Stereoselective Synthesis of a Key Precursor of Halicholactone and Neohalicholactone†

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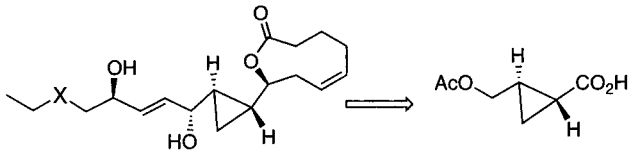
An efficient synthesis of a known precursor of halicholactone (**1a**) and neohalicholactone (**1b**) has been developed using the strategically functionalized key cyclopropane intermediate **2**, which in turn has been synthesized via stereoselective cyclopropanation of *trans*-cinnamyl alcohol in the presence of the chiral dioxaborolane ligand **4**. Elaboration of the above bifunctional cyclopropane to the target molecule was achieved in a relatively short reaction sequence and in good overall yield, representing a formal synthesis of the title compounds.

Introduction

Cyclopropyl and lactone containing oxylipins are a growing class of natural products, isolated from a wide spectrum of marine organisms. Among these compounds, constanolactones,[1] halicholactone, and neohalicholactone[2] possess a linear C_{20} carbon skeleton, derived from eicosanoid precursors, while solandelactones,[3] having a C_{22} carbon skeleton, are thought to be of docosanoid origin. Because of their important physiological properties[2,3] and the presence of interesting structural features, such as a trans-substituted cyclopropane subunit and saturated or unsaturated lactones of various ring size, these compounds have attracted the attention of a number of synthetic organic chemists worldwide. In the approaches reported so far for the syntheses of the above eicosanoid oxylipins, the central cyclopropyl core and the lactone ring are generally constructed from an intermediate of appropriate carbon chain at a fairly advanced stage of the synthesis.[4−6] This strategy renders these methods specific only to a particular target molecule, thereby limiting their scope as a general approach for synthesizing the above-mentioned class of oxylipins. Our own endeavor toward the synthesis of this class of compounds was thus motivated by the need to establish a general route that will be sufficiently flexible and practical to allow the synthesis of all or a majority of these compounds and their analogues from an advanced common intermediate.

Scheme 1



2

1a, X = -CH_2CH_2- (Halicholactone)
1b, X = *cis*-CH:CH (Neohalicholactone)

Our strategy involved (i) stereoselective synthesis of a pivotal trans-substituted bifunctional cyclopropane ring and (ii) utilization of this intermediate for synthesizing the above-mentioned class of oxylipins. The present report describes the synthesis of a versatile cyclopropane intermediate **2** (Scheme 1) and its elaboration to a known precursor of halicholactone (**1a**) and neohalicholactone (**1b**).

Results and Discussion

Cyclopropanation of *trans*-cinnamyl alcohol (**3**) according to Charette's protocol,[7] in the presence of the dioxaborolane chiral ligand **4** [derived from (*S,S*)-(−)-*N,N,N′,N′*-tetramethyltartaric acid diamide], cleanly afforded the (1*R*,2*R*)-cyclopropyl alcohol **5** with good enantioselectivity[8] and high yield (Scheme 2). Acetylation of the hydroxy group followed by oxidative degradation of the phenyl moiety to a carboxylic acid under standard conditions provided the key cyclopropane intermediate **2** in high overall yield. The carboxylic acid carbonyl and the acetate protected latent aldehyde functionality in this molecule allows for rapid construction of the target compounds, as has been illustrated below. Conversion of acid **2** to the corresponding Weinreb amide **7** and its reaction with allylmagnesium bromide yielded the allyl ketone **8**. Protection of the free hydroxy group as its TBDMS ether and stereoselective reduction

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(1) (a) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.* **1990**, *31*, 2995−2998. (b) Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.* **1994**, *59*, 9, 7227−7237.

(2) (a) Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543−4546. (b) Kigoshi, H.; Niwa, H.; Yamada, K.; Stout, T. J.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2427−2430.

(3) Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron*, **1996**, *52*, 10583−10596.

(4) (a) Synthesis of constanolactones A and B: White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224−6233. (b) Synthesis of constanolactone E: Miyaoka, H.; Shigemoto, T.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7407−7408.

(5) Synthesis of halicholactone and neohalicholactone: Crichter, D. J.; Connoly, S.; Wills, M. *Tetrahedron Lett.* **1995**, *36*, 3763−3766.

(6) Synthesis of related eicosanoids: (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970−2971. (b) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31−39.

(7) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081−1083.

