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.; Hong-bin Zhai, Ph.D.

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Total Synthesis of Diterpenoid (+)-Harringtononolide


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

Abstract: Described herein is the first asymmetric total synthesis of (+)-harringtononolide, 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.

(+)-Harringtononolide (1, Figure 1), a structurally unique diterpenoid, was first isolated from the seeds of Cephalotaxus harringtonia by Buta and co-workers in 1978,[14] and subsequently from the bark of the Chinese species Cephalotaxus hainanensis by Sun et al. in 1979, yet under the name of hainanolide.[10] Hainanolide (2), the structural congener of hainanolide was also isolated[10] X-ray crystallographic analysis[10] 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. (+/-)-Harringtononolide 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[26] In contrast, diterpenoid 2 was biologically inactive,[27] 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 tetracetate, though the yield was not given in the literature.[4]

Owing to their intriguing architecture and outstanding biological activities, harringtononolide and its derivatives have attracted considerable attention from the synthetic community. Many synthetic efforts have been devoted to harringtononolide since its isolation.[15,16] In 1998, Mander’s group demonstrated a groundbreaking total synthesis of (±)-hainanolide, which constituted a formal synthesis of (±)-harringtononolide.[16] 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.[16,17] More recently, Tang et al. reported an efficient total synthesis of (±)-harringtononolide through an intramolecular oxidopyrylum-based [3+2] cycloaddition to assemble the tetracyclic carbon skeleton.[19] 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 (+)-harringtononolide (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 harringtononolide 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 stereocentric 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]
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.\(^\text{11}\) 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.\(^\text{12}\) 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.\(^\text{13}\) 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.

Next, bicycle 14 was employed to investigate the intramolecular [3+2] cycloaddition (i.e., 5 → 3, Scheme 3). Preliminary studies\(^\text{14,15}\) 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)\(^\text{16}\) to afford chlorohydrin 15 stereoselectively and regioselectively. The Cl\(^+\) species generated \textit{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 nuceophile attack of water at the less hindered side from the \(\alpha\)-face.
Protection of the hydroxyl group in 15 by TBS led to 16. The side chain in acylidazol 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_3N_2. 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 by-products would increase substantially. As the stereogenic centers in acylidazol 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, the Rh(OAc)_2-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 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 Sn2 reaction, furnishing the desired cyclic ether 20 as the major product. 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.

The endgame for the total synthesis of (+)-harringtonolide (1) was the formation of the tropone unit. According to the literature procedure, cleavage of the C5-O bond, elimination of the proton at C6 (adjacent to the tertiary carbonium at C5), and dehydration involving the hydroxyl group at C2 would generate the tropone moiety. In our case, treatment of 22 with Me_3AlCl led to a diene compound. We speculated that preferential elimination of C6-H (adjacent to the tertiary carbonium 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_3AlCl. The spectroscopic data (HRMS; ^1H & ^13C NMR) were fully consistent with those reported for the natural product.

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. 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 tropon e as a silyl enol ether.

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

[14] We attempted to construct the lactone and THF rings in a one-step fashion in the presence of Yb(OOTf)3, after the carbon−carbon bond was converted into epoxypropene stereochemically according to the literature,34 and then the S-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 tropon 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.
[17] In order to identify the stereochemical structure of the by-product in the saponification step, a (S)-β 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 epoxypropene 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 tropon was proposed in the Supporting Information.
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, Raining 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 (CH₂Cl₂), diisopropylamine (i-Pr₂NH), and triethylamine (Et₃N) 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 MgSO₄ and concentrated by rotary evaporation below 30 °C unless otherwise noted. Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were obtained at the indicated field as solutions in CDCl₃. Chemical shifts are referenced to the deuterated solvent (CDCl₃, δ = 7.27 ppm and 77.0 ppm for ¹H and ¹³C NMR, respectively) and are reported in parts per million (ppm, δ)
relative to tetramethylsilane (TMS, $\delta = 0.00$ 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 SGWøX-4A melting point apparatus. X-ray diffraction was recorded on a Supernova apparatus.

