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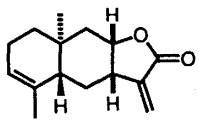
The Total Synthesis of Optically-Active Diplophyllolide A and Diplophyllin[1)]

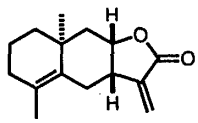
Nobuo KATO,* Hideyuki NISHIKAWA, and Hitoshi TAKESHITA*

Optically-active diplophyllolide A and diplophyllin, mould metabolites having the opposite absolute configuration to the metabolites of higher plants, were synthesized.

Diplophyllolide A and diplophyllin (**1a** and **1b**)[2)] are components of plagiospirolides A and B (**2a** and **2b**), isolated from *Plagiochila moritziana*.[3)] The planar structures of **1a** and **1b** are equivalent to the 2-deoxo derivative of pinnatifidin, isolated from *Helenium pinnatifidum*,[4)] and 1-deoxy derivative of ivangustin, isolated from *Iva angustifolia*,[5)] and both have partially been synthesized from artemisin.[6)]



Diplophyllolide A (**1a**)



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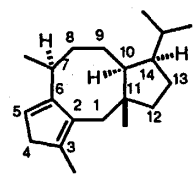
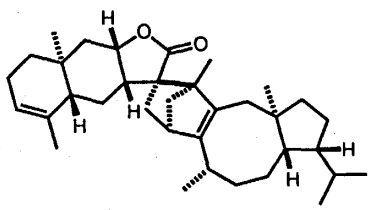
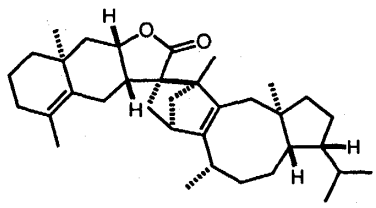


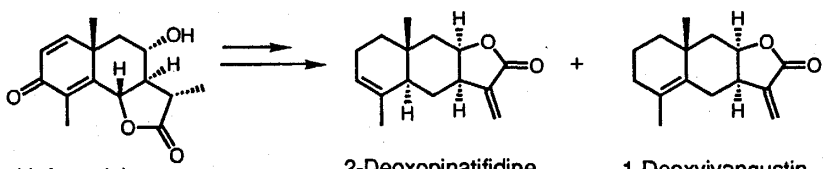
Fusicocca-2,5-diene (**3**)



Plagiospirolide A (**2a**)



Plagiospirolide B (**2b**)



(-)-Artemisin　　2-Deoxopinatifidine　　1-Deoxyivangustin

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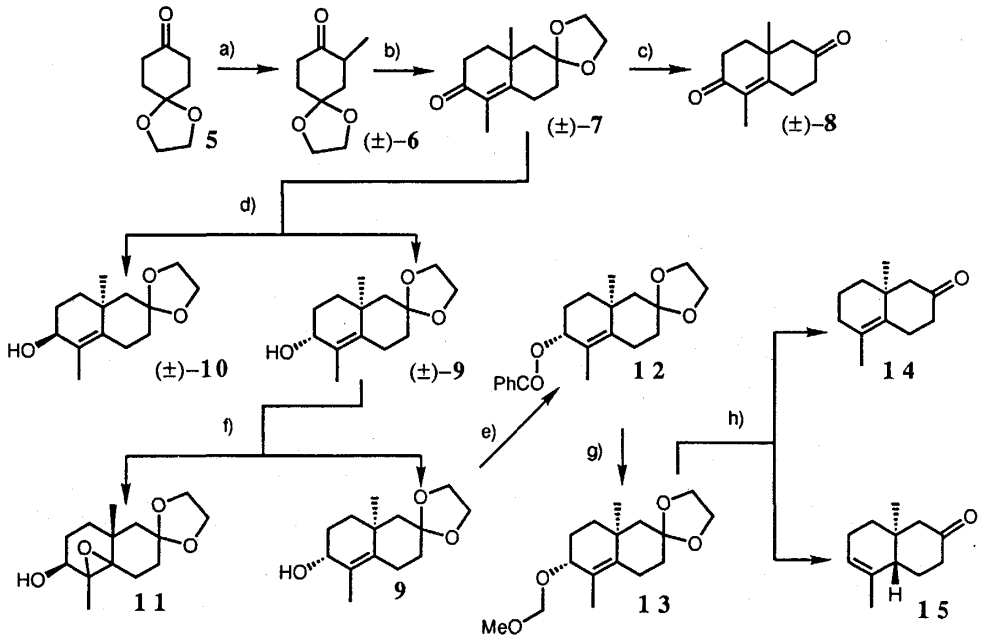
We have been interested in the unique strucures of **2a** and **2b**, which might be biosynthesized via Diels-Alder reaction between the 5-8-5-membered tricyclic diterpene (**3**) and **1a** and **1b**.[3] Although the absolute configuration of **2a** and **2b** is not described precisely, the source of the compounds suggested to have the opposite configuration from the metabolites of higher plants. Therefore, there might be no easily available optically active relay compound. Fortunately, there is a paper[7] describing a total synthesis of (±) -3-oxodiplophyliln ((±)-**4**), a closely related compound. Although the original procedure showed a few points to overcome, we thought it could be practical to prepare eudesmanolide skeleton. Herein we describe the results.

