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Total Syntheses of (+)-1893B and Its Three Diastereomers and Evaluation of Their Biological Activities

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This paper is dedicated to the memory of Professor Kenneth L. Rinehart.

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Abstract The total syntheses of natural (+)-1893B (**2**) and three other diastereomers **14**, **18**, and **21** were accomplished. Starting from the sequential metathesis product **5** prepared in turn from a 7-oxanorbornene derivative (+)-**4**, **2** was synthesized by means of an epoxy-ring opening of **9a** with trimethylsilylacetylide followed by Wacker-type oxidation of the resulting alkyne **10** for the construction of the γ-lactone moiety. By applying the same synthetic sequence, three additional diastereomers of **2**, **14**, **18**, and **21** were also synthesized. The biological activities of previously synthesized 1893A (**1**), 1893B (**2**), and the diastereomers of 1893B **14**, **18**, and **21** were investigated.

Keywords (+)-1893B, total synthesis, oxabicyclo[4.2.1]-nona-2,4-diene, γ-lactone

Introduction

1893A (**1**) and 1893B (**2**) were isolated in 2003 during the course of antitumor natural products searching from a marine endophytic fungus designated as No. 1893, which exists in mangroves (Fig. 1) [1]. Lin and Chen reported that the extract mixture of No. 1893 appeared to exhibit cytotoxic and insecticidal activities. However, the biological activity of the pure metabolites **1** and **2** has not reported. The structure of **1** was elucidated by extensive spectroscopic studies and finally determined by X-ray crystallographic analysis. As structurally related natural product, (+)-mycoepoxydiene (**3**) was isolated in 1999 [2, 3]. We already reported the total syntheses of **1** and **3**, which were characterized by a sequential ring-opening/cross/ring-closing metathesis strategy [4, 5]. Although the stereostructures of **1** and **3** were confirmed by our synthetic studies, the stereochemistry of **2** was not unambiguously established at that time. Later, we were concerned with the stereochemically defined total synthesis of **2** through the total syntheses of all four possible stereoisomers regarding the vicinal diol moiety in **2**. The first total synthesis of natural (+)-**2** was reported as a preliminary communication [6]. Herein, we describe in detail the total syntheses of **2** and three additional diastereomers. The evaluation of their biological activities is also presented.

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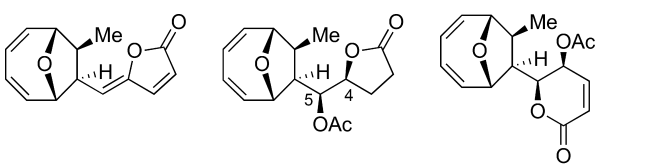
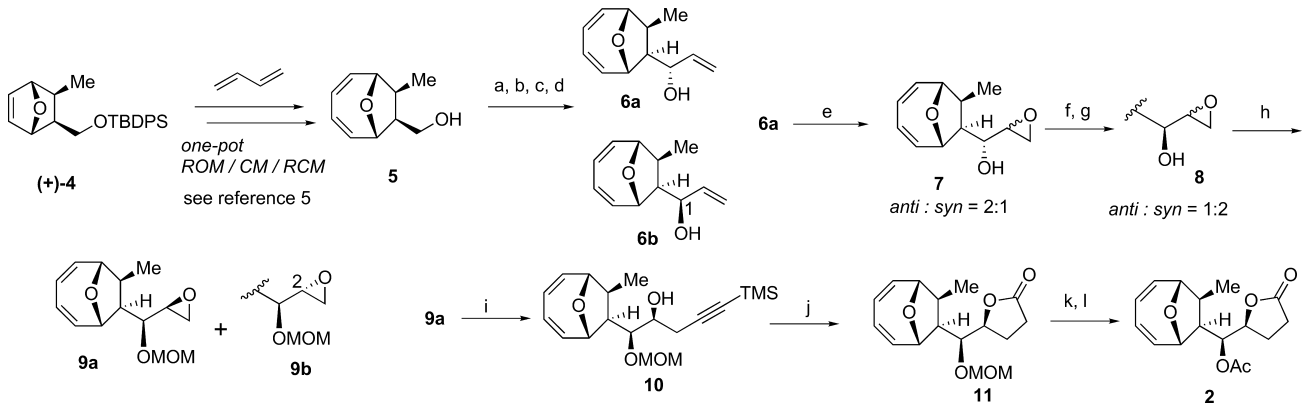
Results and Discussion

According to our previous report [5], we converted the enantioenriched 7-oxanorbornene derivative (+)-**4** (>95% ee) into the cyclooctadiene **5** through a one-pot ring-expansion metathesis strategy (Scheme 1). The



(–)-1893A (**1**) (+)-1893B (**2**) (+)-mycoepoxydiene (**3**)

Fig. 1 Structures of 1893s and mycoepoxydiene.



Scheme 1 Total synthesis of natural (+)-**2**.