(8) The enantiomeric excess was determined by comparison of the specific rotation of **5** ($[\alpha]_D = -62.2$ ($c = 1.9$, EtOH)) with *ent*-**5** ($[\alpha]_D = 66$ ($c = 1.9$, EtOH; at 93% ee) as reported in ref 7 above.

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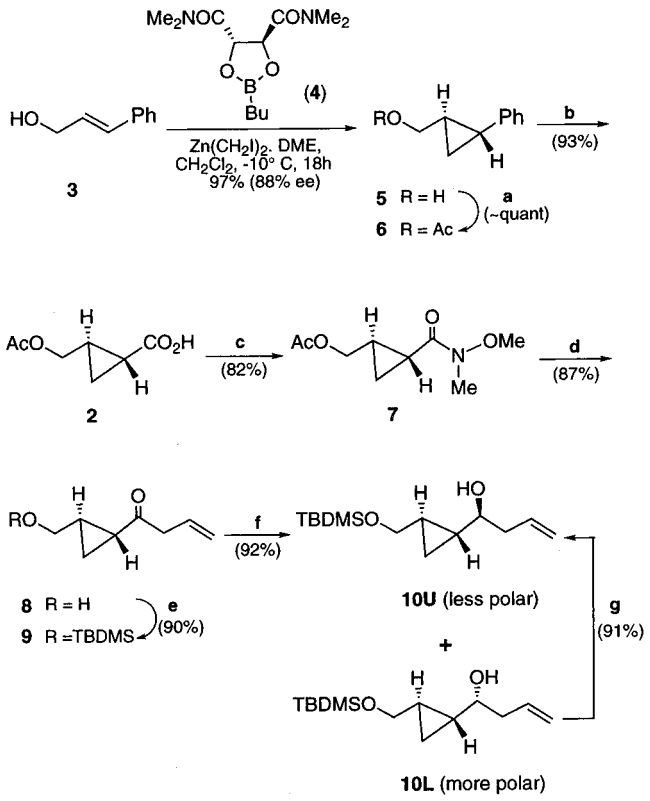
Scheme 2[a]



[a] (**a**) Ac_2O, DMAP, CH_2Cl_2; (**b**) $RuCl_3 \cdot H_2O$, $NaIO_4$, $CH_3CN-CCl_4-H_2O$; (**c**) MeNH(OMe)·HCl, 1,1′-carbonyldiimidazole, Et_3N, CH_2Cl_2; (**d**) allylmagnesium bromide, Et_2O-THF; (**e**) TBDMSCl, imidazole, CH_2Cl_2; (**f**) K-Selectride, THF, −78 °C; (**g**) (i) Ph_3P, DEAD, glacial AcOH, THF; (ii) NaOMe, MeOH.

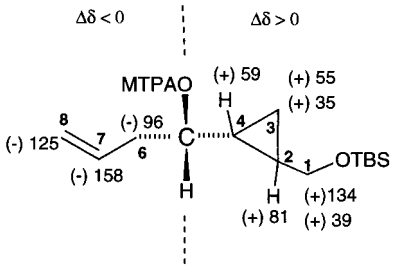


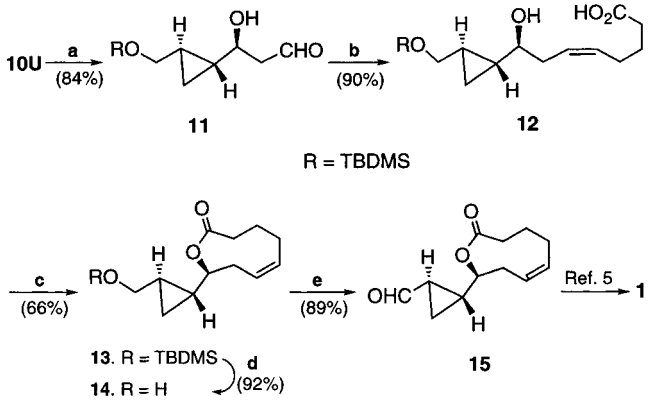
Figure 1. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (*R*)- and (*S*)-MTPA esters of compound **10U**.

of the ketone **9** using K-Selectride (potassium tri-*sec*-butylborohydride) afforded a 9:1 ratio of diastereomeric alcohols **10U** (less polar) and **10L** (more polar), which were easily separated by column chromatography.

Stereochemical assignment of the newly created asymmetric center was achieved by Mosher's modified method.[9] Thus, esterification of the major isomer **10U** with both (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) demonstrated positive chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C-1 through C-4 (Figure 1), while protons on C-6 through C-8 showed negative differences, which is consistent with C-5 bearing an *S* configuration.

