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TOTAL SYNTHESIS OF (+)-1893B AIMED AT ESTABLISHING ITS STEREOCHEMISTRY[‡]

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Abstract – The total synthesis of (+)-1893B (**2**) has been completed. The one-pot ring-opening/cross/ring-closing metathesis of (1*S*,2*S*,3*S*,4*R*)-2-(*t*-butyldiphenylsilyloxy)methyl-3-methyl-7-oxabicyclo[2.2.1]hept-5-ene (**4**) provided (1*R*,6*S*,7*S*,8*S*)-7-hydroxymethyl-8-methyl-9-oxabicyclo[4.2.1]nona-2,4-diene (**6**) after deblocking. The epoxy-ring opening of an advanced intermediate (1*R*,6*S*,7*S*,8*S*)-7-[(1*S*,2*S*)-1-methoxymethoxy-2,3-epoxypropyl]-8-methyl-9-oxabicyclo[4.2.1]nona-2,4-diene (**11a**) with trimethylsilylacetylide, followed by palladium(II)-catalyzed oxidation for construction of the γ -lactone moiety in **2**.

1893A (**1**) and 1893B (proposed to be **2'**) (Figure 1), which exhibit cytotoxic and insecticidal activities, were isolated recently from a marine endophytic fungus in mangroves grown on the coast of South China Sea.¹ The structure of **1** was determined by X-Ray crystallographic analysis, while the structure of 1893B was tentatively assigned by ¹H-NMR spectral analysis. As a structurally related natural product, (+)-mycoepoxydiene (**3**) was also isolated.² These natural products (**1-3**) have a common oxygen-bridged cyclooctadiene core skeleton. After the completion of the total syntheses of (–)-**1** and (+)-**3**,³ we embarked on the total synthesis of 1893B, envisaging that 1893B possesses the same relative configuration as that of **3**. Herein, we disclose the total synthesis of natural (+)-1893B, thereby establishing its relative and absolute stereochemistry to be **2**.

In the total syntheses of (–)-**1** and (+)-**3**,³ we demonstrated the usefulness of a ring-expansion strategy by

[‡] This paper is dedicated to Professor Barry M. Trost with respect and admiration on the occasion of his 65th birthday.

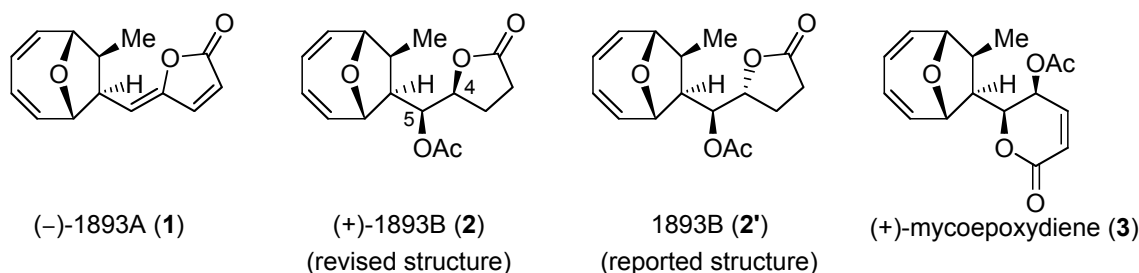
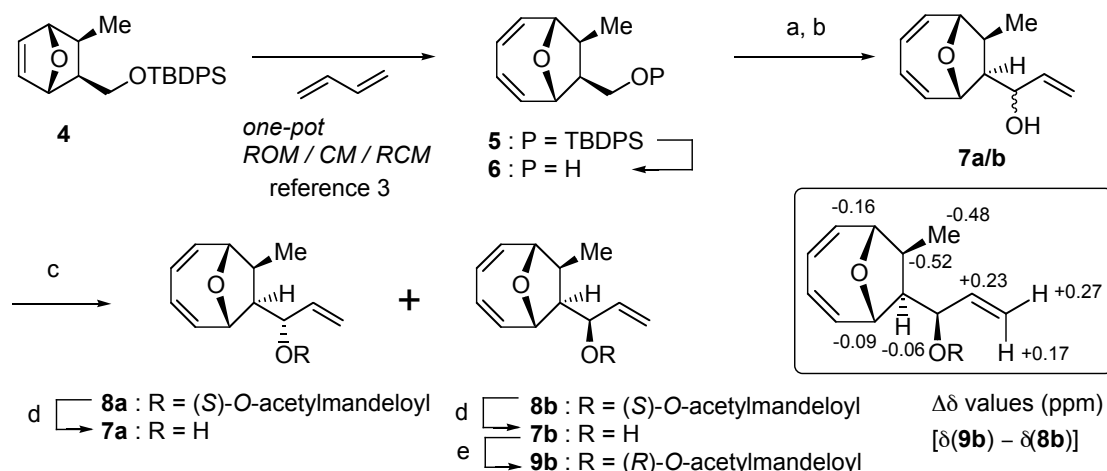