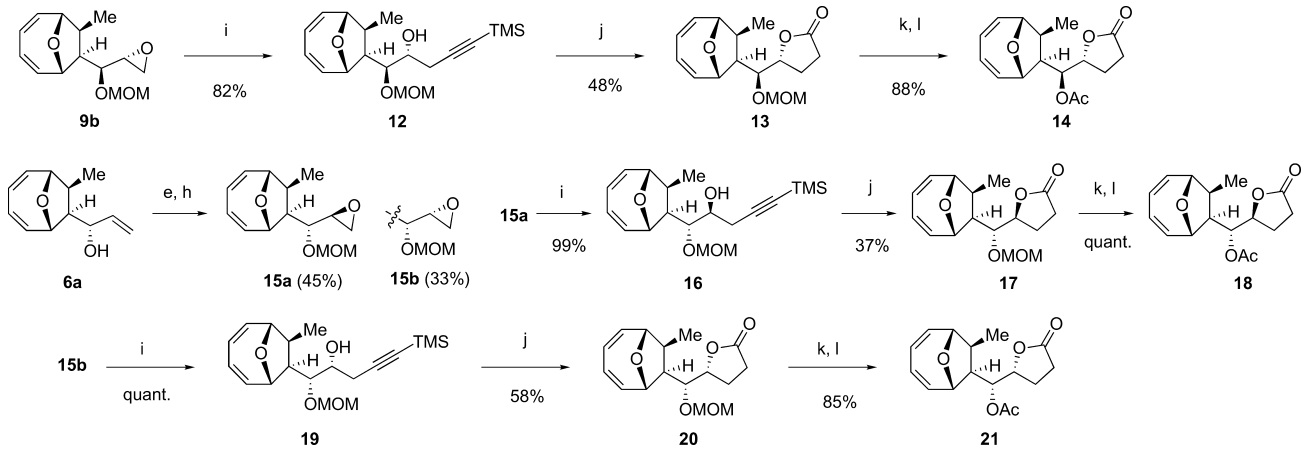
Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2; (b) CH_2=CHMgBr, THF, 70% for 2 steps; (c) (*S*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH_2Cl_2; (d) LiOH, MeOH/H_2O, 40% of **6a** for 2 steps, 52% for **6b**; (e) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 60%; (f) PPh_3, DEAD, *p*-nitrobenzoic acid, THF; (g) LiOH, MeOH/H_2O, 84% for 2 steps; (h) MOMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, reflux, 54% for **9a**, 35% for **9b**; (i) TMS-acetylene, *n*-BuLi, $BF_3\cdot Et_2O$, THF, −78 to −30°C, 99%; (j) $PdCl_2(MeCN)_2$, $CuCl_2$, DMF containing 1% water, 71%; (k) 2 M HCl, THF, 50°C, 98%; (l) Ac_2O, DMAP, pyridine, 84%.

primary alcohol in this cascade metathesis product **5** was oxidized to an aldehyde, which was then reacted with vinylmagnesium bromide, affording diastereomeric allylic alcohols **6a** and **6b** as an inseparable 1 : 1 mixture. To establish the stereochemistry of the diatereomers **6a** and **6b**, the mixture was esterified with (*S*)-*O*-acetylmandelic acid. The resulting two mandelic esters were cleanly separated by chromatography on silica-gel. After removal of the mandeloyl group from each ester, diastereomerically pure **6a** and **6b** were obtained. The newly introduced stereocenter of C-1 in **6b** was determined as depicted using the $\Delta\delta$ values of the (*S*)- and (*R*)-mandelic esters derived from **6b** in their ^{1}H-NMR spectra [7]. The stereochemically defined allylic alcohol **6a** was subjected to the Sharpless $VO(acac)_2$-catalyzed epoxidation [8], affording epoxy alcohols **7** as a 2 : 1 diastereomeric mixture. We deduced from the Sharpless empirical rule that the major isomer was *anti*-epoxy alcohol unsuitable for the synthesis of **2**. Thus the Mitsunobu inversion of the diastereomeric mixture **7** was carried out using *p*-nitrobenzoic acid [9]. As expected, the *anti* : *syn* ratio turned from 2 : 1 to 1 : 2. The resulting *p*-nitrobenzoates were hydrolyzed to epoxy alcohols **8** as the *syn*-enriched form. After protection of the hydroxyl groups, *syn*- and *anti*-epoxy MOM ethers **9a** and **9b** were cleanly separated. The stereochemistry at C-2 of **9b** was unambiguously established based on the ^{1}H NMR difference ($\Delta\delta$) of the corresponding (*S*)- and (*R*)-*O*-acetylmandeloyl esters prepared from **9b** by regioselective hydride opening of the epoxy ring followed by esterification [7]. The opening of the epoxy ring of **9a** with a two-carbon nucleophile was investigated. After several attempts, we found that lithium trimethylsilylacetylide efficiently provided the desired product **10**. For an introduction of the γ-lactone part, **10** was subjected to a Wacker-oxidation-like reaction using a palladium catalyst, providing the desired lactone **11**. This oxidative cyclization was considered to proceed *via* regioselective *trans*-hydroxypalladations followed by [PdCl/TMS] *syn*-elimination [10]. After deprotection of **11** followed by acetylation, (+)-1893B (**2**) was obtained. The spectroscopic data (IR, ^{1}H- and ^{13}C-NMR, HRMS, $[\alpha]_D$) of synthetic **2** were identical with those reported for natural (+)-1893B in all respects.

Furthermore, we synthesized three diastereomers of **2**, *i.e.*, **14**, **18** and **21**, from the stereochemically defined intermediates **6a** (for **18** and **21**) or **9b** (for **14**) *via* exactly the same synthetic routes used for the conversion of **6a** to **2** (Scheme 2).

Biological Activities of 1893 Series

Finally, the biological activities of (+)-1983 A (**1**) and (+)-1983B (**2**) and the three stereoisomers **14**, **18**, and **21** were explored (Table 1). Compound **1** was found to exhibit weak cytotoxicity *in vitro* against human chronic myelogenous leukemia K562 and human hepatocellular carcinoma HepG2 cells. However, neither compounds **2**, nor diastereomers **14**, **18**, and **21** showed either antibacterial activities against a variety of Gram-positive and Gram-negative bacteria and cytotoxicity against the two tumor cell lines.



Scheme 2 Syntheses of other diastereomers **14**, **18** and **21**.

Reagents and conditions: The same reaction conditions as described in Scheme 1 were used.

Table 1 Biological activities of 1893 series

K562 cells	IC_{50} (μg/ml)				
batch	1893A (**1**)	1893B (**2**)	**14**	**18**	**21**
1st	26	>64	>64	>64	>64
2nd	19	>64	>64	>64	>64
Ave.	23	>64	>64	>64	>64
HepG2 cells	IC_{50} (μg/ml)				
batch	1893A (**1**)	1893B (**2**)	**14**	**18**	**21**
1st	26	>64	>64	>64	>64
2nd	21	>64	>64	>64	>64
Ave.	23	>64	>64	>64	>64

Experimental

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H-NMR spectra were recorded at JEOL GSX-270 (270 MHz) and ^{13}C NMR spectra at JEOL GSX-270 (68 Hz). All spectra were recorded in $CDCl_3$. High-resolution mass spectra were measured by JEOL JMS-GCMATE spectrometer. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 F_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel Silica Gel 60 (Merck) or Wakogel C300 (Wako Pure Chemical Industries). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Commercially available solvents were dried (drying reagent in brackets) and distilled prior to use: *N*,*N*-dimethylformamide (DMF) [CaH_2], CH_2Cl_2 [CaH_2], benzene [CaH_2], and pyridine [NaOH].

