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Total synthesis of (+)-epiepoformin and (−)-phyllostine

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Abstract—An efficient asymmetric total synthesis of naturally occurring cyclohexeneoxides, (+)-epiepoformin and (−)-phyllostine has been achieved using the chiral building block available from the base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone. Since (−)-theobroxide was derived from the same precursor of (+)-epiepoformin, the formal total synthesis of (−)-theobroxide has also been achieved.

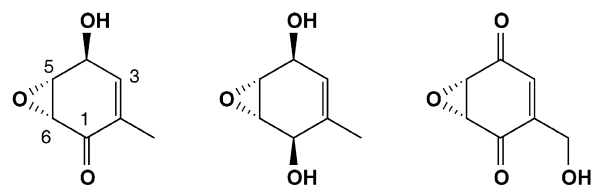
1. Introduction

A cyclohexeneoxide is a common backbone of natural organic compounds. In particular, many cyclohexeneoxides consisting of seven carbons have been isolated mainly from fungi and higher plants, and attract synthetic interest because of their various biological properties.[1] For example, (+)-epiepoformin (**1**) was first obtained from the culture filtrate of an unidentified fungus isolated from a diseased leaf of *Lagerstroemia indica L.*, and showed marked inhibition activity against the germination of lettuce seeds.[2] (−)-Theobroxide (**2**), isolated from the culture filtrate of the fungus *Lasiodiplodia theobromae*, is known as a potato micro-tuber inducing substance.[3] Furthermore, recent research disclosed that this compound also induces the flowering of buds in morning glory plants.[3b] (−)-Phyllostine (**3**) was isolated from the culture broth of *Phyllosticta sp.*, known as the pathogenic red clover fungus, and is one of the phytotoxic compounds produced by the fungus[4] (Fig. 1).

The structural feature of these compounds constitutes fully functionalized six-membered rings. In the case of compounds (+)-**1** and (−)-**2**, the six-membered rings are substituted with three oxygen atoms and one carbon–carbon double bond. Compound (−)-**3** is even more highly oxygenated, as it contains with four oxygen atoms and one carbon–carbon double bond.

Along with many useful biological properties, interest in a stereoselective construction of these highly oxygenated six-membered ring motivates synthetic chemists towards total synthesis of these compounds. Indeed, various synthetic methods have already been reported by several groups.[5–9]

In 1995, we developed the base-catalyzed Diels–Alder (DA) reaction of 3-hydroxy-2-pyrone (**4**) with various dienophiles.[10a] Although compound **4** is a less reactive diene because of its aromatic character,[11] we found that some amine bases activate the diene, so enabling it to react with dienophiles under mild conditions. This type of reaction mechanism involving activation of the diene by base is very rare, as it is completely opposite to the usual catalytic DA reactions catalyzed by Lewis acids in order to activate the dienophile.[12] The reaction proceeded with very high *endo* selectivity and afforded highly functionalized bicyclic lactones in almost quantitative yields. Additionally, the base-catalyzed asymmetric DA reaction has been developed using optically pure dienophiles (−)-**5** or (+)-**5** and cinchona alkaloids as catalysts and the product (+)-**6** or (−)-**6** was obtained with high diastereoselectivity (>95% de), respectively.[10b] Furthermore, since the resulting product precipitated out from the reaction mixture, isolation of the optically pure product only involved filtration and washing, affording more than 10 g of the pure product from



1: (+)-epiepoformin **2**: (-)-theobroxide **3**: (-)-phyllostine

Figure 1. Naturally occuring cyclohexeneoxides.

Keywords: total synthesis; epiepoformin; phyllostine; theobroxide; Diels–Alder reaction.