Figure 1. Structures of 1893A, 1893B and (+)-mycoepoxydiene

olefin metathesis for the construction of the core 9-oxabicyclo[4.2.1]nona-2,4-diene framework. In fact, an enantioenriched (95% ee) 7-oxabicyclo[2.2.1]hept-2-ene derivative (**4**) underwent ring-opening/cross metathesis (ROM/CM) with 1,3-butadiene, followed by ring-closing metathesis (RCM) of the resulting triene mixture, providing a cyclooctadiene derivative (**5**) in one pot (Scheme 1). Deblocking of the *t*-butyldiphenylsilyl (TBDPS) ether in **5** provided **6**, which was eventually transformed into (-)-**1** and (+)-**3**. The total synthesis of 1983B was started with this intermediate (**6**). Dess-Martin oxidation⁴ of **6** and the subsequent vinyl Grignard addition to the resulting aldehyde provided an inseparable diastereomeric mixture of allylic alcohol (**7a/b**)⁵ in a ratio of *ca.* 1:1.⁶ An attempt to separate this mixture (**7a/b**) by a Sharpless asymmetric epoxidation procedure [(−)-DIPT, Ti(O*i*-Pr)₄, *t*-BuOOH] resulted in the recovery of the starting mixture.

For complete separation of **7a/b**, we then investigated the acylation with optically active carboxylic acid. Condensation of **7a/b** with (*S*)-*O*-acetylmandelic acid and separation of the products on silica gel provided esters (**8a** and **8b**). In this acylation, a reaction with excess acid and a low temperature was required to prevent epimerization at the α -carbon of the ester. Basic hydrolysis of **8a** and **8b** provided **7a** and **7b**, respectively. To establish the configuration of the introduced allylic carbon in **7b** (and thus