Preparation of Diastereomeric Mixture of Allylic Alcohols 6a and 6b

The following reaction was carried out under Ar. To a cooled (0°C) stirred solution of crude aldehyde (65.5 mg, 370 μmol) in THF (1 ml), prepared from enantioenriched **5** (>95% ee) by Dess-Martin oxidation according to the previous report [5], was added vinylmagnesium bromide (1.0 M solution in THF, 0.6 ml, 0.6 mmol). After being stirred for 10 minutes at 0°C, the solution was quenched with saturated aqueous NH_4Cl (1 ml), diluted with saturated aqueous NH_4Cl (10 ml), and extracted with CH_2Cl_2 (5 ml×4). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 4), providing 49.5 mg (70%) of the inseparable mixture of **6a** and **6b** as a colorless oil.

Separation of Allylic Alcohols 6a and 6b

To a cooled (0°C) stirred solution of the mixture of **6a** and **6b** (49.4 mg, 257 μmol) in CH_2Cl_2 (2 ml) were added (*S*)-(+)-*O*-acetylmandelic acid (200 mg, 1.03 mmol), EDCI·HCl (197 mg, 1.03 mmol), and 4-DMAP (12.6 mg, 103 μmol). The mixture was stirred for 10 minutes at 0°C, diluted with EtOAc (10 ml), and washed with 1 M aqueous HCl (5 ml×3), saturated aqueous $NaHCO_3$ (5 ml×3), then H_2O (5 ml). The organic layer was dried and concentrated *in vacuo*. The residue was purified by column

chromatography on silica gel (EtOAc/toluene, 1 : 80) to provide 47.0 mg (53%) of (1*R*)-ester derived from **6b** and 36.3 mg (41%) of (1*S*)-ester derived from **6a**. The (1*R*)-ester was isoleted as a colorless oil: TLC Rf 0.17 (EtOAc/toluene, 1 : 15); $[\alpha]_D^{21.5}$ +58.2 (*c* 1.1, $CHCl_3$); IR (neat) 2940, 1750 cm^{-1}; ^1H NMR δ 1.00 (d, 3H, *J*=6.6 Hz), 2.19 (s, 3H), 2.72 (m, 1H), 2.80 (m, 1H), 4.26 (d, 1H, *J*=4.4 Hz), 4.28 (d, 1H, *J*=5.5 Hz), 5.10 (dd, 1H, *J*=0.9, 10.2 Hz), 5.13 (dd, 1H, *J*=0.9, 17.2 Hz), 5.21 (dd, 1H, *J*=7.4, 10.4 Hz), 5.49 (ddd, 1H, *J*=7.4, 10.2, 17.2 Hz), 5.85 (s, 1H), 5.82～5.91 (m, 2H), 6.02～6.11 (m, 2H), 7.33～7.52 (m, 5H); ^{13}C NMR δ 14.1, 20.6, 52.4, 55.5, 74.6, 75.5, 77.6, 86.8, 119.2, 124.5, 125.7, 127.7, 128.7, 129.3, 135.1×2, 137.6×2, 138.6×2, 167.7, 170.4; EIHRMS calcd for $C_{22}H_{24}O_5$ (M^+) *m*/*z* 368.1624, found 368.1625. The (1*S*)-ester was isoleted as white crystals: mp 125.2～127.0°C; TLC Rf 0.19 (EtOAc/toluene, 1 : 15); $[\alpha]_D^{23.5}$ +110 (*c* 0.97, $CHCl_3$); IR (KBr disk) 2940, 1745 cm^{-1}; ^1H NMR δ 0.92 (d, 1H, *J*=7.0 Hz), 2.19 (s, 3H), 2.55～2.62 (m, 2H), 3.99 (t, 1H, *J*=5.3 Hz), 4.11 (d, 1H, *J*=4.8 Hz), 5.23 (m, 1H), 5.28 (d, 1H, *J*=10.7 Hz), 5.42 (d, 1H, *J*=17.2 Hz), 5.62 (dd, 1H, *J*=6.8, 10.7 Hz), 5.70～5.86 (m, 2H), 5.90 (s, 1H), 5.90～5.97 (m, 2H), 7.21～7.40 (m, 5H); ^{13}C-NMR δ 14.3, 20.7, 52.0, 54.8, 74.6, 75.9, 78.8, 86.4, 119.2, 124.6, 124.7, 128.1, 128.9, 129.6, 133.6, 134.4, 136.7×2, 139.0×2, 167.9, 170.3; EIHRMS calcd for $C_{22}H_{24}O_5$ (M^+) *m*/*z* 368.1624, found 368.1623.

To a cooled (0°C) stirred solution of the (1*S*)-ester (30.0 mg, 81.4 μmol) in H_2O/MeOH (1 : 1, v/v, 1 ml) was added $LiOH \cdot H_2O$ (17.1 mg, 407 μmol). The mixture was stirred for 3 hours, diluted with saturated brine (10 ml), and extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 4) to provide 15.3 mg (98%) of **6a** as a colorless oil: TLC Rf 0.57 (EtOAc/hexane, 1 : 1); $[\alpha]_D^{20.0}$ +12.1 (*c* 1.27, $CHCl_3$); IR (neat) 3420, 2950 cm^{-1}; ^1H NMR δ 1.16 (d, 3H, *J*=7.0 Hz), 2.26 (br m, 1H), 2.53 (dt, 1H, *J*=4.3, 7.0 Hz), 2.66 (m, 1H), 4.16 (m, 1H), 4.26 (dd, 1H, *J*=2.9, 5.1 Hz), 4.72 (t, 1H, *J*=4.3 Hz), 5.20 (td, 1H, *J*=1.5, 10.6 Hz), 5.37 (td, 1H, *J*=1.5, 16.9 Hz), 5.82～5.94 (m, 3H), 6.09～6.17 (m, 2H); ^{13}C NMR δ 14.0, 49.6, 60.1, 72.2, 80.0, 85.7, 115.6, 124.9, 125.1, 137.4, 138.5, 140.2; EIHRMS calcd for $C_{12}H_{16}O_2$ (M^+) *m*/*z* 192.1150, found 192.1163.

