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CONCISE FORMAL SYNTHESIS ON SOLANDELACTONE E BASED ON A REGIOSELECTIVE CYCLOPROPANATION

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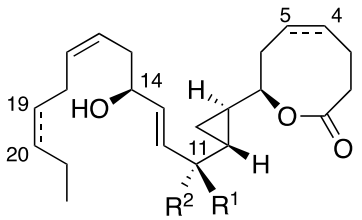
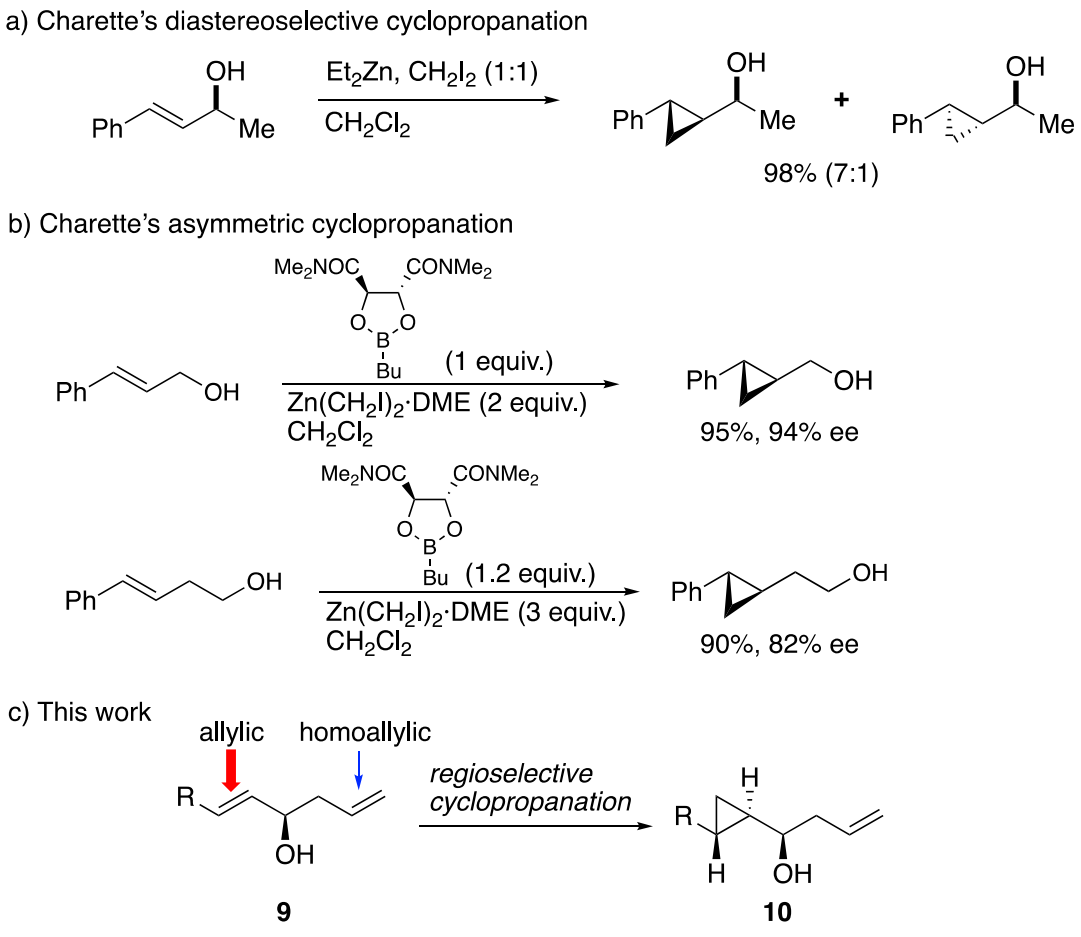
Abstract - A concise synthetic approach to solandelactone E has been developed based on a regio- and stereoselective cyclopropanation using $Zn(CH_2I)_2 \cdot$DME and butyldioxaborolane.

The solandelactones, isolated from the hydroid *Solanderia secunda* by Shin *et al.* in 1996, constitute a family of structurally unique C22 oxylipins, with eight congeners identified to date (Figure 1).[1] The solandelactones possess an eight-membered lactone, a *trans*-cyclopropane motif and a long alkyl chain. These oxylipins were found to exhibit inhibitory activity against 5-lipoxygenase and farnesyl transferase, found in cancer cells. Their intriguing chemical structure and biological activities make the solandelactones attractive targets for synthesis. Since Martin achieved the total synthesis of solandelactone E (**5**) in 2007,[2] White,[3] Pietruszka,[4] Aggarwal,[5] and Raghavan[6] have disclosed their syntheses; and the synthetic studies have been also reported so far.[7] We describe herein a new concise route to solandelactone E based on the regio- and stereoselective cyclopropanation of a *sec*-dienol.