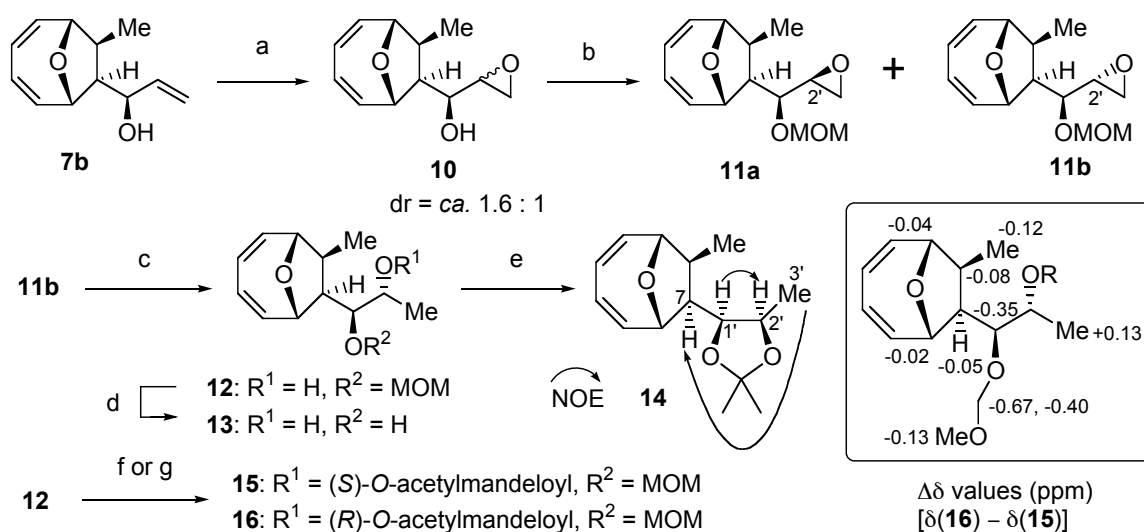


Reagents and conditions: a) Dess-Martin periodinane, CH₂Cl₂; b) CH₂=CHMgBr, THF, 70% for 2 steps; c) (*S*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH₂Cl₂, 47% for **8a**, 51% for **8b**; d) LiOH, 50% aq. MeOH, quant. for **7a**, 98% for **7b**; e) (*R*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH₂Cl₂, 90%.

Scheme 1. Preparation of allylic alcohols (**7a/b**) and determination of their stereochemistries

that in **7a**), the (*R*)-acetylmandelic acid ester (**9b**) of **7b** was also prepared. The chemical shift difference in the ¹H NMR spectra for **9b** and **8b** [$\Delta\delta$, $\delta(\mathbf{9b})-\delta(\mathbf{8b})$], as shown in Scheme 1, verified the (*R*)-configuration.⁷ The stereochemically defined **7b** was subjected to Sharpless VO(acac)₂-mediated oxidation,⁸ providing an inseparable 1.6:1 diastereomeric mixture of epoxy alcohol (**10**) (Scheme 2). This diastereomeric mixture (**10**) was etherified as the MOM (methoxymethyl) ethers, providing *syn*-isomer (**11a**) (34%) and *anti*-isomer (**11b**) (55%) by chromatographic separation on silica gel. To confirm the stereochemistry at C-2' in **11b** (and thus that of **11a**), the major isomer (**11b**) was converted into isopropylidene acetal (**14**) by 1) a hydride attack on the epoxy ring in **11b**, 2) acidic removal of the MOM group in the resulting epoxy-ring opening product (**12**), and then 3) cyclic acetal formation of the resulting diol (**13**). During NOE difference experiments of **14**, signal enhancements of H-2' (4.2%) and H-7 (8.0%) were observed when H-1' and H-3' (Me), respectively, were irradiated. No NOE was observed between H-1' and H-3'(Me). The coupling constant for $J_{1',2'}$ was 5.1 Hz. On the other hand, compound (**12**) was converted into (*S*)- and (*R*)-*O*-acetylmandelic acid esters (**15** and **16**). The $\Delta\delta$ values [$\delta(\mathbf{16})-\delta(\mathbf{15})$] confirmed the *R*-configuration at C-2' in **12**. The structures of the epoxy alcohols (**11a** and **11b**) were established to be those depicted.

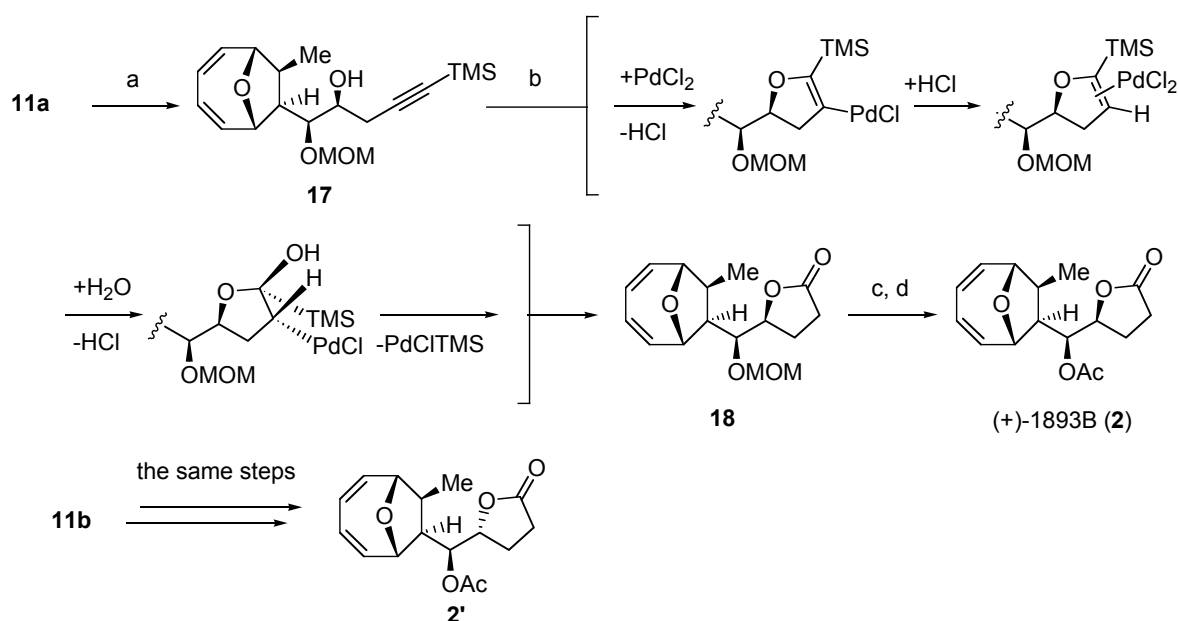
The completion of the total synthesis of **2** from **11a** is depicted in Scheme 3. The introduction of a two-carbon unit to **11a** was efficiently achieved by epoxy-ring opening using trimethylsilylacetylide as a nucleophile,⁹ providing alkyne (**17**).¹⁰ Compound (**17**) was then converted into γ -lactone (**18**) by intramolecular Wacker-type oxidation.^{11,12} As shown in Scheme 3, this palladium(II)-catalyzed γ -lactone formation involves 1) *trans*-selective intramolecular hydroxypalladation to the acetylene group and 2) the