Having found the major diastereoisomer **10U** to be of appropriate stereochemistry for the proposed synthesis

Scheme 3[a]



[a] (**a**) (i) OsO_4, NMO, acetone; (ii) $NaIO_4$, $NaHCO_3$, MeOH, H_2O; (**b**) $HO_2C(CH_2)_4PPh_3Br$, NaHMDS, THF; (**c**) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene; (**d**) TBAF, THF; (**e**) IBX, DMSO.

of **1**, the minor isomer **10L** was also converted to the required isomer via a Mitsunobu inversion of the hydroxy group (Scheme 2). Surprisingly, attempted ozonolysis of the terminal alkene of **10U** led to an intractable mixture of products. This problem was however overcome by following a two-step sequence via OsO_4-catalyzed dihydroxylation of **10U** followed by oxidation with $NaIO_4$, which resulted in the clean formation of the expected hydroxy aldehyde **11** (Scheme 3). Cis-selective Wittig reaction of this aldehyde with the reagent derived from (4-carboxybutyl)triphenylphosphonium bromide in the presence of NaHMDS at −78 °C[10] yielded the lactone precursor hydroxy acid **12**. Lactonization of the acid **12** under Yamaguchi conditions[11] cleanly afforded the expected nine-membered lactone **13** in 66% yield.

The smooth formation of the lactone ring has been attributed to the presence of the cis-double bond, which provides both an enthalpic and entropic assistance to the above cyclization.[10] Finally, deprotection of the TBDMS linkage and oxidation of the resulting alcohol **14** culminated in the synthesis of the aldehyde **15**, a known precursor of halicholactone (**1a**) and neohalicholactone (**1b**),[5] thereby representing a formal synthesis of the above compounds.

Conclusion

In summary, our strategy of initial synthesis of an enantiopure bifunctional cyclopropane ring with differential substitution followed by construction of the rest of the target molecule on this cyclopropane framework represents an effective convergent approach for the title compounds. Moreover, following the above approach and starting from the versatile cyclopropane intermediate **2**, it should also be possible to synthesize the other members of the described oxylipin family. Efforts in this direction are currently underway.

Experimental Section

General. Reagents and solvents were obtained from commercial suppliers and used as received, unless otherwise noted. Moisture- or air-sensitive reactions were conducted under a

(9) (a) Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Yoshida, W. Y.; Bryan P. J.; Baker, B. J.; McClintock, J. B. *J. Org. Chem.* **1995**, *60*, 780−782.

(10) Crichter, D. J.; Connoly, S.; Mahon, M. F.; Wills, M. *J. Chem. Soc. Chem. Commun.* **1995**, 139−140 and references therein.

(11) Inaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

nitrogen atmosphere in oven-dried (120 °C) glass apparatus. Diethyl ether and THF were distilled from sodium benzophenone ketyl prior to use. Toluene was dried over sodium, whereas dichloromethane and triethylamine were distilled from CaH_2 and stored over molecular sieves and anhydrous KOH, respectively. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. Column chromatography was performed on silica gel 60 (60−120 mesh), using ethyl acetate/hexane mixture as eluent, unless specified otherwise. The NMR spectra were recorded in $CDCl_3$ on a 200 MHz spectrometer with TMS as the internal standard. Elemental analyses were carried out at the Indian Association for the Cultivation of Science, Jadavpur, Calcutta, India.

Preparation of Dioxaborolane 4. This reagent was prepared according to the reported procedure,[7] by reacting (*S*,*S*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide with 1-butaneboronic acid to yield a light yellow oil: ^{1}H NMR δ 0.73−0.88 (m, 5H), 1.18−1.42 (m, 4H), 2.94 (s, 6H), 3.18 (s, 6H), 5.45 (s, 2H); EIMS 272 ($M^+ + 2$).

Preparation of the $Zn(CH_2I)_2$·DME Complex Solution in CH_2Cl_2.[7] To a solution of 3.8 mL (37.3 mmol) of Et_2Zn in 37 mL of CH_2Cl_2 and 3.9 mL (37.3 mmol) of freshly distilled DME at −15 °C was added 6 mL (75 mmol) of CH_2I_2 over a period of 30 min, as the internal temperature was maintained below −10 °C. The resulting colorless solution was used as such in the cyclopropanation reaction.