**Experimental Procedures and Characterization Data for (±)-Harringtononolide**

![Chemical Structure](image)

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$_2$O (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 °C and then cooled to about 10 °C. Concentrated HCl (72 mL) was added at 0 °C until the pH = 2. The aqueous solution was extracted with DCM:$^3$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 SOCl₂ (44 g, 0.37 mol) at 0 °C. 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 NaHCO₃ (aq) and brine sequentially. The organic layer was dried over Na₂SO₄, 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 CHCl₃ (858 mL) was added DBU (56 g, 0.37 mmol) at 0 °C. 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 Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rf = 0.29) to give 9 (35 g, 50% over three steps) as a light yellow oil.

9 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 200.0, 167.0, 148.7, 133.1, 52.6, 37.7, 24.8, 22.1; HRMS (ESI) for C₈H₁₀O₃ + H (M + H), 155.0703 (Calc), found 155.0705.

To a solution of 9 (28.4 g, 184 mmol) in MeOH (367 mL) was added NaBH₄ (6.99 g, 184 mmol) at 0 °C. The mixture was stirred for 10 min before it was quenched with NH₄Cl (aq). The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rf = 0.22) to give the alcohol (±)-8 (27.8 g, 98%) as a light yellow oil.

(±)-8 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 139.7, 132.5, 66.0, 51.8, 31.1, 24.2, 19.1. HRMS (ESI) for C₈H₁₂O₃ + Na (M + Na), 179.0679 (Calc), found 179.0676.
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), NEt3 (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 NaHCO3(aq), dried over Na2SO4, 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. [α]D18.2 = -46.1 (c 1.28, CHCl3).

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 °C, 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 NaHCO3(aq) and 1.0 M HCl (aq) sequentially. The organic layer was dried over Na2SO4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rf = 0.77) to give 7 (47.1 g, 98%) as a light yellow oil.

7 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 C14H18O4 + Na (M + Na), 273.1097 (Calc), found 273.1095. [α]D18.9 = -36.6 (c 1.61, CHCl3).

S4
The mixture of 7 (57.8 g, 231 mmol) and BHT (5.09 g, 23.1 mmol) was heated to 180 °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, Rf = 0.32) to give a mixture of 10 and the epimer 10' (40.0 g). ¹H 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 CHCl₃ 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 Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rf = 0.32) to give the compound 10 as a light yellow oil (0.095 g, 95%). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₁₈O₄ + H (M + H), 251.1278 (Calc), found 251.1275. [α]D²⁰ = -46.1 (c 1.02, CHCl₃).

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 °C. After 20 min, the solution was cooled to - 78 °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 NaHCO₃ (aq) until pH = 9 in aqueous. The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rᵣ = 0.38) to give the compound 6 as a light yellow oil (10.2 g, 35 % over two steps).

6 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₁₀O₄ + Na (M + Na), 273.1097 (Calc), found 273.1093. [α]D¹⁸.⁶ = - 54.1 (c 1.09, CHCl₃).

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 °C. The mixture was gradually warmed to - 40 °C over 3 h and then the reaction was quenched with saturated potassium sodium tartrate at - 78 °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 MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 3, Rᵣ = 0.27) to give 11 (5.0 g, 97%) as a colorless oil that contains another unseparated diastereomer in a 1:1 ratio.

11 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₁₂O₄ + Na (M + Na), 275.1254 (Calc), found 275.1256. [α]D¹⁸.⁸ = - 32.4 (c
1.82, CHCl<sub>3</sub>.

1-Propinylmagnesium bromide (0.5 M in THF, 114 mL, 57 mmol) was added to 11 (4.99 g, 19.8 mmol) at 0 °C. The solution was heated to reflux for 36 h. The reaction was quenched with NH<sub>4</sub>Cl (aq) at 0 °C and extracted with DCM three times. The combined organic layers were dried over MgSO<sub>4</sub>, 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 TBSCI (5.94 g, 39.6 mmol) at room temperature. After being stirred for 12 h, the mixture was diluted with Et<sub>2</sub>O (300 mL) and washed with H<sub>2</sub>O three times. The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, R<sub>f</sub> = 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<sub>3</sub> (4.99 g, 59.4 mmol) at room temperature. The mixture was stirred for 24 h before quenching with NaHCO<sub>3</sub> (aq) and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq) at 0 °C. The mixture was extracted with Et<sub>2</sub>O. The organic layer was dried with MgSO<sub>4</sub>, 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<sub>f</sub> = 0.47) and 14′ (2.8 g, 35% over three steps, EtOAc : hexanes = 1 : 10, R<sub>f</sub> = 0.36) as light yellow oil.