Reagents and conditions: a) VO(acac)₂, *t*-BuOOH, CH₂Cl₂, 62%; b) MOMCl, *i*-Pr₂NEt, DMAP, CH₂Cl₂, reflux, 34% for **11a**, 55% for **11b**; c) Dibal-H, CH₂Cl₂, 0 °C, 59%; d) 2 M HCl, THF, 50 °C, quant.; e) 2,2-dimethoxypropane, PPTS, 84%; f) (*S*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH₂Cl₂, 37%; g) (*R*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH₂Cl₂, 35%.

Scheme 2. Preparation of epoxy alcohols (**11a** and **11b**) and determination of the stereochemistry for **11b**

addition of H₂O to the intermediary η^2 -olefin complex, followed by 3) *syn*-elimination of a PdCITMS. Finally, deprotection of the MOM group in **18**, followed by acetylation, provided 1893B (**2**).¹³ The spectroscopic data (IR, ¹H- and ¹³C- NMR) of synthetic **2** were identical to those reported for natural 1893B in all respects.¹ The dextrorotatory property of the synthetic **2** established the absolute stereochemistry [for synthetic **2**: $[\alpha]_D^{27} +10.8^\circ$ (*c* 0.25, acetone), for natural **2**: $[\alpha]_D^{20} +10.8^\circ$ (*c* 0.02, acetone)]. On the other hand, the major epoxy alcohol (**11b**) was transformed into **2'** (the proposed structure for 1893B)¹ by the analogous reaction sequence used for **11a**, whose spectroscopic data (¹H- and ¹³C- NMR) did not coincide with those of the natural 1893B.^{14, 15}



Reagents and conditions: a) TMS-acetylene, *n*-BuLi, BF₃·Et₂O, THF, -78 to -30 °C, 99%; b) PdCl₂(MeCN)₂, CuCl₂, 1% aq. DMF, 71%; c) 2 M HCl, THF, 50 °C, 98%; d) Ac₂O, DMAP, pyridine, 84%.

Scheme 3. Construction of the γ -lactone moiety and completion of the total synthesis

In conclusion, we have accomplished the total synthesis of (+)-1893B (**2**) for the first time. The total synthesis started from our previously reported ROM/CM/RCM product (**5**). The efficient formation of the γ -lactone moiety was achieved by an intramolecular Wacker-type oxidation approach. The present total synthesis verifies the stereochemistry of 1893B. It is obvious that 1893B is a rearrangement product of mycoepoxydiene, as reported previously.