(1*R*,2*R*)-*trans*-1-(Hydroxymethyl)-2-phenylcyclopropane (5). To a mixture of dioxaborolane **4** (2.2 g, 8.2 mmol), cinnamyl alcohol (1 g, 7.5 mmol), and 4 Å molecular sieves (300 mg) in 40 mL of CH_2Cl_2 at −15 °C was added the Zn-$(CH_2I)_2$·DME complex solution as prepared above, over a period of 30 min, as the internal temperature was kept below −10 °C. After completion of addition, the mixture was stirred for 2 h at −10 °C and kept in the refrigerator (−10 °C) for another 20 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (25 mL), the organic layer separated, the aqueous layer extracted with ether (3 × 50 mL) and the combined organic layers stirred vigorously with aqueous KOH (5M, 30 mL) for 16 h. The organic layer was separated, washed sequentially with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water, and brine, dried (anhydrous Na_2SO_4), and concentrated. Column chromatography of the crude residue afforded the pure product **5** (1.04 g, 97%) as a colorless liquid: $[\alpha]_D = -62.2$ ($c = 1.9$, EtOH), [for *ent*-**5** $[\alpha]_D = +66$ ($c = 1.9$, EtOH)];[7] ^{1}H NMR δ 0.95 (m, 2H), 1.42 (m, 1H), 1.9 (m, 1H), 3.58 (d, $J = 6.66$ Hz, 2H), 7.13 (m, 5H); ^{13}C NMR δ 142.4, 128.1, 125.6, 125.3, 65.9, 24.9, 21.0, 13.6; EIMS 148 (M^+). Anal. Calcd for $C_{10}H_{12}O$ (148.2): C, 81.04; H, 8.16. Found: C, 80.82; H, 8.24.

(1*R*,2*R*)-*trans*-1-(Acetoxymethyl)-2-phenylcyclopropane (6). To an ice-cooled solution of the cyclopropyl methanol **1** (600 mg, 4.05 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (15 mg) in CH_2Cl_2 (15 mL) was added dropwise freshly distilled acetic anhydride (1.98 mL, 21 mmol); the mixture was stirred for 10 min at 0 °C followed by 45 min at room temperature. The mixture was then diluted with CH_2Cl_2 (25 mL) and poured into water, and the organic layer was separated and washed sequentially with saturated aqueous $NaHCO_3$, water and brine. After drying over Na_2SO_4 and removal of solvent using a rotary evaporator, the residue was chromatographed to afford the pure product **6** (613 mg, 96.5%) as a colorless liquid: $[\alpha]_D = -64.8$ ($c = 1.25$, $CHCl_3$); IR (neat) 1744, 1488 cm^{-1} ; ^{1}H NMR δ 0.98 (m, 2H), 1.47 (m, 1H), 1.89 (m, 1H), 2.08 (s, 3H), 4.06 (d, $J = 7.2$ Hz, 2H), 7.15 (m, 5H); ^{13}C NMR δ 171.0, 141.9, 128.2, 125.8, 125.7, 67.8, 21.7, 21.3, 20.9, 13.8; HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0993, found 190.1001. Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 76.05; H, 7.35.

(1*R*,2*R*)-*trans*-2-(Acetoxymethyl)cyclopropanecarboxylic Acid (2). To a stirred mixture of the acetoxycyclopropane **6** (1.56 g, 8.2 mmol) and $NaIO_4$ (30.12 g, 147.7 mmol) in acetonitrile (20 mL), carbon tetrachloride (20 mL), and water (30 mL) at room temperature was added $RuCl_3$·H_2O (38 mg, 0.18 mmol) portionwise; the mixture was stirred vigorously for 24 h. CH_2Cl_2 (50 mL) was then added to the mixture, which was then filtered. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4. Removal of solvent and purification of the residue by column chromatography afforded the cyclopropane carboxylic acid **2** (1.2 g, 93%) as a colorless liquid: $[\alpha]_D = -18.6$ ($c = 1$, EtOH); IR (neat) 3240, 1740, 1694 cm^{-1}; ^{1}H NMR δ 0.9 (m, 1H), 1.25 (m, 1H), 1.55 (m, 1H), 1.77 (m, 1H), 2.12 (s, 3H), 3.8 (dd, $J = 4.2$ and 10.5 Hz, 1H), 4.02 (dd, $J = 4.2$ and 10.7 Hz, 1H), 9.85 (br s, 1H); CIMS 159 (MH^+). Anal. Calcd for $C_7H_{10}O_4$ (158.16): C, 53.16; H, 6.33. Found: C, 52.94; H, 6.70.