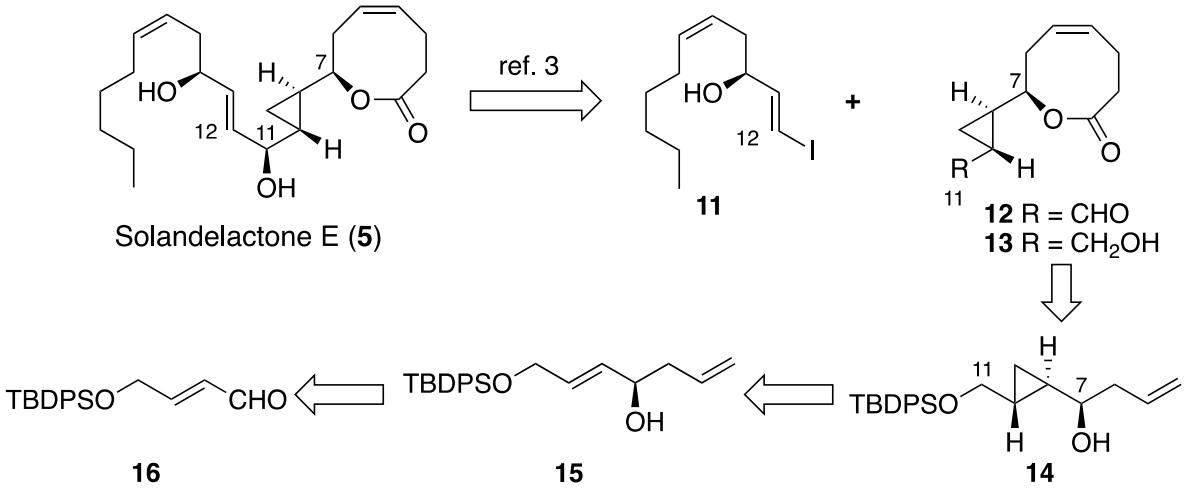
Solandelactone A (**1**); R^1 = OH, R^2 = H
Solandelactone B (**2**); R^1 = H, R^2 = OH
Solandelactone C (**3**); R^1 = OH, R^2 = H, $\Delta_{19,20}$
Solandelactone D (**4**); R^1 = H, R^2 = OH, $\Delta_{19,20}$
Solandelactone E (**5**); R^1 = OH, R^2 = H, $\Delta_{4,5}$
Solandelactone F (**6**); R^1 = H, R^2 = OH, $\Delta_{4,5}$
Solandelactone G (**7**); R^1 = OH, R^2 = H, $\Delta_{4,5}$, $\Delta_{19,20}$
Solandelactone H (**8**); R^1 = H, R^2 = OH, $\Delta_{4,5}$, $\Delta_{19,20}$

For the synthesis of solandelactone, we planned a synthetic strategy focused on the regioselective formation of the cyclopropane ring. In general, zinc-mediated Simmons-Smith reactions of alkenols afford high selectivity due to the coordination of the zinc species to the adjacent hydroxy group regardless of using cyclic or acyclic allylic alcohols (Scheme 1).[8] For this reason, the Simmons-Smith reaction is a promising method for cyclopropanation, and has been used in many natural product syntheses. However, only moderate success has been achieved in the stereoselective cyclopropanation of acyclic homoallylic alcohols by Charette,[9] Mohr,[10] and Landais.[11] Charette demonstrated an enantioselective cyclopropanation using $Zn(CH_2I)_2$·DME and chiral dioxaborolane;[12] however, it was reported that the enantioselectivity of the reaction of homoallylic alcohols was lower than that of allylic alcohols, and a larger molar amounts of reagents was needed in the case of homoallylic alcohols. From these pioneering studies, we hypothesized that cyclopropanation of an allylic alcohol would proceed more rapidly than with a homoallylic alcohol. If our hypothesis is correct, compound **9**, possessing both allylic and homoallylic alcohol in the same molecule, would selectively afford product **10**, an important intermediate for our synthesis of solandelactone, as zinc would coordinate to the hydroxy group to give cyclopropanation at the adjacent olefin.



