 1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.6, 145.4, 139.6, 136.0, 134.2, 129.7, 118.7, 67.6, 51.8, 27.6, 24.1, 19.0, 18.6. HRMS (ESI) for $C_{14}H_{18}O_4$ + Na (M + Na), 273.1097 (Calc), found 273.1095. $[\alpha]_D^{18.9}$ = - 36.6 (*c* 1.61, $CHCl_3$).

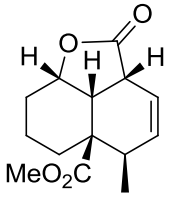


10

The mixture of **7** (57.8 g, 231 mmol) and BHT (5.09 g, 23.1 mmol) was heated to 180 ^{o}C. After 24 h, the mixture was cooled to room temperature and the residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.32) to give a mixture of **10** and the epimer **10'** (40.0 g). ^{1}H NMR spectra indicated that the ratio of **10** and **10'** was 2.5:1.

The pure sample of **10** was obtained after **6** was separated in the next step. To a solution of **6** (0.10 g, 0.40 mmol) in $CHCl_3$ was added DBU (0.091 g). After 1 h, the mixture was deluted with EtOAc and washed with 0.1 M HCl (aq). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.32) to give the compound **10** as a light yellow oil (0.095 g, 95%).

10 ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 7.2, 3.2 Hz, 1H), 4.94 - 4.88 (m, 1H), 3.74 (s, 3H), 3.40 - 3.38 (m, 1H), 2.62 - 2.54 (m, 1H), 2.27 - 2.20 (m, 1H), 2.19 - 2.11 (m, 2H), 1.79 (d, J = 13.2 Hz, 1H), 1.58 - 1.53 (m, 1H), 1.25 - 1.18 (m, 1H), 1.11 - 0.97 (m, 2H), 0.82 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 169.7, 132.8, 126.7, 76.9, 52.2, 49.6, 37.0, 32.8, 30.6, 30.3, 29.0, 19.3, 17.0; HRMS (ESI) for $C_{14}H_{18}O_4$ + H (M + H), 251.1278 (Calc), found 251.1275. $[\alpha]_D^{20.2}$ = - 46.1 (*c* 1.02, $CHCl_3$).

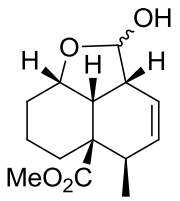


6

To a solution of freshly distilled diisopropylamine (33.9 mL, 240 mmol) in dry THF (114 mL) was added *n*-BuLi (2.5 M in hexane, 80 mL, 200 mmol) dropwise at - 50 ^{o}C. After 20 min, the solution was cooled to - 78 ^{o}C and HMPA (55.7 mL, 320 mmol) was added dropwise. After stirring for 10 min, a solution of **10** and **10'** (20 g, 80 mmol, **10**:**10'** = 2.5:1) in dry THF (40 mL)

was added dropwise. The reaction mixture was stirred at this temperature for 1 h before AcOH (30 mL) was added as quickly as possible. The mixture was warmed to rt in 0.5 h, diluted with EtOAc (500 mL) and washed with $NaHCO_3$ (aq) until pH = 9 in aqueous. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.38) to give the compound **6** as a light yellow oil (10.2 g, 35 % over two steps).

6 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 - 5.83 (m, 2H), 4.93 (dt, J = 6.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.57 - 3.52 (m, 1H), 3.36 (d, J = 10.8 Hz, 1H), 2.24 - 2.18 (m, 1H), 1.95 - 1.89 (m, 1H), 1.81 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.59 - 1.51 (m, 3H), 0.80 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 176.6, 131.3, 119.9, 77.8, 52.1, 45.2, 39.1, 37.2, 32.7, 25.9, 22.0, 17.5, 14.3; HRMS (ESI) for $C_{14}H_{18}O_4$ + Na (M + Na), 273.1097 (Calc), found 273.1093. $[\alpha]_D^{18.6}$ = - 54.1 (*c* 1.09, $CHCl_3$).

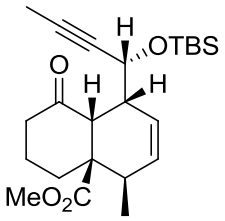


11

To a solution of **6** (5.12 g, 20.5 mmol) in dry THF (100 mL) were added Dibal-H (1.0 M in toluene, 24.6 mL, 24.6 mmol) at - 78 ^{o}C. The mixture was gradually warmed to - 40 ^{o}C over 3 h and then the reaction was quenched with saturated potassium sodium tartrate at - 78 ^{o}C. The mixture was warmed to room temperature and stirred for additional 2 h. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, R_f = 0.27) to give **11** (5.0 g, 97%) as a colorless oil that contains another unseparated diastereomer in a 1:10 ratio.

11 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 - 5.73 (m, 2H), 5.24 (t, J = 2.8 Hz, 1H), 4.70 - 4.66 (m, 1H), 3.71 (s, 3H), 3.34 - 3.24 (m, 2H), 2.85 (dd, J = 10.0, 2.4 Hz, 1H), 2.27 - 2.21 (m, 1H), 1.88 - 1.64 (m, 2H), 1.63 - 1.55 (m, 3H), 1.50 - 1.40 (m, 1H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 131.4, 124.7, 103.1, 76.9, 51.8, 46.8, 46.4, 37.0, 36.7, 27.7, 23.2, 16.9, 15.5; HRMS (ESI) for $C_{14}H_{20}O_4$ + Na (M + Na), 275.1254 (Calc), found 275.1256. $[\alpha]_D^{18.8}$ = - 32.4 (*c*

1.82, $CHCl_3$).



14

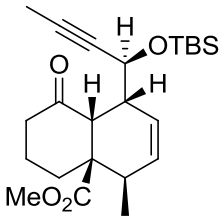
1-Propinylmagnesium bromide (0.5 M in THF, 114 mL, 57 mmol) was added to **11** (4.99 g, 19.8 mmol) at 0 ^oC. The solution was heated to reflux for 36 h. The reaction was quenched with NH_4Cl (aq) at 0 ^oC and extracted with DCM three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to give the crude product as a yellow foam that required no further purification.

To a solution of the crude product in dry DMF (40 mL) was added imidazole (5.39 g, 79.2 mmol) and TBSCl (5.94 g, 39.6 mmol) at room temperature. After being stirred for 12 h, the mixture was diluted with Et_2O (300 mL) and washed with H_2O three times. The organic solution was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R_f = 0.47) to give a mixture of the product.

To a solution of the crude product in dry DCM (40 mL) was added DMP (13.0 g, 30.7 mmol) and $NaHCO_3$ (4.99 g, 59.4 mmol) at room temperature. The mixture was stirred for 24 h before quenching with $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) at 0 ^oC. The mixture was extracted with Et_2O. The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give the product **14** (2.6 g, 32% over three steps, EtOAc : hexanes = 1 : 10, R_f = 0.47**)** and **14'** (2.8 g, 35% over three steps, EtOAc : hexanes = 1 : 10, R_f = 0.36) as light yellow oil.

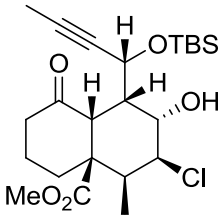
14 ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, J = 10.0 Hz, 1H), 5.49 (dt, J = 10.4, 2.4 Hz, 1H), 4.88 (dd, J = 10.8, 2.4 Hz, 1H), 3.71 (s, 3H), 3.34 (d, J = 4.4 Hz, 1H), 2.45 - 2.27 (m, 5H), 2.10 - 2.03 (m, 2H), 1.91 - 1.82 (m, 1H), 1.79 (d, J = 4.4 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 0.86 (s, 9H); 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 173.3, 131.0, 124.0, 81.2, 80.6, 63.1, 54.7, 51.9, 51.6, 44.2, 42.3, 31.5, 30.9, 25.8, 24.0, 18.0, 14.6, 3.5, - 4.3, - 5.4; HRMS (ESI) for

$C_{23}H_{36}O_4Si$ + Na (M + Na), 427.2275 (Calc), found 427.2283. $[\alpha]_D^{20.2}$ = - 35.4 (*c* 0.96, $CHCl_3$).



14'

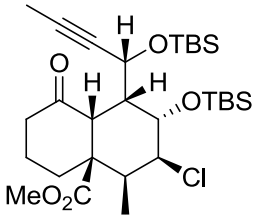
14' ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 4.90 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.70 (s, 3H), 3.42 (d, *J* = 4.4 Hz, 1H), 2.44 (td, *J* = 12.8, 6.8 Hz, 1H), 2.36 - 2.24 (m, 4H), 2.11 - 2.05 (m, 2H), 1.90 - 1.75 (m, 1H), 1.79 (d, *J* = 2.0 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H); 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 173.4, 130.6, 124.6, 81.7, 79.2, 63.9, 54.9, 54.3, 52.0, 43.7, 42.0, 31.3, 30.8, 25.9, 23.8, 18.2, 14.7, 3.5, - 4.5, - 5.0; HRMS (ESI) for $C_{23}H_{36}O_4Si$ + Na (M + Na), 427.2275 (Calc), found 427.2280. $[\alpha]_D^{19.9}$ = - 104.8 (*c* 1.04, $CHCl_3$).



15

To a solution of **14** (573 mg, 1.42 mmol) in acetone (7.1 mL) was added $(CONCl)_3$ (263 mg, 1.14 mmol) at 0 ^{o}C. After being stirred for 0.5 h, the mixture was quenched with $NaHSO_3$ (aq) and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 8, R_f = 0.56) to give the compound **15** (401 mg, 62%) as a colorless foam.

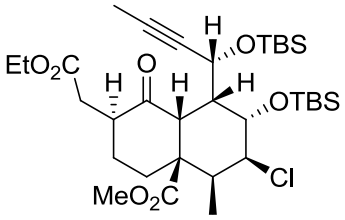
15 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (d, *J* = 8.0 Hz, 1H), 4.80 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.26 - 4.23 (m, 1H), 4.05 (t, *J* = 2.4 Hz, 1H), 4.01 (d, *J* = 4.4 Hz, 1H), 3.73 (s, 3H), 2.80 (dt, *J* = 10.8, 4.0 Hz, 1H), 2.51 - 2.44 (m, 1H), 2.36 - 2.30 (m, 1H), 2.22 - 2.16 (m, 1H), 2.10 - 1.95 (m, 3H), 1.84 (d, *J* = 2.0 Hz, 3H), 1.82 - 1.76 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8, 174.9, 82.3, 78.9, 71.1, 67.2, 61.7, 52.1, 52.0, 50.7, 42.0, 41.2, 34.9, 34.8, 25.8, 22.1, 18.0, 14.5, 3.6, - 4.2, - 5.3; HRMS (ESI) for $C_{23}H_{37}ClO_5Si$ + Na (M + Na), 479.1991 (Calc), found 479.2002. $[\alpha]_D^{20.1}$ = + 3.5 (*c* 1.16, $CHCl_3$).



16

To a solution of **15** (1.69 g, 3.71 mmol) in DCM (19 mL) was added Et_3N (750 mg, 7.42 mmol) and TBSOTf (1.47 g, 5.57 mmol) at 0 ^oC. After the starting material disappeared as monitored by TLC, the mixture was quenched with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R_f = 0.65) to give the compound **16** (1.5 g, 71%) as a colorless foam.

16 ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.29 (t, *J* = 2.4 Hz, 1H), 3.87 (t, *J* = 2.4 Hz, 1H), 3.69 (s, 3H), 3.40 (d, *J* = 4.8 Hz, 1H), 2.67 (ddd, *J* = 10.4, 4.8, 2.0 Hz, 1H), 2.62 - 2.56 (m, 1H), 2.37 - 2.26 (m, 2H), 2.20 - 2.12 (m, 1H), 1.88 (s, 3H), 1.87 - 1.68 (m, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H) 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; 207.7, 175.7, 81.8, 80.7, 72.3, 67.4, 62.9, 51.8, 49.5, 48.3, 43.3, 40.6, 33.9, 33.3, 25.8, 25.7, 18.9, 18.1, 17.9, 14.6, 3.5, - 4.3, - 4.8, - 5.3, - 5.6; HRMS (ESI) for $C_{29}H_{51}ClO_5Si_2$ + Na (M + Na), 593.2856 (Calc), found 593.2865. $[\alpha]_D^{20.0}$ = + 55.5 (*c* 1.55, $CHCl_3$).

