Synthesis of a Germination Self-Inhibitor, (−)-Gloeosporone, and Related Compounds and Evaluation of Their Activities

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Synthesis of (−)-gloeosporone (1a), isolated from spores of *Colletotrichum gloeosporioides* as a self-inhibitor for germination, and its three diastereomers was accomplished starting from (*S*)- and (*R*)-1-tridecen-8-ol obtained from their (*S*)-naphthyl ethylcarbamates (8a and 8b), both of which were isolated from the mixture of diastereoisomers derived from racemic 1-tridecen-8-ol (7) and the Pirkle reagent. Biological testing of the compounds showed weak self-inhibitor activity toward germination of the spores.

Keywords gloeosporone; self-inhibitor; germination; diastereoisomer; resolution; epoxydation; 14-membered lactone; ruthenium tetroxide; α-diketone

There have been several reports[1-6] concerning the synthesis of (−)-gloeosporone (**1a**),[7] isolated from spores of *Colletotrichum gloeosporioides* as a self-inhibitor for germination, because of its novel biological activity and its unique structure. We are interested in synthesizing biologically active compounds related to plant pathology. Recently, we have reported the synthesis of AK- and AF-toxins, which are toxic to Japanese white pear, and their congeners in optically active forms and revealed that the stereochemistry of two chiral centers of these toxins is important for the toxicity.[8] We report here the synthesis of (−)-gloeosporone and its stereoisomers and we discuss the structure–self-inhibitor activity relationship.

In order to synthesize (−)-gloeosporone and its three diastereoisomers in optically active forms, we planned to perform the resolution of the alcohol (**7**) through the diastereoisomeric carbamates (**8a** and **8b**) obtained by condensation of 1-tridecen-8-ol (**7**) and the Pirkle reagent.[9]

Treatment of 5-hexen-1-ol (**2**) with methanesulfonyl chloride gave the mesylate (**3**), which was smoothly transformed to the bromide (**4**) with tetrabutylammonium bromide in tetrahydrofuran (THF). An oxidation of 1-heptene (**5**) with *m*-chloroperbenzoic acid (MCPBA) gave the oxide (**6**). Grignard reaction on **6** with the Grignard reagent of **4** in the presence of cuprous iodide gave the alcohol (**7**). Treatment of **7** with the Pirkle reagent ((*S*)-(+)-1-(1-naphthyl)ethyl isocyanate) in the presence of boron trifluoride etherate[10] in ether gave a mixture of the diastereoisomeric carbamates in 97% yield. Repeated and careful flash chromatography of this mixture allowed us to separate the enantiomeric alcohols (**7a** and **7b**), after reduction with lithium aluminum hydride. The absolute configurations of these alcohols were not determined at this stage, being ultimately confirmed by the synthesis of (−)-gloeosporone (**1a**).

After protection of the hydroxyl group of the (*R*)-alcohol (**7a**) as its tetrahydropyranyl (THP) ether, oxidation of the THP ether (**9a**) with MCPBA gave a mixture of diastereoisomeric epoxides (**10a**). Attempts to isolate each oxide in pure form were unsuccessful. Treatment of the mixture with the dianion of 4-pentynoic acid according to Seebach's procedure[4] and treatment of the resulting acid with diazomethane gave the methyl ester (**11a**) in 45% yield. Protection of the hydroxyl group of **11a** as the *tert*-butyldiphenylsilyl ether (TBDPS) and removal of the THP group gave the mono-hydroxy ester (**13a**). Alkaline hydrolysis of **13a** followed by intramolecular lactonization