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5. All new compounds were fully characterized by spectroscopic means [¹H-NMR (270 MHz in CDCl₃), ¹³C-NMR (68 MHz in CDCl₃), IR] and gave satisfactory HRMS spectrum. Yields referred to homogeneous samples purified by chromatography on silica gel.
6. In a large-scale experiment, the diastereomer (**7b**) was isolated in some extent from the mixture by recrystallization with ethyl acetate.
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10. We examined the ring-opening reactions of epoxy alcohols (**10**, **11a** or **11b**) by using nucleophiles such as acetic acid dianion, acetonitrile anion, or dimethyl malonate anion. None of these nucleophiles afforded the desired ring-opened products.
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12. Conversion of **17** into **18**: To a stirred solution of **17** (11.0 mg, 31.4 μmol) in DMF containing 1 vol% H₂O (1 mL) was added PdCl₂(MeCN)₂ in aqueous DMF solution (100 μL of 6.1 mg in 1.5 mL DMF containing 1 vol% H₂O) and CuCl₂ in aqueous DMF solution (100 μL of 10.6 mg in 1.0 mL DMF containing 1 vol% H₂O). The mixture was stirred for 4 days at rt 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 **18** as a colorless oil; TLC R_f 0.37 (EtOAc/hexane, 3:2); [α]_D^{27.5} +16.9° (c 0.325,

- CHCl₃); ¹H NMR (270 MHz) δ 1.12 (d, 3H, *J* = 7.0 Hz), 2.08~2.27 (m, 2H), 2.54 (dd, 2H, *J* = 6.2, 10.2 Hz), 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), 4.68~4.78 (m, 1H), 4.75 (d, 2H, *J* = 1.8 Hz), 5.87~5.94 (m, 2H), 6.02~6.09, 6.23~6.29 (2m, each 1H); ¹³C NMR (68 MHz) 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, 170.7; IR (neat) 2920, 1775 cm⁻¹; HRMS calcd for C₁₆H₂₂O₅ (M⁺) *m/z* 294.1467, found 294.1478.
13. 1893B (**2**) was obtained as white crystals: mp 138.5-140.7 °C (recrystallized from ethyl acetate/hexane); TLC *R_f* 0.48 (EtOAc/hexane, 4:1); IR 2920, 1775, 1730, 1460 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) 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), 2.70-2.73 (m, 1H), 2.98 (ddd, 1H, *J*=6.5, 6.5, 10.3 Hz), 4.24 (d, 1H, *J*=4.4 Hz), 4.42 (t, 1H, *J*=5.9 Hz), 4.57 (ddd, 1H, *J*=2.5, 6.5, 7.6 Hz), 5.15 (dd, 1H, *J*=2.4, 10.4 Hz), 5.90-5.97 (m, 2H), 6.01-6.08 (m, 1H), 6.21-6.27 (m, 1H); ¹³C-NMR (68 MHz, CDCl₃) 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; HRMS calcd for C₁₆H₂₀O₅ (M⁺) *m/z* 292.1311, found 292.1316.
14. Compound (**2'**) was obtained as white solids: TLC, *R_f* 0.50 (EtOAc/hexane, 4:1) [α]_D^{25.2} +121° (*c* 0.05, acetone); IR (neat) 2920, 1775, 1750 cm⁻¹; ¹H NMR (270 MHz) δ 1.04 (d, 3H, *J* = 6.6 Hz), 2.00-2.36 (m, 2H), 2.08 (s, 3H), 2.43-2.55 (m, 2H), 2.65-2.78 (m, 2H), 4.24 (d, 1H, *J*=4.4 Hz), 4.43-4.50 (m, 2H), 5.31 (dd, 1 H, *J* = 4.4, 9.5 Hz), 5.88-5.97 (m, 2H), 6.06-6.13 (m, 1H), 6.23-6.29 (m, 1H); ¹³C NMR (68 MHz) δ 14.3, 20.9, 22.9, 29.7, 52.4, 52.5, 71.5, 77.2, 80.5, 85.6, 124.9, 126.4, 137.6, 137.8, 169.9, 176.0; HRMS calcd for C₁₆H₂₀O₅ (M⁺) *m/z* 292.1311, found 292.1305.
- 15 We have also synthesized two other diastereomers of 1893B starting from another allylic alcohol (**7a**) by the synthetic schemes similar to those used for **7b**. It was verified that the ¹H-NMR spectra of these diastereomers did not match that of the natural 1893B.