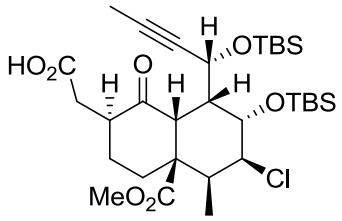


17

To a solution of freshly distilled diisopropylamine (0.66 g, 6.5 mmol) in dry THF (13 mL) was added a solution of *n*-BuLi (2.4 M in hexane, 2.2 mL, 5.2 mmol) dropwise at - 50 ^oC. After 0.5 h, the solution was cooled to - 78 ^oC and then a solution of **16** (1.5 g, 2.6 mmol) in dry THF (13 mL) was added dropwise. After additional 1 h, HMPA (1.4 g, 7.8 mmol) was added dropwise at this temperature. The resulting solution was stirred for 10 min and $BrCH_2CO_2Et$ (0.65 g, 3.9 mmol) was added dropwise. The mixture was allowed to warm to - 40 ^oC and stirred for additional 1 h at

this temperature. The mixture was quenched with NH_4Cl (aq) at the temperature and extracted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R_f = 0.57) to give the compound **17** (0.92 g, 54%) as a colorless oil along with 0.46 g (31%) of recovered starting material.

17 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.34 (s, 1H), 4.15 - 4.06 (m, 2H), 3.91 (s, 1H), 3.68 (s, 3H), 3.37 (d, *J* = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.76 - 2.72 (m, 2H), 2.64 (d, *J* = 16.4 Hz, 1H), 2.43 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.23 - 2.12 (m, 2H), 1.83 (d, *J* = 2.0 Hz, 3H), 1.81 - 1.76 (m, 1H), 1.60 (brs, 1H), 1.37 (d, *J* = 6.4 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 175.3, 172.1, 82.3, 80.5, 72.8, 66.8, 62.8, 60.4, 51.9, 47.9, 46.7, 44.5, 42.3, 36.6, 33.8, 31.5, 26.0, 25.7, 23.3, 18.2, 17.9, 15.0, 14.2, 3.5, - 4.2, - 4.9, - 5.1, - 5.1; HRMS (ESI) for $C_{33}H_{57}ClO_7Si_2$ + Na (M + Na), 679.3224 (Calc), found 679.3233. $[\alpha]_D^{20.0}$ = + 5.7 (*c* 1.22, $CHCl_3$).

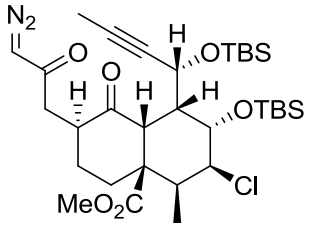


18

To a solution of the crude **17** (0.92 g, 1.4 mmol) in a 4:1 mixture of THF/H_2O (14 mL) was added LiOH (0.29 g, 7.1 mmol). After the solution was stirred vigorously for 36 h at 30 ^{o}C, the mixture was diluted with DCM and washed with 1.0 M HCl (aq). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, R_f = 0.35) to give the compound **18** (0.33 g, 38%) as a colorless solid that contains another unseparated diastereomer in a 1:10 ratio along with 0.36 g (39%) of recovered starting material.

18 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, *J* = 9.6 Hz, 1H), 4.34 (s, 1H), 3.91 (s, 1H), 3.69 (s, 3H), 3.39 (d, *J* = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.74 - 2.70 (m, 3H), 2.53 - 2.46 (m, 1H), 2.26 - 2.18 (m, 2H), 1.88 - 1.75 (m, 1H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.62 (brs, 1H), 1.38 (d, *J* = 5.6 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 209.3, 177.6, 175.2, 82.4, 80.4, 72.8, 66.7, 62.8, 51.9, 47.8, 46.8, 44.6, 41.9, 36.3, 33.9, 31.6, 25.9, 25.7, 23.4, 18.2, 18.0, 15.0, 3.5, - 4.2, - 4.9, - 5.1, - 5.2; HRMS (ESI) for $C_{31}H_{53}ClO_7Si_2$ + Na (M + Na), 651.2911 (Calc), found 651.2907. $[\alpha]_D^{19.7}$ = + 9.0 (*c* 1.22, $CHCl_3$). m.p. = 59 - 61 ^oC

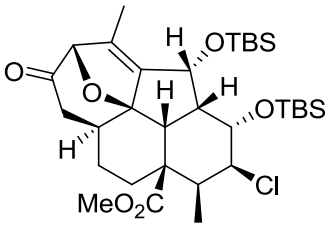


5

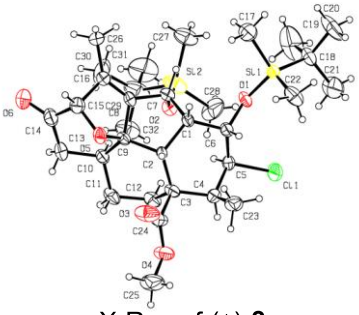
Preparation of CH_2N_2: Under continuously shaking, the precursor compound $CH_3N(NO)CONH_2$ (2.6 g, 25 mmol) was added to a mixture of KOH (40% in H_2O, 8.6 mL) and Et_2O (26 mL) at 0 ^oC. Decantation of the light yellow solution gave the solution of CH_2N_2 (1.0 M in Et_2O). The solution was dried over dusty KOH and used for the next reaction step.

To a solution of acid **18** (0.32 g, 0.50 mmol) in Et_2O (5.0 mL) was added Et_3N (0.15 g, 1.5 mmol) and $ClCO_2{}^iBu$ (0.14 g, 1.0 mmol) sequentially at 0 ℃. After 0.5 h, a freshly prepared solution of CH_2N_2 in Et_2O (1.0 M, 26 mL) was added to the mixture at 0 ^oC. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, R_f = 0.46) to give the compound **5** (0.25 g, 77%) as a yellow foam that contains another unseparated diastereomer in a 1:10 ratio.

5 ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 4.33 (s, 1H), 3.90 (s, 1H), 3.68 (s, 3H), 3.38 (d, *J* = 5.2 Hz, 1H), 2.94 (brs, 1H), 2.74 - 2.71 (m, 3H), 2.40 - 2.37 (m, 1H), 2.22 - 2.12 (m, 2H), 1.83 (d, *J* = 1.6 Hz, 3H), 1.81 - 1.70 (m, 1H), 1.58 - 1.55 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 192.8, 175.3, 82.4, 80.4, 72.7, 66.8, 62.8, 54.8, 51.9, 47.9, 46.8, 44.4, 42.9, 42.8, 34.0, 31.4, 25.9, 25.6, 23.3, 18.2, 17.9, 15.0, 3.5, - 4.1, - 4.9, - 5.1, - 5.2; HRMS (ESI) for $C_{32}H_{53}ClN_2O_6Si_2$ + Na (M + Na), 675.3023 (Calc), found 675.3016. $[\alpha]_D^{21.2}$ = - 5.5 (*c* 1.09, $CHCl_3$).



3

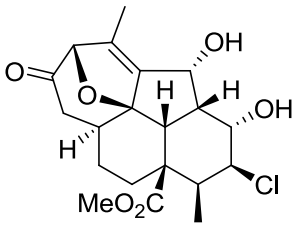


X-Ray of (±)-**3**
ccdc: 1457123

To a suspension of $Rh_2(OAc)_4$ (0.016 g, 0.037 mmol) in toluene (7.4 mL) was added a solution of diazoketone **5** (0.24 g, 0.37 mmol) in toluene (7.4 mL) over 0.5 h via a syringe pump under refluxing. After additional 0.5 h, the solution was cooled to rt and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, R_f = 0.41) to afford **3** (0.19 g, 81%) as a colorless solid.

3 ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, J = 3.6 Hz, 1H), 4.68 (dd, J = 10.8, 3.6 Hz, 1H), 4.62 (s, 1H), 4.11 - 4.07 (m, 1H), 3.75 (s, 3H), 3.56 (d, J = 11.6 Hz, 1H), 2.89 - 2.83 (m, 1H), 2.66 - 2.45 (m, 4H), 2.11 (td, J = 12.8, 2.8 Hz, 1H), 1.96 (d, J = 11.6 Hz, 1H), 1.79 (s, 3H), 1.64 (brs, 1H), 1.12 - 1.04 (m, 1H), 0.99 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 176.2, 149.5, 127.3, 95.2, 93.8, 69.8, 67.8, 63.4, 52.7, 52.4, 50.1, 44.6, 44.3, 39.8, 39.3, 30.7, 27.9, 26.3, 25.7, 18.7, 18.1, 11.3, 11.2, - 4.3, - 4.4, - 4.6, - 4.9; HRMS (ESI) for $C_{32}H_{53}ClO_6Si_2$ + Na (M + Na), 647.2961 (Calc), found 647.2953. $[\alpha]_D^{21.3}$ = - 104.6 (*c* 1.08, $CHCl_3$).

m.p. = 52 - 54 ^{o}C



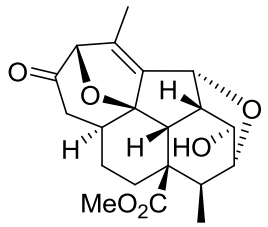
19

To a solution of **3** (0.17 g, 0.27 mmol) in dry THF (11 mL) was added TBAF (0.42 g, 1.4 mmol) at room temperature. The solution was quenched with H_2O until the starting material disappeared as monitored by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified

by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.31) to give the compound **19** (91 mg, 85%) as a colorless solid.

19 ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.65 (s, 1H), 4.48 (dd, *J* = 11.2, 3.6 Hz, 1H), 4.14 (td, *J* =10.4, 2.8 Hz, 1H), 3.77 (s, 3H), 3.60 (d, *J* = 12.8 Hz, 1H), 3.18 - 3.12 (m, 1H), 3.00 (d, *J* = 2.4 Hz, 1H), 2.77 (d, *J* = 3.2 Hz, 1H), 2.62 (d, *J* = 2.4 Hz, 1H), 2.60 (d, *J* = 2.0 Hz, 1H), 2.52 - 2.42 (m, 2H), 2.05 - 2.02 (m, 2H), 1.81 (s, 3H), 1.70 - 1.62 (m, 1H), 1.15 - 1.00 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.7, 147.3, 130.2, 95.1, 94.1, 70.4, 67.8, 66.6, 52.6, 50.7, 49.0, 44.6, 43.5, 39.9, 39.1, 30.7, 28.3, 11.3, 10.7; HRMS (ESI) for $C_{20}H_{25}ClO_6$ + Na (M + Na), 419.1232 (Calc), found 419.1225. $[\alpha]_D^{21.6}$ = - 192.7 (*c* 1.10, $CHCl_3$).

m.p. = 156 - 158 ^{o}C

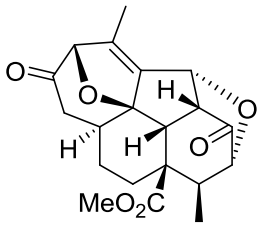


20

To a solution of **19** (76 mg, 0.19 mmol) in dry THF (7.0 mL) was added NaH (60% dispersion in mineral oil, 76 mg, 1.9 mmol) at 0 ^{o}C. The solution was allowed to warm to room temperature over 2 h. While the starting material was disappeared, the solution was quenched with H_2O and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.25) to give the compound **20** (49 mg, 71%) as a colorless solid.

20 ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, *J* = 2.4 Hz, 1H), 4.54 (s, 1H), 4.38 (d, *J* = 1.2 Hz, 1H), 3.88 (s, 1H), 3.69 (s, 3H), 3.03 (q, *J* = 9.6 Hz, 2H), 2.91 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.59 - 2.52 (m, 1H), 2.25 (q, *J* = 7.6 Hz, 1H), 2.18 (dd, *J* = 18.8, 3.6 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.91 - 1.86 (m, 1H), 1.89 (s, 3H), 1.84 - 1.70 (m, 2H), 1.59 (brs, 1H), 1.06 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 177.6, 147.3, 134.1, 95.7, 94.0, 88.4, 74.9, 72.3, 54.3, 51.9, 46.9, 45.5, 43.3, 42.4, 31.3, 28.9, 26.0, 16.3, 11.5; HRMS (ESI) for $C_{20}H_{24}O_6$ + Na (M + Na), 383.1465 (Calc), found 383.1457. $[\alpha]_D^{18.5}$ = - 309.7 (*c* 1.03, $CHCl_3$).

m.p. = 253 - 255 °C

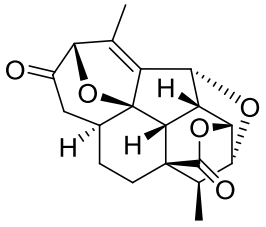


21

To a solution of **20** (35 mg, 0.098 mmol) in DCM (4.0 mL) was added $NaHCO_3$ (0.16 g, 1.9 mmol) and DMP (0.21 g, 0.49 mmol). The mixture was stirred for 24 h before quenching with $Na_2S_2O_3$ (aq) and $NaHCO_3$ (aq). The solution was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.65) to give the compound **21** (23 mg, 66%) as a colorless solid along with 9 mg (25%) of recovered starting material.