(1*R*,2*R*)-*trans*-2-(Acetoxymethyl)cyclopropane-1-(*N*-methoxy-*N*-methyl)carboxamide (7). To a solution of the carboxylic acid **2** (839 mg, 5.3 mmol) in CH_2Cl_2 (20 mL) was added 1,1′-carbonyldiimidazole (1.11 g, 6.9 mmol); the mixture was stirred for 30 min. The solution was then cooled to 0 °C and a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (671 mg, 6.9 mmol) in 0.9 mL (6.9 mmol) of Et_3N was added. The mixture was stirred at 0 °C for 1 h and at room temperature for 14 h, after which CH_2Cl_2 (50 mL) was added; the mixture was washed sequentially with 1 N HCl (2 × 50 mL), saturated aqueous $NaHCO_3$, and brine. Drying (Na_2SO_4) of the organic phase and removal of solvent followed by column chromatography of the residue yielded the pure amide **7** (875 mg, 82%) as a colorless liquid: $[\alpha]_D = -20.8$ ($c = 1$, $CHCl_3$); IR (neat) 1738, 1655 cm^{-1} ; ^{1}H NMR δ 0.79 (m, 1H), 1.21 (m, 1H), 1.67 (m, 1H), 2.01 (s, 3H), 2.08 (m, 1H), 3.15 (s, 3H), 3.71 (s, 3H), 3.87 (dd, $J = 7.1$ and 11.55 Hz, 1H), 4.06 (dd, $J = 6.7$ and 11.55 Hz, 1H); ^{13}C NMR δ 172.9, 170.5, 66.4, 61.5, 32.6, 20.9, 20.2, 16.2, 12.6; HRMS (EI) calcd for $C_9H_{15}NO_4$ 201.1001, found 201.1006. Anal. Calcd for $C_9H_{15}NO_4$ (201.23): C, 53.72; H, 7.51; N, 6.96. Found: C, 53.99; H, 7.30; N, 6.70.

(1*R*,2*R*)-*trans*-2-(Hydroxymethyl)-1-(1-oxo-but-3-enyl)-cyclopropane (8). To an ice-cooled solution of the amide **7** (1.6 g, 7.96 mmol) in THF (20 mL) was added dropwise an ether solution of allylmagnesium bromide (1.2 M, 40 mL, 48 mmol); the mixture was stirred for 30 min at 0 °C and 6 h at room temperature. The reaction was then quenched with aqueous HCl (5%, 25 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by column chromatography to afford the allylcyclopropyl ketone **8** (970 mg, 87%) as a colorless liquid: $[\alpha]_D = -59.4$ ($c = 1$, $CHCl_3$); IR (neat) 3416, 1684 cm^{-1} ; ^{1}H NMR δ 0.87 (m, 1H), 1.29 (m, 1H), 1.65 (m, 1H), 1.89 (m, 1H), 2.48 (br s, 1H, exchangeable with D_2O), 3.25 (d, $J = 7.6$ Hz, 2H), 3.32 (dd, $J = 4.4$ and 12.2 Hz, 1H), 3.62 (dd, $J = 4.4$ and 12.2 Hz, 1H), 5.11 (m, 2H), 5.89 (m, 1H); HRMS (EI) calcd for $C_8H_{12}O_2$ 141.0915 (MH^+), found 141.0901. Anal. Calcd for $C_8H_{12}O_2$ (140.18): C, 68.55; H, 8.62. Found: C, 68.73; H, 8.29.

(1*R*,2*R*)-*trans*-2-[(*tert*-Butylsilyloxy)methyl]-1-(1-oxo-but-3-enyl)cyclopropane (9). A solution of the cyclopropyl methanol **8** (500 mg, 3.5 mmol) and imidazole (595 mg, 8.7 mmol) in CH_2Cl_2 (6 mL) at 0 °C was treated with *tert*-butyldimethylsilyl chloride (580 mg, 3.8 mmol) and the solution was stirred at 0 °C for 30 min and 7 h at room temperature. After quenching the reaction by addition of water (3 mL), the resulting mixture was diluted with CH_2Cl_2 (10 mL), the organic layer was separated, dried over Na_2SO_4, and concentrated, and the residue was purified by column chromatography to yield the silyl ether derivative **9** (816 mg, 90%) as a colorless liquid: $[\alpha]_D = -62.4$ ($c = 1$, $CHCl_3$); IR (neat) 1706 cm^{-1}; ^{1}H NMR δ 0.02 (s, 6H), 0.85 (s, 9H), 0.89 (m, 1H), 1.19 (m, 1H), 1.59 (m, 1H), 1.9 (m, 1H), 3.27 (d, $J = 7.2$ Hz, 2H), 3.46 (dd, $J = 4.2$ and 10.5 Hz, 1H), 3.71 (dd, $J = 4.2$ and 10 Hz, 1H), 5.13 (m, 2H), 5.94 (m, 1H); ^{13}C NMR δ 199.2, 134.2, 118.4, 70.8, 45.6, 29.7, 25.9, 23.6, 18.2, 14.4, −5.2; EIMS 255 (MH^+). Anal. Calcd for $C_{14}H_{26}SiO_2$ (254.44): C, 66.08; H, 10.30. Found: C, 66.15; H, 10.29.