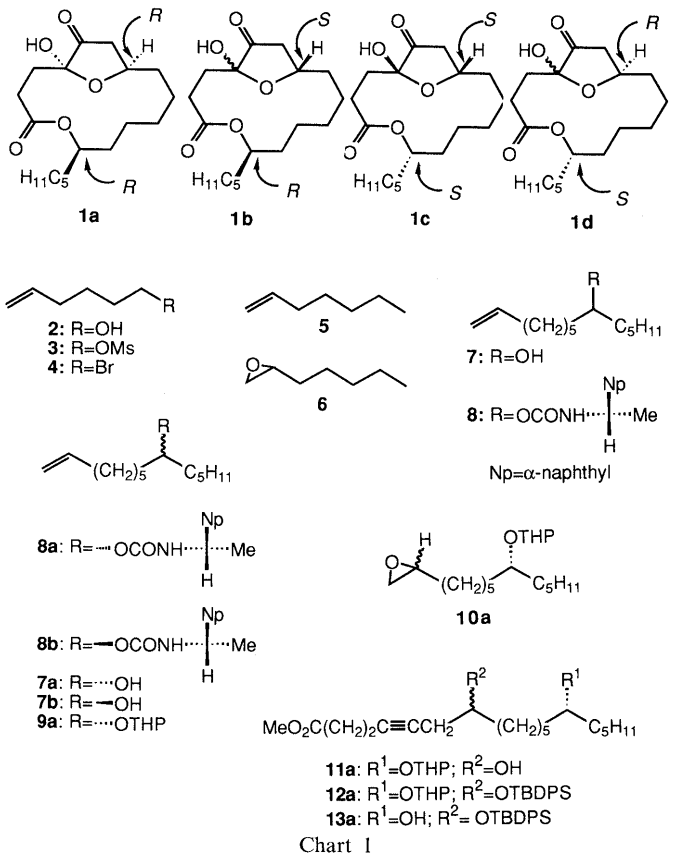

Chart I

TABLE I. Germination of Conidia in Gloeosporone Solutions

Compound	Concentration (ppm)	
	100	30
1a (−) Gloeosporone	68	87
1b	61	89
1c (+) Gloeosporone	65	68
1d	69	88
Water (control)	87	

Germination (percent) of conidia.

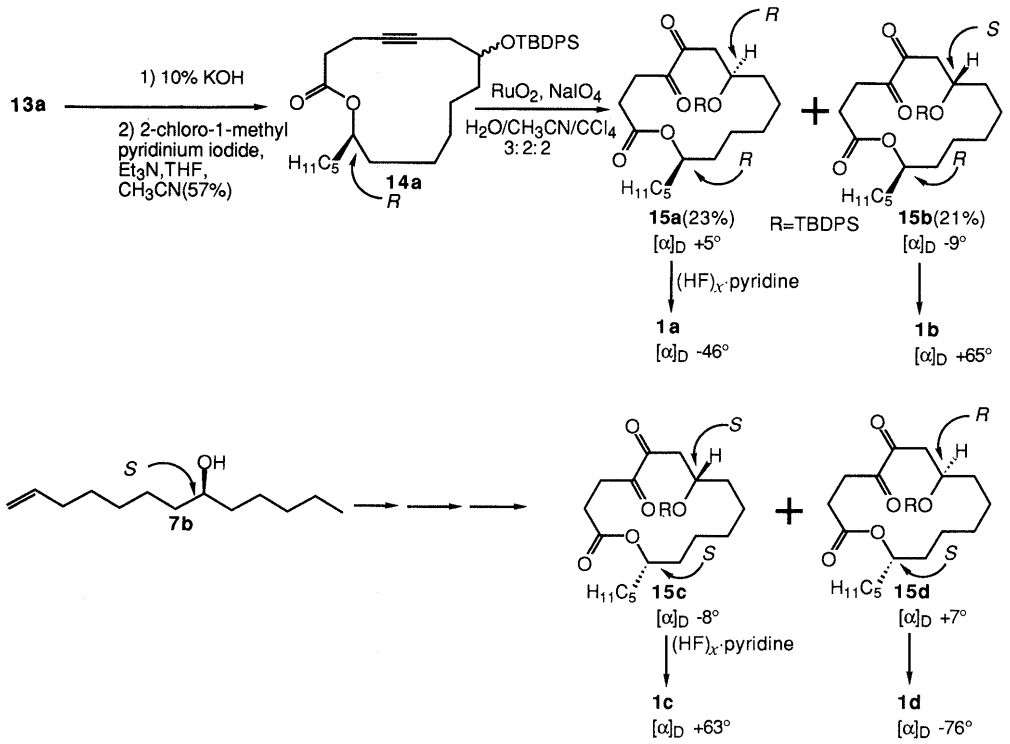

Chart 2

using Schreiber's method[3] gave the lactone (**14a**) in 57% yield. Oxidation of **14a** with ruthenium dioxide and sodium periodate gave the diketones as a mixture of diastereomers. At this stage, both isomers (**15a** and **15b**) were separated by preparative thin layer and flash chromatography. Removal of the TBDPS protecting group in each diketone with fluoride ion accomplished the synthesis of (−)-gloeosporone (**1a**) and 7-epigloeosporone (**1b**). The former showed identical spectroscopic properties with those of (−)-gloeosporone (**1a**), thus confirming the stereochemistry of the alcohol (**7a**). The same reaction sequence on the enantiomeric alcohol (**7b**) gave (+)-gloeosporone (**1c**) and its 7-epimer (**1d**). The rather small $[\alpha]_D$ values of (−)- and (+)-gloeosporone are thought to be due to insufficient purification of the carbamates.