21 ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, J = 2.4 Hz, 1H), 4.58 (s, 1H), 3.65 (s, 3H), 3.60 (s, 1H), 3.21 (d, J = 9.6 Hz, 1H), 3.05 (dd, J = 9.2, 2.4 Hz, 1H), 2.96 (dd, J = 18.8, 8.4 Hz, 1H) 2.81 - 2.73 (m, 1H), 2.57 (q, J = 7.6 Hz, 1H), 2.28 (dd, J = 18.4, 3.6 Hz, 1H), 2.15 - 2.06 (m, 1H), 2.00 - 1.91 (m, 2H), 1.89 (s, 3H), 1.86 - 1.82 (m, 1H), 0.98 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 202.5, 175.0, 147.7, 135.8, 95.3, 94.4, 79.8, 72.4, 53.9, 53.3, 51.7, 48.6, 43.1, 42.4, 31.4, 27.5, 25.9, 15.0, 11.7; HRMS (ESI) for $C_{20}H_{22}O_6$ + Na (M + Na), 381.1309 (Calc), found 381.1302. $[\alpha]_D^{18.4}$ = - 245.8 (*c* 1.20, $CHCl_3$).

m.p. = 165 - 167 °C



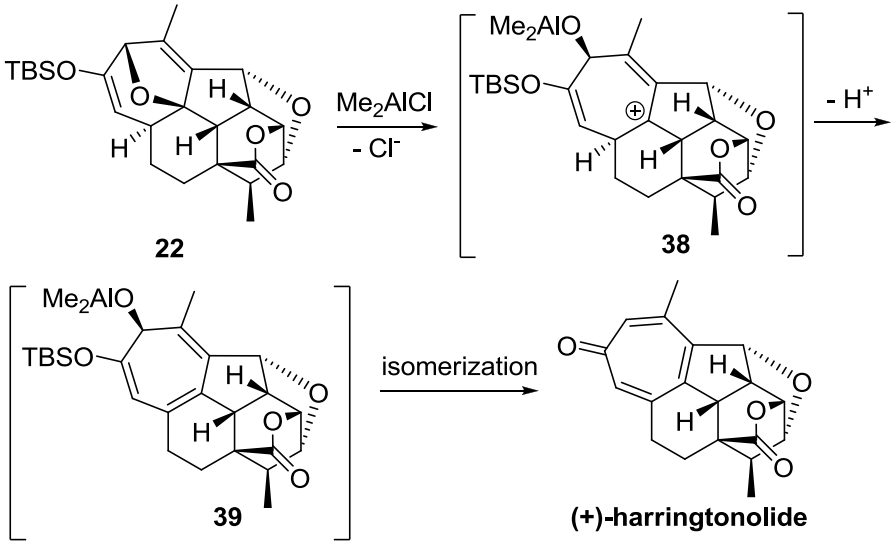
22

To a solution of **21** (23.2 mg, 0.0648 mmol) in MeOH (2.6 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at 0 °C. After 5 min, K_2CO_3 (45 mg, 0.32 mmol) was added to the mixture. The mixture was warmed to 60 °C and stirred for 20 min before quenching with H_2O. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered

and concentrated under vacuum. The crude product was used for the next reaction without further purification.

To a solution of the crude product in DCM (2.6 mL) was added $NaHCO_3$ (54 mg, 0.65 mmol) and DMP (0.14 g, 0.32 mmol) at rt. The mixture was stirred until the starting material disappeared as indicated by TLC. The mixture was quenched with $Na_2S_2O_3$ (aq) and $NaHCO_3$ (aq) and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.44) to give the compound **22** (19.1 mg, 90% over three steps) as a colorless foam.

22 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (t, J = 6.0 Hz, 1H), 4.82 (d, J = 4.0 Hz, 1H), 4.50 (s, 1H), 4.07 (d, J = 6.0 Hz, 1H), 3.28 - 3.23 (m, 1H), 2.88 - 2.81 (m, 1H), 2.52 (d, J = 10.0 Hz, 1H), 2.46 - 2.36 (m, 2H), 2.27 - 2.17 (m, 2H), 1.96 - 1.89 (m, 2H), 1.92 (s, 3H), 1.85 - 1.76 (m, 1H), 0.97 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 174.0, 149.0, 142.3, 95.6, 92.8, 78.3, 77.8, 75.1, 47.8, 45.2, 43.7, 42.7, 41.3, 32.7, 26.5, 20.3, 15.0, 12.5; HRMS (ESI) for $C_{19}H_{20}O_5$ + H (M + H), 329.1384 (Calc), found 329.1390. $[\alpha]_D^{21.2}$ = - 364.2 (c 1.85, $CHCl_3$).



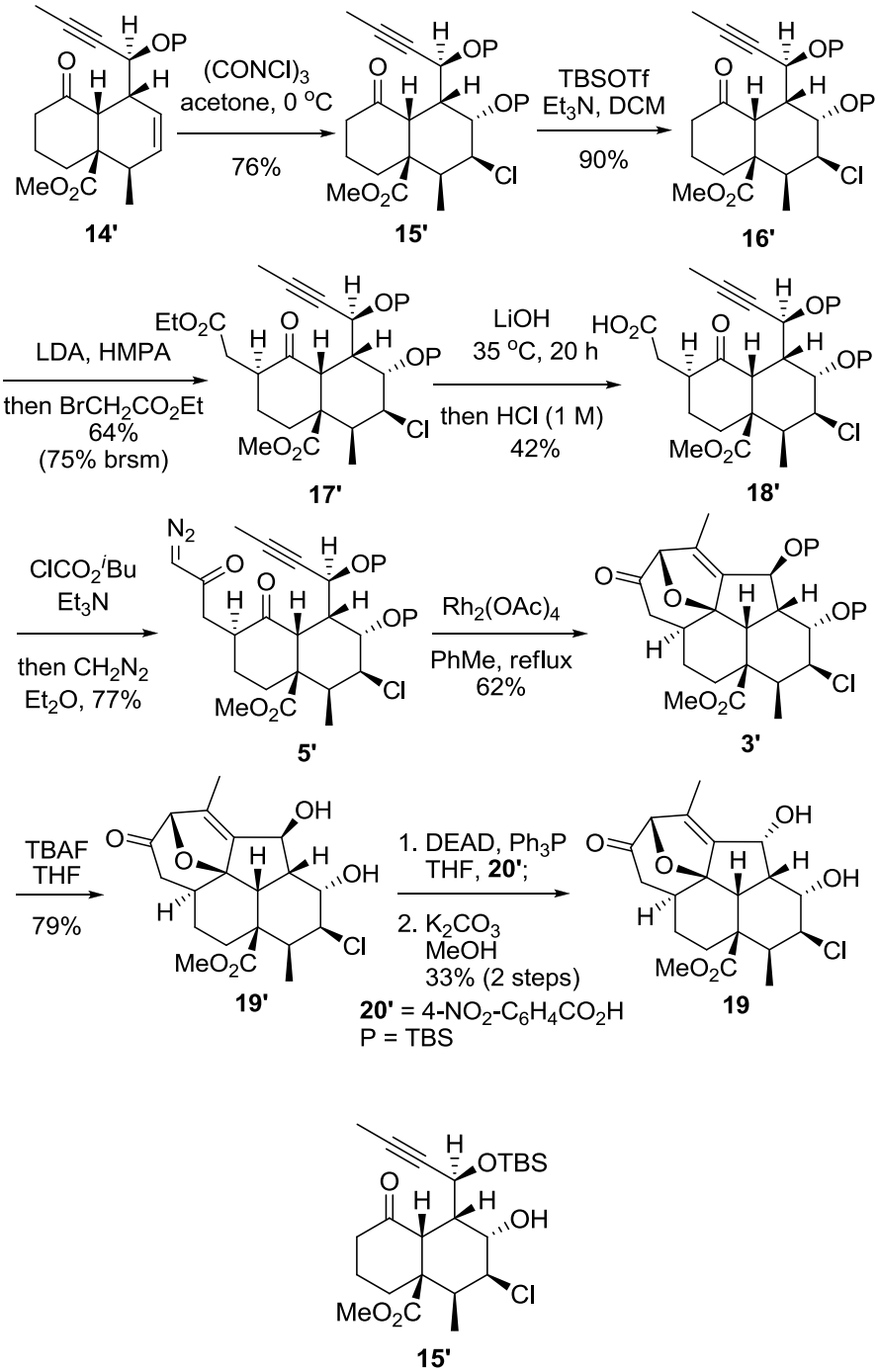
To a solution of **22** (13.4 mg, 0.0409 mmol) in DCM (0.8 mL) was added Et_3N (29 μL, 0.21 mmol) and TBSOTf (38 μL, 0.16 mmol) at room temperature. When the starting material disappeared, the mixture was quenched with H_2O. The solution was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was used for the next reaction without further purification.

To a solution of the crude product in DCM (3.0 mL) was added Me_2AlCl (0.9 M in heptane, 2.3 mL, 2.1 mmol) at - 78 ^oC. The solution was allowed to warm to 40 ^oC. After the starting material disappeared as indicated by TLC, the solution was cooled to - 78 ^oC again and quenched with MeOH dropwise at the temperature. Then the solution was warmed to room temperature. The mixture was diluted with DCM, washed with NH_4Cl (aq) and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.15) to give natural product (+)-harringtonolide (5.8 mg, 46% over two steps) as a light yellow solid.

(+)-**harringtonolide** ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.90 (s, 1H), 5.36 (t, J = 2.8 Hz, 1H), 5.21 (t, J = 5.2 Hz, 1H), 3.99 (d, J = 5.6 Hz, 1H), 3.42 - 3.36 (m, 2H), 2.91 - 2.82 (m, 2H), 2.66 - 2.60 (m, 1H), 2.37 (d, J = 0.8 Hz, 3H), 1.76 (q, J = 7.6 Hz, 1H), 1.36 - 1.28 (m, 1H), 0.90 (d, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.5, 173.5, 145.8, 145.6, 145.0, 143.6, 141.6, 139.3, 86.0, 80.0, 79.7, 49.9, 45.8, 41.8, 40.0, 32.3, 23.9, 22.4, 14.7; HRMS (ESI) for $C_{19}H_{18}O_4$ + H (M + H), 311.1278 (Calc), found 311.1283. $[\alpha]_D^{17.8}$ = + 81.0 (*c* 1.16, $CHCl_3$).

m.p. = 255 - 258 ^oC

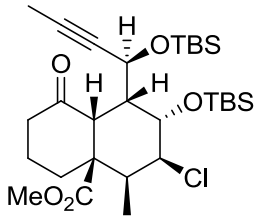
Construction of Oxapentacycle 19 from Compound 14'



To a solution of **14'** (504 mg, 1.25 mmol) in acetone (5.6 mL) was added $(CONCl)_3$ (0.23 g, 1.0 mol) at 0 °C. After being stirred for 0.5 h, the mixture was quenched with $NaHSO_3$ (aq) and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes

= 1 : 8, R_f = 0.53) to give the compound **15'** (434 mg, 76%) as a colorless foam that contains another unseparated diastereomer in a 1:16 ratio.

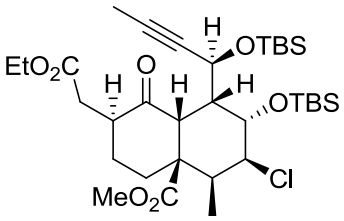
15' ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, J = 7.2 Hz, 1H), 4.85 (dd, J = 10.4, 2.4 Hz, 1H), 4.17 - 4.13 (m, 1H), 4.04 (t, J = 2.8 Hz, 1H), 4.01 (d, J = 4.0 Hz, 1H), 3.74 (s, 3H), 2.70 (dt, J = 10.0, 4.0 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.38 - 2.32 (m, 1H), 2.22 - 2.17 (m, 1H), 2.11 - 1.93 (m, 3H), 1.84 (d, J = 2.0 Hz, 3H), 1.80 - 1.76 (m, 1H), 1.30 (d, J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4, 175.1, 82.4, 79.0, 69.4, 67.0, 61.2, 53.0, 52.2, 52.2, 41.8, 40.8, 34.8, 34.5, 25.8, 21.8, 18.2, 14.6, 3.6, - 4.5, - 5.2; HRMS (ESI) for $C_{23}H_{37}ClO_5Si$ + Na (M + Na), 479.1991 (Calc), found 479.1997. $[\alpha]_D^{19.8}$ = - 111.1 (*c* 1.26, $CHCl_3$).



