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Synthetic studies on soft coral norcembranolides: total synthesis of (+)-10-epigyrosanolide E

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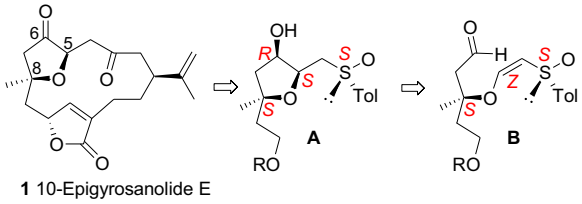
ABSTRACT

Total synthesis of (+)-10-epigyrosanolide E was accomplished employing SmI_2-mediated 5-*exo* cyclization of an aldehydo β-alkoxyvinyl sulfoxide and ring-closing metathesis reaction.

1. Introduction

Soft corals are known to be a rich source of cembrane diterpenoids. In particular, *Sinularia* spp. (family Alcyoniidae) produce a plethora of unique norcembranolides each featuring an oxolanone unit imbedded in a 14-membered carbon ring system.[1] Interestingly, there are no reports yet in the literature concerning synthesis of this class of natural products, and we wish to communicate here a total synthesis of 10-epigyrosanolide E (**1**), a representative member of soft coral norcembranolides. 10-Epigyrosanolide E (**1**) was isolated from *Sinularia numerosa* collected in habitats within the Archipelago of Palau by Fenical and co-workers in 1985.[1b,2] The most characteristic feature in the structure of **1** is the substituted oxolanone structure, which is derived from a tertiary alcohol. We intended to obtain the key structural element **A** through 5-*exo* cyclization of an aldehydo β-alkoxyvinyl sulfoxide **B**. It is known[3] that 5-*exo* cyclizations of aldehydo (*E*)- and (*Z*)-β-alkoxyvinyl sulfoxides derived from a tertiary alcohol proceed under sulfoxide chirality control, and synthesis of (5*S*,6*R*)-**A** requires use of (*Z*)-(*S*)-β-alkoxyvinyl sulfoxide **B** (Scheme 1).



Scheme 1. Retrosynthetic analysis.

2. Results and discussions

In practice, the known (*S*)-epoxide PMP ether **3**[4] was obtained from 3-methyl-3-buten-1-ol (**2**). Reaction of **3** with lithiated dithiane produced tertiary alcohol **4**. Reaction of **4** with (*S*)-alkynyl sulfoxide **5** in the presence of ethylmagnesium bromide and lithium chloride[3] led to aldehydo (*Z*)-(*S*)-β-alkoxyvinyl sulfoxide **6** after hydrolysis of the dithiane unit.

Reaction of **6** with SmI_2 in THF/methanol (1:1)[5] yielded efficiently the (5*S*,6*R*)-hydroxyoxolane product **7**, which was isolated in 85% yield (Scheme 2). This reaction proceeded under high stereo control and minor products were not isolated. Mitsunobu reaction on **7** with *p*-nitrobenzoic acid, hydrolysis, and TBS-protection afforded the hydroxyoxolane intermediate **8**. The inversion at C-6 was necessary for efficiency in the later manipulations.[6] Direct formation of the (5*S*,6*S*)-isomer was attempted using the (*E*)-(*R*)-β-alkoxyvinyl sulfoxide,[3] but the reaction produced the (5*S*,6*S*)-hydroxyoxolane product in 28% yield along with the epimeric (5*S*,6*R*)-isomer (24% yield). Aldehyde **9** was obtained from sulfoxide **8** via Pummerer rearrangement mediated by trifluoroacetic

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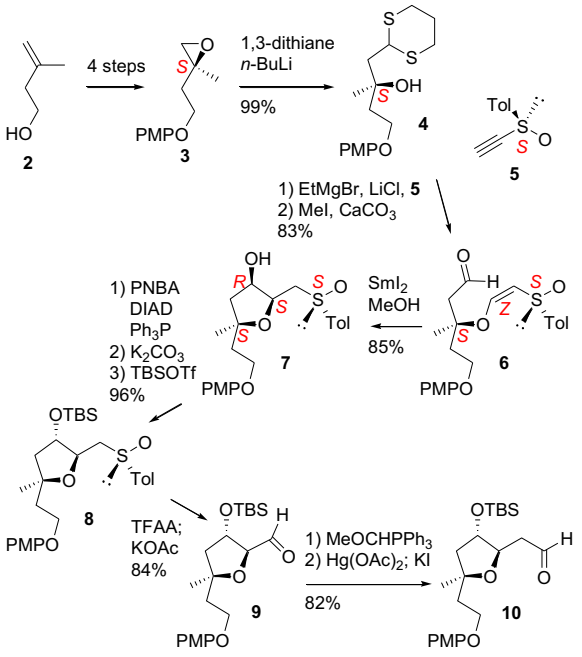
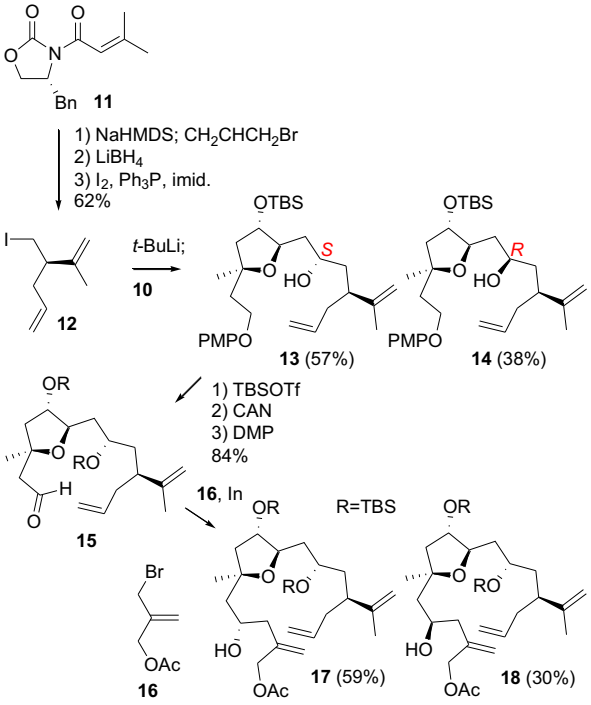


Scheme 2. Synthesis of hydroxyoxolane intermediates.

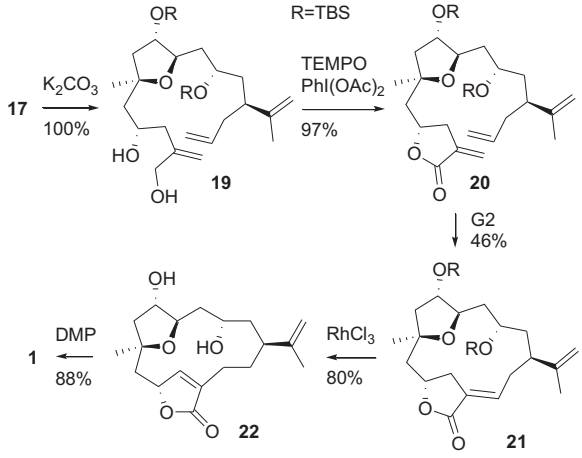
anhydride. Wittig methoxymethylenation of **9** and then mercuric ion-catalyzed hydrolysis yielded the homologous aldehyde **10**.