Analogously, **6b** was obtained from the (1*R*)-ester in 52% yield for tow steps: TLC Rf 0.57 (EtOAc/hexane, 1 : 1); $[\alpha]_D^{25.0}$ +125 (*c* 1.83, $CHCl_3$); IR (KBr disk) 3420, 2940 cm^{-1}; ^1H NMR δ 1.15 (d, 3H, *J*=7.0 Hz), 1.56 (br s, 1H), 2.53 (ddd, 1H, *J*=3.3, 6.6, 10.3 Hz), 2.83 (m, 1H), 4.10 (m, 1H), 4.21～4.28 (m, 2H), 5.16 (ddd, 1H, *J*=0.7, 1.5, 11.4 Hz), 5.29 (td, 1H, *J*=1.5, 17.2 Hz), 5.76～5.89 (m, 3H), 6.01～6.15 (m, 2H); ^{13}C NMR δ 14.2, 52.7, 57.9, 73.0, 78.0, 86.8, 116.2, 124.4, 125.5, 137.4, 138.9, 141.1; EIHRMS calcd for $C_{12}H_{16}O_2$ (M^+) *m*/*z* 192.1150, found 192.1169.

$VO(acac)_2$-catalyzed Epoxidation of 6a. Preparation of Diatereomeric Mixture of Epoxy-alcohols 7

To a cooled (0°C) stirred solution of **6a** (79.8 mg, 415 μmol) in CH_2Cl_2 (1.5 ml) were added $VO(acac)_2$ (20.8 mM solution in CH_2Cl_2, 1.0 ml, 20.8 μmol) and *t*-BuO_2H (5.53 M solution in isooctane, 0.22 ml, 1.25 mmol). The mixture was stirred for 3 hours, diluted with EtOAc (10 ml), and washed with saturated aqueous Na_2SO_3 (5 ml×3), saturated aqueous $NaHCO_3$ (5 ml), and saturated brine (5 ml). The organic layer was dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 2) to provide 51.9 mg (60%) of the 2 : 1 mixture of *anti*- and *syn*-epoxy alcohols **7** as a colorless oil: TLC, Rf 0.49 (EtOAc/hexane, 3 : 2); IR (neat) 3430, 2940 cm^{-1}; ^1H NMR for the major *anti*-isomer δ 1.16 (d, 3H, *J*=7.0 Hz), 2.41 (br d, 1H, *J*=3.2 Hz), 2.54 (td, 1H, *J*=4.5, 6.9 Hz), 2.74～2.81 (m, 3H), 3.05 (ddd, 1H, *J*=3.3, 3.8, 4.3 Hz), 3.81 (ddd, 1H, *J*=3.2, 3.3, 6.9 Hz), 4.27 (dd, 1H, *J*=2.4, 4.9 Hz), 4.78 (dd, 1H, *J*=3.8, 4.9 Hz), 5.85～5.92 (m, 2H), 6.01～6.23 (m, 2H); ^{13}C NMR for the major *anti*-isomer δ 14.6, 43.9, 50.4, 53.8, 56.5, 68.6, 79.4, 85.8, 125.1×2, 137.2, 138.5; EIHRMS calcd for $C_{12}H_{16}O_3$ (M^+) *m*/*z* 208.1099, found 208.1088.

Mitsunobu Inversion of the Diastereomeric Mixture 7. Preparation of the 1 : 2 Mixture of *anti*- and *syn*-Epoxy-alcolols 8

To a cooled (0°C) stirred solution of the inseparable mixture of epoxy-alcohols **7** (7.9 mg, 38 μmol), PPh_3 (40.0 mg, 152 μmol), and 4-nitrobenzoic acid (25.9 mg, 155 μmol) in THF (1.0 ml) was added dropwise diethyl azodicarboxylate (73 μl, 0.16 mmol). After being stirred for 5 hours, the solution was diluted with 1 M aqueous HCl (5 ml) and extracted with EtOAc (3×10 ml). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 5) to provide 18.6 mg of mixture of the 4-nitrobenzoate esters.

To a cooled (0°C) stirred solution of thus obtained mixture (18.6 mg) in H_2O/MeOH, (1 : 1, v/v, 1 ml) was added $LiOH \cdot H_2O$ (7.9 mg, 0.19 mmol). This was stirred for 4 hours, diluted with saturated brine (10 ml), and extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried

and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 2) to provide 6.6 mg (84% for 2 steps) of the 1 : 2 mixture of *anti*- and *syn*-epoxy alcohols **8** as a colorless oil: TLC, Rf 0.49 (EtOAc/hexane, 3 : 2); IR (neat) 3425, 2940 cm^{-1}; ^1H NMR for the major *syn*-isomer δ 1.13 (d, 3H, J=7.0 Hz), 1.95 (br d, 1H, J=5.4 Hz), 2.61 (td, 1H, J=6.6, 10.7 Hz), 2.80～2.98 (m, 4H), 3.45 (td, 1H, J=5.4, 10.7 Hz), 4.28 (d, 1H, J=4.4 Hz), 4.34 (t, 1H, J=6.0 Hz), 5.86～5.95 (m, 2H), 6.09, 6.22 (2m, each 1H); ^{13}C NMR for the major *syn*-isomer δ 14.1, 45.9, 53.3, 55.3, 62.3, 70.9, 77.3, 86.2, 124.5, 126.3, 137.6, 137.8; EIHRMS calcd for $C_{12}H_{16}O_3$ (M^+) *m/z* 208.1099, found 208.1088.