16'

To a solution of **15'** (1.01 g, 2.21 mmol) in DCM (11 mL) was added Et_3N (671 mg, 6.63 mmol) and TBSOTf (1.46 g, 5.53 mmol) at 0 ^{o}C. After being stirred for 3 h, the mixture was quenched with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R_f = 0.63) to give the compound **16'** (1.1g, 90%) a colorless foam.

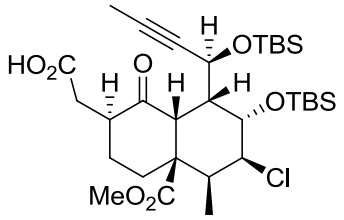
16' ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, J = 10.0, 2.4 Hz, 1H), 4.30 (dd, J = 2.8, 1.6 Hz, 1H), 3.89 (t, J = 2.8 Hz, 1H), 3.71 (s, 3H), 3.36 (d, J = 4.8 Hz, 1H), 2.70 - 2.61 (m, 2H), 2.43 - 2.31 (m, 2H), 2.24 - 2.15 (m, 1H), 1.89 - 1.76 (m, 2H), 1.82 (d, J = 2.0 Hz, 3H), 1.67 (td, J = 13.6, 5.2 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.13 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 176.0, 82.1, 79.4, 70.5, 67.1, 62.9, 51.9, 51.4, 49.3, 43.8, 39.5, 33.1, 32.5, 26.1, 25.7, 18.4, 18.2, 17.9, 14.5, 3.8, - 3.1, - 3.9, - 4.7, - 5.2; HRMS (ESI) for $C_{29}H_{51}ClO_5Si_2$ + Na (M + Na), 593.2856 (Calc), found 593.2846. $[\alpha]_D^{19.7}$ = - 25.9 (*c* 1.16, $CHCl_3$).



17'

To a solution of freshly distilled diisopropylamine (1.08 g, 10.7 mmol) in dry THF (21 mL) was added a solution of *n*-BuLi (2.5 M in hexane, 3.4 mL, 8.5 mmol) dropwise at - 50 ^{o}C. After 0.5 h, the solution was cooled to - 78 ^{o}C and then a solution of **16'** (2.4 g, 4.3 mmol) in dry THF (21 mL) was added dropwise. After additional 1 h, HMPA (2.29 g, 12.8 mmol) was added dropwise at the temperature. The resulting solution was stirred for 10 min and $BrCH_2CO_2Et$ (1.06 g, 6.39 mmol) was added dropwise. The mixture was allowed to warm to - 40 ^{o}C and stirred for additional 1 h at the temperature. The mixture was quenched with NH_4Cl (aq) at the temperature, extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R_f = 0.62) to give the compound **17'** (1.80 g, 64%) as a colorless oil along with 0.36 g (15%) of recovered starting material.

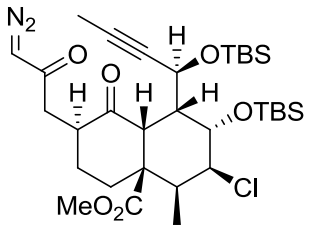
17' ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.31 (q, *J* = 1.6 Hz, 1H), 4.13 - 4.08 (m, 2H), 3.91 (t, *J* = 2.8 Hz, 1H), 3.71 (s, 3H), 3.47 (d, *J* = 4.8 Hz, 1H), 2.88 - 2.81 (m, 1H), 2.74 - 2.66 (m, 3H), 2.42 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.21 - 2.11 (m, 1H), 2.09 - 2.03 (m, 1H), 1.92 - 1.87 (m, 1H), 1.85 (d, *J* = 2.0 Hz, 3H), 1.61 - 1.55 (m, 1H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.83 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 175.5, 172.0, 82.5, 79.6, 70.6, 66.5, 62.6, 60.5, 51.9, 49.5, 48.2, 44.0, 42.5, 36.8, 34.2, 31.7, 26.1, 25.6, 23.4, 18.2, 17.9, 14.9, 14.2, 3.8, - 3.1, - 3.8, - 4.8, - 5.1; HRMS (ESI) for $C_{33}H_{57}ClO_7Si_2$ + Na (M + Na), 679.3224 (Calc), found 679.3232. $[\alpha]_D^{19.7}$ = - 61.5 (*c* 0.95, $CHCl_3$).



18'

To a solution of the crude **17'** (1.7 g, 2.6 mmol) in a 4:1 mixture of THF/H_2O (26 mL) was added LiOH (551 mg, 13.1 mmol). After the mixture was stirred vigorously for 36 h at 30 ^oC, the mixture was diluted with DCM and washed with 1.0 M HCl (aq). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, R_f = 0.21) to give the compound **18'** (0.65 g, 42%) as a colorless foam that contains another unseparated diastereomer in a 1:14 ratio.

18' ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 - 4.96 (m, 1H), 4.32 (s, 1H), 3.91 (s, 1H), 3.72 (s, 3H), 3.47 (d, *J* = 5.2 Hz, 1H), 2.86 - 2.84 (m, 1H), 2.80 - 2.69 (m, 3H), 2.46 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.25 - 2.14 (m, 1H), 2.11 - 2.02 (m, 1H), 1.91 - 1.81 (m, 1H), 1.86 (d, *J* = 1.6 Hz, 3H), 1.63 - 1.58 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 177.5, 175.5, 82.6, 79.5, 70.6, 66.4, 62.6, 52.0, 49.5, 48.1, 44.1, 42.2, 36.4, 34.3, 31.7, 26.1, 25.6, 23.5, 18.2, 17.9, 15.0, 3.8, - 3.1, - 3.8, - 4.9, - 5.1; HRMS (ESI) for $C_{31}H_{53}ClO_7Si_2$ + Na (M + Na), 651.2911 (Calc), found 651.2919. $[\alpha]_D^{21.8}$ = - 54.7 (*c* 1.17, $CHCl_3$).



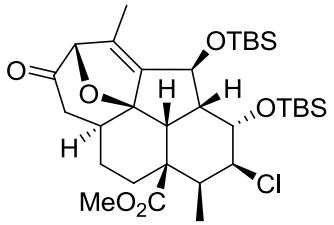
5'

Preparation of CH_2N_2: under continuously shaking, the precursor compound $CH_3N(NO)CONH_2$ (3.4 g, 33 mmol) was added to a mixture of KOH (40% in H_2O, 11.2 mL) and Et_2O (34 mL) at 0 ^oC. Decantation of the light yellow solution gave the solution of CH_2N_2 (1.0 M in Et_2O). The solution was dried over dusty KOH and used for the next reaction step.

To a solution of acid **18'** (0.41 g, 0.65 mmol) in Et_2O (6.5 mL) was added Et_3N (0.20 g, 2.0 mmol) and $ClCO_2{}^iBu$ (0.18 g, 1.3 mmol) sequentially at 0 ^oC. After 0.5 h, a freshly prepared solution of CH_2N_2 (34 mL, 1.0 M in Et_2O) was added to the mixture at 0 ^oC. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica

gel (EtOAc : hexanes = 1 : 4, R_f = 0.23) to give the compound **5'** (0.33 g, 77%) as a yellow oil that contains another unseparated diastereomer in a 1:14 ratio.

5' ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 1H), 4.99 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.31 (d, *J* = 1.6 Hz, 1H), 3.90 (t, *J* = 2.8 Hz, 1H), 3.70 (s, 3H), 3.46 (d, *J* = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.74 - 2.67 (m, 3H), 2.41 (brs, 1H), 2.18 - 2.12 (m, 1H), 2.10 - 2.04 (m, 1H), 1.91 - 1.81 (m, 1H), 1.85 (d, *J* = 2.0 Hz, 3H), 1.60 - 1.55 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 192.7, 175.5, 82.4, 79.6, 70.6, 66.5, 62.6, 54.7, 51.9, 49.5, 48.1, 44.1, 42.8, 42.8, 34.2, 31.6, 26.1, 25.6, 23.5, 18.2, 17.9, 14.9, 3.8, - 3.1, - 3.8, - 4.8, - 5.2; HRMS (ESI) for $C_{32}H_{53}ClN_2O_6Si_2$ + Na (M + Na), 675.3023 (Calc), found 675.3032. $[\alpha]_D^{19.7}$ = - 47.6 (*c* 1.37, $CHCl_3$).

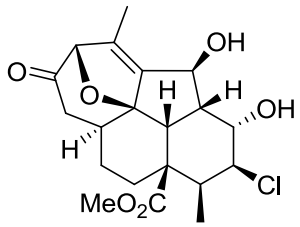


3'

To a suspension of $Rh_2(OAc)_4$ (0.022 g, 0.050 mmol) in toluene (10 mL) was added a solution of diazoketone **5'** (0.33 g, 0.50 mmol) in toluene (10 mL) over 0.5 h via a syringe pump under refluxing. After additional 0.5 h, the solution was cooled to rt and the solvent was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, R_f = 0.57) to afford **3'** (0.20 g, 62%) as a colorless solid.

3' ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.57 (s, 1H), 4.25 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.19 (d, *J* = 4.8 Hz, 1H), 3.69 (s, 3H), 3.47 (d, *J* = 12.0 Hz, 1H), 2.93 (dq, *J* = 12.0, 2.4 Hz, 1H), 2.83 (dd, *J* = 18.4, 8.4 Hz, 1H), 2.55 - 2.50 (m, 2H), 2.31 - 2.21 (m, 1H), 2.12 (d, *J* = 18.4 Hz, 1H), 1.87 - 1.83 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.73 - 1.65 (m, 1H), 1.51 - 1.42 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 175.8, 149.7, 135.1, 96.2, 96.1, 75.0, 68.1, 65.0, 52.6, 52.1, 46.6, 41.3, 38.2, 35.1, 30.9, 28.0, 27.3, 25.7, 25.6, 18.0, 17.9, 14.2, 11.5, - 3.6, - 4.1, - 4.7, - 4.8; HRMS (ESI) for $C_{32}H_{53}ClO_6Si_2$ + Na (M + Na), 647.2961 (Calc), found 647.2973. $[\alpha]_D^{22.0}$ = - 213.5 (*c* 1.26, $CHCl_3$).

m.p. = 36 - 37 °C

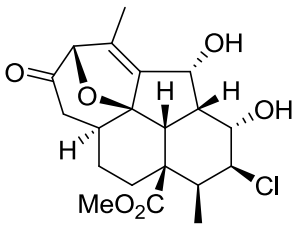


19'

To a solution of **3'** (0.18 g, 0.29 mmol) in dry THF (12 mL) was added TBAF (0.28 g, 0.87 mmol) at room temperature. The solution was quenched with H_2O until the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.33) to give the compound **19'** (92 mg, 79%) as a colorless solid.

19' ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, J = 10.8 Hz, 1H), 4.63 (s, 1H), 4.34 (dd, J = 10.8, 3.2 Hz, 1H), 4.19 (t, J =10.0 Hz, 1H), 3.77 (s, 3H), 3.67 (d, J = 13.2 Hz, 1H), 3.63 (s, 1H), 3.10 - 3.01 (m, 1H), 2.76 (s, 1H), 2.64 - 2.52 (m, 2H), 2.45 - 2.39 (m, 1H), 2.15 - 2.11 (m, 1H), 1.87 (d, J = 1.6 Hz, 3H), 1.80 - 1.72 (m, 1H), 1.68 - 1.54 (m, 2H), 1.07 (q, J = 12.8 Hz, 1H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 175.1, 146.7, 127.4, 94.4, 90.9, 70.4, 70.2, 65.2, 52.7, 50.5, 48.3, 43.5, 43.4, 42.1, 38.0, 32.1, 27.8, 10.5, 9.8; HRMS (ESI) for $C_{20}H_{25}ClO_6$ + Na (M + Na), 419.1232 (Calc), found 419.1238. $[\alpha]_D^{22.2}$ = - 225.7 (*c* 1.13, $CHCl_3$).

m.p. = 78 - 81 °C



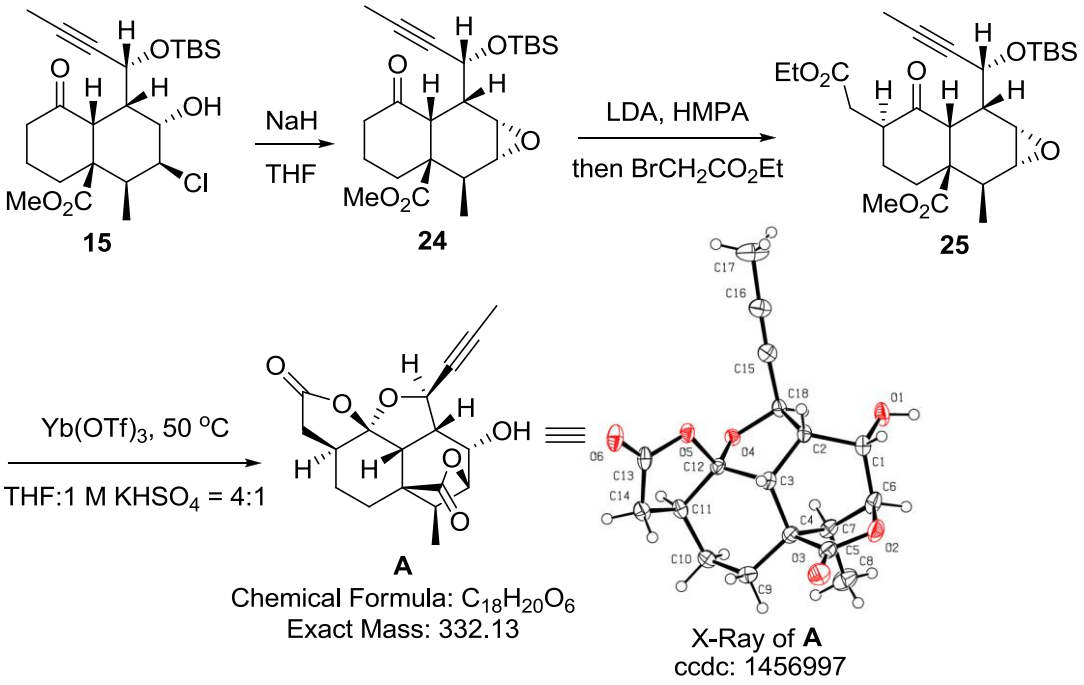
19

To a solution of **19'** (78 mg, 0.20 mmol) in dry THF (4.0 mL) was added Ph_3P (0.16 g, 0.59 mmol), 4-NO_2-$C_6H_4CO_2H$ (99 mg, 0.59 mmol) and DEAD (0.10 g, 0.59 mmol) sequentially at room temperature. The solution was quenched with H_2O until the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by

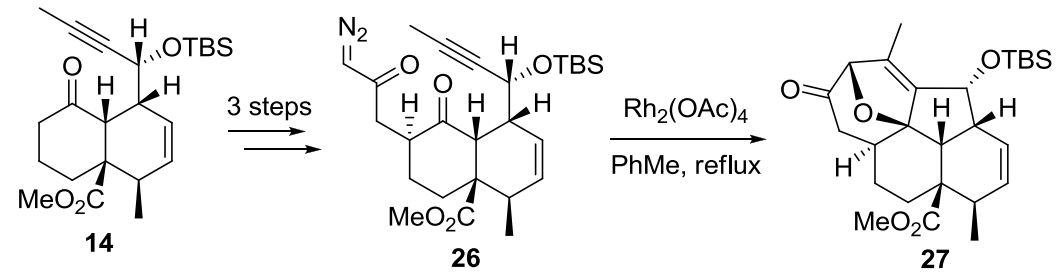
flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R_f = 0.40) to give a crude product used for the next step.

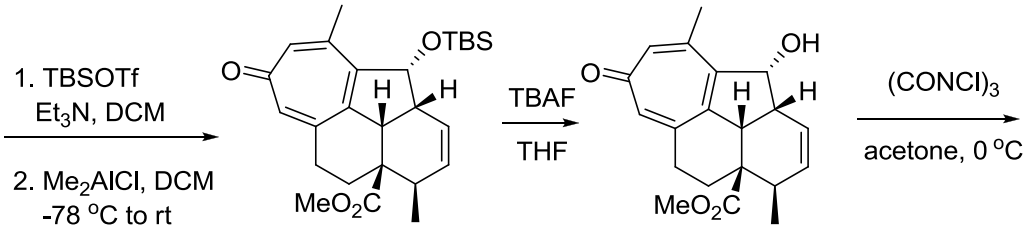
To a solution of the crude product in MeOH (2.0 mL) was added K_2CO_3 (54 mg, 0.59 mmol). The solution was quenched with H_2O until the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give **19** (25 mg, 33 % over two steps) as a colorless solid. The ^{1}H NMR and ^{13}C NMR was in agreement with those measured above.

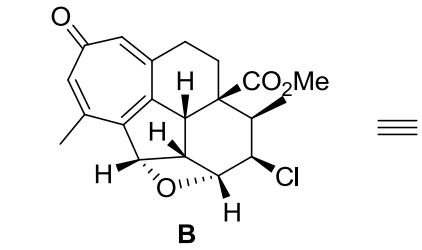
Some Important Intermediates (A、B、C、D and E)



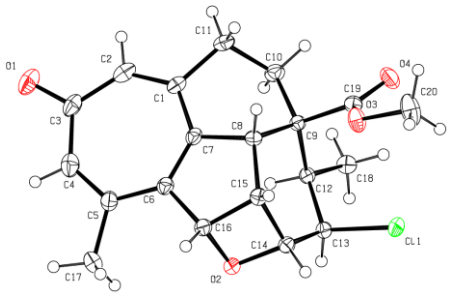
A ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 - 5.24 (m, 1H), 4.36 - 4.30 (m, 1H), 4.28 (s, 1H), 3.42 (q, J = 8.4 Hz, 1H), 2.93 - 2.86 (m, 1H), 2.71 - 2.55 (m, 3H), 2.50 - 2.41 (m, 2H), 1.93 - 1.85 (m, 4H), 1.80 - 1.73 (m, 1H), 1.71 - 1.58 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 172.5, 116.7, 85.2, 83.0, 78.8, 72.4, 66.8, 46.9, 45.7, 45.6, 37.1, 34.2, 33.1, 19.3, 19.2, 13.3, 3.9.





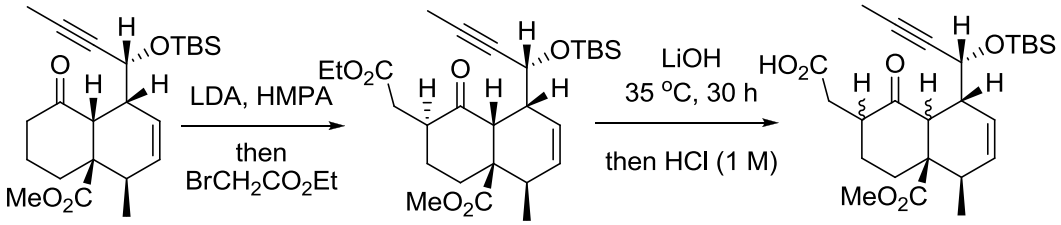


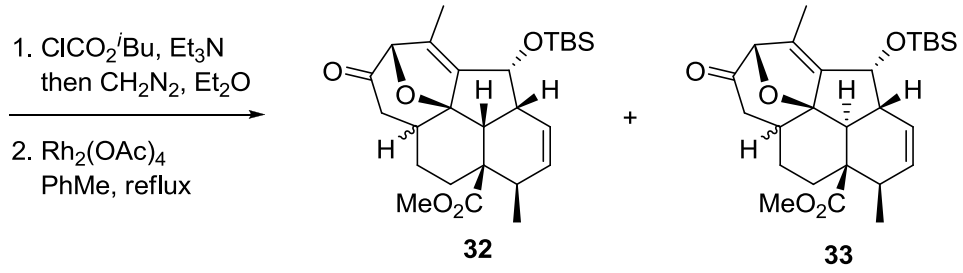
Chemical Formula: $C_{20}H_{21}ClO_4$
Exact Mass: 360.11

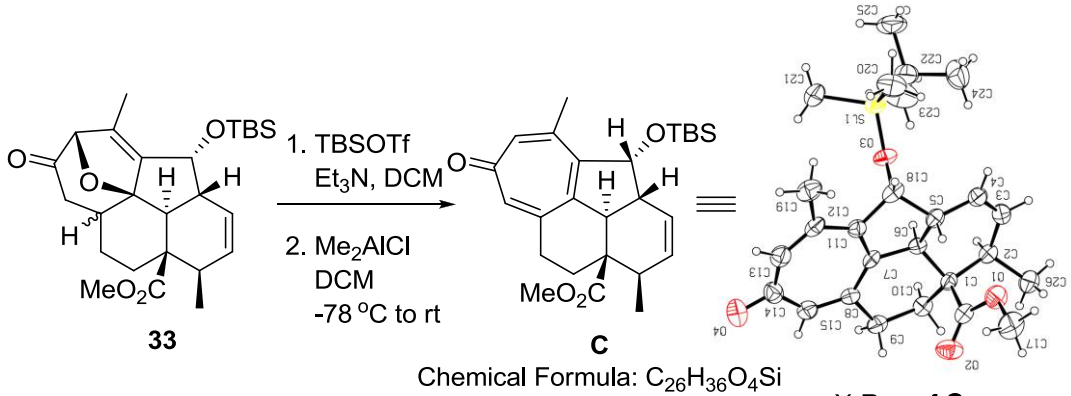


X-Ray of **B**
ccdc: 1457121

B ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.89 (s, 1H), 5.95 (d, J = 5.6 Hz, 1H), 5.20 (dd, J = 7.2, 2.8 Hz, 1H), 3.96 (t, J =2.8 Hz, 1H), 3.90 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 3.69 - 3.63 (m, 1H), 2.67 - 2.43 (m, 3H), 2.28 (s, 3H), 1.69 - 1.65 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H).





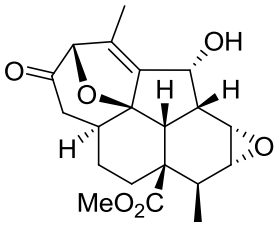


33 **C**

Chemical Formula: $C_{26}H_{36}O_4Si$
Exact Mass: 440.24

X-Ray of **C**
ccdc: 1457120

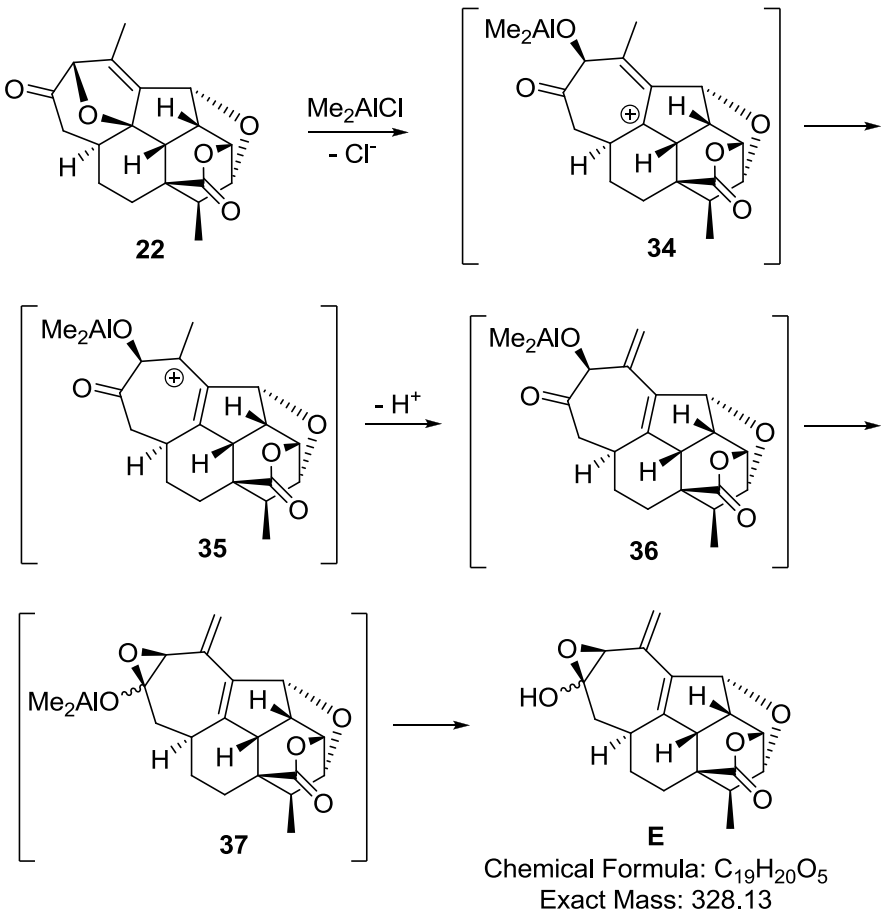
C ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 5.95 (dt, J = 10.0, 2.4 Hz, 1H), 5.51 (dt, J = 10.0, 2.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H), 3.62 (s, 3H), 3.38 (d, J = 10.8 Hz, 1H), 3.23 - 3.19 (m, 1H), 3.00 - 2.81 (m, 2H), 2.65 - 2.60 (m, 1H), 2.44 - 2.42 (m, 1H), 2.35 (s, 3H), 1.54 (td, J = 13.2, 6.0 Hz, 1H), 1.10 (d, J = 7.6 Hz, 3H), 0.82 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 173.0, 148.8, 146.3, 144.7, 144.0, 141.5, 141.2, 134.9, 125.7, 77.2, 52.9, 51.3, 46.6, 45.9, 43.2, 32.1, 30.3, 26.0, 24.1, 18.5, 15.4, - 3.2, - 4.0.