The primary iodide **12** was prepared from the chiral imide **11**[7] via reaction with sodium hexamethyldisilazide and allyl bromide, lithium borohydride reduction of the imide allylation product, and iodide substitution. Treatment of the primary iodide **12** with 2 equiv of *tert*-butyllithium, and then aldehyde **10** led to the efficient formation of a mixture (~3:2) of alcohols **13** and **14**. Stereoselectivity did not improve under different reaction conditions. TBS-protection of the hydroxyl group in **13**, ceric ammonium nitrate-mediated PMP-deprotection, and Dess–Martin oxidation provided aldehyde **15**. In the presence of indium and the allylic bromide **16**, a mixture (~2:1) of secondary alcohols **17** and **18** was obtained from aldehyde **15** (Scheme 3).



Scheme 3. Synthesis the triene intermediates.

Diol **19** was obtained cleanly from **17** upon hydrolysis. The same diol **19** was prepared from **18** in 69% yield via Dess–Martin oxidation and L-selectride reduction, which proceeded with a ~7:1 stereoselectivity. Oxidation of **19** with TEMPO and (diacetoxyiodo)benzene[8] afforded methylene lactone **20** in excellent yield. The crucial ring-closing olefin metathesis reaction of **20** was successfully carried out in the presence of the second generation Grubbs catalyst and 1,4-benzoquinone providing macrocycle **21**.[9] Formation of internal olefin isomers from the starting material was a serious problem in the absence of 1,4-benzoquinone. Double bond translocation in macrocycle **21** proceeded smoothly in the presence of rhodium chloride in ethanol,[10] which also effected global TBS-deprotection yielding diol **22**. Dess–Martin oxidation of **22** produced (+)-10-epigyrosanolide E [(**1**) (Fig. 1)[11]] in good yield[12] (Scheme 4). In view of the rotation values reported by Fenical,[13] the natural product should be represented as *ent*-**1**.



Scheme 4. Synthesis of (+)-10-epigyrosanolide E (**1**).

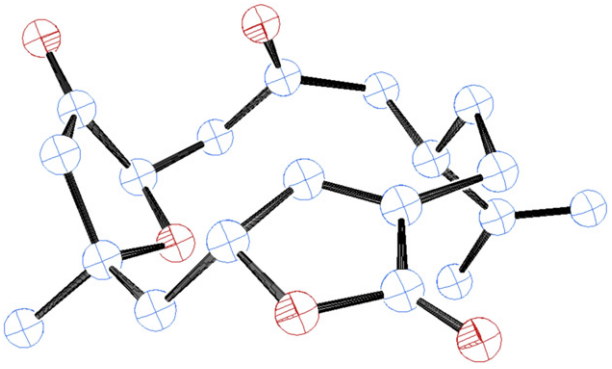


Fig. 1. The structure of (+)-10-epigyrosanolide E (**1**).

In summary, the key oxolanone fragment of (+)-10-epigyrosanolide E (**1**) was prepared through SmI_2-mediated 5-*exo* cyclizations of an aldehydo β-alkoxyvinyl sulfoxide. Ring-closing olefin metathesis reaction of a methylene lactone provided the 13-membered macrocycle. A member of the soft coral norcembranolides is now synthesized for the first time, establishing the absolute stereochemistry of the natural products.

3. Experimental

3.1. General

NMR spectra were obtained on a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were

recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in hertz. Mass spectra were recorded on a XEOL JMS-600 W or a XEOL JMS-700 spectrometer using fast atom bombardment (FAB) method. Significant fragments are reported in the following fashion: *m*/*z* (relative intensity). Optical rotation data were obtained on a JASCO P-1030 automatic polarimeter.

The progress of reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F_{254}), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (1.8 g of vanillin and 8.0 mL of concentrated sulfuric acid in 250 mL of methanol) or a $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of water). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexanes/EtOAc (v/v) or hexanes/acetone (v/v). The solvents were simple distilled unless otherwise noted.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhydrous $MgSO_4$ or Na_2SO_4 and evaporating under reduced pressure using a rotary evaporator.

Solvents used in reaction were dried under nitrogen atmosphere. THF was distilled from sodium-benzophenone and CH_2Cl_2 was distilled from P_2O_5. Et_2O was distilled from LAH.

3.1.1. Alcohol ***4****.* *n*-BuLi (2.5 M in hexane, 1.32 mL, 3.29 mmol) was added to a solution of 1,3-dithiane (424 mg, 3.53 mmol) in THF (18 mL) at −20 °C under argon. After 1 h, the solution was treated with a solution of epoxide **3** (508 mg, 2.35 mmol) in THF (5 mL) and allowed to warm to room temperature. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl solution (10 mL). The reaction mixture was extracted with Et_2O (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 5:1) provided the tertiary alcohol **4** (761 mg, 99%). R_f 0.26 (hexanes/EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86–6.82 (m, 4H), 4.27–4.25 (t, *J*=6.9 Hz, 1H), 4.16–4.09 (m, 2H), 3.77 (s, 3H), 2.98 (s, 1H), 2.96–2.91 (m, 2H), 2.87–2.83 (m, 2H), 2.13–1.96 (m, 5H), 1.94–1.85 (m, 1H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 152.9, 115.6, 114.8, 77.3, 65.3, 55.8, 47.5, 42.3, 40.7, 30.4, 27.3, 25.5. IR (neat): ν_{max}=3463, 2930, 2898, 1509, 1465, 1231, 1038, 900, 729, 626 cm^{-1}. MS *m*/*z* (EI, relative intensity): 328 (M^+, 23), 310 (5), 205 (100), 194 (7), 187 (27), 178 (9), 163 (9), 159 (11), 145 (7), 137 (17), 124 (42), 119 (27), 109 (13), 101 (10), 81 (7), 75 (29), 61 (5), 55 (4). HRMS (EI) calcd for $C_{16}H_{24}O_3S_2$ (M^+) 328.1167, found 328.1169. $[\alpha]_D^{25}$ +12.5 (*c* 0.805, $CHCl_3$).

3.1.2. Aldehydo (Z)-β-alkoxyvinyl sulfoxide ***6****.* Ethylmagnesium bromide (3.0 M in Et_2O, 0.734 mL, 2.20 mmol) was added to a solution of tertiary alcohol **4** (761 mg, 2.32 mmol) and lithium chloride (492 mg, 11.6 mmol) in THF (20 mL) at room temperature under argon. After stirring for 5 min, (+)-(*S*)-ethynyl *p*-tolyl sulfoxide **5** (419 mg, 2.55 mmol) in THF (3 mL) was added dropwise. After stirring for 12 h at room temperature, the reaction was quenched by addition of satd NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/acetone, 5:1) provided (*Z*)-β-alkoxyvinyl sulfoxide **4A** (946 mg, 83%). R_f 0.25 (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.0 Hz, 2H), 6.82 (s, 4H), 6.79 (d, *J*=5.5 Hz, 1H), 5.47 (d, *J*=5.5 Hz, 1H), 4.24 (t, *J*=5.7 Hz, 1H), 4.04 (t, *J*=6.5 Hz, 2H), 3.77 (s, 3H), 3.02–2.94 (m, 2H), 2.83–2.80 (m, 2H), 2.38 (s, 3H), 2.28–2.15 (m, 2H), 2.14–2.04 (m, 3H), 1.88–1.79 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1, 152.7, 146.8, 142.8, 140.8, 129.9, 124.2, 115.5, 115.2, 114.9, 82.4, 63.9, 55.9, 45.7, 41.9, 38.7, 31.4, 25.3, 24.6, 21.6. IR (neat): ν_{max}=2932, 1613, 1508, 1231, 1085, 1035, 908, 827, 811, 738, 516 cm^{-1}. MS *m*/*z* (EI, relative intensity): 492 (M^+, 4), 476 (8), 369 (4), 353 (6), 310 (26), 187 (60), 177 (39), 166 (12), 137 (20), 119 (100), 107 (11), 92 (6), 81 (7). HRMS (EI) calcd for $C_{25}H_{32}O_4S_3$ (M^+) 492.1463, found 492.1465. $[\alpha]_D^{25}$ −211.8 (*c* 0.580, $CHCl_3$).