All of these synthesized compounds, including (−)-gloeosporone (**1a**), exhibited weak activity as self-inhibitors for the germination of the spores (Table I).[4,6]

Experimental

The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 360, a JEOL FX90Q or a JEOL LNMGX-400 spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. The mass spectra (MS) were recorded on a JEOL 303A spectrometer. The infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrophotometer. The optical rotations were measured at 26—28 °C with a JASCO DIP-181 digital polarimeter. Merck Kieselgel 60 Art. 7734 and Art. 7731 were used for open column chromatography and flash column chromatography, respectively. Magnesium sulfate ($MgSO_4$) was used as the drying reagent unless otherwise specified.

6-Methanesulfonyloxy-1-hexene (3) Methanesulfonyl chloride (24.3 g, 0.24 mol) was added to a solution of 5-hexen-1-ol (**2**) (16.2 g, 0.16 mmol) and dry pyridine (56 g, 0.8 mol) in CH_2Cl_2 (30 ml) at 0 °C under argon. The resulting mixture was stirred at room temperature for 2 h. After dilution with CH_2Cl_2, the resultant solution was successively washed with 3% $NaHCO_3$, 3% HCl and water, and dried. Removal of the solvent gave mesylate (**3**) (28.7 g, 99%) as a colorless oil, bp 58.5 °C (25 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. MS *m/z*: 178 (M^+). ^{1}H-NMR ($CDCl_3$) (60 MHz) δ: 1.12—2.40 (6H, m), 3.04 (3H, s), 4.27 (2H, t, J=6.4 Hz), 4.90—5.26 (2H, m), 5.51—6.19 (1H, m).

6-Bromo-1-hexene (4) A solution of the mesylate (**3**) (30.2 g, 0.17 mol) and tetrabutylammonium bromide (81.9 g, 0.26 mol) in THF (500 ml) was stirred at room temperature overnight. The reaction mixture was diluted with ether and washed with 10% NH_4Cl. Aqueous washes were extracted twice with ether. The combined organic layer was washed with saturated brine and dried. Removal of the solvent gave 6-bromo-1-hexene (**4**) (18.7 g, 67%), bp 58.5 °C (25 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. MS *m/z*: 162 (M^+). ^{1}H-NMR ($CDCl_3$) (60 MHz) δ: 1.20—2.25 (6H, m), 3.40 (2H, t, J=7.0 Hz), 4.90—5.28 (2H, m), 5.50—6.24 (1H, ddt, J=6.3, 8.8, 16.4 Hz).

(±)-Heptane-1,2-oxide (6) A solution of 1-heptene (**5**) (6.02 g, 61.3 mmol) and MCPBA (15.9 g, 73.6 mmol) in CH_2Cl_2 (80 ml) was stirred at room temperature for 2 h. After addition of aqueous 10% $NaHSO_3$, the organic layer was washed with 10% Na_2CO_3, 3% HCl and water, and dried. Evaporation of the solvent left the oily epoxide (**6**), (5.34 g, 76%), bp 56 °C (27 mmHg). ^{1}H-NMR ($CDCl_3$) (60 MHz) δ: 0.91 (3H, t, J=4.0 Hz), 1.07—1.77 (8H, m), 2.27—2.98 (3H, m).