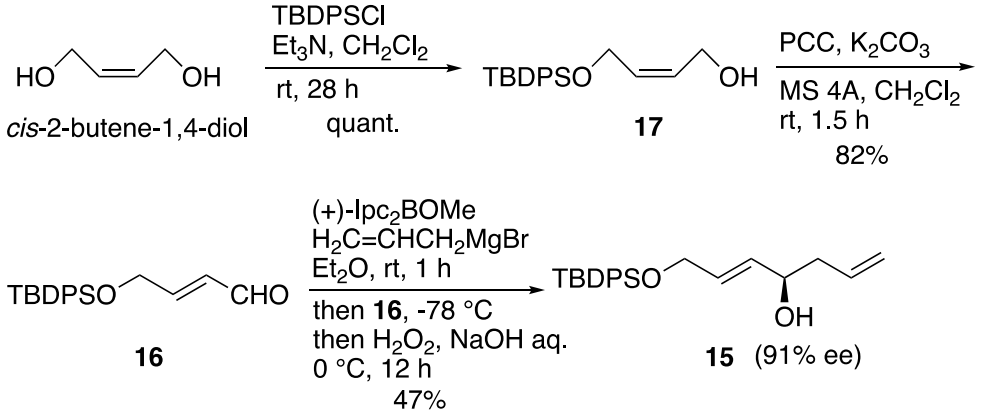
Scheme 1

For the synthesis of solandelactone E, we envisioned eight-membered lactone **13** as a precursor, which is the intermediate in White's synthesis (Scheme 2).[3] Although compound **14** could be transformed to **13** *via* Petasis methylenation by White's protocol, we envisaged that **14** would be converted to intermediate **13** through an alternative approach. Provided that selective cyclopropanation was successful, compound **14** could be obtained from secondary alcohol **15**. Compound **15** would be readily accessible in an enantioenriched form from **16** by Brown's allylation.



Scheme 2. Synthetic strategy of solandelactone E

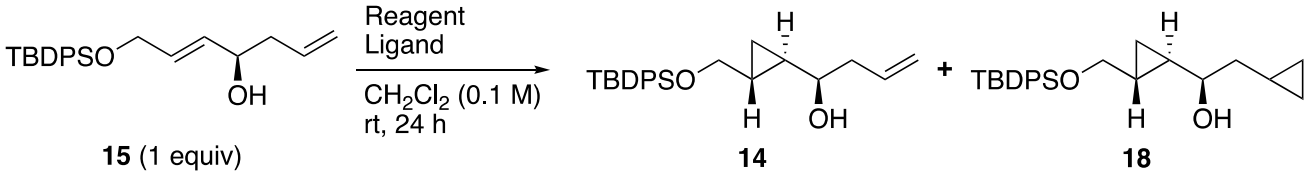
Our synthesis of **15** began with the preparation of aldehyde **16** (Scheme 3). Aldehyde **16** was readily prepared from *cis*-2-butene-1,4-diol by monosilylation and PCC oxidation.[13] Brown's allylation of **16** with (+)-Ipc$_2$BOMe and allylmagnesium bromide afforded compound **15** in 91% ee and in 39% yield from **17**.[14,15]



Scheme 3

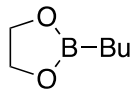
We then explored cyclopropanation of **15** (Table 1). When compound **15** was treated with five equivalents of Et_2Zn and CH_2I_2 ($EtZnCH_2I$) in CH_2Cl_2 at rt, dicyclopropane **18** was produced in 60% yield.[16] In the case of $Zn(CH_2I)_2$·DME generated by Denmark's protocol, the reaction afforded **14** as a single mono-cyclopropane product in low yield (entry 2).[17] Furthermore, it was found that the addition of a dioxaborolane ligand dramatically accelerated the cyclopropanation. When **15** was subjected to $Zn(CH_2I)_2$·DME in the presence of 1.1 equivalent of butyldioxaborolane (**L1**), compound **14** was generated in 51% yield (entry 3). Addition of an excess amount of $Zn(CH_2I)_2$·DME was not effective at increasing the yield further (entry 4). Compared to **L1**, the reaction with phenyldioxaborolane (**L2**) markedly diminished the yield (entry 5). In each case, a diastereomeric isomer of cyclopropane **14** was not detected. Consequently, it was observed that the use of $Zn(CH_2I)_2$·DME and dioxaborolane (**L1**) effectively promoted the regio- and diastereoselective cyclopropanation.

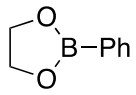
Table 1. Examination of selective cyclopropanation of compound **15**



15 (1 equiv) **14** **18**

Entry	Reagent (equiv)	Ligand[a] (equiv)	**14** (%)	**18** (%)	Recovered **15** (%)
1	$EtZnCH_2I$ (5.0)	none	0	60	0
2	$Zn(CH_2I)_2$·DME (1.25)	none	6	0	74
3[b]	$Zn(CH_2I)_2$·DME (1.25)	**L1** (1.1)	51	0	0
4	$Zn(CH_2I)_2$·DME (2.5)	**L1** (1.1)	47	22	23
5	$Zn(CH_2I)_2$·DME (1.25)	**L2** (1.1)	16	0	53

a)  **L1**

 **L2**

b) The reaction was performed for 21 h.