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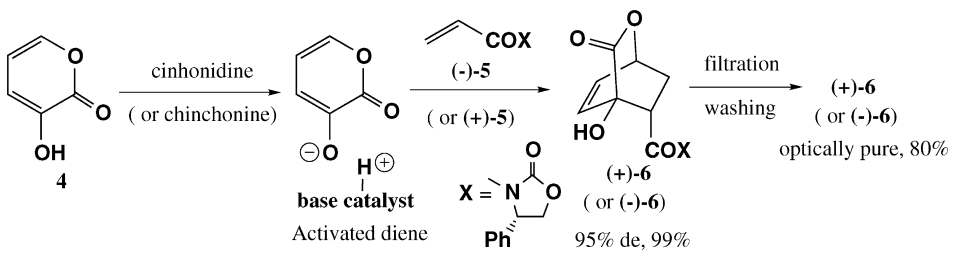


Scheme 1.

one batch (Scheme 1).[10c] For the reasons stated above, these compounds may be considered as easily obtainable and practical starting materials for the asymmetric synthesis of natural cyclohexeneoxides. Along these lines, we have already reported the efficient total synthesis of both enantiomers of eutipoxide B from (+)- and (−)-**6**[10c].

As part of an extensive study of the synthesis of cyclohexeneoxides, we have completed the total synthesis of (+)-**1** and (−)-**3**, and the formal synthesis of (−)-**2**. We describe here the details of the synthesis. Part of this work has already been reported as a letter.[10d]

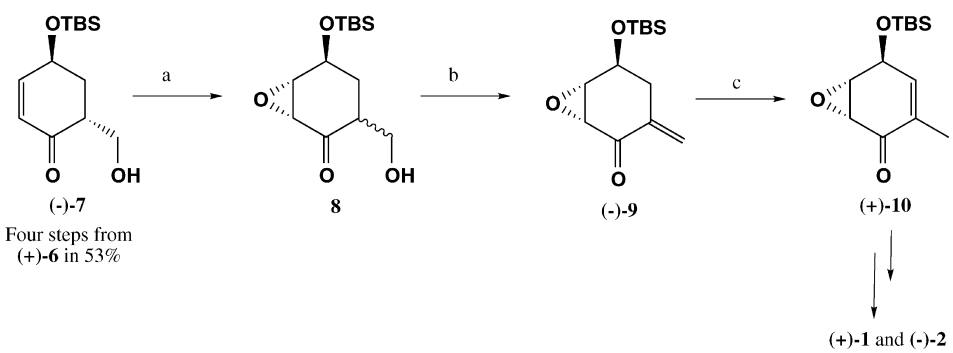
2. Results and discussion

The synthesis started from compound (−)-**7**, which was derived from (+)-**6** via four steps in 53% overall yield, and was used as an intermediate in the synthesis of (−)-eutipoxide B.[10c] Since this compound already contains the main carbon skeleton of the target molecules, including a one-carbon side chain, two oxygen functional groups, and a carbon–carbon double bond that may be transformed into an epoxide, we again chose this compound as the precursor of (+)-**1**, (−)-**2**, and (−)-**3**.

The key steps of the synthesis of (+)-**1** and (−)-**2** involved stereoselective epoxidation of the C-5,6 double bond and introduction of a carbon–carbon double bond into the C-2,3 position (numbers are based on the labeling of (+)-**1**).

First, the epoxidation was examined. The standard reaction conditions for the epoxidation of an electron deficient olefin, employing an aqueous alkaline solution of hydrogen peroxide, were too harsh for the synthesis of the desired product **8**. Hence, only undesired highly polar products were formed, probably due to the hydrolysis of the resulting epoxide. Heterogeneous conditions using THF, hydrogen peroxide, and Triton B® (benzyltrimethylammonium hydroxide) as a base were employed in order to avoid this process.[13] The reaction proceeded very fast under these conditions, and went to completion after 10 min. The yield of **8** was improved to 92% by use of catalytic amount of base. Although the hydroxymethyl group was epimerized during this reaction, resulting in an almost equivalent amount of the diastereomer mixture, the stereochemistry of the resulting epoxide was completely controlled to α-orientation. This may be due to the steric interaction of the β-TBSO-group at the C-4 position (Scheme 2).