Results and Discussions

In order to synthesize optically-active **1a** and **1b**, we selected a rather conventional route with a slight modification of Caine's synthesis of racemic 3-oxodiplophyllin ((±)-**4**).[7] Thus, cyclohexane-1,4-dione monoethylene acetal (**5**) was treated with lithium diisopropylamide (LDA) to form an enolate, and this was used for methylation by treatment with methyl iodide to give 2-methylcyclohexane-1,4-dione monoethylene acetal ((±)-**6**). Then, (±)-**6** was subjected to a Robinson annulation with 1-penten-3-one to give 4, 10-dimethyl-8, 8-ethylenedioxy-Δ^4-3-octalone ((±)-**7**). Upon treatment with aqueous acetic acid, (±)-**7** formed 4, 10-dimethy 1-Δ^4-3,8-octalindione ((±)-**8**). According to the method of Caine, the introduction of a C_2-side chain at C-7 via selective enamine formation from the isolated C-8 keto group was not satisfactory; this rather disappointing result might be due to the presence of two keto functions, one of which is unnecessary for our purpose. In addition, we need an optical resolution at an early stage. Therefore, (±)-**7** was reduced with lithium aluminumhydride (LAH) to give the epimeric allyl alcohols, (±)-**9** and (±)-**10**.

The kinetic resolution of (±)-**9** by means of Sharpless epoxidation[8] with a half molar amount of oxidizing agent yielded an optically-active epoxy alcohol (**11**) and the unreacted **9**. After separation by column chromatography on a silica gel, **9** was esterified with benzoyl chloride to give the benzoate (**12**). The optical purity of **12** at this stage was 75 % e. e. Repeated recrystallizations from hexane and ethyl acetate, followed by saponification afforded the desired (-)-**9** ($[\alpha]_D^{21}$=-50°) enantiomerically pure. Meanwhile, we examined a preferential crystallization procedure at this stage; however, the melting point of the optically-pure **12** was 80-82 ℃, while that of the racemate ((±)-**12**) was 98-99 ℃. Indeed, seeding the optically-pure crystalline **12** afforded the crystals of (±)-**12**. Consequently, Optically-active **12** in sufficient quantity for further synthetic operations was prepared by the kinetic epoxidation. Birch reduction of **12** was somewhat complicated due to the easy



Reagents: a) $(i\text{-}Pr)_2NH$-BuLi, MeI; b) aq. KOH, $ClCH_2CH_2COCH{=}CH_2$; c) aq. AcOH; d) $LiAlH_4$;e) PhCOCl pyridine; f)$Ti(O\text{-}i\text{-}Pr)_4$, (+)-$(CHOHCO_2\text{-}i\text{-}Pr)_2$ /t-BuO_2H; g) KOH/ MeOH;)$(i\text{-}Pr)_2NEt$, MOMCl; h) Li/$EtNH_2$.