The proposed transition state for the reaction of **15** with $Zn(CH_2I)_2$·DME and **L1** is shown in Figure 2. Similar to Charette's chiral cyclopropanation, the zinc alkoxide coordinates to the dioxaborolane to form the ate complex with the dioxaborolane located at the less congested pseudo-equatorial position and the allylic alkoxide located at pseudo-axial position.[12,18] It is

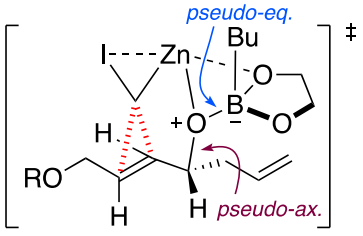
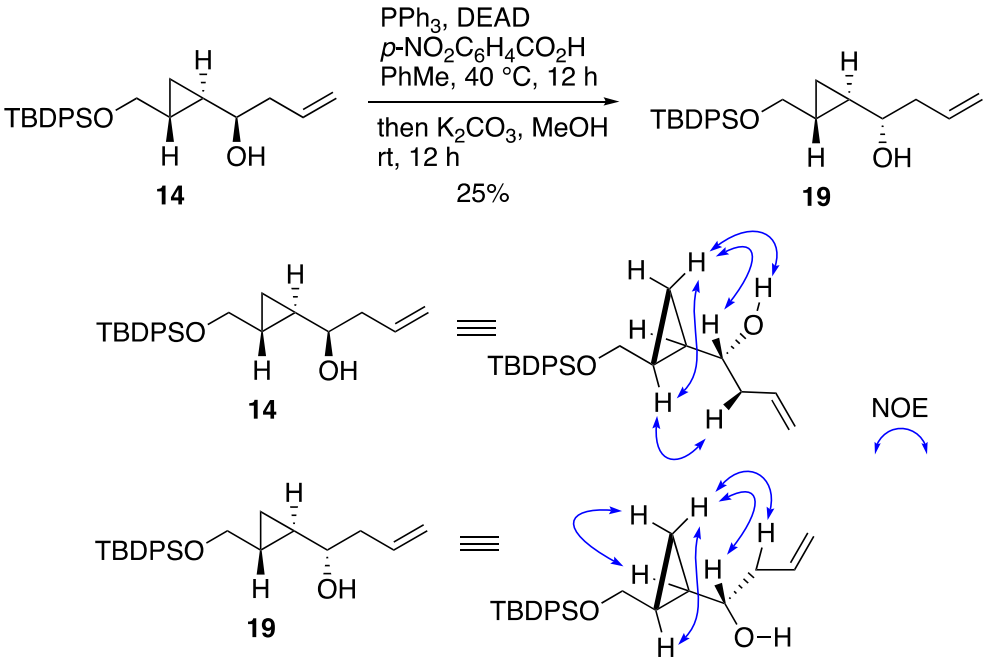