14<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); 13<sup>C</sup> NMR (100 MHz, CDCl<sub>3</sub>) 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, CHCl₃).

14\textsuperscript{1}H NMR (400 MHz, CDCl₃) 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); \textsuperscript{13}C NMR (100 MHz, CDCl₃) 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, CHCl₃).

To a solution of 14 (573 mg, 1.42 mmol) in acetone (7.1 mL) was added (CONCl)\textsubscript{3} (263 mg, 1.14 mmol) at 0 °C. After being stirred for 0.5 h, the mixture was quenched with NaHSO\textsubscript{3} (aq) and extracted with EtOAc. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 8, R\textsubscript{f} = 0.56) to give the compound 15 (401 mg, 62%) as a colorless foam.

15\textsuperscript{1}H NMR (400 MHz, CDCl₃) 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); \textsuperscript{13}C NMR (100 MHz, CDCl₃) 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_2Si + Na (M + Na), 479.1991 (Calc), found 479.2002. [\alpha]^D_{20.1} = +3.5 (c 1.16, CHCl₃).

S8
To a solution of 15 (1.69 g, 3.71 mmol) in DCM (19 mL) was added Et₃N (750 mg, 7.42 mmol) and TBSOTf (1.47 g, 5.57 mmol) at 0 °C. After the starting material disappeared as monitored by TLC, the mixture was quenched with H₂O and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, Rf = 0.65) to give the compound 16 (1.5 g, 71%) as a colorless foam.

16 ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₉H₅₁ClO₅Si₂ + Na (M + Na), 593.2856 (Calc), found 593.2865. [α]D²⁰.⁰ = +55.5 (c 1.55, CHCl₃).

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 °C. After 0.5 h, the solution was cooled to -78 °C 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 BrCH₂CO₂Et (0.65 g, 3.9 mmol) was added dropwise. The mixture was allowed to warm to -40 °C and stirred for additional 1 h at
this temperature. The mixture was quenched with NH₄Cl (aq) at the temperature and extracted with EtOAc and washed with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, Rf = 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** ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₃H₅₇ClO₅Si₂Na+ (M + Na), 679.3224 (Calc), found 679.3233. [α]D²⁰ = + 5.7 (c 1.22, CHCl₃).

![Diagram](image)

To a solution of the crude 17 (0.92 g, 1.4 mmol) in a 4:1 mixture of THF/H₂O (14 mL) was added LiOH (0.29 g, 7.1 mmol). After the solution was stirred vigorously for 36 h at 30 °C, the mixture was diluted with DCM and washed with 1.0 M HCl (aq). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 4, Rf = 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** ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, ...
Preparation of CH$_2$N$_2$: Under continuously shaking, the precursor compound CH$_3$N(NO)CONH$_2$ (2.6 g, 25 mmol) was added to a mixture of KOH (40% in H$_2$O, 8.6 mL) and Et$_2$O (26 mL) at 0 °C. Decantation of the light yellow solution gave the solution of CH$_2$N$_2$ (1.0 M in Et$_2$O). 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$_2$O (5.0 mL) was added Et$_3$N (0.15 g, 1.5 mmol) and ClCO$_2$Bu (0.14 g, 1.0 mmol) sequentially at 0 °C. After 0.5 h, a freshly prepared solution of CH$_2$N$_2$ in Et$_2$O (1.0 M, 26 mL) was added to the mixture at 0 °C. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et$_2$O 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 $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_{33}$ClN$_2$O$_6$Si$_2$ + Na (M + Na), 675.3023 (Calc), found 675.3016. [$\alpha$]$_{D}^{19.7}$ = - 5.5 (c 1.09, CHCl$_3$).
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$_3$) $\delta$ 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); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 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$_{52}$ClO$_6$Si$_2$ + Na (M + Na), 647.2961 (Calc), found 647.2953. [$\alpha$]$_D^{21.3} = - 104.6$ (c 1.08, CHCl$_3$).

m.p. = 52 - 54 °C

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$_2$O 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$_2$SO$_4$, filtered and concentrated under vacuum. The residue was purified
by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R<sub>f</sub> = 0.31) to give the compound 19 (91 mg, 85%) as a colorless solid.