D

Chemical Formula: $C_{20}H_{24}O_6$
Exact Mass: 360.16

D ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.72 (s, 1H), 3.77 (s, 3H), 3.38 - 3.37 (m, 1H), 3.29 - 3.23 (m, 2H), 3.20 (t, J = 4.0 Hz, 1H), 2.75 (dd, J = 16.8, 7.2 Hz, 1H), 2.55 - 2.51 (m, 1H), 2.50 - 2.45 (m, 1H), 2.43 - 2.32 (m, 3H), 1.95 (d, J = 13.6 Hz, 1H), 1.86 (s, 3H), 1.19 - 1.08 (m, 1H), 1.61 - 1.44 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H).



E ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.31 (s, 1H), 5.07 (t, J =5.6 Hz, 1H), 4.88 (d, J = 4.4 Hz, 1H), 4.08 (s, 1H), 3.93 (d, J = 5.6 Hz, 1H), 3.24 - 3.16 (m, 2H), 2.61 (dd, J = 14.0, 6.0 Hz, 1H), 2.49 (s, 1H), 2.02 - 1.89 (m, 3H), 1.77 - 1.65 (m, 2H), 1.61 - 1.41 (m, 2H), 0.95 (d, J = 7.6 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 5.38 (s, 1H), 5.31 (s, 1H), 5.07 (t, J =5.6 Hz, 1H), 4.87 (d, J = 4.4 Hz, 1H), 4.07 (s, 1H), 3.93 (d, J = 5.6 Hz, 1H), 3.23 - 3.16 (m, 2H), 2.61 (dd, J = 14.8, 6.0 Hz, 1H), 2.02 - 1.89 (m, 3H), 1.78 - 1.67 (m, 2H), 1.61 - 1.57 (m, 1H), 1.50 (d, J = 10.8 Hz, 1H), 0.94 (d, J = 7.6 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 174.7, 145.9, 141.7, 137.8, 118.3, 88.6, 83.5, 79.6, 79.2, 74.8, 49.0, 45.0, 42.9, 40.6, 38.7, 34.5, 28.1, 23.7, 15.0. HRMS (ESI) for $C_{19}H_{20}O_5$ - H_2O + H (M - H_2O + H), 311.1278 (Calc), found 311.1282.

Comparison of Spectra of Natural and Synthetic Harringtonolide

Comparison of ^{1}H NMR Spectra of Harringtonolide **1** in $CDCl_3$

(a) ^{1}H NMR spectra provided by B. Nay[1]

(b) ^{1}H NMR spectra provided by W. P. Tang[2]

(c) ^{1}H NMR spectra of our synthetic **1**

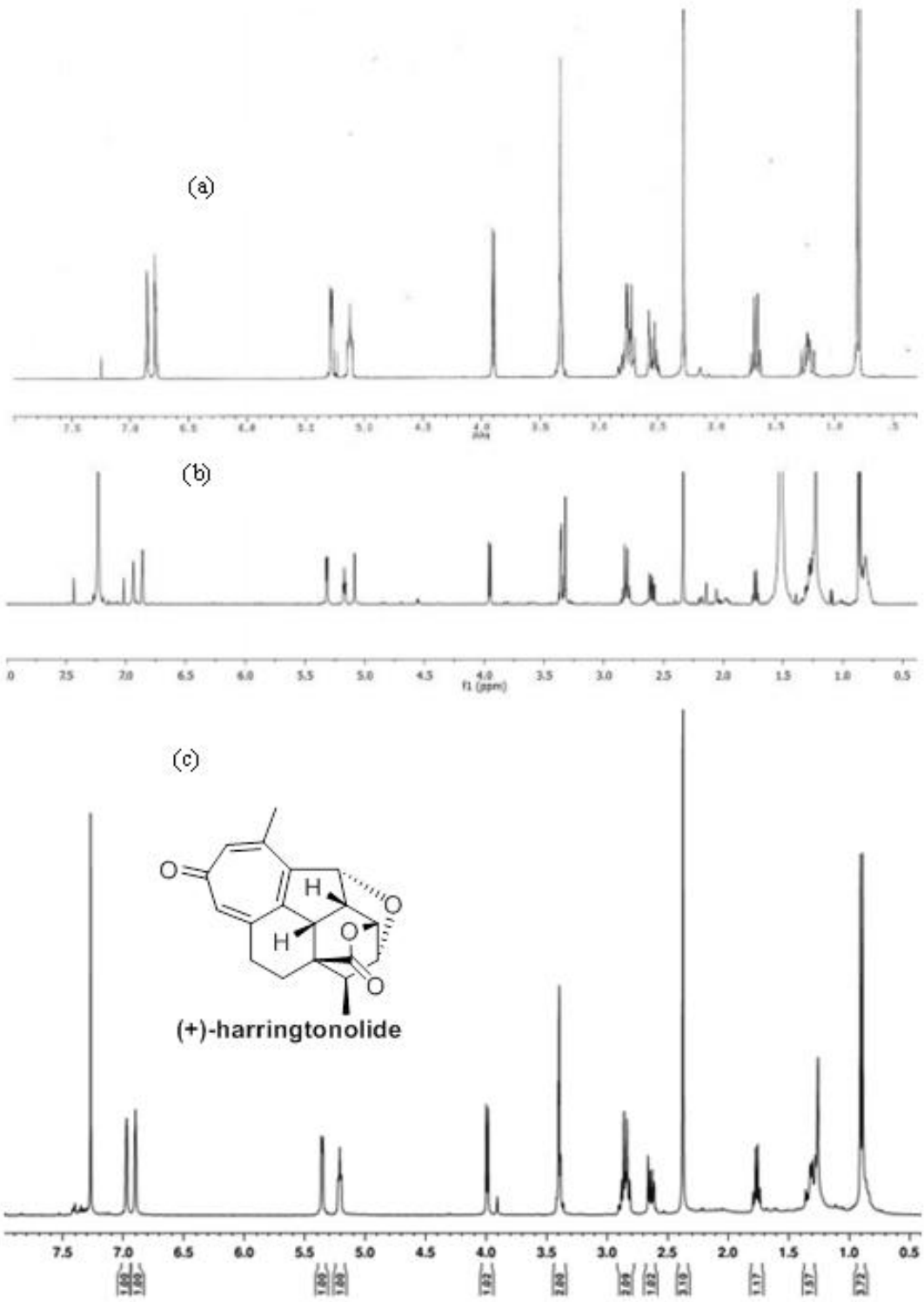


Table S1 ^{1}H NMR Spectroscopic Data of Our Synthetic **1**, Buta's Natural **1**,[3] Sun' Natural **1**,[4] and Tang's Synthetic **1**[2] in $CDCl_3$

δH of our synthetic **1** (400 MHz)	δH of lit. natural **1**[3] (100 MHz)	δH of lit. natural **1**[4] (100 MHz)	δH of Tang's synthetic **1**[2] (500 MHz)
6.97 (s, 1H)	6.98 (s, 1H)	6.95 (d, *J* = 2 Hz, 1H)	6.98 (s, 1H)
6.90 (s, 1H)	6.92 (s, 1H)	6.77 (d, *J* = 2 Hz, 1H)	6.91 (s, 1H)
5.36 (t, *J* = 2.8 Hz, 1H)	5.47 (m, 1H)	5.35 (q, 1H)	5.36 (m, 1H)
5.21 (t, *J* = 5.2 Hz, 1H)	5.32 (m, 1H)	5.19 (m, 1H)	5.22 (dd, *J* = 5.3, 5.3 Hz, 1H)
3.99 (d, *J* = 5.6 Hz, 1H)	4.00 (m, 1H)	3.98 (d, *J* = 6 Hz, 1H)	4.00 (d, *J* = 5.6 Hz, 1H)
3.42 - 3.36 (m, 2H)	3.51 (m, 2H)	3.40 (m, 2H)	3.42 (m, 2H)
2.91 - 2.82 (m, 2H)	2.70 (m, 3H)	2.85 (m, 1H)	2.87 (m, 1H)
2.66 - 2.60 (m, 1H)		2.75 (m, 1H)	2.83 (m, 1H)
		2.65 (m, 1H)	2.64 (dd, *J* = 13.7, 6.5 Hz, 1H)
2.37 (d, *J* = 0.8 Hz, 3H)	2.36 (s, 3H)	2.37 (s, 3H)	2.38 (s, 3H)
1.76 (q, *J* = 7.6 Hz, 1H)	1.75 (q, 1H)	1.74 (q, *J* = 8 Hz, 1H)	1.77 (q, *J* = 7.5 Hz, 1H)
1.36 - 1.28 (m, 1H)	1.25 (m, 1H)	1.32 (m, 1H)	1.31 (m, 1H)
0.90 (d, *J* = 7.6 Hz, 3H)	0.90 (d, 3H)	0.89 (d, *J* = 8 Hz, 3H)	0.91 (d, *J* = 7.6 Hz, 3H)

Table S2. ^{13}C NMR Spectroscopic Data of Our Synthetic **1**, Nay's Natural **1**,[1] Buta's Natural **1**,[3] Sun's Natural **1**,[4] and Tang's Synthetic **1**[2] in $CDCl_3$

δC (I) of our synthetic **1**	δC (II) of lit. natural **1**[1]	δC (III) of lit. natural **1**[3]	δC (IV) of lit. natural **1**[4]	δC of Tang's synthetic **1**[2]
186.5	186.2	186.4	186.9	186.3
173.5	173.3	173.5	173.0	173.3
145.8	145.7	145.9	145.9	145.7
145.6	145.5	145.7	145.2	-
145.0	144.9	145.0	145.0	144.8
143.6	143.4	143.6	143.4	-
141.6	141.3	141.5	141.5	141.5
139.3	139.0	139.1	139.4	139.1
86.0	85.9	85.5	86.0	85.9
80.0	79.8	80.0	79.6	79.9
79.7	79.5	80.0	78.2	79.6
49.9	49.7	49.9	49.7	49.8
45.8	45.6	43.8	45.5	45.7
41.8	41.6	41.7	41.5	41.7
40.0	39.8	40.0	39.7	39.9
32.3	32.1	32.3	31.8	32.2
23.9	23.7	23.8	23.3	23.7
22.4	22.2	22.3	22.0	22.3
14.7	14.6	14.7	14.2	14.6

References:

[1] L. Evanno, A. Jossang, J. Nguyen-Pouplin, D. Delaroche, P. Herson, M. Seuleiman, B. Bodo, B. Nay, *Planta Med*. **2008**, *74*, 870－872.

[2] M. Zhang, N. Liu, W. P. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 12434－12438.

[3] J. G. Buta, J. L. Flippen, W. R. Lusby, *J. Org. Chem.* **1978**, *43*, 1002－1003.

[4] N. J. Sun, Z. Xue, X. T. Liang, L. Huang, *Acta Pharm. Sin*. **1979**, *14*, 39－44.