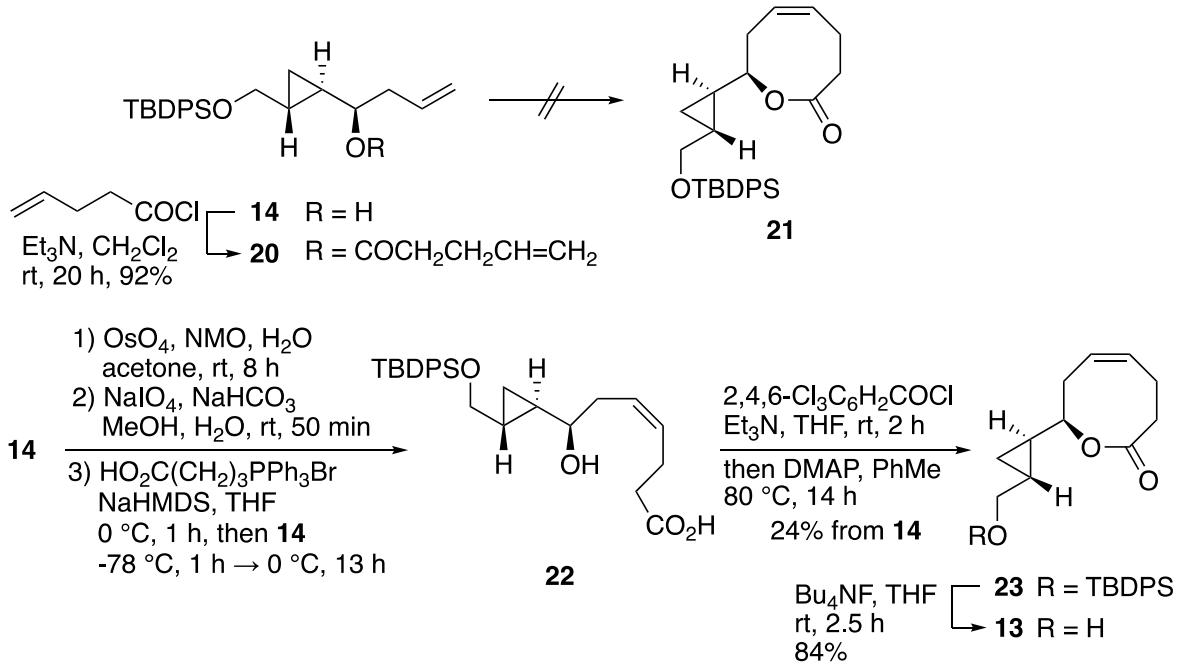
Figure 2

likely that this preferred compact structure of the complex would promote cyclopropanation of the olefin at the spatially closer allylic position. To unambiguously characterize the configuration of **14**, diastereomeric isomer **19** was also synthesized by Mitsunobu inversion (Scheme 4). Since the conformations of cyclopropane derivatives are known to be restricted due to cyclopropyl strain,[19] the configuration of both cyclopropane compounds **14** and **19** was clearly confirmed by NOE correlation.



Scheme 4

With **14** in hand, we attempted to form the eight-membered lactone by ring-closing metathesis (RCM) (Scheme 5). Although White reported that the RCM reaction of a similar substrate failed to construct an eight-membered skeleton in the synthesis of solandelactones A, B, E, and F in 2008,[3] an RCM approach was still attractive, especially considering that RCM methodology and reagents are much more advanced since their report. Thus, treatment of **14** with 4-pentenoyl chloride and triethylamine afforded acyl compound **20** in 92% yield. However, all efforts to engage diene **20** in RCM reactions with 2nd Grubbs, 2nd Hoveyda-Grubbs, or *Z*-selective Grubbs[20] in various solvents such as dichloromethane, 1,2-dichloroethane, toluene, or octafluorotoluene[21] were unsuccessful, leading to complex mixtures. Given these results, we performed cleavage of the terminal alkene of **14** by dihydroxylation and periodate cleavage, which was followed by Wittig reaction with $HO_2C(CH_2)_3PPh_3Br$ and NaHMDS to afford *Z*-product **22**. Yamaguchi lactonization of **22** afforded compound **23** in 24% yield from **14**. Finally, removal of the TBDPS group of **23** using Bu_4NF furnished compound **13**, which exhibited spectral properties identical in all respects to those reported by White *et al*. Therefore, the formal synthesis of solandelactone E was achieved.



Scheme 5. Preparation of compound **13**

In conclusion, we have developed a concise approach to solandelactone E (**5**) in a highly enatioselective manner. The present work illustrates an efficient methodology for the regio- and diastereoselective formation of the cyclopropane ring by $Zn(CH_2I)_2 \cdot DME$ and butyldioxaborolane.

EXPERIMENTAL

Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. Dichloromethane (CH_2Cl_2), pyridine, toluene, and triethylamine (Et_3N) were distilled from CaH_2. Thin-layer chromatography (TLC) was performed using precoated silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flash). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were measured using $CDCl_3$ as solvent, and chemical shifts are reported as δ values in ppm based on internal $CDCl_3$ (7.26 ppm, ^1H; 77.0 ppm, ^{13}C). Mass (MS) and high resolution mass (HRMS) spectra were taken in ESI or DART mode.

(*Z*)-4-(*tert*-Butyldiphenylsilyloxy)-2-buten-1-ol (17). To a solution of *cis*-2-butene-1,4-diol (1.20 g, 13.6 mmol) in CH_2Cl_2 (13.6 mL) was added Et_3N (1.90 mL, 13.6 mmol). To the mixture was added TBDPSCl (1.80 mL, 6.81 mmol) at 0 °C and the mixture was stirred at rt for 28 h. The mixture was diluted with saturated NH_4Cl (15 mL) at 0 °C and extracted with CH_2Cl_2 (10 mL x 3). The extracts were washed with

brine (20 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 80 g, hexane–AcOEt, 5:1) gave **17** (2.30 g, 7.04 mmol, quant.); a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.8, 1.2 Hz, 4H), 7.44-7.37 (m, 6H), 5.74-5.61 (m, 2H), 4.26 (d, *J* = 5.6 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 1.46 (t, *J* = 5.0 Hz, 1H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.4, 130.9, 129.9, 129.7, 127.7, 60.2, 58.7, 26.7, 19.1; FT-IR (neat) 3355, 2932, 2858, 1426, 1107, 821, 701, 611, 506, 420; MS (ESI) *m/z* 349 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{20}H_{26}NaO_2Si$ [(M+Na)$^+$] 349.1600, found 349.1616.

(2*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-butenal (16):[13] To a mixture of K_2CO_3 (825 mg, 5.97 mmol) and dried molecular sieves 4Å powder (1.30 g) in CH_2Cl_2 (20.5 mL) was added pyridinium chlorochromate (1.29 g, 5.97 mmol) and the mixture was stirred at rt for 30 min. To the mixture was added a solution of **17** (1.30 g, 3.98 mmol) in CH_2Cl_2 (20.5 mL) and stirring was continued at rt for 1.5 h. The mixture was diluted with Et_2O (82 mL), and filtered through Celite cake, to give the crude aldehyde **16** (1.06 g, 3.27 mmol, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.2 Hz, 4H), 7.47-7.40 (m, 6H), 6.86 (dt, *J* = 15.3, 3.4 Hz, 1H), 6.58 (ddt, *J* = 15.3, 8.2, 2.2 Hz, 1H), 4.46 (dd, *J* = 2.0, 0.8 Hz, 2H), 1.08 (s, 9H).