The next stage of the synthesis involved the introduction of a double bond at the C-2,3 position, which was achieved by using the hydroxymethyl group at the C-2 position. The undesired primary hydroxyl group was removed by tosylation and subsequent elimination under basic condition. Subsequently, it was necessary to isomerise the *exo* olefin (−)-**9** to the *endo* olefin (+)-**10**. Usually rhodium catalysts are used for this type of isomerization reactions,[14] but no desired product was obtained under the common reaction conditions even after all starting material was consumed. Although Pd/C is also known as a catalyst of isomerization reactions,[15] no conversion was observed in the reaction under air or inert atmosphere. Interestingly however, when Pd/C that was pre-activated under hydrogen atmosphere was used, the reaction proceeded slowly to give the desired (+)-**10** in up to 71% yield. Unfortunately, the yield of the product varied between 31 and 71% because of sensitivity to small changes in the reaction conditions such as the time of pre-activation and the substance/catalyst/solvent purity. Since the resulting (+)-**10** was already



Scheme 2. (a) aq. H_2O_2, Triton B, THF, 92% (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 94% (c) Pd/C, MeOH, 71%.

known as the key intermediate of (+)-**1** and (−)-**2** in previous syntheses reported by Ogasawara's group,[6a] the formal total synthesis of both compounds was achieved at this stage. For further confirmation of the structure, (+)-**10** was converted to (+)-**1** according to the literature procedure,[6a] and the spectral data and [α] value of the resultant product matched those of its literature counterpart.

Synthesis of (−)-**3** was also examined. Since this compound is closely related to (+)-**1** and (−)-**2**, the same structural building block was envisaged for its synthesis. Indeed, dihydroxylation of the *exo*-olefin (−)-**10** and subsequent dehydroxylation of the resulting tertiary hydroxyl group at the C-2 position to introduce the C-2,3 double bond was proposed as a reasonable synthetic route.

First OsO_4 oxidation of (−)-**9** was carried out to give diol **11**. Although this compound was obtained as a 5:1 mixture of diastereomers, it was used in the next step without separation because the stereogenic center of the tertiary hydroxyl group would anyhow be lost in a later step. After acetylation of the resulting diol and deprotection of the TBS group, the secondary hydroxyl group at the C-4 position was oxidized to a ketone. During the oxidation, spontaneous elimination of the tertiary acetate occurred, and, consequently, the isolated compound was indicated as phyllostine acetate **12** by ^{1}H NMR spectrum. Unfortunately, all attempts to hydrolyze **12** to give (−)-**3** failed. Neither acidic (cat. 10-camphorsulfuric acid in methanol) nor basic condition (1N KOH in methanol) were appropriate for this transformation, and no desired product was formed even after all the acetate was consumed (Scheme 3).

In an effort to solve this problem, the protecting group was changed to carbonate with the aim of inducing spontaneous deprotection followed by elimination. Conversion of diol **11** to carbonate **13** was accomplished in high yield by using carbonyldiimidazole and DMAP. As expected, the deprotection of TBS and subsequent oxidation of the resulting alcohol caused the elimination of tertiary oxygen atom and the deprotection of primary oxygen atom in succession, and consequently the desired product (−)-**3** was obtained in good yield. The spectral data and [α] value were in good agreement with the reported values.[6b]

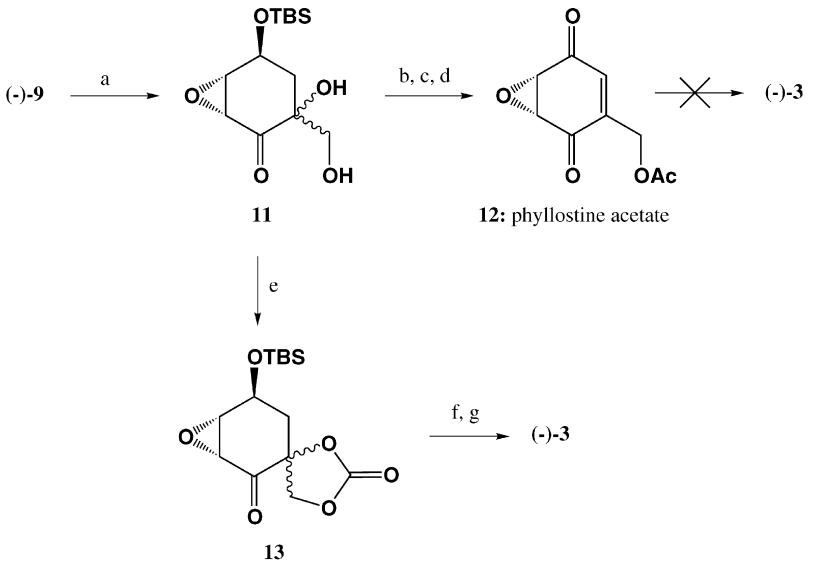
In conclusion, we have reported the total synthesis of (+)-epiepoformin and (−)-phyllostine derived from (−)-**7**, an easily obtainable chiral building block as a result of the base-catalyzed asymmetric DA reaction of 3-hydroxy-2-pyrone. Since compound (+)-**10** is already known as a precursor of (−)-theobroxide, this synthesis also represents the formal total synthesis of (−)-theobroxide.

