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Synthesis of Δ²-OPC-8:0 and OPC-6:0

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Abstract—CuCN-catalyzed reaction of the (1*R*)-isomer of 4-cyclopentene-1,3-diol monoacetate with TBDPSO$(CH_2)_6$MgCl produced an S_N2-type product regioselectively in high yield. Mitsunobu inversion of the product and subsequent Claisen rearrangement furnished aldehyde with the two side chains, from which the title compounds were synthesized efficiently.

1. Introduction

While the biological properties of *epi*-jasmonic acid produced in plants via the linolenic acid cascade (Fig. 1) have been well studied,[1,2] only a little attention has been paid to the upper metabolic intermediates. Tendril coiling response is one such function for 12-oxo-PDA found in 1993.[3] Since then, induction of secondary metabolites,[4] up-regulation of several genes,[5] and expression of the specific genes[6] have been disclosed. Furthermore, the specific enzyme for the β-oxidation was identified.[7] However, the biological profile of OPC-*n*:0 (*n*=8, 6, 4) has not been studied, while biological activity of the trans isomer of 11-*epi*-OPC-6:0 methyl ester in racemic form has been studied to date.[8]

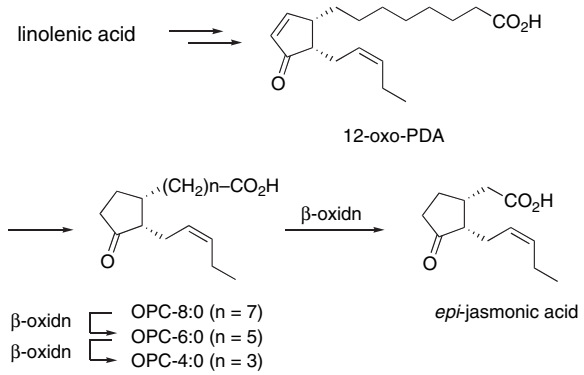

Figure 1. Metabolic sequence to *epi*-jasmonic acid.

Keywords: Allylation; Copper; Stereoselective synthesis; OPC-6:0; Linolenic acid metabolism.
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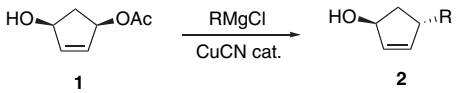
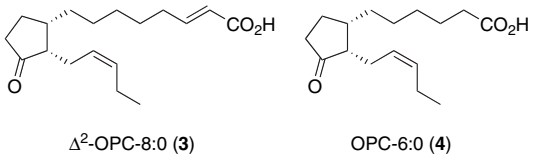
To elucidate the biological function of OPC-*n*:0 (*n*=8, 6, 4), these compounds in chemically pure form are definitely required. In these compounds, the two side chains on the cyclopentane ring are projected in the same direction, and the lower (2*Z*)-pentenyl chain is attached to the α position of the cyclopentanone core. Consequently, synthesis should be designed in a manner that it would not induce isomerization to the thermodynamically more stable trans isomer. However, the previous syntheses[9] of OPC-*n*:0 (*n*=8, 6, 4) have hardly been successful in controlling the stereocenters except for our approach[10] to OPC-8:0, which is briefly described next.

Several years ago, we reported installation of an alkyl group on the ring of 4-cyclopentene-1,3-diol monoacetate (**1**) through CuCN-catalyzed allylation with RMgCl to produce S_N2-type product **2** (Eq. 1).[11,12] The reaction was then applied to the synthesis of OPC-8:0 as well as 12-oxo-PDA with great success.[9] These compounds synthesized as chemically pure forms have been used for the biological studies mentioned above.[6,7]



(1)

Later we studied the synthesis of Δ²-OPC-8:0 (**3**) and OPC-6:0 (**4**) (Fig. 2).[13] The former compound possessing the double bond at the Δ² position would be resistant to the β-oxidation[14] on the analogy of Δ²-prostaglandins,[15] and hence be a useful tool for chemical biology to elucidate the pure property of OPC-8:0.[16] Herein, we present the synthesis in detail.

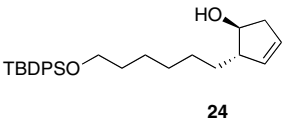


Δ^2-OPC-8:0 (**3**) OPC-6:0 (**4**)

Figure 2. Compounds synthesized through the procedures mentioned in this paper.