(4*S*,5*E*)-7-(*tert*-Butyldiphenylsilyloxy)-1,5-heptadien-4-ol (15): To a mixture of (+)-*B*-methoxydiisopinocampheylborane (1.76 g, 5.55 mmol) in Et_2O (16 mL) was added allylmagnesium bromide (1.0 mol/L in Et_2O, 4.9 mL, 4.90 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. To the stirred mixture was added dropwise the solution of **16** (1.06 g, 3.27 mmol) in Et_2O (17 mL) at -78 °C and the mixture was stirred at that temperature for 1 h. After being stirred at 0 °C for 15 h, the reaction was quenched with aqueous NaOH (1.0 mol/L, 5.4 mL) and 30% aqueous H_2O_2 (2.7 mL) at 0 °C. The mixture was diluted with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (15 mL x 3). The extracts were washed with brine (20 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 100 g, hexane–Et_2O, 9:1) to give **15** (555 mg, 1.52 mmol, 47%, 91% ee); a colorless oil; $[\alpha]_D^{20}$ -6.0 (*c* 1.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.45-7.38 (m, 6H), 5.86-5.73 (m, 3H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.21 (t, *J* = 4.8 Hz, 2H), 4.19-4.16 (m, 1H), 2.37-2.23 (m, 2H), 1.58 (d, *J* = 4.0 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 134.2, 133.6, 131.8, 129.8, 129.6, 127.6, 118.1, 71.1, 63.7, 41.8, 26.8, 19.2; FT-IR (neat) 3370, 2932, 1641, 1428, 1119, 823, 740, 707, 615, 507; MS (ESI) *m/z* 389 [(M+Na)$^+$]; HRMS (ESI) calcd for $C_{23}H_{30}NaO_2Si$ [(M+Na)$^+$] 389.1913, found 389.1900. HPLC conditions: Daicel CHIRALPAK AD-H, 4.6 mm x 250 mm, Particle size 5 μm, hexane/isopropanol = 99/1, 0.5 mL/min, 254 nm, tR = 25.0 min ((-)-**15**), tR = 26.2 min ((+)-**15**).

(*R*)-1-((1*R*,2*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopropyl)but-3-en-1-ol (14): To a solution of 1,2-dimethoxyethane (0.014 mL, 0.14 mmol) in CH_2Cl_2 (0.25 mL) were added dropwise diethylzinc (1.0 mol/L in hexane, 0.14 mL, 0.14 mmol) and diiodomethane (0.022 mL, 0.27 mmol) at 0 °C and the mixture

was stirred at that temperature for 15 min. After being stirred at rt for 30 min, a solution of **15** (40 mg, 0.11 mmol) and **L1** (15.4 mg, 0.12 mmol) in CH_2Cl_2 (0.75 mL) was added dropwise and stirring was continued for 21 h. The reaction was quenched with aqueous NH_4Cl (1 mL) and extracted with AcOEt (5 mL x 3). The extracts were washed with brine (3 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 1.2 g, hexane–AcOEt, 10:1) to give compound **14** (21.3 mg, 0.056 mmol, 51%); a pale yellow oil; $[\alpha]_D^{20}$ -14.0 (*c* 0.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 5.95-5.84 (m, 1H), 5.13 (d, *J* = 15.2 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 3.66 (dd, *J* = 10.7, 5.6 Hz, 1H), 3.45 (dd, *J* = 10.7, 6.8 Hz, 1H), 2.45-2.40 (m, 1H), 2.36-2.30 (m, 1H), 1.60 (d, *J* = 3.2 Hz, 1H), 1.05 (s, 9H), 0.99-0.94 (m, 1H), 0.87-0.82 (m, 1H), 0.51 (dt, *J* = 8.4, 4.8 Hz, 1H), 0.43 (dt, *J* = 8.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 134.9, 133.8, 129.6, 127.6, 117.7, 74.8, 66.2, 41.8, 26.8, 22.9, 19.2, 18.7, 7.8; FT-IR (neat) 3382, 2859, 1428, 1111, 915, 823, 741, 704, 613, 504; MS (ESI) *m/z* 403 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{23}H_{30}NaO_2Si$ [$(M+Na)^+$] 403.2069, found 403.2065.