(1*R*,2*R*)-*trans*-2-[(*tert*-Butylsilyloxy)methyl)]-1-[(1*S*)-1-hydroxybut-3-enyl]cyclopropane (10U) and (1*R*,2*R*)-*trans*-2-[(*tert*-Butylsilyloxy)methyl]-1-[(1*R*)-1-hydroxybut-3-enyl]cyclopropane (10L). To a stirred solution of the cyclopropyl ketone **9** (127 mg, 0.5 mmol) in THF (8 mL) at

−78 °C was added dropwise K−Selectride (1M solution in THF, 1 mL, 1 mmol) and stirring continued for 30 min. After quenching the reaction by sequential addition of MeOH (1 mL) and 10% aqueous NaOH solution (5 mL) at −78 °C, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then extracted with ether (3 × 30 mL), and the combined extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (ethyl acetate:hexanes = 1:15), affording the pure diastereoisomers **10U** (R_f = 0.4, 106 mg, 83%) and **10L** (R_f = 0.28, 12 mg, 9%) as colorless liquids. **10U**: $[\alpha]_D = -7.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 0.02 (s, 6H), 0.42 (2d, J = 8 and 10 Hz, 2H), 0.75 (m, 1H), 0.84 (s, 9H), 0.96 (m, 1H), 2.29 (m, 2H), 2.98 (m, 1H), 3.3 (dd, J = 4 and 10.5 Hz, 1H), 3.58 (dd, J = 4.2 and 10 Hz, 1H), 5.08 (m, 2H), 5.82 (m, 1H); ^{13}C NMR δ 134.8, 117.4, 74.4, 65.9, 41.4, 29.6, 25.9, 23.1, 19.1, 7.6, −5.2; CIMS 255 ($M^+ - 1$). Anal. Calcd for $C_{14}H_{28}SiO_2$ (256.45): C, 65.57; H, 11.00. Found: C, 65.49; H, 10.63. **10L**: $[\alpha]_D = -12.99$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 0.01 (s, 6H), 0.44 (m, 2H), 0.74 (m, 1H), 0.84 (m, 1H), 0.90 (s, 9H), 1.4 (m, 1H), 2.3 (m, 2H), 2.98 (m, 1H), 3.35 (dd, J = 5.9 and 10.44 Hz, 1H), 3.55 (dd, J = 5.2 and 11.4 Hz, 1H), 5.06 (m, 2H), 5.82 (m, 1H); ^{13}C NMR δ 134.8, 117.5, 74.7, 65.6, 41.8, 29.5, 25.9, 22.8, 18.9, 7.9, −5.3; CIMS 255 ($M^+ - 1$).

Conversion of the Hydroxymethylene Cyclopropane 10L to the Corresponding β-OH Isomer 10U. To a solution of **10L** (75 mg, 0.2 mmol) in THF (3 mL) was added Ph_3P (138 mg, 0.5 mmol) and glacial acetic acid (0.03 mL, 0.5 mmol) and the mixture was cooled to 0 °C. To this stirred solution was added dropwise diethyl azodicarboxylate (0.104 mL, 0.6 mmol) dissolved in THF (1 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. After removal of solvent under vacuum, the residue was dissolved in CH_2Cl_2 (15 mL) and washed sequentially with dilute aqueous $NaHCO_3$, water, and brine. After drying over Na_2SO_4 and removal of solvent under vacuum, the crude residue was dissolved in 2 mL of MeOH and treated with a solution of NaOMe (0.05 M in MeOH, 5 mL). After stirring for 3 h at room temperature, the reaction mixture was concentrated, and the residue was taken up in CH_2Cl_2 (10 mL) and washed successively with water and brine. Removal of solvent and purification of the residue by column chromatography yielded the pure product **10U** (68 mg, 91%, two steps), similar in all respects to the major isomer **10U**, as obtained previously via reduction of the ketone **9**.

***(S)*- and *(R)*-Mosher Esters of Alcohol 10U.** A solution of the cyclopropyl alcohol **10U** (13 mg, 0.05 mmol), (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*S*-MTPA) (16 mg, 0.07 mmol), *N*,*N*-dicyclohexylcarbodiimide (18 mg, 0.09 mmol), and a catalytic amount of DMAP (4 mg) in CH_2Cl_2 (1 mL) was stirred at room temperature for 8 h. The precipitated solid was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography to yield the pure (*S*)-MTPA ester: ^{1}H NMR δ 0.008 (s, 6H), 0.51 (m, 1H), 0.61 (m, 1H), 0.85 (s, 9H), 1.04 (m, 1H), 1.18 (m, 1H), 2.42 (m, 2H), 3.35 (dd, J = 4.6 and 12.6 Hz, 1H), 3.56 (s, 3H), 3.63 (dd, J = 4.2 and 12.6 Hz, 1H), 4.59 (m, 1H), 4.95 (m, 2H), 5.63 (m, 1H), 7.38 (m, 5H).