A stirred solution of (*Z*)-β-alkoxyvinyl sulfoxide **4A** (161 mg, 0.327 mmol), CH_3I (1.02 mL, 16.4 mmol), and $CaCO_3$ (818 mg, 8.18 mmol) in CH_3CN (26 mL) and H_2O (7 mL) was heated to 40 °C. After stirring for 12 h, the reaction was quenched by addition of satd NH_4Cl solution (10 mL) at room temperature. The reaction mixture was extracted with EtOAc (25 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude aldehydo (*Z*)-β-alkoxyvinyl sulfoxide **6** (132 mg, 100%) was not subjected to further purification. R_f 0.18 (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.87 (t, *J*=2.2 Hz, 1H), 7.50 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=7.9 Hz, 2H), 6.85 (d, *J*=5.6 Hz, 1H), 6.85–6.78 (m, 4H), 5.53 (d, *J*=5.6 Hz, 1H), 4.10–4.01 (m, 2H), 3.77 (s, 3H), 2.92–2.80 (m, 2H), 2.39 (s, 3H), 2.31–2.20 (m, 2H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 154.3, 152.5, 146.4, 142.4, 141.1, 130.1, 124.1, 116.0, 115.4, 114.9, 81.1, 63.6, 55.9, 52.4, 38.4, 25.1, 21.6. IR (neat): ν_{max}=3335, 2925, 2651, 1723, 1672, 1614, 1509, 1384, 1231, 1085, 1036, 827, 811, 729, 514 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 403 (M^++1, 10), 337 (3), 307 (3), 282 (7), 220 (3), 211 (11), 183 (12), 154 (32), 136 (25), 95 (53), 69 (85), 55 (100), 43 (61), 29 (12). HRMS (FAB) calcd for $C_{22}H_{27}O_5S$ (M^++1) 403.1579, found 403.1579. $[\alpha]_D^{25}$ +70.9 (*c* 0.520, $CHCl_3$).

3.1.3. Hydroxyoxolane ***7****.* To a solution of aldehydo (*Z*)-β-alkoxyvinyl sulfoxide **6** (1.02 g, 2.53 mmol) in THF (12.5 mL) and MeOH (12.5 mL) was added a 0.1 M solution of SmI_2 in THF (53 mL, 5.31 mmol) at 0 °C under argon. After stirring for 10 min, the mixture was diluted with EtOAc (10 mL) and washed with H_2O (10 mL×2). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (hexanes/acetone, 5:1) to give hydroxyoxolane **7** (870 mg, 85%). R_f 0.30 (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J*=8.2 Hz, 2H), 7.34 (d, *J*=8.2 Hz, 2H), 6.86–6.81 (m, 4H), 4.50–4.45 (m, 1H), 4.19 (d, *J*=6.8 Hz, 1H), 4.13–4.07 (m, 3H), 3.76 (s, 3H), 3.38 and 3.19 (ABX, J_{AB}=14.0 Hz, J_{AX}=8.5 Hz, J_{BX}=3.2 Hz, 2H), 2.43 (s, 3H), 2.22–2.13 (m, 2H), 2.15–2.08 (m, 2H), 1.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 153.1, 141.9, 138.6, 130.3, 124.3, 115.6, 114.8, 81.6, 76.6, 73.3, 65.2, 55.9, 55.3, 46.1, 40.7, 26.6, 21.6. IR (neat): ν_{max}=3378, 2927, 1735, 1593, 1509, 1443, 1397, 1232, 1085, 1038, 826, 812, 739, 505 cm^{-1}. MS *m*/*z* (EI, relative intensity): 404 (M^+, 21), 388 (52), 281 (44), 265 (47), 194 (5), 177 (25), 137 (100), 124 (80), 97 (17), 84 (20), 69 (23), 55 (10). HRMS (EI) calcd for $C_{22}H_{28}O_5S$ (M^+) 404.1657, found 404.1652. $[\alpha]_D^{25}$ −73.2 (*c* 0.245, $CHCl_3$).

3.1.4. Hydroxyoxolane derivative ***8****.* DIAD (1.06 mL, 5.38 mmol) was added dropwise to a solution of hydroxyoxolane **7** (870 mg, 2.15 mmol), *p*-nitrobenzoic acid (899 mg, 5.38 mmol), and PPh_3 (1.41 g, 5.38 mmol) in toluene (21 mL) at room temperature under argon. After stirring for 1 h, the reaction mixture was concentrated and the residue was purified by flash column chromatography to provide *p*-nitrobenzoate **7A** (1.16 g, 100%). R_f 0.37 (hexanes/acetone, 2:1).

K_2CO_3 (298 mg, 2.15 mmol) was added to a solution of *p*-nitrobenzoate **7A** (1.16 g, 2.15 mmol) in MeOH (20 mL) at room temperature. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/acetone, 5:1) provided

the alcohol **7B** (868 mg, 100%). R_f 0.24 (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J=8.2 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 6.82 (m, 4H), 5.05 (d, J=1.9 Hz, 1H), 4.22–4.17 (m, 1H), 4.00–3.96 (m, 2H), 3.77 (s, 3H), 3.77–3.73 (m, 1H), 3.32 and 3.02 (ABX, J_{AB}=14.0 Hz, J_{AX}=9.6 Hz, J_{BX}=2.9 Hz, 2H), 2.43 (s, 3H), 1.97–1.94 (m, 2H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 153.1, 141.8, 137.4, 130.3, 124.6, 115.5, 114.9, 82.5, 78.7, 76.0, 65.0, 57.0, 55.9, 45.3, 41.6, 27.7, 21.7. IR (neat): ν_{max}=3354, 2929, 1734, 1509, 1444, 1377, 1231, 1180, 1085, 1038, 827, 739, 506 cm^{-1}. MS m/z (EI, relative intensity): 420 (14), 404 (M^+, 61), 388 (26), 281 (100), 265 (26), 177 (33), 137 (87), 124 (84), 109 (18), 95 (20), 69 (15), 55 (5). HRMS (EI) calcd for $C_{22}H_{28}O_5S$ (M^+) 404.1657, found 404.1660. $[\alpha]_D^{25}$ −75.1 (c 0.895, $CHCl_3$).