These syntheses have made evident the high potential of the chiral building block **7** as a starting material in the asymmetric synthesis of polyoxygenated cyclohexane derivatives. The other analogous preparation of biologically active compounds in this category is now under way.

3. Experimental

3.1. General

All reagents and solvents were used as supplied commercially, except for THF and CH_2Cl_2, which were distilled from Na/Ph_2CO and CaH_2, respectively. Melting points were determined on a Yanagimoto micro melting point apparatus and are reported uncorrected. Infrared spectra were measured as KBr discs or as a thin film using NaCl plates on a JASCO FT/IR 5300 spectrophotometer, and only diagnostic absorptions in the infrared spectrum are listed. ^{1}H and ^{13}C NMR spectra were measured on a JEOL GSX400 spectrometer at 400 and 100 MHz, respectively. All chemical shifts were recorded in δ (ppm) relative to tetramethylsilane (TMS). Optical rotation was measured with a JASCO DIP-370S Digital Polarimeter. Reactions were carried out under inert atmosphere, unless otherwise



Scheme 3. OsO_4, NMO, THF–H_2O, 99%; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (c) TBAF, THF; (d) PDC, CH_2Cl_2, 24% after three steps; (e) $COIm_2$, DMAP, CH_2Cl_2, 84%; (f) CSA, MeOH, 82%; (g) CrO_3, aq. H_2SO_4–acetone, 76%.

specified. TLC analysis was performed on Silica gel 60 F_{254}-coated aluminum sheets (Merck). Visualization was accomplished with 254 nm UV light and a 12-molybdo(VI) phosphoric acid ethanol solution was used as a developing agent.

3.1.1. (−)-(2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methylene-1-cyclohexanone (9). To a solution of (−)-**7** (200 mg, 0.78 mmol) in dry THF (7.8 mL) were added Triton B® (40% in H_2O, 92 μL, 0.23 mmol) and H_2O_2 (30% in H_2O, 270 μL, 2.34 mmol) at 0°C. After stirring for 10 min, the reaction was quenched with dimethyl sulfide (130 μL, 1.79 mmol) and a few drop of acetic acid. The whole mixture was poured onto water and extracted three times with ethyl acetate (10 mL). The combined organic layer was dried over $MgSO_4$, filtered through a glass filter, and evaporated under reduce pressure. Purification of the residue via silica gel column chromatography (hexane/ethyl acetate, 1:1) gave a diastereomeric mixture of epoxyalcohol **8** (194 mg, 92%) as a colorless oil. The mixture was used without separation in the next step.

To a solution of **8** (940 mg, 3.45 mmol) in CH_2Cl_2 (15 mL) at 0°C were added DMAP (120 mg, 1.03 mmol), Et_3N (2.00 mL, 13.8 mmol) and tosyl chloride (986 mg, 5.18 mmol). After stirring for 5 h, the reaction mixture was poured onto water (20 mL) and extracted three times with ethyl acetate (10 mL). The combined organic layer was dried over $MgSO_4$, filtered through a glass filter, and evaporated. The residue was purified via silica gel column chromatography to give (−)-**9** (822 mg, 94%) as a colorless oil. R_f 0.38 (dry benzene/hexane, 10:1); $[\alpha]_D^{27}=-50.6$ (*c* 0.710, $CHCl_3$); IR (film): 1693, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.24 (br s, 1H), 5.29 (br s, 1H), 4.51 (dd, *J*=6.2, 2.9 Hz, 1H), 3.56 (dt, *J*=6.2, 4.0 Hz, 1H), 3.44 (d, *J*=4.0 Hz, 1H), 2.83 (ddd, *J*=16.0, 6.2, 2.9 Hz, 1H), 2.45 (dd, *J*=16.0, 2.9 Hz, 1H), 0.85 (s, 9H), 0.10, 0.08 (each s, 3H); ^{13}C NMR ($CDCl_3$): δ 193.5, 137.4, 125.7, 65.4, 57.8, 55.1, 33.9, 25.6, 18.0, −4.7, −4.8. Anal. calcd for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.33; H, 8.69.