19 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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<sub>20</sub>H<sub>25</sub>ClO<sub>6</sub> + Na (M + Na), 419.1232 (Calc), found 419.1225. [α]<sub>D</sub><sup>21.6</sup> = - 192.7 (c 1.10, CHCl<sub>3</sub>),

m.p. = 156 - 158 °C

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 °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<sub>2</sub>O and extracted with DCM. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, R<sub>f</sub> = 0.25) to give the compound 20 (49 mg, 71%) as a colorless solid.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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<sub>20</sub>H<sub>24</sub>O<sub>6</sub> + Na (M + Na), 383.1465 (Calc), found 383.1457. [α]<sub>D</sub><sup>18.5</sup> = - 309.7 (c 1.03, CHCl<sub>3</sub>).
m.p. = 253 - 255 °C

To a solution of 20 (35 mg, 0.098 mmol) in DCM (4.0 mL) was added NaHCO₃ (0.16 g, 1.9 mmol) and DMP (0.21 g, 0.49 mmol). The mixture was stirred for 24 h before quenching with Na₂S₂O₅ (aq) and NaHCO₃ (aq). The solution was extracted with DCM three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, Rf = 0.65) to give the compound 21 (23 mg, 66%) as a colorless solid along with 9 mg (25%) of recovered starting material.

21 H NMR (400 MHz, CDCl₃) 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); 13C NMR (100 MHz, CDCl₃) 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 C₂₀H₂₂O₆ + Na (M + Na), 381.1309 (Calc), found 381.1302. [α]D^18.4 = -245.8 (c 1.20, CHCl₃).

m.p. = 165 - 167 °C

To a solution of 21 (23.2 mg, 0.0648 mmol) in MeOH (2.6 mL) was added NaBH₄ (10 mg, 0.26 mmol) at 0 °C. After 5 min, K₂CO₃ (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 H₂O. The mixture was extracted with DCM three times. The combined organic layers were dried over Na₂SO₄, 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$_2$S$_2$O$_3$ (aq) and NaHCO$_3$ (aq) and extracted with DCM three times. The combined organic layers were dried over Na$_2$SO$_4$, 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$N (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$_2$O. The solution was extracted with DCM. The organic layer was dried over Na$_2$SO$_4$, 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 Me₂AlCl (0.9 M in heptane, 2.3 mL, 2.1 mmol) at - 78 °C. The solution was allowed to warm to 40 °C. After the starting material disappeared as indicated by TLC, the solution was cooled to - 78 °C 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 NH₄Cl (aq) and extracted with DCM three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, Rf = 0.15) to give natural product (+)-harringtonolide (5.8 mg, 46% over two steps) as a light yellow solid.

(+)-harringtonolide

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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 C₁₉H₁₈O₄ + H (M + H), 311.1278 (Calc), found 311.1283. [α]D¹⁷ = + 81.0 (c 1.16, CHCl₃).

m.p. = 255 - 258 °C
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$_2$SO$_4$, 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\(_3\)) \( \delta \) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 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\(_2\)Si + Na (M + Na), 479.1991 (Calc), found 479.1997. \([\alpha]_D^{19.8} = -111.1 \) (c 1.26, CHCl\(_3\)).

\[ \text{16’} \]

To a solution of 15’ (1.01 g, 2.21 mmol) in DCM (11 mL) was added Et\(_3\)N (671 mg, 6.63 mmol) and TBSOTf (1.46 g, 5.53 mmol) at 0 °C. After being stirred for 3 h, the mixture was quenched with H\(_2\)O and extracted with EtOAc. The organic layer was dried over Na\(_2\)SO\(_4\), 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’ (1.1 g, 90%) a colorless foam.