Preparation of Separable MOM Ethers 9a and 9b

To a stirred solution of **8** (21.9 mg, 105 μmol) in CH_2Cl_2 (1 ml) were added *i*-Pr_2NEt (259 μl, 1.05 mmol), chloromethyl methyl ether (41 μl, 0.53 mmol), and 4-DMAP (6.4 mg, 53 μmol). The mixture was refluxed for 24 hours, diluted with saturated aqueous $NaHCO_3$ (10 ml), and extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 4) to provide 14.4 mg (54%) of **9a** and 9.1 mg (35%) of **9b**. Compound **9a** was isolated as a colorless oil: TLC Rf 0.43 (EtOAc/hexane, 3 : 2); $[\alpha]_D^{21.5}$ +25.4 (*c* 0.25, $CHCl_3$); IR (neat) 2930 cm^{-1}; ^1H NMR δ 1.10 (d, 3H, J=7.0 Hz), 2.62～2.71 (m, 2H), 2.81～2.90 (m, 2H), 2.96 (m, 1H), 3.25 (dd, 1H, J=7.7, 10.6 Hz), 3.42 (s, 3H), 4.26 (d, 1H, J=4.4 Hz), 4.32 (t, 1H, J=6.2 Hz), 4.70 (d, 1H, J=6.6 Hz), 4.97 (d, 1H, J=6.6 Hz), 5.87～5.94 (m, 2H), 6.09, 6.21 (2m, each 1H); ^{13}C NMR δ 13.8, 44.0, 53.2, 53.6, 54.9, 56.3, 76.7, 77.6, 86.0, 95.9, 124.7, 126.2, 137.7, 138.2; EIHRMS calcd for $C_{14}H_{20}O_4$ (M^+) *m/z* 252.1362, found 252.1366. Compound **9b** was isolated as a colorless oil: TLC Rf 0.44 (EtOAc/hexane, 3 : 2); $[\alpha]_D^{24.0}$ +64.3 (*c* 0.54, $CHCl_3$); IR (neat) 2940 cm^{-1}; ^1H NMR δ 1.07 (d, 3H, J=7.0 Hz), 2.67～2.87 (m, 5H), 3.19～3.25 (m, 1H), 3.38 (s, 3H), 4.23 (d, 1H, J=4.4 Hz), 4.60 (d, 1H, J=7.0 Hz), 4.61 (t, 1H, J=6.8 Hz), 4.76 (d, 1H, J=7.0 Hz), 5.86～5.93 (m, 2H), 6.07, 6.36 (2m, each 1H); ^{13}C NMR δ 13.8, 46.5, 52.6, 53.1, 55.8, 56.1, 76.4, 77.1, 85.5, 96.2, 124.8, 125.5, 137.5, 139.2; EIHRMS calcd for $C_{14}H_{20}O_4$ (M^+) *m/z* 252.1362, found 252.1359.

Epoxy-ring Opening of 9a by Lithium TMS-acetylide. Preparation of 10

The following reaction was carried out under Ar. To a cooled (−78°C) stirred solution of trimethylsilylacetylene (50 μl, 0.36 mmol) in THF (1 ml) was added *n*-BuLi (2.67 M in hexane, 0.14 ml, 0.36 mmol). The solution was stirred at −78°C for 10 minutes and a solution of **9a** (9.1 mg, 36 μmol) in THF (1.5 ml) was added. The mixture was stirred at −78°C for 10 minutes and then $BF_3{\cdot}Et_2O$ (45 μl, 0.36 mmol) was added. The mixture was stirred while gradually warmed to −30°C over 5 hours. The mixture was quenched with saturated aqueous NH_4Cl (1 ml), diluted with saturated aqueous NH_4Cl (10 ml), and extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 4) to provide 11.0 mg (99%) of **10** as a colorless oil: TLC Rf 0.48 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{24.5}$ +8.8 (*c* 0.55, $CHCl_3$); IR (neat) 3450, 2960, 2180 cm^{-1}; ^1H NMR δ 0.15 (s, 9H), 1.14 (d, 3H, J=7.0 Hz), 2.48～2.57 (m, 2H), 2.74 (m, 1H), 2.87 (m, 1H), 3.25 (br d, 1H, J=5.9 Hz), 3.42 (s, 3H), 3.78～3.81 (m, 1H), 3.87 (dd, 1H, J=1.8, 7.7 Hz), 4.27 (dd, 1H, J=2.6, 4.8 Hz), 4.65 (t, 1H, J=5.0 Hz), 4.73 (d, 1H, J=7.0 Hz), 4.81 (d, 1H, J=7.0 Hz), 5.87～5.95 (m, 2H), 6.12～6.26 (m, 2H); ^{13}C NMR δ 0.2×3, 13.8, 25.3, 50.1, 55.3, 56.0, 71.4, 78.0, 78.1, 85.4, 87.6, 97.5, 103.3, 125.2, 125.4, 137.5, 138.3; EIHRMS calcd for $C_{19}H_{30}O_4Si$ (M^+) *m/z* 350.1913, found 350.1924.

γ-Lactone Formation. Preparation of 11

To a stirred solution of **10** (11.0 mg, 31.4 μmol) in DMF containing 1% water (1 ml) were added $PdCl_2(MeCN)_2$ (16 mM solution in DMF containing 1% water, 0.1 ml, 1.6 μmol) and $CuCl_2$ (79 mM solution in DMF containing 1% water, 0.1 ml, 7.9 μmol). The mixture was stirred for 4 days and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2 : 1) to provide 6.5 mg (71%) of **11** as a colorless oil: TLC Rf 0.37 (EtOAc/hexane, 3 : 2); $[\alpha]_D^{27.5}$ +16.9 (*c* 0.33, $CHCl_3$); IR (neat) 2920, 1775 cm^{-1}; ^1H NMR δ 1.12 (d, 3H, J=7.0 Hz), 2.08～2.27 (m, 2H), 2.54～2.61 (m, 2H), 2.65～2.81 (m, 2H), 3.40 (s, 3H), 3.82 (dd, 1H, J=4.4, 8.8 Hz), 4.23 (d, 1H, J=4.4 Hz), 4.52 (t, 1H, J=6.0 Hz), 4.73 (m, 1H), 4.75 (s, 2H), 5.87～5.94 (m, 2H), 6.06, 6.26 (2m, each 1H); ^{13}C NMR δ 14.7, 23.7, 28.5, 50.8, 53.4, 56.3, 77.2, 79.0, 80.8, 85.9, 97.9, 124.8, 125.9, 137.3, 138.6, 176.7; EIHRMS calcd for $C_{16}H_{22}O_5$ (M^+) *m/z* 294.1467, found 294.1478.