3.1.2. (+)-(2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-methyl-cyclohex-5-en-1-one (10). A suspension of Pd/C (5% Pd in active charcoal, 10 mg) in anhydrous MeOH (2.0 mL) was subjected to H_2 at 1 atm provided by a rubber balloon. After stirring for 4 h at room temperature, the atmosphere of the reaction vessel was changed to N_2, and the compound (−)-**9** (20 mg, 0.079 mmol) was then added. After stirring for 1 week at 40°C, the reaction mixture was filtered through a pad of celite, and evaporated to afford a concentrate residue. Chromatography of the residue on silica gel (dry benzene/hexane, 10:1) gave Ogasawara's intermediate (+)-**10** as a colorless oil (14 mg, 71%). R_f 0.33 (dry benzene/hexane, 10:1); $[\alpha]_D^{31}=+252$ (*c* 0.820, $CHCl_3$); [lit.: $[\alpha]_D^{28}=+250.72$ (*c* 1.17, $CHCl_3$);[6a] $[\alpha]_D^{28}=+251.3$ (*c* 1.40, $CHCl_3$)];[7a] IR (film): 1684 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (br s, 1H), 4.64 (dd, *J*=4.8, 1.1 Hz, 1H), 3.63 (ddd, *J*=4.8, 3.7, 1.1 Hz, 1H), 3.48 (dd, *J*=3.7, 1.1 Hz, 1H), 1.83 (d, *J*=1.1 Hz, 3H), 0.92 (s, 9H), 0.17, 0.15 (each s, 3H); ^{13}C NMR ($CDCl_3$): δ 194.0, 139.5, 133.4, 64.0, 58.4, 53.4, 25.7, 18.2, 15.9, −4.4, −4.6. Anal. calcd for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.33; H, 8.69.

3.1.3. (+)-Epiepoformin (1). In accordance with the literature method,[6a] Ogasawara's intermediate (+)-**10** (15.4 mg, 0.061 mmol) was converted to (+)-epiepoformin (8.5 mg, 99%) as a white solid. R_f 0.33 (hexane/AcOEt, 1:1); mp 86.5–88.5°C; $[\alpha]_D^{27}=+310$ (*c* 0.460, EtOH); [lit.: mp 87.5–88.5°C;[6a] $[\alpha]_D^{28}=+316.04$ (*c* 0.37, EtOH);[6a] mp 84–85°C;[7b] $[\alpha]_D^{28}=+314.5$ (*c* 0.49, EtOH);[7b] $[\alpha]_D^{25}=+221$ (*c* 0.83, EtOH)];[2] IR (film): 3431, 1676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.47 (br s, 1H), 4.66 (m, 1H), 3.79 (ddd, *J*=3.7, 1.5, 1.1 Hz, 1H), 3.50 (dd, *J*=3.7, 1.1 Hz, 1H), 2.29 (d, *J*=8.8 Hz, 1H, −OH), 1.85 (t, *J*=1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 194.2, 138.8, 134.5, 63.4, 57.6, 53.3, 15.9. Anal. calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.11; H, 5.83.