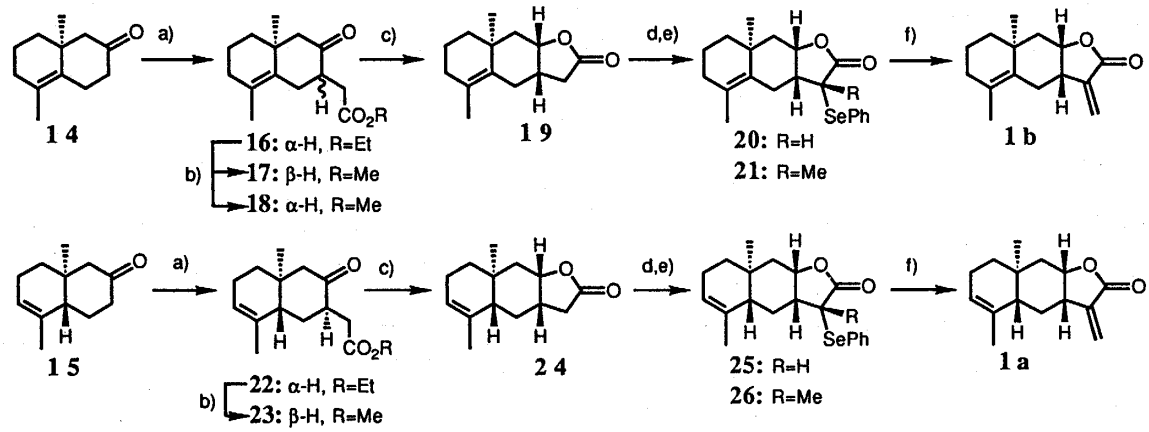
cleavage of the benzoyl group. Therefore, **9** was converted to the methoxymethyl ether (**13**) and reduced with lithium and ethylamine; after hydrolysis of the acetal group, 1, 4-dimethyl-Δ^4-8-octalone (**14**) and *trans*-1, 4-dimethyl-Δ^3-8-octalone (**15**) were obtained in 72 and 18 % yields, respectively.

For the next step to **1b**, an introduction of the acetic acid moiety of the α-position of the major isomer **14** was investigated. For the introduction of the acetic acid unit into **14**, the best result was obtained by means of lithium hexamethyldisilylazide and ethyl bromoacetate to stereospecifically from the α-*axial* derivative (**16**).[9] Then the epimerization of the ethoxycarbonylmethyl group of **16** by an alkali-treatment and reesterification gave **17** and unepimerized methyl ester (**18**). The sodium borohydride reduction of **17** gave a γ-lactone (**19**), which was converted to the α-methylene derivative **1b** by the method developed by Grieco and Miyashita;[10] treatment of **19** with diphenyl diselenide afforded a stereoisomeric mixture of α-phenylselenyl derivatives (**20**), which were directly treated with base and methyl iodide to give the methylation product (**21**). Oxidation of **21** with hydrogen peroxide afforded **1b**. The identity of synthetic and natural **1b** was assured by pertinent ^1H and ^{13}CNMR spectral comparisons.[2]

Diplophyllolide (**1a**) was prepared from the by-product (**15**) of the Birch reduction of **13**: The acetic acid moiety was introduced into **15** by the method mentioned as above to give **22**, which was epimerized by saponification and methylation with diazomethane to afford **22**. The reductive lactonization of **23** yielded **24** as the single compound. Finally, **24** was converted, via the phenylselenyl derivative (**25**) and the α-methyl-α-phenylselenyl

derivative (**26**), into **1a**. The identity of both synthetic and natural **1a** was unambiguously established by ^{1}H and $^{13}CNMR$ specteoscopy, and by its conversion to plagiospirolides A and B.[1)]

In conclusion, this constitutes the first total synthesis of **1a** and **1b**.



Reagents: a) ($Me_3Si)_2NH$-BuLi, $BrCH_2CO_2Et$; b) KOH/EtOH; CH_2N_2I; c) $NaBH_4$; d) $(i\text{-}Pr_2)NH$-BuLi, $(PhSe)_2$/HMPA; e) $(i\text{-}Pr_2)NH$-BuLi, MeI/HMPA; f) H_2O_2.

Experimental

The mps were measured with a Yanagimato Micro Melting Point Apparatus and are uncorrected. The NMR Spectra were measured by JEOL FX 100 Model and GSX 270H Model spectrometers in $CDCl_3$; the chemical shifts were expressed in the unit of δ. The stationary phase for column chromatography was Wakogel C-300, and the eluent was a mixture of ethyl acetate and hexane.

Preparation of (±)-7. To a tetrahydrofuran (THF) solution (50 cm^3) of $(i\text{-}Pr)_2NH$ (5.4 cm^3), BuLi (39.2 mmol in 24.2 cm^3 of hexane) was added while cooling with ice and stirred for 30 min. The mixture was then cooled to −78 ℃, to which, **5** (5.11 g; 32.7 mmol) was introduced dropwise and after being stirred for another 30 min, MeI (6.1 cm^3) was introduced and gradually warmed up to 0 ℃. The mixture was treated with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and chromatographed on a silica-gel column to give (±)-**6** (3.72 g; 67%).