(±)-12-Tridecen-6-ol (7) The bromide (**4**) (9.68 g, 59.4 mmol) was added dropwise to a mixture of Mg (1.49 g, 62 mmol) and dry THF (5 ml) under argon. After the reaction started, the mixture was maintained at reflux for 2 h. The resulting solution of the Grignard reagent was added to a suspension of CuI (10.3 mg, 5.4 mmol) in THF (10 ml) at −78 °C under argon and stirred for 10 min. To this cuprate solution, a solution of the epoxide (**6**) (6.20 g, 54 mmol) in THF (20 ml) was added dropwise at the same temperature and stirring was continued for 20 min. The reaction was quenched with aqueous NH_4Cl and ether. The ether extract was washed with 10% NH_4Cl. The aqueous layer was again extracted with $CHCl_3$, and the organic layers were combined, dried and concentrated to give the (±)-alcohol (**7**) (8.54 g, 79%), bp 120 °C (3 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630, 3550. MS *m/z*: 198 (M^+). ^{1}H-NMR ($CDCl_3$) (60 MHz) δ: 0.86—2.62 (22H, m), 3.62 (1H, br s), 4.82—5.27 (2H, m), 5.40—6.28 (1H, m).

(8*R*)-8-[*N*-(2*S*)-2-Naphthylethyl]carbamyl-1-tridecene (8a) A solution of $BF_3 \cdot Et_2O$ (426 mg, 3.04 mmol) in dry ether (2 ml) was added dropwise to a solution of the (±)-alcohol (**7**) (300 mg, 1.52 mmol) and (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate[9,10] (300 mg, 1.52 mmol) in ether (2 ml) under argon. The reaction mixture was stirred at room temperature for 2 h. After dilution with ether, the mixture was washed with 3% HCl, 3% $NaHCO_3$ and water, and dried. Removal of the solvent left a residue, which was purified by column chromatography (hexane–ether, 4:1) to give a mixture of diastereoisomeric carbamates (**8a** and **8b**) (580 mg, 97%). Careful flash column chlomatography of the mixture in hexane–ether afforded pure **8a** and **8b**, each as white crystals. **8a**: mp 50—51 °C, $[\alpha]_D$ −11° (c=4.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 3440. *Anal.* Calcd for

$C_{26}H_{37}NO_2$: C, 78.93; H, 9.43; N, 3.57. Found: C, 78.53; H, 9.43; N, 3.50. HR-MS Calcd for $C_{26}H_{37}NO_2$: 395.282. Found: 395.284. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, t, J=3.6 Hz), 1.20—1.71 (21H, m), 1.99 (1H, m), 4.76 (1H, m), 4.85—5.02 (2H, m), 5.55—5.71 (1H, m), 5.73—5.85 (1H, m), 6.72—7.63 (7H, m). **8b**: 43—49 °C, $[\alpha]_D$ −0.9° (c=4.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 3440. *Anal.* Calcd for $C_{26}H_{37}NO_2$: C, 78.93; H, 9.43; N, 3.57. Found: C, 77.95; H, 9.27; N, 3.39. HR-MS Found: 395.282. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t), 0.97—1.84 (21H, m), 2.03 (1H, m), 4.75 (1H, m), 4.85—5.02 (2H, m), 5.71 (1H, m), 5.72—5.87 (1H, m), 7.24—7.80 (7H, m).

(6*R*)-12-Tridecen-6-ol (7a) A mixture of the carbamate (**8a**) (1.5 g, 3.7 mmol), lithium aluminum hydride (285 mg, 7.4 mmol) and dry THF (25 ml) was heated at gentle reflux for 1 h under argon. After addition of ether, the excess reagent was decomposed by dropwise addition of water and the resulting mixture was filtered. The precipitate was thoroughly washed with hot $CHCl_3$. The combined organic layers were washed 4% HCl, 3% $NaHCO_3$ and brine, and dried. Concentration *in vacuo* left an oily residue, which was chromatographed on silica gel with hexane–ether (4 : 1—2 : 1) to give the alcohol (**7a**) (712 mg, 94%). (**7a**): $[\alpha]_D$ −13° (c=4.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600. *Anal.* Calcd for $C_{13}H_{26}O$: C, 78.71; H, 13.22. Found: C, 78.48; H, 12.56. HR-MS Calcd for $C_{13}H_{26}O$: 198.198. Found: 198.193. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, t, J=6.0 Hz), 1.11—1.81 (18H, m), 1.81—2.21 (1H, m), 3.57 (1H, m), 4.84—5.10 (2H, m), 5.59—6.04 (1H, ddt, J=6.3, 8.8, 16.4 Hz). **7b**: $[\alpha]_D$ +12° (c=0.46, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600. *Anal.* Calcd for $C_{13}H_{26}O$: C, 78.71; H, 13.22. Found: C, 77.61; H, 12.79. HR-MS Found: 198.199. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, t, J=6.0 Hz), 1.11—1.81 (18H, m), 1.81—2.21 (1H, m), 3.57 (1H, m), 4.84—5.10 (2H, m), 5.59—6.04 (1H, ddt, J=6.3, 8.8, 16.4 Hz).