2. Results and discussion

According to our original method for the S_N2-type reaction of **1** (Eq. 1),[11] 3 equiv of RMgCl is required to complete the reaction. To reduce the quantity of the reagent **5**, monoacetate (1*R*)-**1** (>99% ee), prepared according to the literature procedure,[17] was treated first with 1 equiv of *t*-BuMgCl at 0 °C (Scheme 1). Subsequently, 2 equiv of TBDPSO$(CH_2)_6$MgCl (**5**) was added to the solution of the resulting magnesium alkoxide at −18 °C. The reaction proceeded with 92% regioselectivity giving the S_N2-type product **6**, which was isolated as a mixture with TBDPSO$(CH_2)_6$OH (calculated yield of **6** by ^{1}H NMR was 81%) after chromatographic separation of the minor regioisomer **24**. Mitsunobu inversion of the mixture using AcOH, DIAD, and PPh_3 in toluene at −78 °C afforded **7** and TBDPSO$(CH_2)_6$OAc, and the mixture was separated by chromatography to afford pure **7** in 77% yield from (1*R*)-**1**. Hydrolysis of the acetate **7** yielded alcohol **8** in high yield. Claisen rearrangement of alcohol **8** with CH_2=CHOEt proceeded at 180–190 °C to afford aldehyde **9**, which upon Jones oxidation produced acid **10** in 90% yield. Lactonization with KI_3 provided iodo-lactone **11**, which underwent reaction with Bu_3SnH to afford lactone **12** in high yield.

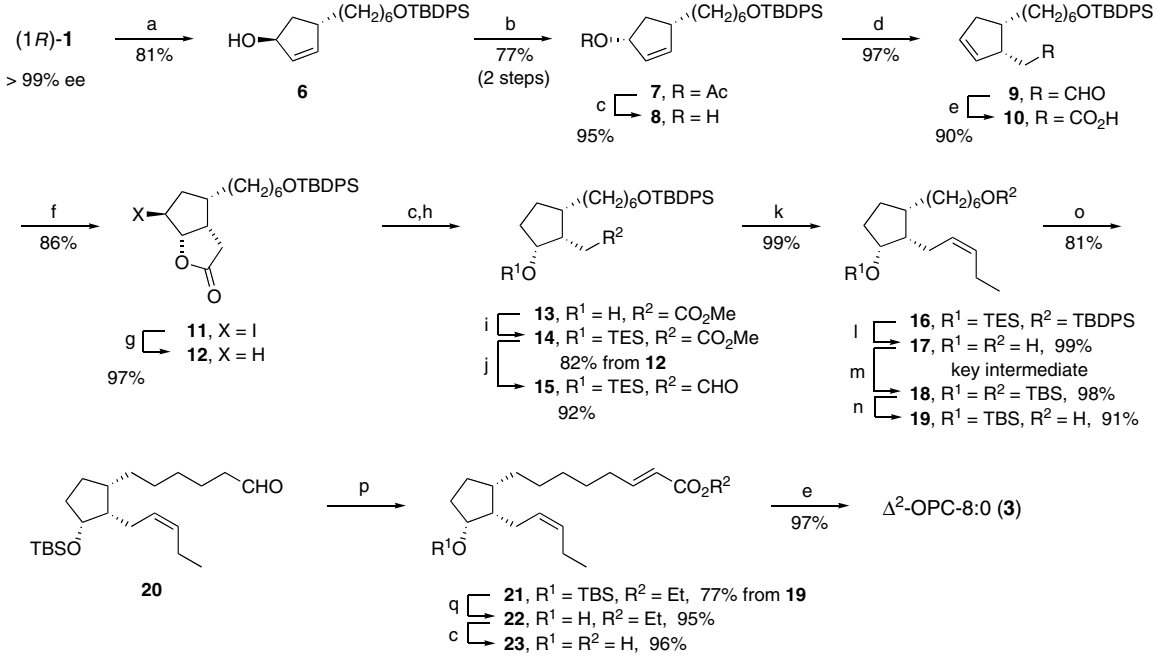


24

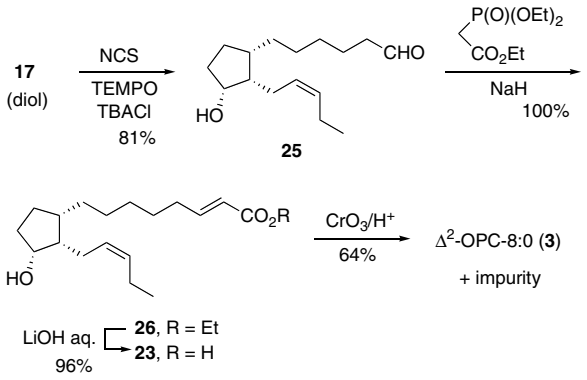
To construct the complete (2*Z*)-pentenyl side chain, lactone **12** was hydrolyzed into the hydroxyl acid, which upon esterification with CH_2N_2 afforded the hydroxyl methyl ester **13**. Subsequently, the silylation of **13** with TESCl immediately after filtration through a short silica gel column produced silyl ether **14** in 82% yield from **12**.[18,19] DIBAL-H reduction of ester **14** followed by Wittig reaction of the resulting aldehyde **15** with Ph_3P=CHEt furnished *cis*-olefin **16**, which underwent deprotection with Bu_4NF to afford the key diol **17** in quantitative yield.