2-Butyl-1,3,2-dioxaborolane (L1): To a solution of butylboronic acid (5.00 g, 49.1 mmol) in pentane (49 mL) was added ethylene glycol (2.74 mL, 49.1 mmol) at 0 °C and the mixture was stirred at rt for 25 h. To the mixture was added $MgSO_4$, and stirring was continued for 30 min. The mixture was filtered, and concentrated to give compound **L1** (5.10 g, 39.9 mmol, 81%); a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (s, 4H), 1.41 (quint, *J* = 7.4 Hz, 2H), 1.32 (sext, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.3, 26.1, 25.3, 13.8; FT-IR (neat) 2927, 1483, 1397, 1229, 1186, 1022, 946, 894, 828, 723; MS (ESI) *m/z* 151 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_6H_{13}BNaO_2$ [$(M+Na)^+$] 151.0906, found 151.0932.

(*S*)-1-((1*R*,2*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)cyclopropyl)but-3-en-1-ol (19): To a solution of **14** (40 mg, 0.105 mmol) in toluene (1.1 mL) were added triphenylphosphine (110 mg, 0.42 mmol), 4-nitrobenzoic acid (70 mg, 0.42 mmol) and diethyl azodicarboxylate (262 μL, 0.52 mmol) and the mixture was stirred at rt for 15 h. The mixture was diluted with H_2O (1 mL) at 0 °C, extracted with AcOEt (5 mL x 3), and washed with brine (1 mL). The extracts were dried, and concentrated. The residue was purified by column chromatography (SiO_2 0.8 g, hexane–AcOEt, 10:1) to give a crude acyl product, which was used for the next reaction without purification.

To a solution of the crude acyl product in MeOH (0.21 mL) was added K_2CO_3 (29 mg, 0.21 mmol) and mixture was stirred at rt for 15 h. The mixture was diluted with saturated aqueous NH_4Cl (1 mL), extracted with AcOEt (5 mL x 3), and washed with brine (1 mL). The extracts were dried, concentrated. The residue was purified by column chromatography (SiO_2 0.8 g, hexane–AcOEt, 10:1) to give compound **19** (10.0 mg, 0.0263 mmol, 25%, 2 steps); a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.45-7.36 (m, 6H), 5.93-5.83 (m, 1H), 5.12 (d, *J* = 15.2 Hz, 1H), 5.09 (d, *J* = 9.2 Hz, 1H), 3.70 (dd, *J* = 10.8, 5.6 Hz,

1H), 3.40 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.05 (td, *J* = 7.8, 4.8 Hz, 1H), 2.41-2.25 (m, 2H), 1.05 (s, 9H), 1.05-1.02 (m, 1H), 0.83-0.76 (m, 1H), 0.43 (t, *J* = 7.0 Hz, 2H).

(*R*,*Z*)-3,4,7,8-Tetrahydro-8-((1*R*,2*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)cyclopropyl)oxocin-2-one (23): To a mixture of **14** (20 mg, 0.0525 mmol) in acetone (0.45 mL) and H_2O (0.15 mL) was added OsO_4 (0.157 mol/L in H_2O, 17 μL, 0.0026 mmol) at 0 °C. After being stirred for 15 min, a solution of *N*-methylmorpholine *N*-oxide (7.4 mg, 0.0631 mmol) was added, and stirring was continued at rt for 8 h. The mixture was diluted with saturated aqueous $Na_2S_2O_3$ (1 mL) and extracted with AcOEt (2 mL x 3). The extracts were washed with brine (1 mL), dried, and concentrated to give a crude diol, which was used for the next reaction without purification.

To a solution of crude diol in MeOH (0.4 mL) and H_2O (0.2 mL) were added $NaIO_4$ (56.2 mg, 0.263 mmol) and $NaHCO_3$ (4.86 mg, 0.0578 mmol) at 0 °C and the mixture was stirred at rt for 50 min. The mixture was diluted with H_2O (1 mL), concentrated, and extracted with AcOEt (5 mL x 3). The extracts were washed with brine (1 mL), dried, and concentrated to give a crude aldehyde, which was used for the next reaction without purification.

To a solution of (3-carboxypropyl)triphenylphosphonium bromide (33.8 mg, 0.0788 mmol) in THF (0.2 mL) was added dropwise NaHMDS (1.0 mol/L in THF, 0.22 mL, 0.221 mmol) at 0 °C and the mixture was stirred at that temperature for 1 h. To the mixture was added dropwise a solution of above-mentioned aldehyde in THF (0.33 mL) at -78 °C, and the mixture was stirred for 1 h. The reaction mixture was gradually allowed to warm to 0 °C and the stirring was continued for 13 h. To the mixture was added saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with AcOEt (2 mL x 3). The extracts were washed with brine (1 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 4.0 g, hexane–AcOEt, 1:1) to give product **22**, which was used for the next reaction without purification.