(8*R*)-8-(2-Tetrahydropyranyloxy)-1-tridecene (9a) A mixture of the alcohol (**7a**) (1.41 g, 7.1 mmol), pyridinium *p*-toluenesulfonate (191 mg, 0.17 mmol), dihydropyran (1.19 g, 14.2 mmol) and CH_2Cl_2 (25 ml) was stirred at room temperature for 4 h. The reaction mixture was partitioned between ether and water, and the organic layer was washed with 3% $NaHCO_3$, 3% NH_4Cl and brine. Removal of the solvent gave a residue, which was chromatographed on silica gel with hexane–ether (4 : 1) to give the THP ether (**9a**) (1.69 g, 84.5%). **9a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. HR-MS Calcd for $C_{18}H_{34}O_2$: 282.256. Found; 282.256. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=5.3 Hz), 1.08—2.20 (24H, m), 3.24—3.72 (2H, m), 3.72—4.08 (1H, m), 4.52—4.72 (1H, br s), 4.81—5.10 (2H, m), 5.52—6.08 (1H, ddt, J=6.5, 10.3, 17.0 Hz). **9b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. HR-MS Found: 282.257. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=5.6 Hz), 1.04—2.18 (24H, m), 3.29—3.74 (2H, m), 3.74—4.03 (1H, m), 4.63 (1H, br s), 4.80—5.10 (2H, m), 5.55—6.04 (1H, ddt, J=6.5, 10.3, 17.0 Hz).

(8*R*)-8-(2-Tetrahydropyranyloxy)tridecane-1,2-oxide (10a) MCPBA (694 mg, 3.22 mmol) was added to an ice-cooled solution of the olefin (**9a**) (757 mg, 2.68 mmol) in CH_2Cl_2 (35 ml) and the mixture was stirred at room temperature for 3 h. The usual work-up gave the epoxide (**10a**) (639 mg, 80%) as a diastereoisomeric mixture. **10a**: HR-MS Calcd for $C_{18}H_{34}O_3$: 298.251. Found: 298.253. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=5.4 Hz), 1.04—2.09 (24H, m), 2.45 (1H, dd, J=2.9, 5.1 Hz), 2.73 (1H, dd, J=5.1, 5.1 Hz), 2.78—3.00 (1H, m), 3.27—3.71 (2H, m), 3.71—4.01 (1H, m), 4.67 (1H, m). Similarly, the corresponding diastereomeric mixture of the oxide (**10b**) having 8*S* configuration was obtained from (8*S*)-tetrahydropyranyloxy-1-tridecene (**9b**). **10b**: HR-MS Found: 298.250. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, t, J=5.7 Hz), 1.05—2.09 (24 H, m), 2.45 (1H, dd, J=2.6, 5.1 Hz), 2.74 (1H, dd, J=5.1, 5.1 Hz), 2.81—3.01 (1H, m), 3.29—3.73 (2H, m), 3.73—4.09 (1H, m), 4.62 (1H, m).

(13*R*)-Methyl-7-hydroxy-13-(2-tetrahydropyranyloxy)-4-octadecynoate (11a)[4] A 1.6 M hexane solution of *n*-BuLi (9.5 ml, 15.1 mmol) was added dropwise to a solution of 4-pentynoic acid (439 mg, 5.0 mmol) in hexamethylphosphoramide (HMPA) (6.3 ml) at 0 °C under argon. The mixture was stirred at room temperature for 1 h. To this solution was added a solution of the epoxide (**10a**) in HMPA (6.3 ml) at 0 °C, and the resulting mixture was stirred for an additional 36 h at room temperature. The reaction mixture was acidified with 10% HCl, and extracted with ether. The ether extract was washed with brine, and concentrated to leave a residue. An ethereal solution of the residue was treated with CH_2N_2 at 0 °C, then the mixture was washed with 3% $NaHCO_3$ and 4% NH_4Cl, and dried. After removal of the solvent, the oily residue was purified by flash column chromatography with hexane–ether–acetone (4 : 1 : 0.5) to give the hydroxy methyl ester (**11a**) (265 mg, 40%) as a diastereoisomeric mixture. **11a**: colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 3500. HR-MS Calcd for $C_{24}H_{42}O_5$: 410.303. Found: 410.304. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=5.4 Hz), 1.08—1.89 (24H, m), 2.05 (1H, br s), 2.16—2.37 (2H, m), 2.40—2.56 (4H, m), 3.69 (3H, s), 3.28—4.04 (4H, m), 4.61 (1H, m). **11b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 3500. HR-MS Found: 410.306. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=5.4 Hz), 1.08—1.90 (24H, m), 2.05 (1H, br s), 2.18—2.39 (2H, m), 2.43—2.56 (4H, m), 3.69 (3H, s), 3.28—4.05 (4H, m), 4.62 (1H, m).