3.1.4. (2*R*,3*S*,4*S*)-4-*tert*-Butyldimethylsilyloxy-2,3-epoxy-6-hydroxy-6-hydroxymethyl-1-cyclohexanone (11). To a solution of (−)-**9** (61.8 mg, 0.243 mmol) in dry THF (2.4 mL) were added NMO (85.0 μL, 0.365 mmol) and OsO_4 (0.2 M in *t*-BuOH, 23 μL, 0.0046 mmol), and the mixture was stirred for 1 day. The resulting mixture was poured onto an aqueous saturated solution of $NaHCO_3$ (10 mL) and extracted three times with ethyl acetate (10 mL). The combined organic layer was washed with brine, and dried over $MgSO_4$. After filtration, all volatile compounds were evaporated under reduce pressure. Purification of the residue via silica gel column chromatography (hexane/ethyl acetate, 2:3) afforded a 5:1 diastereomeric mixture of **11** (69.1 mg, 99%) as a colorless oil. R_f 0.59 and 0.49 (hexane/ethyl acetate, 2:3) for major and minor isomers, respectively. IR (film): 3436, 2932, 1725 cm^{-1}; ^1H NMR of major isomer ($CDCl_3$): δ 4.59 (m, 1H), 3.82 (dd, *J*=10.6, 4.0 Hz, 1H), 3.41–3.57 (m, 5H, including 2× −OH), 2.16 (dd, *J*=14.9, 4.0 Hz, 1H), 1.96 (ddd, *J*=14.9, 2.5, 1.2 Hz, 1H), 0.95 (s, 9H), 0.20 (s, 6H); ^1H NMR of minor isomer ($CDCl_3$): δ 4.61 (m, 1H), 4.05 (dd, *J*=11.7, 7.7 Hz, 1H), 3.98 (s, 1H, −OH), 3.91 (dd, *J*=11.7, 6.2 Hz, 1H), 3.49 (dd, *J*=4.0, 1.1 Hz, 1H), 3.40 (br t, *J*=3.5 Hz, 1H), 2.80 (dd, *J*=18.0, 6.6 Hz, 1H), 2.55 (dd, *J*=18.0, 2.6 Hz, 1H), 2.39 (br t, *J*=7.0 Hz, 1H, −OH), 0.93 (s, 9H), 0.15, 0.13 (each s, 3H). Anal. calcd for $C_{13}H_{24}O_5Si$: C, 54.14; H, 8.39. Found for diastereomeric mixture: C, 54.08; H, 8.40.

3.1.5. Phyllostine acetate (12). To a solution of a diastereomeric mixture of **11** (22 mg, 0.076 mmol) in CH_2Cl_2 (0.76 mL) were added Et_3N (36 μL, 0.264 mmol), DMAP (0.8 mg, 0.006 mmol), and Ac_2O (25 μL, 0.26 mmol) at room temperature. After stirring for 12 h, the mixture was filtered through a pad of silica gel, washed with ether, and concentrated.

To a solution of the residue in dry THF (0.76 mL) was added TBAF (1.0 M in THF, 76 μL, 0.076 mmol) at room temperature. After stirring for 1 h at the temperature, the mixture was filtered through a pad of silica gel, washed with ether, and concentrated.

The residue (7.8 mg) was dissolved in CH_2Cl_2 (0.6 mL), and PDC (56.8 mg, 0.151 mmol) was added to the solution

at room temperature. The mixture was stirred for 15 h, and filtered through a pad of silica gel. The filtrate was evaporated and the residue was purified via silica gel column chromatography (hexane/ethyl acetate, 1:1) to give **12** (3.6 mg, 24% after three steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.73 (m, 1H), 4.95 (br d, J=12.0 Hz, 1H), 4.80 (br d, J=12.0 Hz, 1H), 3.80–3.85 (m, 2H), 2.10 (s, 3H).