Then, to an EtOH solution (20 cm^3) of KOH (6.1 g; 85 %; 92.8 mmol), ether (30 cm^3) was added at 0 ℃ under an N_2 atmosphere, and anhydrous ether solution (20 cm^3) of (±)-**6** (7.89 g; 46.4 mmol) was added dropwise for 15 min. The mixture was stirred for another 45 min, and an ether solution (20 cm^3) of 5-chloro-1-penten-3-one (6.7 g; 55.7 mmol) was introduced within 30 min. After being stirred for 5 h at room temperature, the mixture was poured into water and extracted with EtOAc. The organic layer was dried over

Na_2SO_4 and chromatographed on a silica-gel column to give (±)-**7**[7] [a colorless oil, 9.14 g; 83%. ^{1}HNMR δ =1.35 (3H, s), 1.56-1.85 (5H, m), 1.79 (3H, s), 1.85-2.0 (1H, m), 2.3-2.6 (3H, m), 2.74 (1H, ddd, J=15.0, 4.4, 3.3 Hz), 3.93 (2H, m), 4.02 (2H, m). ^{13}CNMR δ =11.5, 24.1, 26.0, 33.9, 35.0, 37.3, 38.4, 48.9, 64.1, 65.0, 108.2, 129.2, 160.9, and 199.1].

Hydrolysis of (±)-7 to (±)-8. An aqueous AcOH solution (1 : 4.2 cm^3) of (±)-**7** (64 mg; 0.27 mmol) was heated at 60 ℃ for 1.5 h. The mixture was poured into icecooled aq. K_2CO_3, and extracted with EtOAc. The organic layer was washed with NaCl solution and dried over Na_2SO_4, and chromatographed on a silica-gel column to give (±)-**8** [a colorless oil, 47 mg; 90 %. ^{1}HNMR δ =1.25 (3H, s), 1.83 (3H, s), 1.85 (1H, m), 1.97 (1H, dt, J= 13, 5 Hz), 2.36 (1H, dd, J=15, 1 Hz), 2.45 (1H, br d, J=15 Hz), 2.45−2.8 (5H, m), and 2.96 (1H, dt, J=16.5, 7 Hz)].

Reduction of (±)-7 with $LiAlH_4$. Formation of (±)-9 and (±)-10. An anhydrous ether solution (80 cm^3) of (±)-**7** (9.14 g; 38.7 mmol) was treated with LAH (736 mg; 19.4 mmol) while being cooled with ice. The mixture was stirred for 1 h at room temperature. The mixture was treated with a small amount of water, dried over Na_2SO_4, and chromatographed on a silica-gel column to give (±)-**9** [colorless crystals, mp 82−83 ℃, 6.79 g; 74%. ^{1}HNMR δ = 1.23 (3H, S), 1.4-2.0 (8H, m), 1.74 (3H, s), 2.17 (1H, tm, J=14 Hz), 2.51 (1H, ddd, J=14.5, 4.5, 3 Hz), and 3.85-4.10 (5H, m)] and (±)-**10** [colorless soild, 881 mg; 10%. ^{1}HNMR δ =1.15 (3H, s), 1.3-1.9 (8H, m), 1.78 (3H, s), 2.16 (1H, tm, J=14 Hz), 2.53 (1H, ddd, J=14.5, 4, 3.5 Hz), and 3.85-4.05 (5H, m)].

Benzoylation of (±)-9 to (±)-12. To a pyridine solution (1 cm^3) of (±)-9 (34 mg; 0.14 mmol) was added PhCOCl (24 mg) at 0 ℃. After 1.5 h, the mixture was diluted with ether, and washed with aq. $KHSO_4$, aq. $NaHCO_3$, and aq. NaCl. The organic layer was dried over Na_2SO_4 and chromatographed on a silica-gel column to give (±)-**12** [colorless crystals, mp 98-99 ℃, 50 mg; 100%. ^{1}HNMR δ =1.30 (3H, s), 1.45-1.70 (5H, m), 1.70-1.90 (2H, m), 2.03 (1H, br. m), 2.25 (1H, tm, J=13.0 Hz), 2.58 (1H, dt, J=14.5, 4.0 Hz), 3.85-4.05 (4H, m), 5.54 (1H, t, J=7.0 Hz), 7.35-7.50 (3H, m), and 8.05-8.15 (2H, m)].