HPLC Data of (±)-8 and 8

Empower software

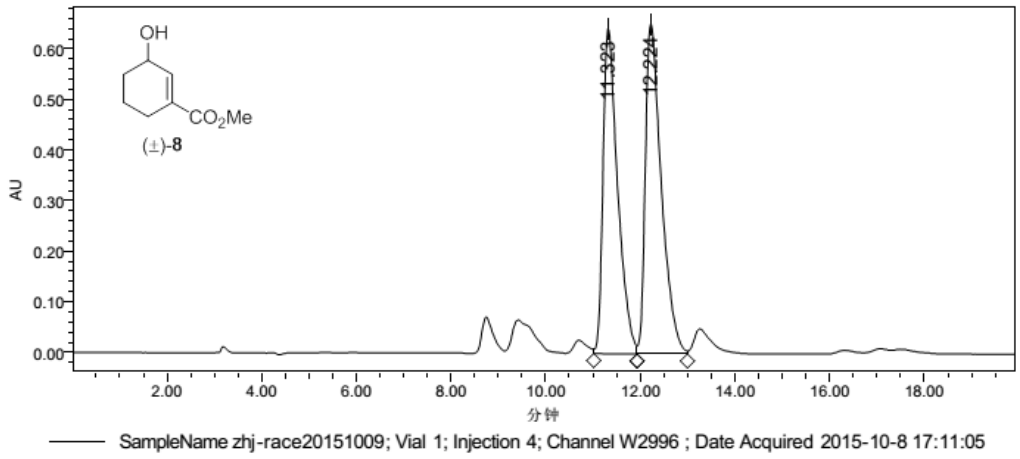
进样综合报告 报告

用户名称: System　　项目名称: a2015

样品信息

样品名称:	zhj-race20151009	采集者:	System
样品类型:	未知	采集时间:	2015-10-8 17:11:05
瓶号:	1	采集方法组:	zhjrace
进样次数:	4	处理日期:	2015-10-8 17:38:33
进样体积:	5.00 ul	处理方法:	zhjrace20151009
运行时间:	60.0 Minutes	通道名称:	Wvln Ch1
样品组名称:		处理通道注释:	PDA 230.0 纳米

自动标尺色谱图



处理通道: **PDA 230.0** 纳米

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2	PDA 230.0 纳米	12.224	15283185	52.57	653100

Empower software

进样综合报告 报告

用户名称: System　　项目名称: a2015

样品信息

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样品类型:	未知	采集时间:	2015-10-21 15:32:05
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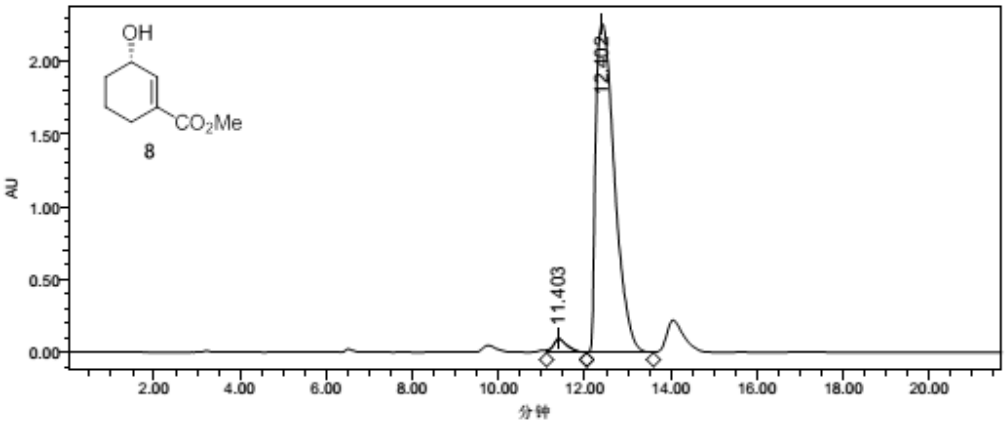
进样次数:	1	处理日期:	2015-10-21 16:00:08
进样体积:	5.00 ul	处理方法:	zhjzjfRuH30g
运行时间:	60.0 Minutes	通道名称:	Wvln Ch1
样品组名称:		处理通道注释:	PDA 230.0 纳米

自动标尺色谱图



SampleName zhj-zjf (RuH30g); Vial 1; Injection 1; Channel W2996 ; Date Acquired 2015-10-21 15:32:05

处理通道: **PDA 230.0** 纳米

	处理通道	保留时间 (分钟)	面积	% 面积	峰高
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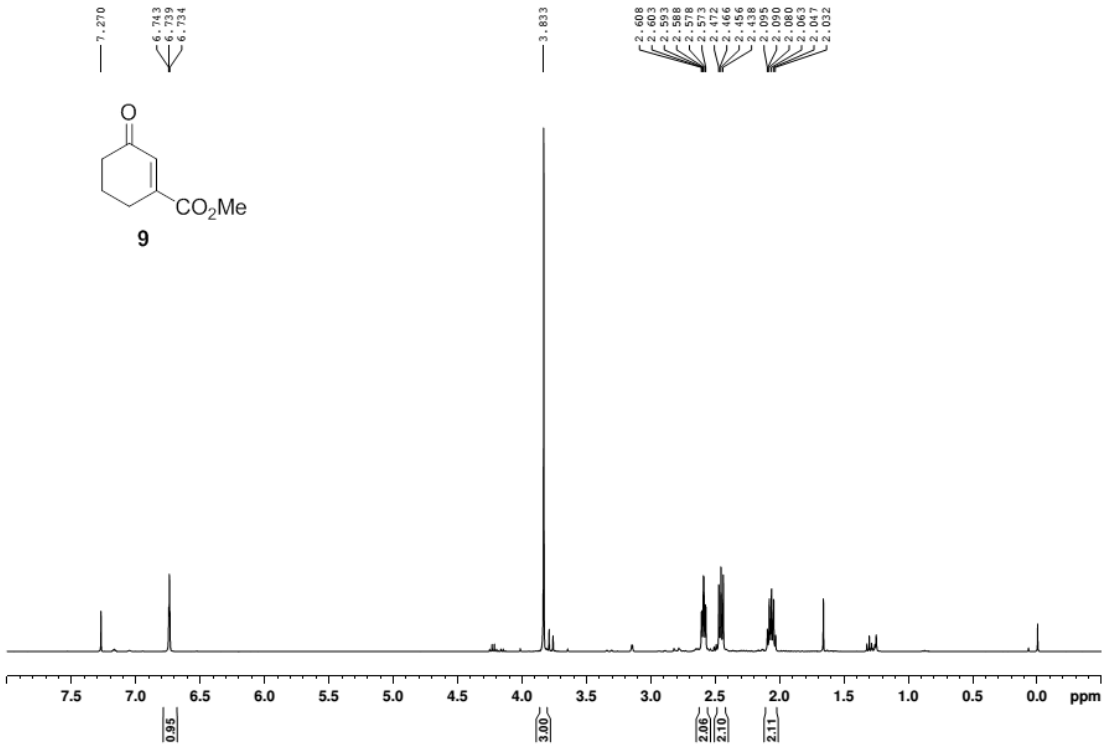
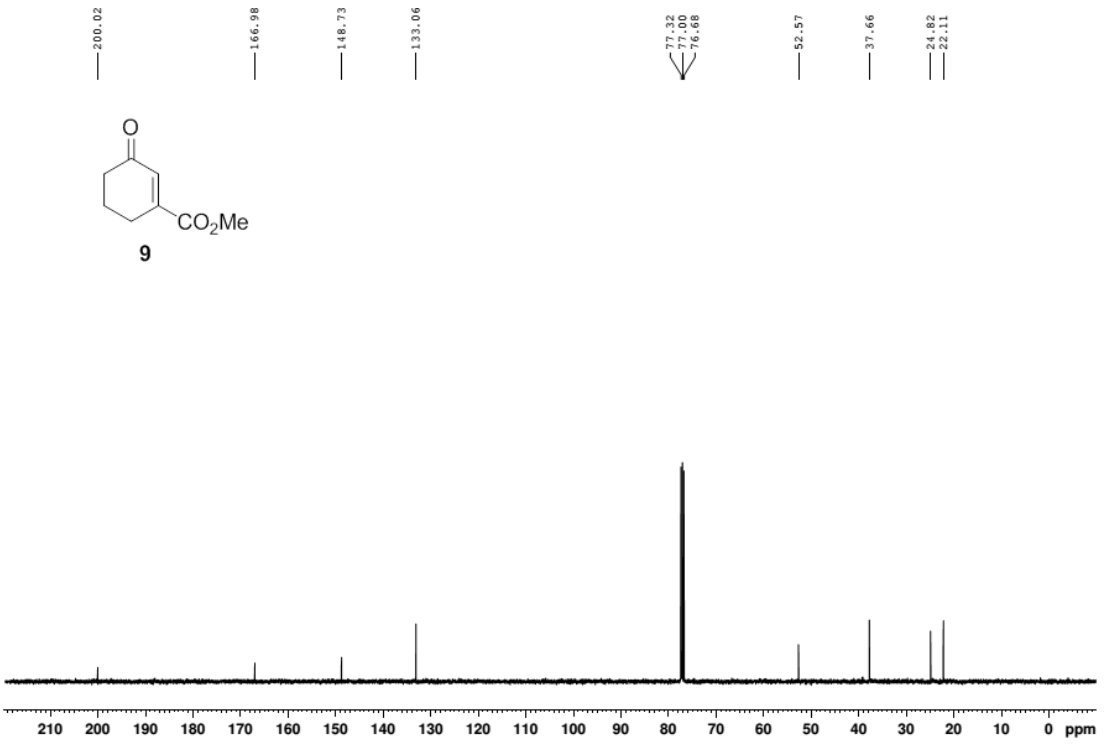
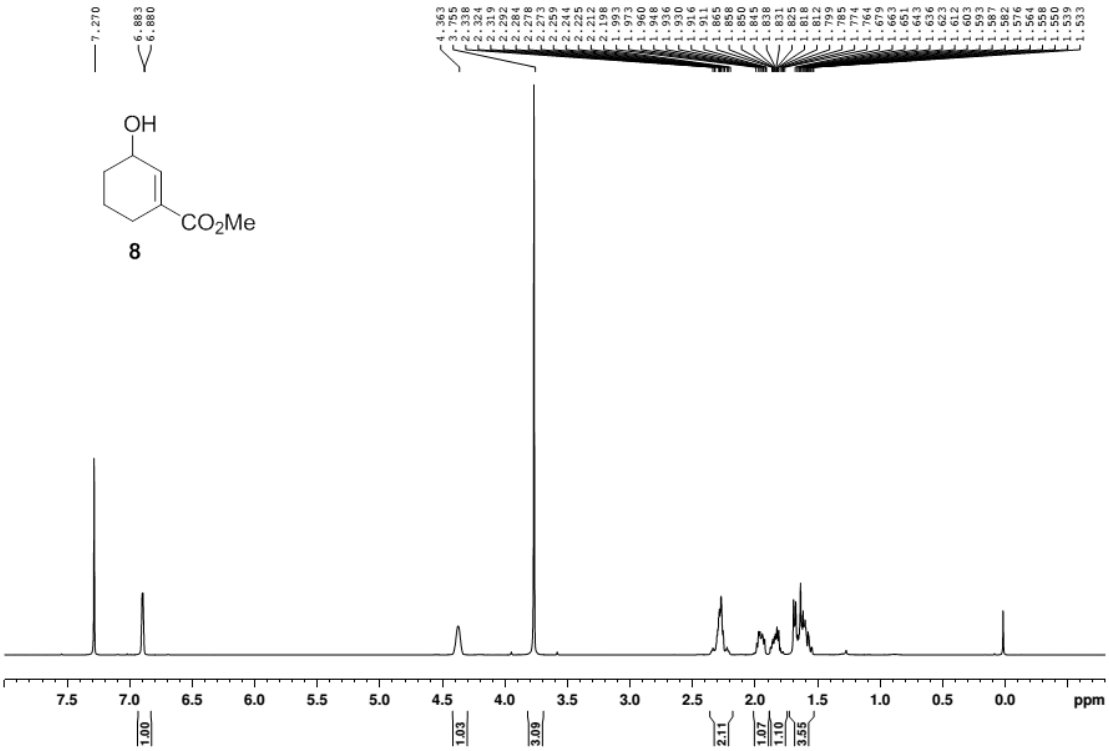
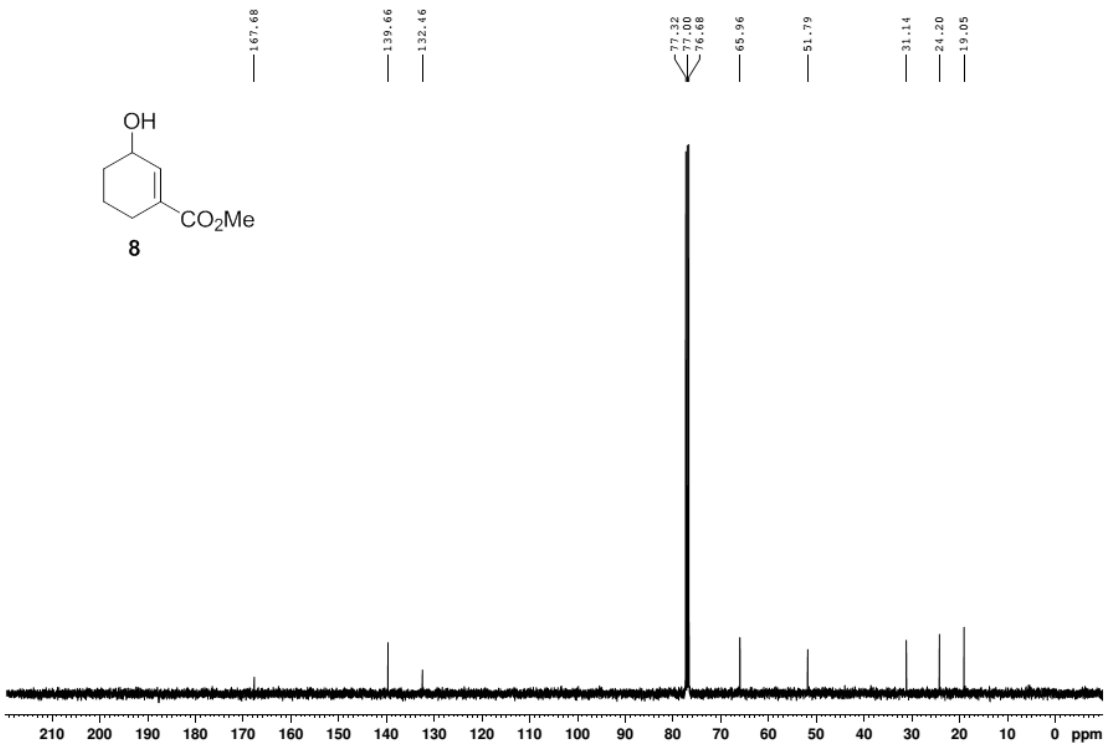
2	PDA 230.0 纳米	12.402	68773533	97.01	2262600