3.1.6. (7*R*,8*S*,9*S*)-9-*tert*-Butyldimethylsilyloxy-2,6-dioxo-7,8-epoxy-1,3-dioxa-spiro[4.5]decane (13). To a solution of **11** (51.3 mg, 0.178 mmol) in CH_2Cl_2 were added DMAP (2.1 mg, 0.0178 mmol) and *N*,*N*′-carbonyldiimidazole (43.3 mg, 0.267 mmol). After stirring for 1 day, the resulting mixture was directly purified by silica gel column chromatography to give a 6:1 diastereomeric mixture of **13** (46.8 mg, 84%) as a colorless oil. R_f 0.60 (CH_2Cl_2/ethyl acetate, 20:1); IR (KBr): 2951, 1822, 1736 cm^{-1}; Major diastereomer: ^{1}H NMR ($CDCl_3$): δ 4.68 (br d, J=3.2 Hz, 1H), 4.42 (dd, J=9.5, 1.5 Hz, 1H), 4.19 (d, J=9.5 Hz, 1H), 3.56 (m, 1H), 3.49 (d, J=3.7 Hz, 1H), 2.64 (br dd, J=13.9, 2.7 Hz, 1H), 2.11 (dd, J=13.9, 3.4 Hz, 1H), 0.91 (s, 9H), 0.17, 0.16 (each s, 3H). Minor diastereomer: ^{1}H NMR ($CDCl_3$): δ 4.64 (m, 1H), 4.39 (d, J=9.5 Hz, 1H), 4.32 (d, J=9.5 Hz, 1H), 3.60 (m, 1H), 3.56 (m, 1H), 2.73 (dd, J=18.3, 3.7 Hz, 1H), 2.56 (br d, J=18.3 Hz, 1H), 0.89 (d, J=1.5 Hz, 9H), 0.14, 0.12 (each s, 3H). Anal. calcd for $C_{14}H_{22}O_6Si$: C, 53.48; H, 7.05. Found for diastereomeric mixture: C, 53.52; H, 7.08.

3.1.7. (−)-Phyllostine (3). To a solution of **13** (90 mg, 0.28 mmol) in methanol (4.0 mL) was added DL-10-camphorsulfonic acid (7.0 mg, 0.028 mmol), and the mixture was stirred for 15 h at room temperature. The resulting mixture was evaporated, and directly purified via silica gel column chromatography to give a diastereomeric mixture of alcohol (46 mg, 82%) as colorless oil. R_f 0.33 (AcOEt); IR (film): 3418, 1800, 1732, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.62 (m, 1H), 4.50 (d, J=9.9 Hz, 1H), 4.41 (d, J=9.9 Hz, 1H), 3.70 (t, J=4.0 Hz, 1H), 3.62 (t, J=4.0 Hz, 1H), 2.69 (dd, J=18.7, 3.7 Hz, 1H), 2.62 (dd, J=18.7, 2.6 Hz, 1H). Anal. calcd for $C_8H_8O_6$: C, 48.01; H, 4.03. Found: C, 48.05; H, 4.11.

To a solution of the resulting alcohol (10 mg, 0.052 mmol) in acetone (520 μL) containing in a round-bottomed flask in an ice bath was added Jones reagent (2.0 M CrO_3 in aq. H_2SO_4, 31 μL, 0.062 mmol), and the mixture was stirred for 2.5 h in the ice bath. The mixture was poured onto aq. saturated solution of $NaHCO_3$ (10 mL) and extracted three times with ethyl acetate (10 mL). The combined organic layer was washed with brine, and dried over $MgSO_4$. Upon filtration, the mixture was evaporated under reduced pressure. Purification of the residue via column chromatography provided (−)-phyllostine (**3**) (6.0 mg, 76%) as a yellowish oil:[16] R_f 0.50 (hexane/ethyl acetate, 3:7); $[\alpha]_D^{28}$=−120 (*c* 0.28, EtOH); [lit.: $[\alpha]_D^{31}$=−100.4 (*c* 0.6, EtOH);[6b] $[\alpha]_D^{26}$=−118.7 (*c* 0.05, EtOH);[6a] $[\alpha]_D^{20}$=−105.6 (*c* 1.0, EtOH)];[4] IR (film): 3400, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.69 (dt, J=4.0, 2.0 Hz, 1H), 4.58 (ddd, J=17.4, 5.8, 2.0 Hz, 1H), 4.40 (ddd, J=17.4, 5.8, 2.0 Hz, 1H), 3.82–3.85 (m, 2H), 1.98 (t, J=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$):[17] δ 191.5, 190.6, 147.6, 130.8, 59.2, 54.0. Anal. calcd for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.69; H, 4.00.

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16. Phyllostine was originally reported as a solid,[4,6a,b] but we isolated pure phyllostine as a yellowish oil, which agrees with the calculated values of elemental analysis. The product is relatively unstable and after 24 h at room temperature, it changed into pale brown solid that no longer satisfied the elemental analysis.
17. Since the overlapped signal at 54.0 ppm corresponding to the epoxy carbons, only five signals were observed. The signal intensity at 54.0 ppm was higher than its methylene carbon at 59.2 ppm.