Kinetic Resolution of (±)-9 by Means of The Sharpless Epoxidation. Formation of 11 and 9. To a CH_2Cl_2 solution (200 cm^3) of (±)-**9** (6.36 g; 26.7 mmol) were added Ti (O-i-Pr)$_4$ (7.59 g; 26.7 mmol) and diisopropyl L-tartrate (9.39 g). The mixture was cooled to −25 ℃, and treated with t-BuOOH (80%, 1.53 g; 13.6 mmol) and kept 2 d at that temperature. The mixture was then diluted with water, and extracted with CH_2Cl_2. The organic extract was washed with aq. NaCl, dried over Na_2SO_4, and chromatographed on a silica-gel column to give a mixture of unreacted **9** and diisopropyl tartrate (7.3 g) and **11** [colorless solid, 3.49 g; quantitative yield. ^{1}HNMR δ =0.94 (1H, m), 1.21 (3H, s), 1.3-1.64 (4H, m), 1.47 (3H, S), 1.85 (2H, m), 2.1-2.35 (3H, m), and 3.8-4.0 (5H, m)].

Benzoylation of 9 to 12. The above fractions containing **9** were dissolved in pyridine (30 cm^3) and treated with PhCOCl (5.3 cm^3; 46 mmol) at room temperature for 1.5 h. The mixture was diluted with ether, washed with aq. $KHSO_4$ and aq. NaCl, and dried over Na_2SO_4. After evaporation of the sovent in vacuo, the residue thus obtained was chromatographed on a silica-gel column to give **12** [colorless crystals, mp 80-82 ℃, 4.66 g; 50%]. Optical purity of this product was ca. 70% e.e., judged by chiral HPLC analysis. Recrystallization from EtOH gave optically-pure **12** [$[\alpha]_D^{28}$ = +23 ℃ (c 1.00, $CHCl_3$)].

Saponification of 12. Formation of Optically-Pure 9. To an MeOH solution (30 cm^3) of **12** (1.91 g; 5.38 mmol) was added KOH (85%, 550 mg; 8.38 mmol) and refluxed for 2.5 h. The residue thus obtained was extracted with EtOAc, washed with aq. $NaHCO_3$ and aq. NaCl, dried over Na_2SO_4, and chromatographed on a silica-gel column chromatography to give **9** [a colorless crystals, mp 82-84 ℃, 1.30 g; 98% from **12**, and 41% from (±)-**9**; $[\alpha]_D^{26}$ = −50° (c 1.00, $CHCl_3$)].

Methoxymethyl Ether (13) of 9. To a CH_2Cl_2 solution (15 cm^3) of **9** (1.30 g; 5.46 mmol) were added $(i\text{-}Pr)_2NH$ (2.86 cm^3) and MOMCl (830 mg; 10.9 mmol) at room temperature for 2 h. The mixture was then diluted with CH_2Cl_2, washed with aq. $KHSO_4$, aq. $NaHCO_3$, and aq. NaCl, and dried over Na_2SO_4. After evaporation of the solvent, the residue thus obtained was chromatographed on a slilica-gel column to give **13** [a colorless oil, 1.50 g; 97 %. $[\alpha]_D^{25}$ = −56° (c 1.08, $CHCl_3$)].

Birch Reduction of 13. Formation of 14, and 15. The Li (830 mg) was added to an $EtNH_2$ solution (50 cm^3) of **13** (1.3 g; 5.46 mmol) at −78℃ and under N_2 atmosphere. The mixture was then warmed up to 0 ℃ in a 3-h period and treated with $PhCO_2Na$ and aq. NH_4Cl. After evaporation of the amine, the residue was diluted with water and extracted with hexane. After a brief filtration of the hexane solution through a slilica-gel column, the mixture was heated in vacuo to remove the solvent, and thus-obtained residue was dissolved in aq. AcOH (1:3, 16 cm^3), and heated at 60 ℃ for 45 min. The mixture was then poured into ice-cooled aq. K_2CO_3 and extracted with hexane. Slilica-gel column chromatography of the organic layer afforded **14** [a colorless oil, 676 mg; 72%. $[\alpha]_D^{26}$ = −56° (c 1.08, $CHCl_3$). ^{13}HNMR δ = 1.04 (3H, s), 1.49 (1H, dd, J=9.0, 3.5 Hz), 1.5-1.7 (4H, m), 1.70 (3H, s), 2.02 (1H, m), 2.14 (1H, dd, J=13.5, 2 Hz), 2.25-2.45 (4H, m), and 2.88 (H, m). ^{13}CNMR δ = 19.3, 19.6, 25.2, 26.4, 32.9, 38.5, 39.5, 41.4, 55.8, 127.5, 131.4, and 212.0] and **15** [a colorless oil, 239 mg; 25% as a mixture with 5-*epi*-**15** (3 : 1). ^{1}HMNR δ = 1.00 (3H, s), 1.26 (1H, dt, J=13.6 Hz), 1.4-1.6 (2H, m), 1.67 (1H, m), 1.74 (3H, d, J=2 Hz), 1.9−2.1 (2H, m), 2.1−2.6 (5H, m), and 5.38 (1H, m)].