The reaction of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*R*-MTPA) with the alcohol **10U** similarly afforded the (*R*)-MTPA ester: ^{1}H NMR δ 0.011 (s, 6H), 0.45 (m, 1H), 0.58 (m, 1H), 0.85 (s, 9H), 0.96 (m, 1H), 1.12 (m, 1H), 2.52 (m, 2H), 3.22 (dd, J = 6.6 and 12.3 Hz, 1H), 3.54 (s, 3H), 3.59 (dd, J = 4.8 and 12.3 Hz, 1H), 4.60 (m, 1H), 5.07 (m, 2H), 5.78 (m, 1H), 7.39 (m, 5H).

(3*S*)-3-Hydroxy-3-[(1*R*,2*R*)-*trans*-2-[(*tert*-butylsilyloxy)methyl]cyclopropyl]propionaldehyde (11). To a stirred solution of compound **10U** (210 mg, 0.6 mmol) and *N*-methylmorpholine *N*-oxide (325 mg, 2.4 mmol) in acetone (3 mL) and water (3 mL) at room temperature was added a catalytic amount of OsO_4 solution in toluene (5% solution, 5 mol %). After 8 h a saturated aqueous Na_2SO_3 solution was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 25 mL). The combined extracts were dried over Na_2SO_4 and concentrated to afford the crude dihydroxylated compound (195 mg), which was dissolved in a mixture of methanol (4.5 mL) and water (3 mL), and solid $NaHCO_3$ (340 mg, 0.66 mmol) was added. This stirred mixture was then treated with $NaIO_4$ (870 mg, 4 mmol). After 30 min the reaction mixture was diluted by adding water (10 mL), the methanol was removed under vacuum, and the residue was extracted with ethyl acetate (3 × 25 mL). Drying (Na_2SO_4), removal of solvent, and purification of the residue by column chromatography afforded the pure hydroxy aldehyde **11** (133 mg, 86%, two steps) as a colorless liquid. This aldehyde was however found to degrade on storage and was used immediately in the next reaction: $[\alpha]_D = -25.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6H), 0.46 (m, 2H), 0.8 (m, 1H), 0.9 (s, 9H), 1.01 (m, 1H), 1.58 (m, 1H), 1.9 (m, 1H), 3.34 (m, 1H), 3.52 (m, 1H), 4.8 (m, 1H), 9.84 (s, 1H).

(5*Z*,8*S*)-8-Hydroxy-8-[(1*R*,2*R*)-*trans*-2-[(*tert*-butylsilyloxy)methyl]cyclopropyl]oct-5-enoic Acid (12). To an ice-cooled solution of (4-carboxybutyl)triphenylphosphonium bromide (474 mg, 1.07 mmol) in THF (10 mL) was added dropwise sodium hexamethyldisilazide (1.3 M solution in THF, 2.2 mL, 2.86 mmol); the mixture was stirred for 30 min. The reaction mixture was then cooled to −78 °C, and the hydroxyaldehyde **11** (185 mg, 0.71 mmol), dissolved in 5 mL of THF, was added dropwise. After stirring for 2 h at −78 °C and 2 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated to afford the crude product, which on column chromatography yielded the pure hydroxy acid **12** (220 mg, 90%) as a colorless liquid: $[\alpha]_D = -5.73$ ($c = 1.5$, $CHCl_3$); IR (neat) 3456, 1708 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6H), 0.46 (m, 2H), 0.8 (m, 1H), 0.88 (s, 9H), 1.01 (m, 1H), 1.72 (m, 2H), 2.15 (m, 2H), 2.34 (m, 4H), 3.04 (m, 1H), 3.36 (dd, J = 5.2 and 12.4 Hz, 1H), 3.65 (dd, J = 4.8 and 12.4 Hz, 1H), 5.48 (m, 2H); ^{13}C NMR δ 178.1, 132.2, 126.6, 75.0, 66.0, 34.7, 33.3, 26.5, 25.9, 24.5, 23.2, 19.1, 18.3, 7.7, −5.1; CIMS 343 (MH^+).