1893B (2)

Compound **11** (6.5 mg, 22 μmol) was dissolved in 2 M aqueous HCl/THF (1 : 1, v/v, 1 ml). After being stirred at 50°C for 1.5 hours, the solution was diluted with H_2O (10 ml) and extracted with EtOAc (5 ml×3). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 3 : 1) to provide 5.4 mg (98%) of de-*O*-

MOM derivative as a colorless oil: TLC Rf 0.28 (EtOAc/hexane, 4 : 1); $[\alpha]_D^{26.0}$ +56.0 (*c* 0.25, $CHCl_3$); IR (neat) 3450, 2930, 1775 cm^{-1}; ^1H NMR δ 1.15 (d, 3H, *J*=6.6 Hz), 2.17 (br s, 1H), 2.26～2.47 (m, 2H), 2.53～2.65 (m, 2H), 2.70～2.83 (m, 2H), 3.58 (m, 1H), 4.28 (d, 1H, *J* =4.8 Hz), 4.32 (t, 1H, *J*=5.7 Hz), 4.42 (dt, 1H, *J*=1.5, 7.3 Hz), 5.88～5.95 (m, 2H), 6.05, 6.23 (2m, each 1H); ^{13}C NMR δ 14.1, 24.2, 28.6, 53.0, 54.4, 72.0, 76.8, 81.9, 86.5, 124.8, 126.4, 137.1, 137.4, 169.6; EIHRMS calcd for $C_{14}H_{18}O_4$ (M^+) *m/z* 250.1205, found 250.1203.

To a stirred solution of thus obtained compound (5.4 mg, 22 μmol) in pyridine/Ac_2O (1 : 1, v/v, 1 ml) was added 4-DMAP (1.3 mg, 11 μmol). After being stirred for 30 minutes, the solution was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2 : 1) to provide 5.3 mg (84%) of **2** as colorless crystals: mp 138.5～140.7°C; TLC Rf 0.48 (EtOAc/hexane, 4 : 1); $[\alpha]_D^{27.4}$ +10.8 (*c* 0.25, acetone); IR (neat) 2920, 1775, 1730 cm^{-1}; ^1H NMR δ 0.98 (d, 3H, *J*=7.0 Hz), 2.00～2.36 (m, 2H), 2.11 (s, 3H), 2.43～2.55 (m, 2H), 2.72 (m, 1H), 2.98 (td, 1H, *J*=6.5, 10.3 Hz), 4.24 (d, 1H, *J*=4.4 Hz), 4.42 (t, 1H, *J*=5.9, 5.9 Hz), 4.57 (ddd, 1 H, *J*=2.5, 6.5, 7.6 Hz), 5.15 (dd, 1H, *J*=2.4, 10.4 Hz), 5.91 (m, 1H), 5.95 (m, 1H), 6.04 (m, 1H), 6.24 (m, 1H); ^{13}C NMR δ 14.4, 21.0, 23.9, 28.0, 51.5, 52.3, 72.6, 76.7, 80.1, 86.2, 125.0, 126.3, 136.9, 137.5, 170.5, 176.2; EIHRMS calcd for $C_{16}H_{20}O_5$ (M^+) *m/z* 292.1311, found 292.1316.

Preparation of 12

Compound **9b** was converted to **12** analogously as the conversion of **9a** to **10**. Compound **12** as a coloress oil: TLC Rf 0.60 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{25.0}$ +45.8 (*c* 2.41, $CHCl_3$); IR (neat) 3450, 2950, 2180 cm^{-1}; ^1H NMR δ 0.16 (s, 9H), 1.04 (d, 3H, *J*=7.3 Hz), 2.31～2.53 (2m, 3H), 2.78 (m, 1H), 3.44 (s, 3H), 3.59 (m, 1H), 3.68 (dd, 1H, *J*=1.7, 10.8 Hz), 4.25 (d, 1H, *J*=4.4 Hz), 4.34 (t, 1H, *J*=6.0 Hz), 4.69 (d, 1H, *J*=7.0 Hz), 4.78 (d, 1H, *J*=7.0 Hz), 5.86～5.97 (m, 2H), 6.06, 6.26 (2m, each 1H); ^{13}C NMR δ 0.1×3, 14.0, 22.8, 52.8, 53.0, 56.1, 72.8, 76.7, 84.1, 86.1, 98.5, 103.9, 124.66, 126.31, 137.5, 137.9; EIHRMS calcd for $C_{19}H_{30}O_4Si$ (M^+) *m/z* 350.1913, found 350.1903.

Preparation of 13

Compound **12** was converted to **13** analogously as the conversion of **10** to **11**. Compound **13** as a coloress oil: TLC Rf 0.50 (EtOAc/hexane, 3 : 2); $[\alpha]_D^{24.5}$ +46.2 (*c* 1.0, $CHCl_3$); IR (neat) 2940, 1775 cm^{-1}; ^1H NMR δ 1.13 (d, 3H, *J*=7.3 Hz), 2.04～2.59 (m, 5H), 2.81 (m, 1H), 3.36 (s, 3H), 3.94 (dd, 1H, *J*=1.7, 9.9 Hz), 4.25 (d, 1H, *J*=4.3 Hz), 4.35 (t, 1H, *J*=5.8 Hz), 4.46 (dt, 1H, *J*=1.7, 7.5 Hz), 4.65 (d, 1H), 4.76 (d, 1H), 5.87～5.95 (m, 2H), 6.09～6.20 (2m, 2H); ^{13}C NMR δ 13.5, 20.7, 28.5, 52.0, 53.0, 56.0, 76.5, 77.2, 82.5, 85.7, 98.0, 124.8, 126.5, 137.4, 138.0, 176.9; EIHRMS calcd for $C_{16}H_{22}O_5$ (M^+) *m/z* 294.1467, found 294.1463.