2,6-Lutidine (0.300 mL, 2.58 mmol) and TBSOTf (0.474 mL, 2.06 mmol) were added to a solution of alcohol **7B** (694 mg, 1.72 mmol) in CH_2Cl_2 (18 mL) at 0 °C under argon. This reaction mixture was stirred for 2 h and the reaction was quenched by addition of H_2O (10 mL). The reaction mixture was extracted with Et_2O (40 mL×3) and the organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 5:1) gave the hydroxyoxolane derivative **8** (853 mg, 96%). R_f 0.68 (hexanes/EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J=8.2 Hz, 2H), 7.32 (d, J=7.9 Hz, 2H), 6.84 (s, 4H), 4.31–4.28 (m, 1H), 4.09–4.01 (m, 2H), 3.77 (s, 3H), 3.76–3.73 (m, 1H), 3.12 and 2.91 (ABX, J_{AB}=13.0 Hz, J_{AX}=6.8 Hz, J_{BX}=4.4 Hz, 2H), 2.41 (s, 3H), 2.32 and 1.69 (ABX, J_{AB}=12.8 Hz, J_{AX}=7.4 Hz, J_{BX}=5.6 Hz, 2H), 2.03 (t, J=6.6 Hz, 2H), 1.36 (s, 3H), 0.82 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 153.1, 141.8, 140.8, 130.1, 124.6, 115.4, 114.8, 82.5, 79.6, 76.2, 64.9, 61.1, 55.9, 46.1, 41.5, 27.4, 25.9, 21.6, 18.0, −4.46, −4.67. IR (neat): ν_{max}=2954, 2929, 2856, 1509, 1471, 1376, 1231, 1121, 1042, 837, 778 cm^{-1}. MS m/z (EI, relative intensity): 518 (M^+, 21), 502 (44), 477 (18), 461 (74), 445 (100), 395 (19), 379 (16), 222 (14), 177 (38), 137 (69), 115 (18), 73 (48), 57 (28). HRMS (EI) calcd for $C_{28}H_{42}O_5SiS$ (M^+) 518.2522, found 518.2515. $[\alpha]_D^{25}$ −6.53 (c 0.49, $CHCl_3$).

*3.1.5. Aldehyde **10**.* To a solution of hydroxyoxolane derivative **8** (863 mg, 1.66 mmol) in CH_3CN (33 mL) was added pyridine (0.270 mL, 3.32 mmol) and trifluoroacetic anhydride (0.470 mL, 3.32 mmol) at 0 °C under argon. After stirring for 1 h, H_2O (0.85 mL) and potassium acetate (815 mg, 8.30 mmol) were added. The reaction mixture was then allowed to warm up to room temperature. After stirring for 12 h, the reaction mixture was partitioned between H_2O (15 mL) and Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL×2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 8:1) to give aldehyde **9** (554 mg, 84%). R_f 0.32 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, J=1.3 Hz, 1H), 6.83 (s, 4H), 4.48–4.45 (m, 1H), 4.26 (q, J=1.7 Hz, 1H), 4.13–4.01 (m, 2H), 3.77 (s, 3H), 2.11 and 1.87 (ABX, J_{AB}=13.0 Hz, J_{AX}=6.8 Hz, J_{BX}=3.4 Hz, 2H), 2.06 (t, J=7.9 Hz, 2H), 1.47 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 154.0, 152.9, 115.4, 114.8, 90.7, 84.6, 74.9, 64.9, 55.9, 46.8, 41.4, 26.7, 25.8, 18.0, −4.7, −4.8. IR (neat): ν_{max}=2954, 2930, 2657, 1736, 1509, 1471, 1232, 1180, 1041, 829, 778, 522 cm^{-1}. MS m/z (EI, relative intensity): 394 (M^+, 18), 319 (5), 227 (2), 213 (5), 203 (4), 177 (100), 145 (30), 137 (35), 124 (34), 117 (18), 109 (11), 84 (12), 75 (25), 73 (25). HRMS (EI) calcd for $C_{21}H_{34}O_5Si$ (M^+) 394.2176, found 394.2179. $[\alpha]_D^{25}$ +28.1 (c 0.485, $CHCl_3$).

Potassium *tert*-butoxide (1.0 M in THF, 1.52 mL, 1.52 mmol) was added to a solution of (methoxymethyl)triphenylphosphonium chloride (626 mg, 1.82 mmol) in THF (10 mL) at 0 °C under argon. The resulting red solution was stirred for 1 h at the same temperature, followed by dropwise addition of a solution of aldehyde **9** (240 mg, 0.608 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched by addition of satd $NaHCO_3$ solution (5 mL) and the product mixture was extracted with Et_2O (10 mL×3). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude enol ether was dissolved in THF (12 mL) and H_2O (1.2 mL) then cooled to 0 °C. Mercuric acetate (194 mg, 0.608 mmol) was added to the solution in one portion and the mixture was stirred for 30 min at 0 °C, and then treated with satd KI solution (10 mL). The reaction mixture was extracted with Et_2O (10 mL×3), and the organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc, 10:1) provided aldehyde **10** (203 mg, 82%). R_f 0.55 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (t, J=2.5 Hz, 1H), 6.83 (m, 4H), 4.20–4.16 (m, 1H), 4.05–3.94 (m, 3H), 3.77 (s, 3H), 2.66–2.60 (m, 1H), 2.54–2.48 (m, 1H), 2.30 and 1.74 (ABX, J_{AB}=12.8 Hz, J_{AX}=7.4 Hz, J_{BX}=6.0 Hz, 2H), 1.97 (t, J=6.6 Hz, 2H), 1.39 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.2, 153.9, 153.1, 115.4, 114.9, 81.9, 79.3, 76.7, 64.9, 55.9, 47.5, 46.1, 41.6, 27.7, 25.9, 18.1, −4.4, −4.7. IR (neat): ν_{max}=2954, 2930, 2857, 2729, 1728, 1509, 1472, 1389, 1232, 1117, 1041, 837, 778 cm^{-1}. MS m/z (EI, relative intensity): 408 (M^+, 52), 333 (4), 241 (4), 215 (4), 209 (8), 195 (18), 183 (9), 177 (100), 157 (25), 137 (28), 131 (18), 124 (36), 109 (24), 101 (10), 81 (7), 73 (31), 69 (15). HRMS (EI) calcd for $C_{22}H_{36}O_5Si$ (M^+) 408.2332, found 408.2332. $[\alpha]_D^{25}$ +27.5 (c 0.790, $CHCl_3$).

*3.1.6. Iodide **12**.* NaHMDS (1.0 M in THF, 11.4 mL, 11.37 mmol) was added to a solution of imide **11** (2.68 g, 10.33 mmol) in THF (35 mL) at −78 °C under argon. After 1 h, the solution was treated with allyl bromide (1.89 mL, 20.66 mmol) at −78 °C and then stirred for 5 h at the same temperature. The reaction was quenched by addition of satd NH_4Cl solution and the reaction mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 10:1) provided imide **11A** (2.21 g, 71%). R_f 0.41 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.30–7.26 (m, 1H), 7.24–7.20 (m, 2H), 5.87–5.78 (m, 1H), 5.13 (dd, J=17.2, 1.6 Hz, 1H), 5.03 (dd, J=10.2, 1.0 Hz, 1H), 4.90 (s, 2H), 4.68–4.63 (m, 1H), 4.56 (dd, J=8.9, 5.7 Hz, 1H), 4.17–4.12 (m, 2H), 3.30 and 2.74 (ABX, J_{AB}=13.4 Hz, J_{AX}=9.7 Hz, J_{BX}=3.2 Hz, 2H), 2.70–2.64 (m, 1H), 2.44–2.37 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 153.2, 142.8, 135.7, 135.5, 129.6, 129.0, 127.4, 116.9, 113.9, 65.9, 55.8, 49.8, 38.1, 35.1, 21.4. IR (neat): ν_{max}=3078, 2923, 1782, 1698, 1642, 1386, 1366, 1208, 1099, 912, 748, 702 cm^{-1}. MS m/z (EI, relative intensity): 299 (M^+, 22), 284 (12), 258 (48), 208 (10), 178 (20), 122 (100), 95 (65), 79 (36), 55 (14). HRMS (EI) calcd for $C_{18}H_{21}O_3N$ (M^+) 299.1521, found 299.1523. $[\alpha]_D^{25}$ −98.6 (c 0.740, $CHCl_3$).