To a solution of **22** (8.1 mg, 0.0179 mmol) in THF (2.5 mL) were added dropwise Et_3N (37.7 μL, 0.268 mmol) and 2,4,6-trichlorobenzoyl chloride (28.0 μL, 0.179 mmol) at 0 °C and the mixture was stirred at rt for 2 h. To the mixture was added toluene (24 mL) and the mixture was allowed to warm 80 °C. A solution of *N,N*-dimethyl-4-aminopyridine (21.9 mg, 0.179 mmol) in toluene (11.8 mL) was then added to the mixture, and stirring was continued for 14 h. The mixture was diluted with saturated aqueous NH_4Cl (15 mL) and extracted with AcOEt (20 mL x 3). The extracts were washed with brine (15 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 2.0 g, hexane–AcOEt, 10:1) to give compound **23** (5.4 mg, 0.0124 mmol, 24%, 4 steps); a colorless oil; $[\alpha]_D^{20}$ +2.6 (*c* 0.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.43-7.36 (m, 6H), 5.78-5.74 (m, 2H), 3.96-3.91 (m, 1H), 3.73 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.40 (dd, *J* = 10.7, 3.2 Hz, 1H), 2.90-2.81 (m, 1H), 2.73 (ddd, *J* = 13.2, 5.6, 3.2 Hz, 1H), 2.61 (ddd, *J* = 14.0, 10.4, 5.6 Hz, 1H), 2.33-2.23 (m, 1H), 2.16-2.09 (m, 1H), 1.05 (s, 9H),

1.04-1.02 (m, 1H), 1.01-0.93 (m, 1H), 0.64 (dt, *J* = 8.4, 5.2 Hz, 1H), 0.50 (dt, *J* = 8.4, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 135.6, 133.8, 132.6, 129.6, 127.7, 81.7, 66.0, 37.7, 34.3, 26.8, 24.4, 20.4, 19.6, 19.2, 8.5; FT-IR (neat) 3015, 2933, 2857, 1745, 1427, 1329, 1213, 1110, 705, 507; MS (ESI) *m/z* 457 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{23}H_{30}NaO_2Si$ [$(M+Na)^+$] 457.2175, found 457.2188.

(*R*,*Z*)-8-((1*R*,2*R*)-2-(Hydroxymethyl)cyclopropyl)-3,4,7,8-tetrahydro-2*H*-oxocin-2-one (13): To a solution of **23** (3.40 mg, 0.00782 mmol) in THF (0.4 mL) was added tetrabuylammonium fluoride (1.0 mol/L in THF, 12.0 μL, 0.012 mmol) at 0 °C and the mixture was stirred at rt for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl (1 mL) at 0 °C and extracted with AcOEt (1 mL x 3). The extracts were washed with brine (1.5 mL), dried, and concentrated. The residue was purified by column chromatography (SiO_2 0.5 g, hexane–AcOEt, 2:1) gave **13** (1.3 mg, 0.00662 mmol, 84%); a colorless oil; $[\alpha]_D^{20}$ -3.8 (*c* 0.13, $CHCl_3$) (*lit*., $[\alpha]_D^{23}$ +5.8 (*c* 0.4, $CHCl_3$))[3b, 22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.74 (m, 2H), 4.05 (ddd, *J* = 10.2, 8.2, 1.9 Hz, 1H), 3.56 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.40 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.91-2.81 (m, 1H), 2.74 (ddd, *J* = 13.4, 6.0, 3.2 Hz, 1H), 2.67-2.59 (m, 1H), 2.34-2.21 (m, 2H), 2.16-2.09 (m, 1H), 1.17-1.09 (m, 1H), 1.01 (ddd, *J* = 13.6, 8.4, 4.5 Hz, 1H), 0.75 (dt, *J* = 8.4, 5.2 Hz, 1H), 0.56 (dt, *J* = 8.4, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 132.8, 128.0, 80.9, 66.0, 37.7, 34.3, 24.4, 20.7, 19.7, 8.6; FT-IR (neat) 3410, 2924, 1741, 1428, 1218, 1063, 802, 731, 466, 426 ; MS (DART) *m/z* 197 [$(M+H)^+$]; HRMS (DART) calcd for $C_{11}H_{17}O_3$ [$(M+H)^+$] 197.1178, found 197.1163.

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SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra of new compounds are available.

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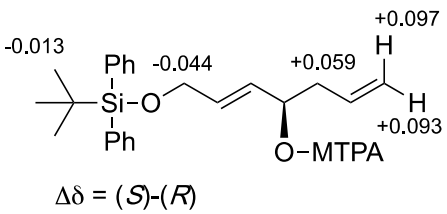
15. The assignment of the ^{1}H NMR spectra of both compounds followed by calculation of Δδ (*S*-*R*) led to the absolute stereochemistry of compound **15** as *R*.



Δδ = (*S*)-(*R*)

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22. The difference in optical rotation value would be attributed to substrate's inherently low optical rotation.