(13*R*)-Methyl-7-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-13-(2-tetrahydropyranyloxy)-4-octadecynoate (12a)[3] A solution of imidazole (314 mg, 4.62 mmol), the hydroxy ester (**11a**) (610 mg, 1.54 mmol) and *tert*-butyldiphenylsilyl chloride (843 mg, 3.08 mmol) in dimethylformamide (DMF) (5 ml) was stirred at room temperature for 36 h. After dilution with ether, the mixture was successively washed with 2% HCl, 2% $NaHCO_3$ and brine, and dried. Removal of the solvent left an oily residue, which was purified by flash column chromatography (hexane–benzene–acetone–ether, 30 : 10 : 1 : 1) to give the silylether (**12a**) (590 mg, 63%) as a colorless oil. **12a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. MS m/z: 648 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=3.6 Hz), 1.05 (9H, s), 1.10—2.00 (24H, m), 2.14—2.30 (3H, m), 2.33—2.46 (4H, m), 3.66 (3H, s), 3.29—4.05 (4H, m), 4.63 (1H, br s), 7.24—7.76 (10H, m).

Although **12b** was prepared under the same conditions, the product was used in the next step, without purification.

(13*R*)-Methyl-7-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-13-hydroxy-4-octadecynoate (13a) A solution of the silylether (**12a**) (362 mg, 0.61 mmol) and pyridinium *p*-toluenesulfonate (250 mg) in MeOH (8 ml) was stirred at room temperature for 48 h. After removal of the solvent, the residue was taken up in ether. The ethereal solution was washed with half-saturated brine, dried, and concentrated to leave a residue, which was chromatographed on silica gel with hexane–ether (4 : 1) to give the hydroxy methyl ester (**13a**) (274 mg, 88%) as a colorless oil. **13a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 3700. MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.90 (3H, br t, J=5.4 Hz), 1.05 (9H, s), 1.10—1.80 (19H, m), 2.13—2.30 (2H, m), 2.34—2.46 (4H, m), 3.32—3.92 (2H, m), 3.66 (3H, s), 7.18—7.74 (10H, m). **13b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 3700. MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.90 (3H, br t, J=5.4 Hz), 1.05 (9H, s), 1.12—1.70 (19H, m), 2.14—2.30 (2H, m), 2.36—2.47 (4H, m), 3.36—3.96 (2H, m), 3.66 (3H, s), 7.16—7.74 (10H, m).

(13*R*)-8-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-13-pentyloxacyclotetradec-5-yn-2-one (14a)[3] An aqueous 10% KOH solution (2 ml) was added to a solution of **13a** (453 mg, 0.80 mmol) in EtOH (10 ml) and the mixture was stirred at room temperature for 3 h, washed with water, dried and evaporated. A solution of the crude acid thus obtained in THF (35 ml) containing Et_3N (826 mg, 8.0 mmol) was then added dropwise to a refluxing solution of 2-chloro-1-methylpyridinium iodide (816 mg, 3.2 mmol) in acetonitrile (150 ml) over 8 h. When the addition was completed, the mixture was further refluxed for 2 h, then cooled to room temperature, and concentrated. The residue was dissolved in ether, and the solution was washed with 3% NH_4Cl and brine, dried and evaporated. Purification by column chromatography with hexane–ether (8 : 1) gave a 14-membered lactone (**14a**) (242 mg, 57%). **14a**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. HR-MS Calcd for $C_{34}H_{48}O_3Si$: 532.337. Found: 532.336. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.87 (3H, br t, J=5.4 Hz), 1.03 (9H, s), 1.09—1.88 (18 H, m), 2.09—2.31 (2H, m), 2.31—2.48 (4H, m), 3.56—3.96 (1H, m), 4.72—5.12 (1H, m), 7.22—7.69 (10H, m). **14b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. HR-MS Found: 532.337. ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.87 (3H, br t, J=5.4 Hz), 1.03 (9H, s), 1.09—1.88 (18H, m), 2.12—2.32 (2H, m), 2.32—2.50 (4H, m), 3.60—4.00 (1H, m), 4.72—5.12 (1H, m), 7.24—7.74 (10H, m).