$LiBH_4$ (2.0 M in THF, 9.72 mL, 19.4 mmol) was added to a solution of imide **11A** (1.94 g, 6.48 mmol) and catalytic amount of EtOH (0.7 mL) in Et_2O (65 mL) at 0 °C under argon. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl solution at 0 °C. The reaction mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 15:1) provided the alcohol **11B** (799 mg, 98%). R_f 0.57 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79–5.70 (m, 1H), 5.08–4.99 (m, 2H), 4.95 (s, 1H), 4.83 (s, 1H), 3.61–3.49 (m, 2H), 2.39–2.32 (m, 1H), 2.16 (t, J=7.2 Hz, 2H), 1.70 (s, 3H), 1.38 (dd, J=7.5, 4.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 136.6, 116.2, 113.7, 63.7, 49.5, 34.3, 19.6. IR (neat): ν_{max}=3364, 2930, 1748, 1265, 1054, 911, 837, 738 cm^{-1} $[\alpha]_D^{25}$ −2.2 (c 0.835, $CHCl_3$).

To a solution of alcohol **11B** (602 mg, 4.77 mmol) in THF (48 mL) was added imidazole (810 mg, 11.9 mmol) and PPh_3 (3.12 g, 11.9 mmol), followed by I_2 (3.02 g, 11.9 mmol) at 0 °C. After stirring for 2 h, the reaction was quenched by addition of H_2O at 0 °C. The

reaction mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (pentanes/Et_2O, 10:1) gave iodide **12** (1.02 g, 90%). R_f 0.83 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72–5.64 (m, 1H), 5.10–5.02 (m, 2H), 4.92 (t, J=1.5 Hz, 1H), 4.76 (t, J=0.8 Hz, 1H), 3.28 and 3.19 (ABX, J_{AB}=9.9 Hz, J_{AX}=7.4 Hz, J_{BX}=6.0 Hz, 2H), 2.39–2.18 (m, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 136.0, 116.9, 113.4, 48.8, 37.7, 19.6, 11.1. IR (neat): ν_{max}=3076, 2973, 2925, 1642, 1439, 1375, 1180, 992, 916, 897, 602 cm^{-1}. MS m/z (CI, relative intensity): 253(25), 235 (M^+−1, 29), 217 (5), 199 (5), 181 (2), 157 (3), 143 (35), 127 (100), 109 (6), 91 (87), 71 (16), 57 (1). HRMS (CI) calcd for $C_8H_{12}I$ (M^+−1) 234.9984, found 234.9978. $[\alpha]_D^{25}$ +2.9 (c 1.02, $CHCl_3$).

*3.1.7. Alcohols **13** and **14**.* To a solution of iodide **12** (592 mg, 2.51 mmol) in Et_2O (20 mL) at −80 °C was added *t*-BuLi (1.7 M in pentane, 2.95 mL, 5.02 mmol) dropwise over 10 min under argon. After 1 h, the solution was treated with a solution of aldehyde **10** (640 mg, 1.57 mmol) in THF (5 mL) and allowed to warm to room temperature. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl solution (10 mL). The reaction mixture was extracted with Et_2O (20 mL×2). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 25:1) provided alcohols **13** (463 mg, 57%) and **14** (306 mg, 38%). (**13**) R_f 0.61 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 4H), 5.75–5.70 (m, 2H), 5.02–4.95 (m, 1H), 4.81–4.80 (m, 1H), 4.78 (s, 1H), 4.04–3.92 (m, 2H), 3.88–3.84 (m, 2H), 3.80–3.76 (m, 1H), 3.77 (s, 3H), 3.53 (s, 1H), 2.51–2.45 (m, 1H), 2.28–2.24 (m, 1H), 2.13–2.09 (m, 2H), 2.00–1.91 (m, 2H), 1.74–1.70 (m, 1H), 1.69–1.65 (m, 1H), 1.64 (s, 3H), 1.55–1.50 (m, 1H), 1.46–1.39 (m, 2H), 1.39 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 153.1, 147.0, 137.5, 115.6, 115.4, 114.8, 112.3, 84.3, 82.1, 77.6, 69.4, 64.9, 55.9, 46.1, 43.5, 41.7, 41.3, 40.9, 39.0, 27.6, 26.0, 18.7, 18.1, −4.4, −4.7. IR (neat): ν_{max}=3519, 3073, 2930, 2857, 1737, 1642, 1509, 1472, 1231, 1122, 1042, 836, 777 cm^{-1}. MS m/z (EI, relative intensity): 518 (M^+, 39), 422 (4), 307 (5), 279 (3), 251 (7), 233 (6), 215 (8), 181 (12), 177 (100), 139 (20), 137 (23), 124 (34), 109 (14), 81 (20), 73 (42), 55 (13). HRMS (EI) calcd for $C_{30}H_{50}O_5Si$ (M^+) 518.3428, found 518.3427. $[\alpha]_D^{25}$ +26.1 (c 0.480, $CHCl_3$). (**14**) R_f 0.56 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 4H), 5.73–5.65 (m, 1H), 5.02–4.95 (m, 2H), 4.75 (t, J=1.7 Hz, 1H), 4.72 (s, 1H), 4.05–4.01 (m, 1H), 3.99–3.95 (m, 3H), 3.81–3.78 (m, 1H), 3.77 (s, 3H), 3.09 (d, J=4.9 Hz, 1H), 2.27–2.21 (m, 2H), 2.16–2.08 (m, 2H), 1.99–1.96 (m, 2H), 1.78–1.68 (m, 2H), 1.66 (s, 3H), 1.66–1.62 (m, 1H), 1.53–1.48 (m, 2H), 1.38 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 153.1, 147.8, 137.1, 115.9, 115.4, 114.9, 112.0, 82.1, 81.9, 77.0, 67.9, 65.0, 56.0, 46.5, 44.4, 41.8, 40.1, 38.7, 38.3, 27.3, 26.0, 18.6, 18.1, −4.3, −4.6. IR (neat): ν_{max}=3501, 3073, 2930, 2857, 1643, 1509, 1472, 1375, 1231, 1117, 1042, 836, 777, 734 cm^{-1}. MS m/z (EI, relative intensity): 518 (M^+, 40), 307 (5), 251 (8), 233 (7), 215 (8), 195 (8), 177 (100), 159 (12), 139 (24), 124 (35), 109 (16), 95 (21), 73 (44), 57 (14). HRMS (EI) calcd for $C_{30}H_{50}O_5Si$ (M^+) 518.3428, found 518.3420. $[\alpha]_D^{25}$ +21.1 (c 0.510, $CHCl_3$).