(1*R*,2*R*)-*trans*-1-[(4*Z*,2*S*)-2,3,6,7,8,9-Hexahydro-9-oxo-2-oxoninyl]-2-[(*tert*-butylsilyloxy)methyl]cyclopropane (13). To a room-temperature solution of the hydroxy acid **12** (100 mg, 0.29 mmol) and triethylamine (0.05 mL, 0.31 mmol) in THF (2 mL) was added dropwise 2,4,6-trichlorobenzoyl chloride (0.05 mL, 0.29 mmol); the mixture was stirred for 2 h. The precipitated solids were then filtered, the filtrate was diluted with toluene (200 mL) and added dropwise (7−8 h) to a refluxing solution of 4-(dimethylamino)pyridine (141 mg, 1.16 mmol) in toluene (35 mL) followed by stirring at room temperature for 10 h. Toluene was removed under reduced pressure and the residue purified by column chromatography to yield the cyclopropyl lactone **13** (62 mg, 66%) as a colorless liquid: $[\alpha]_D = -54.66$ ($c = 0.3$, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^{1}H NMR δ 0.05 (br s, 6H), 0.49 (m, 2H), 0.86 (br s, 9H), 0.93 (m, 1H), 1.06 (m, 1H), 1.75 (m, 1H), 2.02 (m, 2H), 2.17 (m, 2H), 2.21 (m, 2H), 2.46 (m, 2H), 3.50 (m, 2H), 4.18 (br t, J = 9.7 Hz, 1H), 5.44 (m, 2H); ^{13}C NMR δ 174.4, 134.5, 124.9, 76.4, 65.4, 33.9, 33.6, 26.5, 25.9, 19.9, 19.5, 7.8, 1.0; HRMS (CI) calcd for $C_{14}H_{23}SiO_3$ 267.4194 ($M^+ - {}^t$Bu), found 267.4204.

(1*R*,2*R*)-*trans*-1-[(4*Z*,2*S*)-2,3,6,7,8,9-Hexahydro-9-oxo-2-oxoninyl]-2-(hydroxymethyl)cyclopropane (14). To a stirred solution of the cyclopropyl lactone **13** (80 mg, 0.24 mmol) in THF (4 mL) at 0 °C was added a solution of tetrabutylammonium fluoride (1 M solution in THF, 0.085 mL, 0.29 mmol) and stirring was continued at 0 °C for 30 min and 6 h at room temperature. After removal of the solvent under vacuum, the residue was purified by column chromatography to afford the hydroxymethyl cyclopropane **14** (52 mg, 92%) as a colorless liquid: $[\alpha]_D = -149.2$ ($c = 1$, $CHCl_3$); IR (neat) 3408, 1732 cm^{-1}; ^{1}H NMR δ 0.61 (m, 2H), 0.99 (m, 1H), 1.27 (m, 1H), 1.81 (m, 1H), 2.07 (m, 3H), 2.25 (m, 2H), 2.50 (m, 2H), 3.48 (m, 2H), 4.17 (m, 1H), 5.45 (m, 2H); CIMS 211 (MH^+).

(1*R*,2*R*)-*trans*-2-[(4*Z*,2*S*)-2,3,6,7,8,9-Hexahydro-9-oxo-2-oxoninyl]cyclopropanecarboxaldehyde (15). To a room-temperature solution of 2-iodoxybenzoic acid (67 mg, 0.24 mmol) in DMSO (1 mL) was added a solution of the hydroxymethyl cyclopropane **14** (40 mg, 0.12 mmol) in THF (3 mL); the mixture was stirred for 2 h. Water (6 mL) was then added to the reaction mixture, the precipitated solid was

filtered off, and the filtrate was extracted with ether (3 × 20 mL). The combined filtrate on drying (Na_2SO_4) and removal of solvent afforded the crude product which was column chromatographed to yield the pure cyclopropyl aldehyde **15** (35 mg, 89%) as a colorless liquid: $[\alpha]_D = -155.4$ ($c = 0.7$, $CHCl_3$); IR (neat) 1744, 1696 cm^{-1}; ^1H NMR δ 1.11 (m, 1H), 1.39 (m, 1H), 1.77 (m, 2H), 2.07 (m, 3H), 2.16 (m, 2H), 2.25 (m, 2H), 2.47 (m, 2H), 4.33 (br t, $J = 9.4$ Hz, 1H), 5.45 (m, 2H), 9.21 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR δ 200.0, 173.8, 135.1, 124.0, 74.1, 33.8, 33.4, 27.8, 26.3, 25.5, 25.3, 12.7; CIMS 209 (MH^+). Anal. Calcd for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.75. Found: C, 69.59; H, 7.94.

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