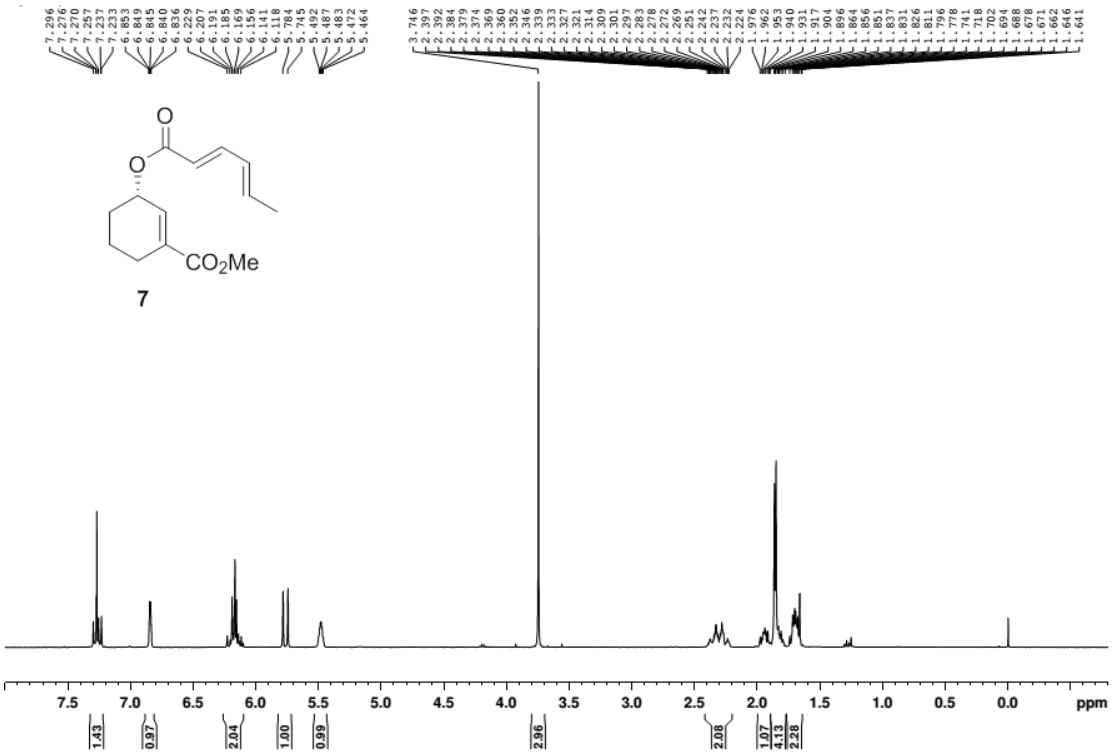
NMR Spectra of the Intermediates and (+)-Harringtonolide

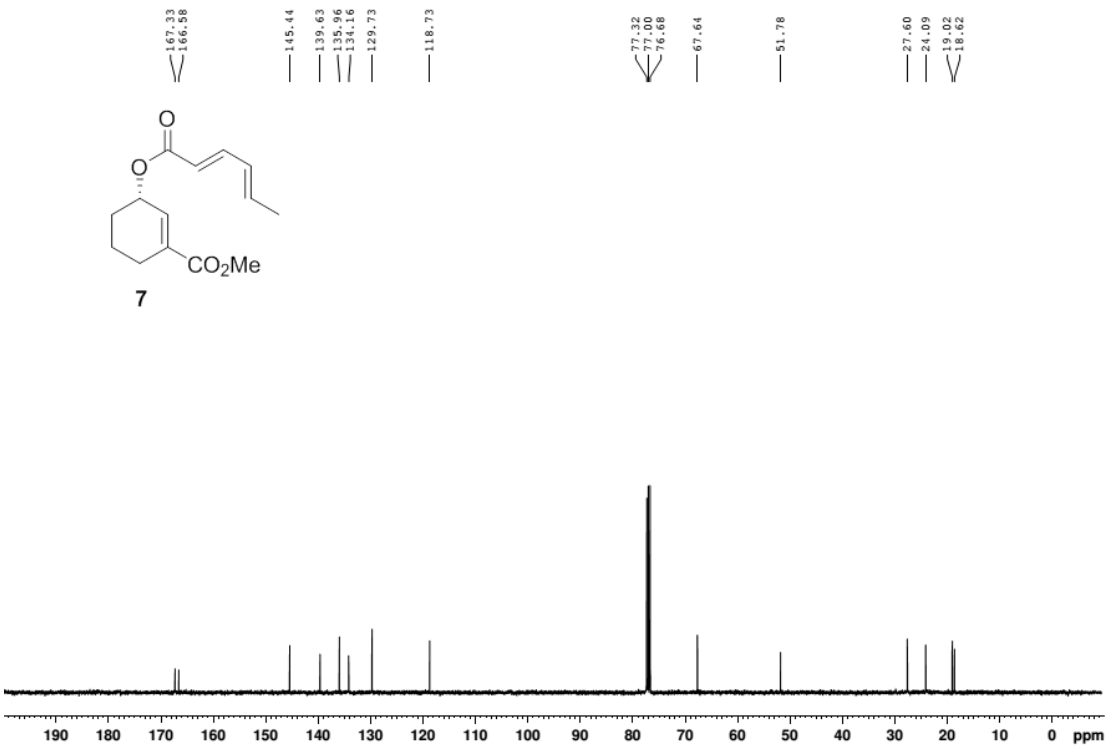


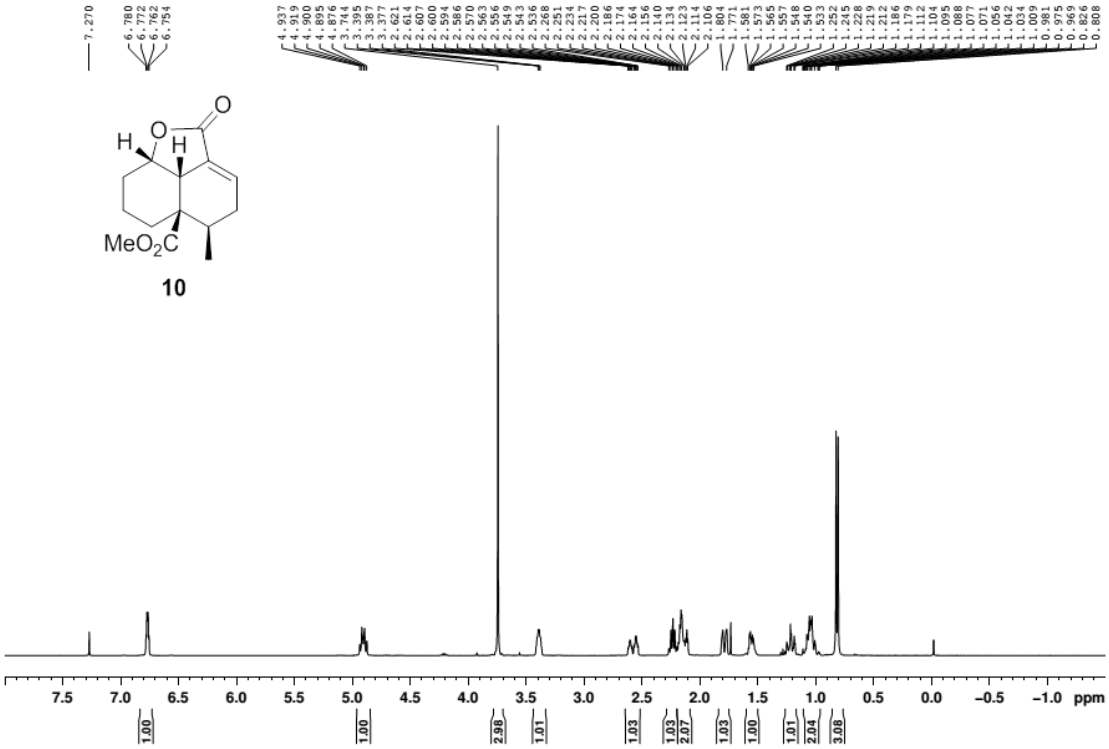


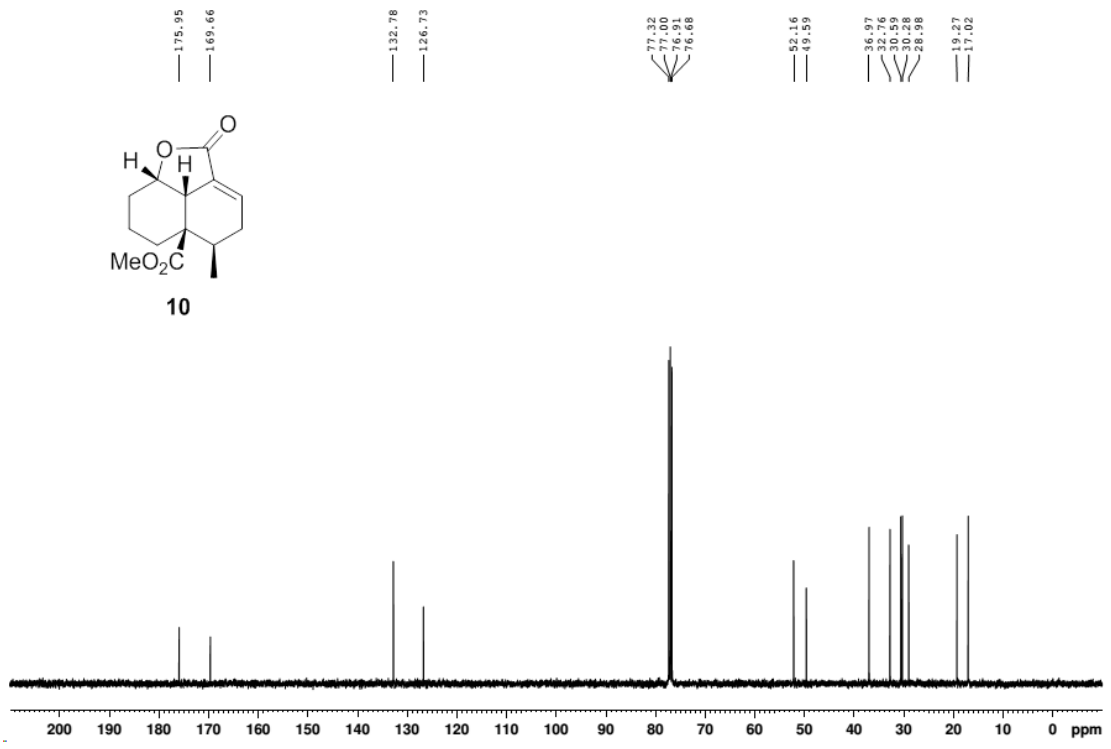












Mixture of 10 and 10':