Preparation of 4-*epi*-1893B (14)

Compound **13** was converted to **14** analogously as the conversion of **11** to **2**. Compound **14** as a coloress oil: TLC Rf 0.56 (EtOAc/hexane, 2 : 1); $[\alpha]_D^{25.2}$ +121.3 (*c* 0.05, acetone); IR (neat) 2950, 1775, 1750 cm^{-1}; ^1H NMR δ 1.04 (d, 3H, *J*=7.0 Hz), 2.08 (s, 3H), 2.13～2.23 (m, 2H), 2.48～2.55 (m, 2H), 2.65～2.78 (m, 2H), 4.24 (d, 1H, *J*=4.8 Hz), 4.43～4.50 (m, 2H), 5.31 (dd, 1H, *J*=4.8, 9.5 Hz), 5.88～5.97 (m, 2H), 6.10, 6.26 (m, each 1H); ^{13}C NMR δ 14.3, 20.9, 22.9, 28.1, 52.4×2, 71.5, 77.2, 80.6, 85.6, 124.9, 126.4, 137.6, 137.8, 169.6, 176.0; EIHRMS calcd for $C_{16}H_{20}O_5$ (M^+) *m/z* 292.1311, found 292.1305.

Preparation of 15a and 15b

Compound **6a** was converted to **15a** and **15b** by $VO(acac)_2$-catalyzed epoxidation followed by MOM etherification. The *ant*-**15a** and *syn*-epoxy alcohols **15b** were separated by chromatography on silica gel. Compound **15a** was isolated as a coloress oil: TLC Rf 0.57 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{24.5}$ +101.8 (*c* 2.0, $CHCl_3$); IR (neat) 2930 cm^{-1}; ^1H NMR δ 1.09 (d, 3H, *J*=7.0 Hz), 2.61～2.80 (m, 4H, H-8), 2.91 (m, 1H), 3.41 (s, 3H), 3.58 (dd, 1H, *J*=4.8, 9.9 Hz), 4.28 (d, 1H, *J*=4.4 Hz), 4.56 (d, 1H), 4.64 (t, 1H, *J*=5.9 Hz), 4.77 (d, 1H), 5.83～5.93 (m, 2H), 6.04, 6.29 (2m, each 1H); ^{13}C NMR δ 15.1, 44.7, 52.5, 53.1, 54.7, 56.0, 75.5, 78.9, 86.9, 96.7, 124.9×2, 137.1, 139.8; EIHRMS calcd for $C_{14}H_{20}O_4$ (M^+) *m/z* 252.1362, found 252.1358. Compound **15b** was isolated as a colorless oil: TLC Rf 0.59 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{24.5}$ +70.0 (*c* 0.45, $CHCl_3$); IR (neat) 2940 cm^{-1}; ^1H NMR δ 1.08 (d, 3H), 2.63～2.81 (m, 4H), 3.00 (m, 1H), 3.44 (s, 3H), 3.57 (dd, 1H, *J*=5.9, 9.2 Hz), 4.27 (d, 1H, *J*=4.4 Hz), 4.64 (d, 1H, *J*=6.6 Hz), 4.64 (t, 1H), 4.89 (d, 1H), 5.83～5.94 (m, 2H), 6.04, 6.29 (2m, each 1H); ^{13}C NMR δ 15.4, 44.4, 52.1, 53.4, 53.9, 56.3, 76.4, 78.8, 86.8, 96.3, 125.0×2, 137.0, 139.7; EIHRMS calcd for $C_{14}H_{20}O_4$ (M^+) *m/z* 252.1362, found 252.1374.

Preparation of 16

Compound **15a** was converted to **16** analogously as the conversion of **9a** to **10**. Compound **16** was isolated as a coloress oil: TLC Rf 0.61 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{25.0}$ +34.8 (*c* 2.19, $CHCl_3$); IR (neat) 3440, 2960, 2190 cm^{-1}; ^1H NMR δ 0.15 (s, 9H), 1.08 (d, 3H, *J*=6.6 Hz), 2.42 (dd, 1H, *J*=7.3, 17.2 Hz), 2.53 (dd, 1H, *J*=5.5, 17.2 Hz), 2.64～2.70 (m, 2H), 3,45 (s, 3H), 3.56～3.74 (m, 3H), 4.26 (d, *J*=4.8 Hz), 4.49 (t, 1H, *J*=5.5 Hz), 4.68 (d, 1H,

J=7.0 Hz), 4.83 (d, 1H, J=7.0 Hz), 5.80～5.91 (m, 2H), 6.01, 6.25 (m, each 1H); ^{13}C NMR δ 0.1×3, 14.5, 23.2, 52.2, 52.8, 56.2, 71.2, 79.7, 85.5, 86.5, 86.9, 98.7, 103.8, 124.7, 125.0, 136.8, 139.8; EIHRMS calcd for $C_{19}H_{30}O_4Si$ (M^+) m/z 350.1913, found 350.1921.