Conversion of 14 into 16. To an anhydrous THF solution (5 cm^3) of $(Me_3Si)_2NH$ (1.07 cm^3; 5.07 mmol) was added BuLi (4.71 mmol in 3.0 cm^3 of hexane) at 0 ℃ and the resulting solution was kept 30 min at that temperature. The mixture was then cooled to −78 ℃

and a THF solution (5 cm^3) of **14** (654 mg; 3.62 mmol) was added drowise. After 30 min, HMPA (3.0 cm^3) and $BrCH_2CO_2Et$ (1.2 cm^3) were added to the mixture and further stirred for another 30 min. The mixture was then gradually warmed up to 0 ℃, and poured into water. After evaporation of the solvent in vacuo, the residue was extracted with EtOAc, washed with aq. NaCl, dried over Na_2SO_4, and chromatographed on a slilica-gel column to give **16** [a colorless oil, 900 mg; 94%. $[\alpha]_D^{26}$ = +38° (c 1.10, $CHCl_3$). ^{1}HNMR δ = 1.00 (3H, s), 1.26 (3H, t, J=7 Hz), 1.45-1.7 (4H, m), 1.63 (3H, s), 1.95-2.1 (2H, m), 2.20 (1H, d, J=14.5), 2.37 (1H, d, J=14.5), 2.43 (1H, dd, J=16, 8 Hz), 2.57 (1H, dd, J=16, 6 Hz), 2.61(2H, m), 2.94 ((1H, dqm, J=8.5, 6 Hz), and 4.14 (2H, q, J=7 Hz). ^{13}CNMR δ = 14.2, 19.1, 19.5, 26.8, 30.0, 32.4, 35.5, 37.6, 39.1, 46.2, 53.0, 60.7, 129.1, 129.4, 171.8, and 212.4].

Epimerization of 16 to 17. To an EtOH solution (15 cm^3) of **16** (845 mg; 0.24 mmol) was sdded KOH (85%, 633 mg; 9.6 mmol) and the mixture was stirred at room temperature for 24 h. The mixture was then acidified with 2 N HCl and the solvent was removed by evaporation. The residue was dissolved in EtOAc, washed with aq. NaCl. The organic layer was dried over Na_2SO_4, and the residue obtained after removing the solvent was treated with an excess of etheral CH_2N_2. The residue obtained by evaporation of the solvent was chromatographed on a slilica-gel column to give **17** [a colorless oil, 540 mg; 68%. $[\alpha]_D^{21}$ = −46° (c 1.50, $CHCl_3$). ^{1}HMNR δ = 1.00 (3H, s), 1.5-1.7 (4H, m), 1.71 (3H, s), 1.95-2.1 (3H, m), 2.17 (1H, d, J=13 Hz), 2.23 (1H, m), 2.40 (1H, br, d, J=13.8 Hz), 2.75-2.9 (2H, m), 2.97 (1H, dd, J=13.5, 6 Hz), and 3.69 (3H, s). ^{13}CNMR δ = 19.2, 19.6, 26.0, 32.1, 32.8, 33.7, 39.3, 39.4, 46.7, 51.5, 55.5, 128.0, 130.9, 172.8, and 210.3]. and the unepimerized **18** [a colorless oil, 153 mg; 19%. ^{1}HNMR δ = 1.11 (3H, s), 1.4-1.7 (4H, m), 1.63 (3H, s), 2.0-2.1 (2H, m), 2.21 (1H, dd, J=14.5, 0.5 Hz), 2.36(1H, d, J=14.5 Hz), 2.45 (1H, dd, J= 16.8 Hz), 2.60 (1H, dd, J=16, 6 Hz), 2.60 (2H, m), 2.95 (1H, m), and 3.68 (3H, s)].