*3.1.8. Aldehyde **15**.* 2,6-Lutidine (0.137 mL, 1.18 mmol) and TBSOTf (0.217 mL, 0.944 mmol) were added to a solution of alcohol **13** (408 mg, 0.786 mmol) in CH_2Cl_2 (8 mL) at 0 °C under argon. This reaction mixture was stirred for 2 h and the reaction was quenched by addition of H_2O (10 mL). The reaction mixture was extracted with Et_2O (10 mL×3) and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 20:1) gave the **13A** (475 mg, 95%). R_f 0.88 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 4H), 5.75–5.67 (m, 1H), 5.00–4.94 (m, 2H), 4.76 (t, J=1.7 Hz, 1H), 4.70 (d, J=2.0 Hz, 1H), 4.06–3.96 (m, 2H), 3.85–3.79 (m, 2H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 2.42–2.36 (m, 1H), 2.20–2.16 (m, 1H), 2.10–2.08 (m, 2H), 1.94–1.91 (m, 2H), 1.70–1.63 (m, 3H), 1.62 (s, 3H), 1.58–1.52 (m, 1H), 1.42–1.37 (m, 1H), 1.32 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H), 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 153.3, 147.1, 137.6, 115.5, 115.4, 114.9, 112.1, 80.9, 80.5, 78.0, 68.6, 65.2, 55.9, 46.7, 43.4, 42.8, 42.0, 39.4, 39.1, 27.5, 26.3, 26.0, 18.8, 18.3, 18.2, −3.5, −4.1, −4.4, −4.5. IR (neat): ν_{max}=3075, 2955, 2930, 2857, 1643, 1509, 1472, 1375, 1252, 1231, 1108, 712, 890, 775, 671 cm^{-1}. MS m/z (EI, relative intensity): 632 (M^+, 17), 575 (4), 521 (10), 443 (42), 383 (23), 365 (13), 329 (12), 291 (75), 251 (23), 189 (100), 177 (50), 159 (38), 137 (18), 121 (51), 93 (21), 73 (75). HRMS (EI) calcd for $C_{36}H_{64}O_5Si_2$ (M^+) 632.4292, found 632.4286. $[\alpha]_D^{25}$ +38.3 (c 0.260, $CHCl_3$).

CAN (1.17 g, 2.14 mmol) was added to a solution of **13A** (452 mg, 0.714 mmol) in CH_3CN (30 mL) and H_2O (3 mL) at 0 °C. After stirring at room temperature for 5 min, the mixture was diluted with EtOAc (30 mL) and washed with satd $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (30 mL×3), and the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude product alcohol **13B** was used without further purification.

Dess–Martin periodinane (454 mg, 1.07 mmol) was added to a solution of crude product alcohol **13B** in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 30 min and the reaction was quenched by addition of satd $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 20:1) gave aldehyde **15** (332 mg, 88%, two steps). R_f 0.85 (hexanes/EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (t, J=2.8 Hz, 1H), 5.75–5.67 (m, 1H), 5.01–4.95 (m, 2H), 4.78 (t, J=1.8 Hz, 1H), 4.70 (d, J=2.0 Hz, 1H), 3.90–3.86 (m, 1H), 3.81–3.76 (m, 2H), 2.56–2.46 (m, 2H), 2.41–2.35 (m, 1H), 2.10–2.07 (m, 3H), 1.78–1.74 (m, 1H), 1.72–1.66 (m, 1H), 1.64–1.61 (m, 1H), 1.62 (s, 3H), 1.59–1.52 (m, 1H), 1.43–1.38 (m, 1H), 1.39 (s, 3H), 0.88 (s, 18H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 147.0, 137.6, 115.5, 112.2, 110.0, 81.5, 80.1, 77.7, 68.3, 55.8, 46.6, 43.3, 42.6, 39.3, 39.1, 27.8, 26.2, 26.0, 18.8, 18.3, 18.2, −3.6, −4.2, −4.4, −4.5. IR (neat): ν_{max}=3076, 2956, 2930, 2857, 1726, 1643, 1473, 1375, 1255, 1124, 1068, 836, 775, 665 cm^{-1}. MS m/z (CI, relative intensity): 509 (M^++1, 10), 481 (17), 467 (8), 415 (13), 393 (22), 377 (19), 349 (61), 329 (59), 291 (42), 257 (100), 217 (96), 189 (21), 159 (26), 121 (36), 95 (20), 73 (13), 57 (7). HRMS (CI) calcd for $C_{29}H_{57}O_4Si_2$ (M^++1) 525.3795, found 525.3799. $[\alpha]_D^{25}$ +38.0 (c 0.295, $CHCl_3$).

*3.1.9. Diol **19**.* In powder (72 mg, 0.624 mmol) was added to a solution of aldehyde **15** (218 mg, 0.416 mmol) and allylic bromide **16** (120 mg, 0.624 mmol) in THF (2.1 mL) and satd NH_4Cl solution (6.2 mL) at room temperature. After 12 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 18:1) gave the secondary alcohols **17** (157 mg, 59%) and **18** (79 mg, 30%). Compound (**17**) R_f 0.68 (hexanes/EtOAc, 4:1). Compound (**18**) R_f 0.64 (hexanes/EtOAc, 4:1).

K_2CO_3 (34 mg, 0.246 mmol) was added to a solution of the secondary alcohol **17** (157 mg, 0.246 mmol) in MeOH (2.5 mL) at room temperature. After stirring for 1 h, the reaction was quenched by addition of satd NH_4Cl solution (5 mL). The reaction mixture was extracted with Et_2O (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 8:1) provided diol **19** (147 mg, 100%). R_f 0.31 (hexanes/EtOAc, 4:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74–5.66 (m, 1H), 5.07 (d, J=1.3 Hz, 1H), 5.01–4.95 (m, 2H), 4.90 (s, 1H), 4.80 (t, J=1.7 Hz, 1H), 4.70 (s, 1H), 4.58 (s, 1H), 4.16–4.11 (m, 1H), 4.11–4.04 (m, 2H), 3.92–3.88 (m,

1H), 3.86–3.84 (m, 1H), 3.80–3.76 (m, 1H), 3.73–3.69 (m, 1H), 2.39–2.33 (m, 1H), 2.32–2.23 (m, 2H), 2.14–2.03 (m, 2H), 1.98 and 1.77 (ABX, J_{AB}=12.7 Hz, J_{AX}=7.3 Hz, J_{BX}=5.7 Hz, 2H), 1.74–1.69 (m, 1H), 1.61 (s, 3H), 1.64–1.51 (m, 2H), 1.42–1.37 (m, 1H), 1.38 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 146.7, 137.4, 115.6, 114.5, 112.4, 83.1, 82.1, 77.0, 68.9, 68.3, 67.0, 48.8, 48.7, 43.3, 42.9, 42.5, 39.3, 39.1, 26.2, 26.0, 25.5, 18.8, 18.3, 18.2, −3.5, −4.3, −4.4, −4.5. IR (neat): ν_{max}=3426, 3075, 2955, 2930, 2857, 1644, 1472, 1441, 1377, 1254, 1073, 837 cm^{-1}. MS *m*/*z* (CI, relative intensity): 597 (M^++1, 47), 581 (19), 539 (30), 465 (67), 447 (40), 407 (18), 393 (19), 309 (80), 291 (73), 257 (31), 215 (97), 197 (100), 159 (46), 139 (49), 121 (80), 73 (27), 57 (19). HRMS (CI) calcd for $C_{33}H_{65}O_5Si_2$ (M^++1) 597.4371, found 597.4374. $[\alpha]_D^{25}$ +16.6 (*c* 0.375, $CHCl_3$).