(8*R*,13*R*)-8-[[(1,1-Dimethylethyl)diphenylsilyl]oxy-14-pentyloxacyclotetradeca-2,5,6-trione (15a) Oxidation of the lactone (**14a**) was carried out by using Seebach's protocol.[4] Thus, RuO_2 (10 mg, 0.054 mmol) and $NaIO_4$ (464 mg, 2.12 mmol) were dissolved in water (3 ml). After 30 min, a solution of the lactone (**14a**) (289 mg, 0.54 mmol) in CCl_4 (2 ml) and acetonitrile (2 ml) was added to the above solution and vigorous stirring was continued for 3 d. The reaction mixture was diluted with ether and the organic layer was washed with 3% $NaHCO_3$, 3% HCl and water, and dried. After removal of the solvent, the oily residue was subjected to flash chromatography with hexane–ether (100 : 4) to give the *trans*-α-diketone (**15b**) (63 mg, 21%) from the first eluate, and the *cis*-α-diketone (**15a**) (71 mg, 23%) from the second eluate. **15a**: $[\alpha]_D$ +5° (c=1.3, $CHCl_3$). MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.86 (3H, br t, J=6.0 Hz), 1.06 (9H, s), 1.17—1.58 (18H, m), 2.49 (1H, dd, J=4.0, 15.0 Hz), 2.65 (2H, t, J=5.9 Hz), 2.80 (1H, dt, J=5.9, 19.4 Hz), 3.04 (1H, dt, J=5.9, 19.4 Hz), 3.40 (1H, dd, J=15.0, 10.3 Hz), 4.25—4.29 (1H, m), 4.88—4.92 (1H, m), 7.34—7.73 (10H, m). **15b**: $[\alpha]_D$ −9° (c=1.4, $CHCl_3$). MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=7.0 Hz), 1.07

(9H, s), 1.14—1.63 (18H, m), 2.54 (1H, dd, J=9.5, 12.5 Hz), 2.65 (2H, t, J=5.9 Hz), 2.87 (1H, dt, J=5.9, 19.1 Hz), 2.99 (1H, dt, J=5.9, 19.7 Hz,) 3.22 (1H, dd, J=3.7, 12.5 Hz), 4.22—4.32 (1H, m), 4.73—4.81 (1H, m), 7.34—7.74 (10H, m). Similar treatment of **14b** with RuO_4 furnished a separable mixture of **15c** and **15d** in comparable yields. **15c**: $[\alpha]_D$ −8° (c=0.84, $CHCl_3$). MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.86 (3H, br t, J=6.0 Hz), 1.06 (9H, s), 1.17—1.58 (18H, m), 2.49 (1H, dd, J=4.0, 15.0 Hz), 2.65 (2H, t, J=5.9), 2.80 (1H, dt, J=5.9, 19.4 Hz), 3.04 (1H, dt, J=5.9, 19.4 Hz), 3.40 (1H, dd, J=15.0, 10.3 Hz), 4.25—4.29 (1H, m), 4.88—4.92 (1H, m), 7.34—7.73 (10H, m). **15d**: $[\alpha]_D$ +7° (c=1.02, $CHCl_3$). MS m/z: 564 (M^+). ^{1}H-NMR ($CDCl_3$) (90 MHz) δ: 0.89 (3H, br t, J=7.0 Hz), 1.07 (9H, s), 1.14—1.63 (18 H, m), 2.54 (1H, dd, J=9.5, 12.5 Hz), 2.65 (2H, t, J=5.9 Hz), 2.87 (1H, dt, J=5.9, 19.7 Hz), 2.99 (1H, dt, J=5.9, 19.7 Hz), 3.22 (1H, dd, J=3.7, 12.5 Hz), 4.22—4.32 (1H, m), 4.73—4.81 (1H, m), 7.34—7.74 (10H, m).