16’ \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 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\(_{23}\)H\(_{37}\)ClO\(_2\)Si + Na (M + Na), 593.2856 (Calc), found 593.2846. \([\alpha]_D^{19.7} = -25.9 \) (c 1.16, CHCl\(_3\)).
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 °C. After 0.5 h, the solution was cooled to -78 °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 BrCH₂CO₂Et (1.06 g, 6.39 mmol) was added dropwise. The mixture was allowed to warm to -40 °C and stirred for additional 1 h at the temperature. The mixture was quenched with NH₄Cl (aq) at the temperature, extracted with EtOAc and washed with brine. The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 10, Rf = 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' ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₃H₅₇ClO₇Si₂ + Na (M + Na), 679.3224 (Calc), found 679.3232. [α]D¹⁹⁷ = -61.5 (c 0.95, CHCl₃).
To a solution of the crude 17' (1.7 g, 2.6 mmol) in a 4:1 mixture of THF/H$_2$O (26 mL) was added LiOH (551 mg, 13.1 mmol). After the mixture was stirred vigorously for 36 h at 30 °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$_f$ = 0.21) to give the compound 18' (0.65 g, 42%) as a colorless foam that contains another unseparated diastereomer in a 1:14 ratio.

18' $^1$H 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$_{3}$H$_{13}$ClO$_{2}$Si$_{2}$ + Na (M + Na), 651.2911 (Calc), found 651.2919. [$\alpha$]$_D$$_{218}^{20}$ = -54.7 (c 1.17, CHCl$_3$).

Preparation of CH$_2$N$_2$: under continuously shaking, the precursor compound CH$_3$N(NO)CONH$_2$ (3.4 g, 33 mmol) was added to a mixture of KOH (40% in H$_2$O, 11.2 mL) and Et$_2$O (34 mL) at 0 °C. Decantation of the light yellow solution gave the solution of CH$_2$N$_2$ (1.0 M in Et$_2$O). 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$_2$O (6.5 mL) was added Et$_3$N (0.20 g, 2.0 mmol) and ClCO$_2$Bu (0.18 g, 1.3 mmol) sequentially at 0 °C. After 0.5 h, a freshly prepared solution of CH$_2$N$_2$ (34 mL, 1.0 M in Et$_2$O) was added to the mixture at 0 °C. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et$_2$O 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.

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gel (EtOAc : hexanes = 1 : 4, Rf = 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\(^{+}\) ¹H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_2\)O\(_6\)Si\(_2\) + Na (M + Na), 675.3023 (Calc), found 675.3032. \([\alpha]_D^{19.7} = - 47.6\) (c 1.37, CHCl\(_3\)).

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, Rf = 0.57) to afford 3\(^{+}\) (0.20 g, 62\%) as a colorless solid.

3\(^{+}\) ¹H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_{53}\)ClN\(_2\)O\(_6\)Si\(_2\) + 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

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 H₂O until the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc : hexanes = 1 : 1, Rf = 0.33) to give the compound 19' (92 mg, 79%) as a colorless solid.

19' ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₂₅ClO₆ + Na (M + Na), 419.1232 (Calc), found 419.1238. [α]D²² = -225.7 (c 1.13, CHCl₃).

m.p. = 78 - 81 °C

To a solution of 19' (78 mg, 0.20 mmol) in dry THF (4.0 mL) was added Ph₃P (0.16 g, 0.59 mmol), 4-NO₂-C₆H₄CO₂H (99 mg, 0.59 mmol) and DEAD (0.10 g, 0.59 mmol) sequentially at room temperature. The solution was quenched with H₂O until the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na₂SO₄, 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 ^1H NMR and ^13C NMR was in agreement with those measured above.
Some Important Intermediates (A, B, C, D and E)

A \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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.
B \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 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).

\[ \text{Chemical Formula: C}_{20}\text{H}_{21}\text{ClO}_{4} \]

**Exact Mass:** 360.11

\[ \text{X-Ray of B} \]

\[ \text{ccdc: 1457121} \]
C $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_2$O) $\delta$ 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$_3$) $\delta$ 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$_2$O (M - H$_2$O + 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

![NMR Spectra](image)
### Table S1 \(^1\)H NMR Spectroscopic Data of Our Synthetic 1, Buta’s Natural 1,[3] Sun’s Natural 1,[4] and Tang’s Synthetic 1[2] in CDCl3