Dess–Martin periodinane (108 mg, 0.254 mmol) was added to a solution of alcohol **18** (108 mg, 0.169 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 3 h and the reaction was quenched by addition of satd $Na_2S_2O_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 20:1) gave ketone **18A** (103 mg, 96%). R_f 0.69 (hexanes/EtOAc, 4:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75–5.67 (m, 1H), 5.25 (d, *J*=1.2 Hz, 1H), 5.04 (d, *J*=0.8 Hz, 1H), 5.01–4.95 (m, 2H), 4.78 (q, *J*=1.2 Hz, 1H), 4.71 (d, *J*=2.1 Hz, 1H), 4.55 (s, 2H), 3.84–3.80 (m, 1H), 3.79–3.76 (m, 1H), 3.73–3.69 (m, 1H), 3.30 and 3.22 (ABq, J_{AB}=16.4 Hz, 2H), 2.65–2.58 (m, 2H), 2.42–2.37 (m, 1H), 2.21–2.17 (m, 1H), 2.11–2.06 (m, 1H), 2.07 (s, 3H), 1.74–1.70 (m, 1H), 1.71–1.66 (m, 1H), 1.64–1.62 (m, 1H), 1.62 (s, 3H), 1.58–1.52 (m, 1H), 1.42–1.37 (m, 2H), 1.32 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.8, 170.6, 147.0, 137.7, 137.5, 117.4, 115.5, 112.2, 81.0, 80.6, 77.6, 68.4, 66.8, 54.3, 49.6, 45.9, 43.3, 42.5, 39.2, 39.1, 27.4, 26.2, 26.0, 21.1, 18.7, 18.3, 18.1, −3.5, −4.1, −4.4, −4.6. IR (neat): ν_{max}=2956, 2930, 2857, 1746, 1715, 1472, 1253, 1228, 1076, 912, 836, 775 cm^{-1}. MS *m*/*z* (CI, relative intensity): 637(M^++1, 6), 621 (4), 579 (6), 505 (12), 489 (20), 447 (16), 383 (11), 349 (100), 291 (31), 251 (9), 217 (91), 159 (24), 121 (22), 95 (13), 61 (10). HRMS (CI) calcd for $C_{35}H_{65}O_6Si_2$ (M^++1) 637.4320, found 637.4320. $[\alpha]_D^{25}$ +27.3 (*c* 2.56, $CHCl_3$).

L-selectride (0.463 mmol) was added dropwise to a solution of ketone **18A** (59 mg, 0.093 mmol) in THF (1 mL) at −78 °C under argon. After stirring for 18 h, the reaction was quenched with satd NH_4Cl solution (5 mL) at −78 °C and the reaction mixture was allowed to warm to room temperature. The product mixture was extracted with Et_2O (10 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 8:1) to give diol **19** (40 mg, 72%).

*3.1.10. Macrocycle **21**.* TEMPO (14 mg, 0.0871 mmol) was added to a solution of diol **19** (52 mg, 0.0871 mmol) and PhI(OAc)2 (84 mg, 0.261 mmol) in CH_2Cl_2 (8 mL) at room temperature. After stirring for 24 h, the reaction was quenched with H_2O (10 mL). The reaction mixture was extracted with CH_2Cl_2 (20 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (toluene/EtOAc, 25:1) to give methylene lactone **20** (52 mg, 97%). R_f 0.60 (hexanes/EtOAc, 4:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 (t, *J*=2.7 Hz, 1H), 5.75–5.67 (m, 1H), 5.60 (s, 1H), 5.01–4.95 (m, 2H), 4.78 (s, 1H), 4.71 (s, 1H), 4.66–4.61 (m, 1H), 3.86–3.82 (m, 1H), 3.79–3.76 (m, 1H), 3.73–3.70 (m, 1H), 3.08–3.03 (m, 1H), 2.68–2.62 (m, 1H), 2.42–2.36 (m, 1H), 2.33–2.29 (m, 1H), 2.11–2.08 (m, 2H), 1.97 and 1.79 (ABX, J_{AB}=14.7 Hz, J_{AX}=6.9 Hz, J_{BX}=5.0 Hz, 2H), 1.74–1.69 (m, 1H), 1.62 (s, 3H), 1.57–1.52 (m, 1H), 1.42–1.35 (m, 1H), 1.31 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 147.1, 137.6, 134.8, 121.9, 115.5, 112.1, 80.9, 80.2, 77.9, 74.9, 68.5, 47.9, 45.1, 43.3, 42.4, 39.3, 39.1, 35.5, 29.0, 26.2, 26.0, 18.8, 18.3, 18.2, −3.5, −4.1, −4.4, −4.6. IR (neat): ν_{max}=3075, 2956, 2930, 2857, 1771, 1472, 1375, 1255, 1121, 837, 775, 738 cm^{-1}. MS *m*/*z* (CI, relative intensity): 593 (M^++1, 2), 577 (33), 535 (43), 483 (14), 461 (41), 445 (8), 399 (9), 351 (8), 325 (100), 291 (20), 267 (21), 251 (6), 217 (13), 189 (13), 159 (12), 121 (16), 85 (8), 57 (13). HRMS (CI) calcd for $C_{33}H_{61}O_5Si_2$ (M^++1) 593.4058, found 593.4049. $[\alpha]_D^{25}$ +52.6 (*c* 0.135, $CHCl_3$).

The second generation Grubbs catalyst (18.6 mg, 0.0219 mmol) was added to a solution of methylene lactone **20** (26 mg, 0.0438 mmol) and 1,4-benzoquinone (7 mg, 0.0658 mmol) in DCE (8.8 mL) under Ar. This reaction mixture was heated to 95 °C. After 48 h, the reaction mixture was quenched under air for 2 h at room temperature. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/EtOAc, 12:1) to afford macrocycle **21** (11.5 mg, 46%). R_f 0.45 (hexanes/EtOAc, 4:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74–6.71 (m, 1H), 4.93–4.90 (m, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 4.00–3.93 (m, 2H), 3.84–3.81 (m, 1H), 3.39 (d, *J*=16.8 Hz, 1H), 2.90–2.83 (m, 1H), 2.52–2.47 (m, 1H), 2.38–2.34 (m, 1H), 2.32–2.28 (m, 1H), 2.29–2.26 (m, 1H), 2.03–1.96 (m, 1H), 1.93–1.89 (m, 1H), 1.82–1.77 (m, 1H), 1.73 (s, 3H), 1.69–1.66 (m, 1H), 1.64–1.61 (m, 1H), 1.42–1.37 (m, 1H), 1.35 (s, 3H), 1.32–1.26 (m, 1H), 0.88 (s, 9H), 0.86 (s, 9H), 0.02(s, 6H), 0.01 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 147.6, 139.0, 129.5, 110.5, 81.5, 80.4, 77.9, 76.1, 68.8, 51.3, 45.4, 42.4, 40.8, 38.2, 35.5, 30.2, 26.2, 25.9, 25.5, 18.3, 18.0, −3.7, −4.5, −4.5, −4.6. IR (neat): ν_{max}=2955, 2930, 2857, 1746, 1670, 1472, 1257, 1231, 1118, 1088, 1062, 1007, 836, 775, 738 cm^{-1}. MS *m*/*z* (CI, relative intensity): 639 (2), 593 (10), 565 (M^++1, 10), 549 (17), 507 (37), 461 (3), 433 (76), 391 (100), 347 (4), 301 (18), 279 (21), 261 (4), 177 (9), 167 (20), 149 (46), 113 (23), 71 (5), 57 (5). HRMS (CI) calcd for $C_{31}H_{57}O_5Si_2$ (M^++1) 565.3745, found 565.3739. $[\alpha]_D^{25}$ +18.2 (*c* 0.150, $CHCl_3$).