(−)-Gloeosporone (1a) The last step in the synthesis was carried out according to the procedure of Seebach *et al.*[4] Hydrogen fluoride-pyridine (0.1 ml) was added to a solution of the *cis*-α-diketone (**15a**) in THF (2.5 ml) at 0 °C and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ether and washed with 2% HCl and water, dried and concentrated. The residue was purified by flash column chromatography (hexane–ether–AcOEt, 8:1:1) followed by recrystallization (ether–hexane) to give (−)-gloeosporone (**1a**) (3 mg, 15%). The synthetic compound was identical with the natural product. **1a**: mp 108—111 °C (lit.[2] 119—120 °C), $[\alpha]_D$ −46° (c=0.11, $CHCl_3$) (lit.[1,4] $[\alpha]_D$ −61°, lit.[3] −63.2°, lit.[6] −14°, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{30}O_5$: C, 66.22; H, 9.27. Found: C, 66.65; H, 9.17. HR-MS Calcd for $C_{18}H_{30}O_5$: 326.209. Found: 326.210. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 0.88 (3H, br t, J=7.0 Hz), 1.18—1.74 (18H, m), 2.04 (1H, dd, J=8.4, 18.7 Hz), 2.10 (1H, ddd, J=3.3, 8.4, 14.3 Hz), 2.27 (1H, ddd, J=3.3, 8.8, 14.6 Hz), 2.37 (1H, ddd, J=3.5, 8.8, 4.3 Hz), 2.44 (1H, ddd, J=3.5, 8.4, 14.6 Hz), 2.74 (1H, dd, J=6.2, 18.7 Hz), 3.55 (1H, s), 4.43 (1H, m), 5.06 (1H, m). **1b**: $[\alpha]_D$ +65° (c=0.02, $CHCl_3$). HR-MS Found: 326.204. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 0.87 (3H, br t, J=7.0 Hz), 1.23—1.82 (18H, m), 2.09 (1H, ddd, J=2.2, 8.1, 14.6 Hz), 2.15 (1H, dd, J=9.6, 18.3 Hz), 2.18 (1H, ddd, J=2.2, 11.0, 14.6 Hz), 2.29 (1H, ddd, J=2.2, 8.4, 15.4 Hz), 2.42 (1H, s), 2.59 (1H, ddd, J=2.2, 11.0, 15.8 Hz), 2.63 (1H, dd, J=5.5, 18.3 Hz), 4.39 (1H, m), 5.05 (1H, m). **1c**: mp 113—115 °C (lit.[1] 117—118 °C), $[\alpha]_D$ +63° (c=0.05, $CHCl_3$) (lit.[1,4] $[\alpha]_D$ +58°, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{30}O_5$: C, 66.22; H, 9.27. Found: C, 66.48; H, 9.38. HR-MS Found: 326.209. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 0.88 (3H, br t, J=7.0 Hz), 1.18—1.74 (18H, m), 2.04 (1H, dd, J=8.4, 18.7 Hz), 2.10 (1H, ddd, J=3.3, 8.4, 14.3 Hz), 2.27 (1H, ddd, J=3.3, 8.8, 14.6 Hz), 2.37 (1H, ddd, J=3.5, 8.8, 4.3 Hz), 2.44 (1H, ddd, J=3.5, 8.4, 14.6 Hz), 2.74 (1H, dd, J=6.2, 18.7 Hz), 3.55 (1H, s), 4.43 (1H, m), 5.06 (1H, m). **1d**: $[\alpha]_D$ −76° (c=0.05, $CHCl_3$). HR-MS Found 326.209. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 0.87 (3H, br t, J=7.0 Hz), 1.23—1.82 (18H, m), 2.09 (1H, ddd, J=2.2, 8.1, 14.6 Hz), 2.15 (1H, dd, J=9.6, 18.3 Hz), 2.18 (1H, ddd, J=2.2, 11.0, 14.6 Hz), 2.29 (1H, ddd, J=2.2, 8.4, 15.4 Hz), 2.42 (1H, s), 2.59 (1H, ddd, J=2.2, 11.0, 15.8 Hz), 2.63 (1H, dd, J=5.5, 18.3 Hz), 4.39 (1H, m), 5.05 (1H, m).

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