Formation of γ-Lactone (19) from 17. An MeOH solution (1 cm^3) of **17** (114 mg; 0.46 mmol) was treated with $NaBH_4$ (17 mg; 0.46 mmol) at 0 ℃ under an N_2 atmosphere. After 10 min, the mixture was treated with acetone and heated in vacuo to remove the solvent. The residue was extracted with EtOAc and chromatographed on a slilica-gel column to give **19** [colorless solid, 91 mg, 91%. $[\alpha]_D^{23}$ = −69° (c 1.08, $CHCl_3$). ^{1}HNMR δ = 1.13 (3H, s), 1.35 (1H, m), 1.5-1.65 (4H, m), 1.63 (3H, br, s), 1.8-2.0 (3H, m), 2.07 (1H, dd, J=15, 4 Hz), 2.28 (1H, dd, J=17.2 Hz), 2.40 (1H, m), 2.59 (1H, dd, J=15, 6.5 Hz), 2.69 (1H, dd, J=17, 7 Hz), and 4.53 (1H, q, J=4.5 Hz). ^{13}CNMR δ = 18.7, 19.4, 26.9, 27.2, 32.6, 33.4, 36.7, 37.6, 39.5, 42.2, 79.8, 127.2, 131.5, and 177.3].

Conversion of 19 into 1b via 20 and 21. The BuLi (0.45 mmol in 0.3 cm^3 of hexane) was added to an anhydrous THF solution (1 cm^3) of (i-Pr_2)NH (67 mg; 0.48 mmol). After 30 min, the strirred mixture was cooled to −78 ℃, and a THF solution (1.5 cm^3) of **19** (66 mg; 0.3 mmol) was added drowise within 30-min period, after which, HMPA (0.26 cm^3)

and $(PhSe)_2$ (94 mg; 0.3 mmol) were introduced and stirred for another 30 min. The mixture was treated with water and extracted with EtOAc and chromatographed on a slilica-gel column to give **20** (59 mg; 81%) and the recovered **19** (24 mg; 36%).

The BuLi (0.31 mmol in 0.2 cm^3 of hexane) was added to an anhydrous THF solution (1 cm^3) of $(i\text{-}Pr)_2NH$ (49 mg; 0.35 mmol) at 0 ℃ under an N_2 atmosphere within 30 min. The mixture was then cooled to −78 ℃, to which, a THF solution (1.5 cm^3) of **20** (59 mg; 0.16 mmol) was added. The mixture was further treated with HMPA (0.2 cm^3) and MeI (19 mg; 0.31 mmol) and stirred for 30 min, after which 2 NHCl was added and extracted with EtOAc. The organic layer was washed with aq. Na_2SO_3 and aq. NaCl, dried over Na_2SO_4, and chromatographed on a slilica-gel column to give **21** (39 mg; 64%).

Then, the 35% H_2O_2 (0.1cm^3) containing AcOH (30 mg) to a THF solution (1 cm^3) of **21** (39 mg; 0.10 mmol) at 0 ℃, and stirred for 30 min. The mixture was then diluted with water and extracted with hexane. The organic layer was, dried over Na_2SO_4, concentrated and chromatographed on a slilica-gel column to give **1b** [a colorless oil, 24 mg; 100 %. ^{1}HNMR δ =1.08 (3H, S), 1.4-1.5 (2H, m), 1.55-1.75 (2H, m), 1.66 (3H, s), 1.74 (2H, d, J=7.5 Hz), 1.9-2.0 (3H, m), 2.80 (1H, dd, J=13.5, 7.5 Hz), 3.05 (1H, m), 4.49 (1H, q, J= 7 Hz), 5.61 (1H, d, J=2 Hz), and 6.24 (1H, d, J=3 Hz)].