Preparation of 17

Compound **16** was converted to **17** analogously as the conversion of **10** to **11**. Compound **17** as a coloress oil: TLC Rf 0.27 (EtOAc/hexane, 3 : 2); $[\alpha]_D^{23.5}$ +65.7 (c 0.67, $CHCl_3$); IR (neat) 2950, 1775 cm^{-1}; ^{1}H NMR δ 1.09 (d, 3H, J=6.6 Hz), 2.07～2.58 (m, 6H), 3.43 (s, 3H), 3.97 (dd, 1H, J=1.7, 10.8 Hz), 4.28 (d, 1H, J=4.4 Hz), 4.53 (dt, 1H, J=1.7, 7.5 Hz), 4.63 (d, 1H, J=6.6 Hz), 4.69 (t, 1H, J=5.9 Hz), 4.81 (d, 1H, J=6.6 Hz), 5.83～5.93 (m, 2H), 6.01, 6.31 (2m, each 1H); ^{13}C NMR δ 14.7, 20.8, 28.3, 51.7, 52.0, 56.5, 78.4, 79.1, 81.2, 86.8, 98.7, 125.0, 125.1, 136.7, 139.8, 176.8; EIHRMS calcd for $C_{16}H_{22}O_5$ (M^+) m/z 294.1467, found 294.1474.

Preparation of 5-*epi*-1893B (18)

Compound **17** was converted to **18** analogously as the conversion of **11** to **2**. Compound **18** as a coloress oil: TLC Rf 0.50 (EtOAc/hexane, 3 : 1) $[\alpha]_D^{23.0}$ +44.3 (c 0.50, acetone); IR (neat) 2950, 1775, 1740 cm^{-1}; ^{1}H NMR δ 1.08 (d, 3H, J=6.6 Hz), 2.10 (s, 3H), 2.12～2.36 (m, 2H), 2.48～2.56 (m, 2H), 2.64～2.73 (m, 2H), 4.26 (d, 1H, J=4.4 Hz), 4.50 (ddd, 1H, J=4.4, 7.2, 7.3 Hz), 4.64 (t, 1H, J=5.7 Hz), 5.30 (dd, 1H, J=4.0, 7.2 Hz), 5.84～5.94 (m, 2H), 6.04 (m, 1H), 6.22 (m, 1H); ^{13}C NMR δ 14.7, 21.1, 22.9, 28.0, 51.1, 53.1, 72.3, 77.4, 80.0, 86.2, 124.9, 125.4, 137.0, 138.8, 169.9, 176.1; EIHRMS calcd for $C_{16}H_{20}O_5$ (M^+) m/z 292.1311, found 292.1315.

Preparation of 19

Compound **15b** was converted to **19** analogously as the conversion of **9a** to **10**. Compound **19** as a coloress oil: TLC Rf 0.48 (EtOAc/hexane, 2 : 3); $[\alpha]_D^{22.0}$ +47.6 (c 0.77, $CHCl_3$); IR (neat) 3400, 2960, 2190 cm^{-1}; ^{1}H NMR δ 0.20 (s, 9H), 1.09 (d, 3H, J=7.0 Hz), 2.38～2.77 (m, 3H), 2.93 (m, 1H), 3.46 (s, 3H), 3.90 (d, 1H, J=9.9 Hz), 4.26 (d, 1H, J=4.0 Hz), 4.52 (m, 1H), 4.67 (t, 1H, J=6.2 Hz), 4.73 (d, 1H), 4.83 (d, 1H, J=6.6 Hz), 5.87～5.92 (m, 2H), 6.02, 6.28 (m, each 1H); ^{13}C NMR δ −0.1×3, 14.6, 25.9, 52.1, 52.3, 56.5, 70.6, 78.9, 80.3, 86.8×2, 98.6, 102.5, 124.9, 125.1, 137.0, 139.6; EIHRMS calcd for $C_{19}H_{30}O_4Si$ (M^+) m/z 350.1913, found 350.1931.

Preparation of 20

Compound **19** was converted to **20** analogously as the conversion of **10** to **11**. Compound **20** as a coloress oil: TLC Rf 0.53 (EtOAc/hexane, 4 : 1); $[\alpha]_D^{20.5}$ +22.5 (c 0.25, $CHCl_3$); IR (neat) 2940, 1775 cm^{-1}; ^{1}H NMR δ 1.07 (d, 3H, J=7.0 Hz), 2.17～2.28 (m, 2H), 2.46～2.69 (m, 3H), 2.83 (m, 1H), 3.43 (s, 3H), 3.71 (dd, 1H, J=3.1, 9.7 Hz), 4.26 (d, 1H, J=4.4 Hz), 4.58 (dt, 1H, J=3.2, 7.3 Hz), 4.62 (t, 1H, J=5.9 Hz), 4.75 (d, 1H, J=3.7 Hz), 4.77 (d, 1H, J=3.7 Hz), 5.83～5.93 (m, 2H), 6.03, 6.25 (2m, each 1H); ^{13}C NMR δ 14.9, 23.4, 28.3, 52.1×2, 56.6, 78.5, 79.7, 80.4, 86.7, 98.4, 125.2×2, 136.9, 139.3, 176.9; EIHRMS calcd for $C_{16}H_{22}O_5$ (M^+) m/z 294.1467, found 294.1455.

Preparation of 4,5-di-*epi*-1893B (21)

Compound **20** was converted to **21** analogously as the conversion of **11** to **2**. Compound **21** as a coloress oil: TLC Rf 0.41 (EtOAc/hexane, 4 : 1) $[\alpha]_D^{23.5}$ +1.5 (c 0.31, acetone); IR (neat) 2940, 1775, 1740 cm^{-1}; ^{1}H NMR δ 1.07 (d, 3H, J=7.0 Hz), 2.13 (s, 3H), 2.24～2.36 (m, 2H), 2.46～2.58 (m, 2H), 2.78 (m, 1H), 2.94 (m, 1H), 4.25 (d, 1H, J=4.4 Hz), 4.49 (t, 1H, J=6.0 Hz), 4.56 (m, 1H), 5.21 (dd, 1H, J=2.6, 8.8 Hz), 5.85～5.94 (m, 2H), 6.03 (m, 1H), 6.17 (m, 1H); ^{13}C NMR δ 14.7, 23.9, 28.0×2, 51.4, 52.4, 73.2, 77.9, 79.6, 86.5, 125.1, 125.6, 136.8, 138.5, 172.8, 176.1; EIHRMS calcd for $C_{16}H_{20}O_5$ (M^+) m/z 292.1311, found 292.1313.

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