*3.1.11. 10-Epigyrosanolide E **1**.* $RhCl_3 \cdot 3H_2O$ (6.7 mg, 0.0319 mmol) was added to a solution of macrocycle **21** (18 mg, 0.0319 mmol) in EtOH (6.4 mL) at room temperature. This reaction mixture was heated under reflux. After stirring for 5 h, the reaction was diluted with EtOH (20 mL), filtered through silica, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/acetone, 2:1) to give diol **22** (8.6 mg, 80%). R_f 0.12 (hexanes/acetone, 2:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H), 5.17 (d, *J*=2.6 Hz, 1H), 4.77 (t, *J*=1.6 Hz, 1H), 4.65 (s, 1H), 4.05–4.01 (m, 1H), 4.00–3.93 (m, 1H), 3.80–3.75 (m, 1H), 2.49–2.46 (m, 1H), 2.44–2.34 (m, 2H), 2.22–2.15 (m, 1H), 1.96–1.87 (m, 3H), 1.86–1.68 (m, 5H), 1.66 (s, 3H), 1.62–1.53 (m, 1H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 151.8, 148.0, 130.5, 112.2, 81.2, 80.3, 79.9, 78.1, 67.9, 50.1, 43.1, 42.9, 42.8, 40.6, 29.4, 24.3, 21.0, 18.8. IR (neat): ν_{max}=3405, 2926, 1733, 1444, 1373, 1265, 1095, 898, 755 cm^{-1}. MS *m*/*z* (EI, relative intensity): 336 (M^+, 5), 318 (9), 237 (4), 208 (4), 178 (9), 163 (5), 143 (100), 135 (8), 123 (6), 115 (8), 108 (18), 95 (16), 83 (21), 69 (12), 55 (13). HRMS (EI) calcd for $C_{19}H_{28}O_5$ (M^+) 336.1937, found 336.1934. $[\alpha]_D^{25}$ −72.2 (*c* 0.130, $CHCl_3$).

Dess–Martin periodinane (26 mg, 0.0606 mmol) was added to a solution of diol **22** (6.8 mg, 0.0202 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of satd $Na_2S_2O_3$ solution (2 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/acetone, 5:1) gave 10-epigyrosanoldie E **1** (5.9 mg, 88%). R_f 0.35 (hexanes/acetone, 2:1). ^{1}H NMR (500 MHz, C_6D_6): δ 6.67 (s, 1H), 4.70 (s, 1H), 4.61 (s, 1H), 4.26 (m, 1H), 3.58 (dd, *J*=8.7, 3.5 Hz, 1H), 2.46 (dd, *J*=15.0, 3.6 Hz, 1H), 2.44–2.36 (m, 1H), 2.39–2.33 (m, 1H), 2.18 (dd, *J*=15.0, 8.7 Hz, 1H), 2.02–1.96 (m, 1H), 1.95 (dd, *J*=11.3, 2.5 Hz, 1H), 1.91–1.84 (m, 1H), 1.82 (t, *J*=11.1 Hz, 1H), 1.70 (d, *J*=17.6 Hz, 1H), 1.59 (d, *J*=17.6 Hz, 1H), 1.57–1.51 (m, 1H), 1.54 (dd,

J=15.0, 6.6 Hz, 1H), 1.39 (s, 3H), 1.27 (dd, J=15.0, 4.7 Hz, 1H), 0.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.0, 208.0, 174.2, 150.8, 145.9, 131.3, 113.2, 78.8, 78.4, 74.8, 48.3, 46.8, 45.7, 43.2, 41.0, 27.7, 25.5, 20.9, 18.2. IR (neat): ν_{max}=3405, 2926, 1733, 1444, 1373, 1265, 1095, 898, 755 cm^{-1}. MS m/z (EI, relative intensity): 332 (M^+, 100), 314 (6), 289 (15), 270 (5), 256 (7), 239 (9), 221 (11), 201 (10), 178 (15), 163 (12), 149 (26), 135 (20), 124 (31), 109 (44), 83 (38), 71 (38), 57 (59). HRMS (EI) calcd for $C_{19}H_{24}O_5$ (M^+) 332.1624 found 332.1627. $[\alpha]_D^{25}$ +139 (c 0.065, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.011.

References and notes

1. For selected reports on isolation of norcembranolide natural products from soft corals, see: (a) Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Mulder, J.; Stokie, G. J. *Aust. J. Chem.* **1978**, *31*, 2049–2056; (b) Sato, A.; Fenical, W.; Zheng, Q.-T.; Clardy, J. *Tetrahedron* **1985**, *41*, 4303–4308; (c) Shoji, N.; Umeyama, A.; Arihara, S. *J. Nat. Prod.* **1993**, *56*, 1651–1653; (d) Rudi, A.; Lev-Ari Dayan, T.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *J. Nat. Prod.* **1998**, *61*, 872–875; (e) Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908; (f) Ahmed, A. F.; Shiue, R.-T.; Wang, G.-H.; Dai, C.-F.; Kuo, Y.-H.; Sheu, J.-H. *Tetrahedron* **2003**, *59*, 7337–7344; (g) Ahmed, A. F.; Su, J.-H.; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2004**, *67*, 2079–2082; (h) Cheng, S.-Y.; Chuang, C.-T.; Wen, Z.-H.; Wang, S.-K.; Chiou, S.-F.; Hsu, C.-H.; Dai, C.-F.; Duh, C.-Y. *Bioorg. Med. Chem.* **2010**, *18*, 3379–3385.
2. As the compound was not named by Fenical at the time of its isolation, it was named in reference to a natural product isolated and named more recently by Duh.[1h]
3. Jung, J. H.; Lee, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 5698–5700.
4. Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696–13697.
5. Higher concentration of methanol probably prevented retro Michael reaction, and higher yield of **7** was obtained.
6. It was difficult to protect the hydroxyl group of the (6*R*)-isomers. For example, TBS-protection did not proceed.
7. Cases, M.; Gonzalez-Lopez de Turiso, F.; Hadjisoteriou, M. S.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 2786–2804.
8. Serra, S.; Fuganti, C. *Helv. Chim. Acta* **2004**, *87*, 2100–2109.
9. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
10. Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102–7104.
11. The structure of **1** was confirmed by X-ray diffraction studies. CCDC 812599 contains the supplementary crystallographic data for this compound. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
12. From **14**, 3-*epi*-**22** was obtained in 27% yield following the same reaction sequence. It was converted into **1** in 84% yield via Dess–Martin oxidation. The mixture of **13** and **14** may be used in the reaction sequence to yield a mixture of **22** and 3-*epi*-**22**.
13. The specific rotation of the natural sample:[1b] $[\alpha]_D$ −47 (c 0.01, $CHCl_3$).