Conversion of 15 into 22. The BuLi (1.88 mmol in 1.2 cm^3 of hexane) was added to an anhydrous THF solution (3 cm^3) of $(Me_3Si)_2NH$ (0.42 cm^3; 2.01 mmol) added while being cooled with ice, and kept for 30 min at that temperature. The mixture was then cooled to −78 ℃, to which a THF solution (3 cm^3) of **15** (239 mg; 1.34 mmol) was added drowise. After 30 min, HMPA (2.0 cm^3) and $BrCH_2CO_2Et$ (0.45 cm^3) were sdded to the mixture, and the mixture was stirred for another 30 min. The mixture was then gradually warmed up to 0 ℃, and poured into water. After evaporation of the solvent in vacuo, the residue was extracted with EtOAc, washed with aq. NaCl, dried over Na_2SO_4, and chromatographed on a slilica-gel column to give **22** (a colorless oil, 158 mg).

Epimerization of 22 to 22. An EtOH solution (5 cm^3) of **22** (158 mg; 0.24 mmol) was treated with KOH (85%, 79 mg) at room temperaeure for 24 h, The mixture was them neutralized with dil. HCl. The mixture was extracted with EtOAc, washed with NaCl, dried over Na_2SO_4, and treated with ethereal CH_2N_2. Distillation of the solvent in vacuo left a colorless oily **23** (111 mg, 70.3%).

Formation of γ-Lactone (24) from 23. An MeOH solution (5 cm^3) of **23** (111 mg; 0.46 mmol) was treated with $NaBH_4$ (32 mg; 0.84 mmol) at 0 ℃ under an N_2 atmosphere. After 10 min, the mixture was treated with acetone and heated in vacuo to remove the solvent. The residue was extracted with EtOAc and chromatographed on a slilica-gel column to give **24** [a colorless oil, 30 mg, 10%. ^{1}HNMR δ =0.90 (3H, s), 1.11-1.16 (4H, m), 1.63 (3H, m), 1.8-2.2 (4H, m), 2.14 (1H, br, d, J=15 Hz), 2.30 (1H, d, J=17 Hz), 2.46 (1H, m), 2.74

(1H, dd, J=17, 6 Hz), 4.60 (1H, tm, J=4.5 Hz), and 5.37 (1H, m)].

Conversion of 24 into 1a via 25 and 26. The BuLi (0.19 mmol in 0.2 cm^3 of hexane) was added to an anhydrous THF solution (0.5 cm^3) of $(i\text{-}Pr)_2NH$ (42 mg; 0.20 mmol). After 30 min, the stirred mixture was cooled to −78 ℃, and a THF solution (1.5 cm^3) of **24** (30 mg; 0.14 mmol) was added dropwise within 30-min, after which, HMPA (0.12 cm^3) and $(PhSe)_2$ (59 mg; 0.2 mmol) were introduced and stirred for another 30 min. The mixture was treated with water and extracted with EtOAc and chromatographed on a slilica-gel column to give **25** (25 mg; 48%).

To an anhydrous THF solution (0.5 cm^3) of $(Me_3Si)_2NH$ (32 mg; 0.15 mmol in 0.1 cm^3 of hexane) for 30 min. The mixture was then cooled to −78 ℃, to which, a THF solution (1.5 cm^3) of **25** (25 mg; 0.067 mmol) was added. The mixture was further treated with HMPA (0.05 cm^3) and MeI (8 mg; 0.13 mmol) and stirred for 30 min, after which 2 N HCl was added and extracted with EtOAc. The organic layer washed with aq. Na_2SO_3 and aq. NaCl, dried over Na_2SO_4, and chromatographed on a slilica-gel column to give **26** (23 mg; 88%).

Then, the 35% H_2O_2 (0.1 cm^3) containing AcOH (30 mg) was added to a THF solution (1 cm^3) of **26** (23 mg; 0.06 mmol) at 0 ℃, and stirred for 30 min. The mixture was then diluted with water and extracted with hexane. The organic layer was, dried over Na_2SO_4, concentrated and chromatographed on a slilica-gel column to give **1a** [a colorless oil, 7 mg; 51%. ^{1}HNMR δ =0.90 (3H, s), 1.15-1.5 (4H, m), 1.62 (3H, m), 1.8-2.1 (4H, m), 2.15 (1H, dd, J=15.5, 1.5 Hz), 3.01 (1H, m), 4.53 (1H, td, J=5.15 Hz), 5.38 (1H, m), 5.60 (1H, d, J=1 Hz), and 6.14 (1H, d, J=1 Hz). ^{13}CNMR δ =17.2, 21.1, 22.2, 27.5, 30.9, 37.9, 41.0, 41.2, 43.9, 77.0, 120.3, 122.4, 133.0, 142.0, and 170.7].

References and Notes

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