<table>
<thead>
<tr>
<th>δH of our synthetic 1 (400 MHz)</th>
<th>δH of lit. natural 1[3] (100 MHz)</th>
<th>δH of lit. natural 1[4] (100 MHz)</th>
<th>δH of Tang’s synthetic 1[2] (500 MHz)</th>
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<tr>
<td>6.97 (s, 1H)</td>
<td>6.98 (s, 1H)</td>
<td>6.95 (d, J = 2 Hz, 1H)</td>
<td>6.98 (s, 1H)</td>
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<td>6.90 (s, 1H)</td>
<td>6.92 (s, 1H)</td>
<td>6.77 (d, J = 2 Hz, 1H)</td>
<td>6.91 (s, 1H)</td>
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<td>5.36 (t, J = 2.8 Hz, 1H)</td>
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<td>5.35 (q, 1H)</td>
<td>5.36 (m, 1H)</td>
</tr>
<tr>
<td>5.21 (t, J = 5.2 Hz, 1H)</td>
<td>5.32 (m, 1H)</td>
<td>5.19 (m, 1H)</td>
<td>5.22 (dd, J = 5.3, 5.3 Hz, 1H)</td>
</tr>
<tr>
<td>3.99 (d, J = 5.6 Hz, 1H)</td>
<td>4.00 (m, 1H)</td>
<td>3.98 (d, J = 6 Hz, 1H)</td>
<td>4.00 (d, J = 5.6 Hz, 1H)</td>
</tr>
<tr>
<td>3.42 - 3.36 (m, 2H)</td>
<td>3.51 (m, 2H)</td>
<td>3.40 (m, 2H)</td>
<td>3.42 (m, 2H)</td>
</tr>
<tr>
<td>2.91 - 2.82 (m, 2H)</td>
<td>2.70 (m, 3H)</td>
<td>2.85 (m, 1H)</td>
<td>2.87 (m, 1H)</td>
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<tr>
<td>2.66 - 2.60 (m, 1H)</td>
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<td>2.65 (m, 1H)</td>
<td>2.64 (dd, J = 13.7, 6.5 Hz, 1H)</td>
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<td>2.37 (s, 3H)</td>
<td>2.38 (s, 3H)</td>
</tr>
<tr>
<td>1.76 (q, J = 7.6 Hz, 1H)</td>
<td>1.75 (q, 1H)</td>
<td>1.74 (q, J = 8 Hz, 1H)</td>
<td>1.77 (q, J = 7.5 Hz, 1H)</td>
</tr>
<tr>
<td>1.36 - 1.28 (m, 1H)</td>
<td>1.25 (m, 1H)</td>
<td>1.32 (m, 1H)</td>
<td>1.31 (m, 1H)</td>
</tr>
<tr>
<td>0.90 (d, J = 7.6 Hz, 3H)</td>
<td>0.90 (d, 3H)</td>
<td>0.89 (d, J = 8 Hz, 3H)</td>
<td>0.91 (d, J = 7.6 Hz, 3H)</td>
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### Table S2. \(^1^C\) 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 CDCl3

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<tr>
<th>δC (I) of our synthetic 1</th>
<th>δC (II) of lit. natural 1[¹]</th>
<th>δC (III) of lit. natural 1[³]</th>
<th>δC (IV) of lit. natural 1[⁴]</th>
<th>δC of Tang’s synthetic 1[²]</th>
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S29
References:


HPLC Data of (±)-8 and 8
样品信息

样品名称: zlj-zg(Ru3D0g)  采样条: System
样品类型: 未知  采样时间: 2015-10-21 15:32:05
数次: 1  采样方法: zlj-zg
检测次数: 1  处理日期: 2015-10-21 16:00:08
检测体积: 5.00 ul  处理方法: zlj-zg(Ru3D0g)
运行时间: 60.0 Minutes  处理名称: PV88 CMe

自动标尺色谱图

处理通道: PDA 230.0 纳米

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NMR Spectra of the Intermediates and (+)-Harringtonolide
Mixture of 10 and 10':

\[ \text{Mixture of 10 and 10':} \]

\[ 10:10' = 2.5:1 \]