In order to transform diol **17** into Δ^2-OPC-8:0 (**3**) in a short way through hydroxyl aldehyde **25** (Scheme 2), diol **17** was oxidized into hydroxyl aldehyde **25** with NCS in the presence of catalytic TEMPO and Bu_4NCl.[20] The reaction proceeded in good yield.[21] However, the ^{13}C NMR spectrum of **25** after chromatography revealed contamination with an olefinic impurity, though in less than 10%, which was probably derived from TEMPO-catalyzed olefin isomerization. Without further purification, **25** was subjected to the Horner–Emmons reaction to produce ester **26**, which was hydrolyzed to give hydroxyl acid **23**. Finally, Jones oxidation produced **3**. However, the impurity could not be eliminated even after these reactions and accompanying chromatographic purification.

After the unsuccessful results mentioned above, a sequence leading to the target compound **3** was established, which is

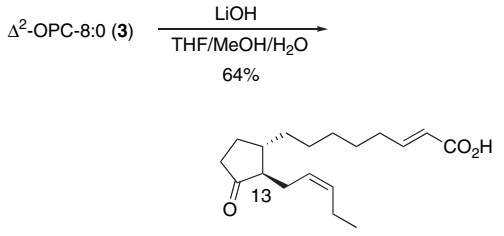


Scheme 1. Synthesis of Δ^2-OPC-8:0. (a) *t*-BuMgCl (1 equiv) then ClMg$(CH_2)_6$OTBDPS (**5**) (2 equiv), CuCN (0.3 equiv), −18 °C; (b) AcOH, DIAD, PPh_3, −78 °C; (c) LiOH aq; (d) CH_2=CHOEt, $Hg(OAc)_2$ (0.23 equiv), 180–190 °C; (e) CrO_3; (f) KI_3, $NaHCO_3$; (g) Bu_3SnH, AIBN; (h) CH_2N_2; (i) TESCl, imidazole; (j) DIBAL-H, −78 °C; (k) $Ph_3PC_3H_7Br$, $NaN(TMS)_2$; (l) Bu_4NF; (m) TBSCl, imidazole; (n) PPTS, EtOH/CH_2Cl_2; (o) PCC; (p) $(EtO)_2P$(=O)CH_2CO_2Et, LiCl, DBU; (q) AcOH, aq THF.



Scheme 2. An attempted synthesis of Δ^2-OPC-8:0.

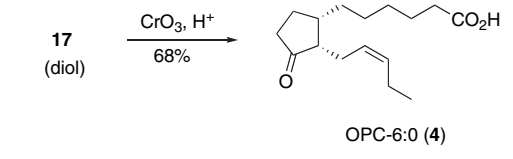
presented in Scheme 1. Silylation of diol **17** with TBSCl afforded **18**, which upon exposure to PPTS in EtOH and CH_2Cl_2 (1:1) at 5–10 °C afforded primary alcohol **19** in 91% yield.[22] PCC oxidation of **19** followed by Horner–Emmons reaction of the resulting aldehyde **20** under the Masamune conditions[23] afforded the α,β-unsaturated ester **21**. Desilylation of **21** followed by hydrolysis of the resulting alcohol **22** gave hydroxyl acid **23** in good yield. Finally, Jones oxidation furnished Δ^2-OPC-8:0 (**3**) in 97% yield.[24] Furthermore, **3** was subjected to epimerization under alkaline conditions to afford the 13-epimer of **3** (i.e., **27**) (Eq. 2). The ^{13}C NMR spectra (75 MHz) of **3** and **27** differed from each other (especially, 35.4, 38.7, and 53.7 ppm for **3**; 38.1, 41.2, 55.1 ppm for **27**), and established <5% contamination of **27** in **3**, while the ^1H NMR spectra and R_f values of **3** and **27** were superimposed on each other.



(2)

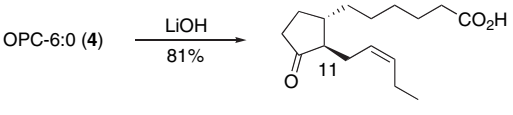
27 (13-epimer of **3**)

Next, Jones oxidation of the key diol **17** afforded OPC-6:0 (**4**) in 68% yield (Eq. 3).[24] In addition, **4** was exposed to aqueous LiOH for epimerization at C(11) (Eq. 4). The 11-epimer of **4** (i.e., **28**) thus synthesized in 81% yield was identical to the racemic 11-epimer reported in the literature[9c] by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Purity of OPC-6:0 (**4**) was >95% by calculation of the specific signal heights at 38.7 and 53.7 ppm for **4** and 41.2 and 55.1 ppm for **28**, in the ^{13}C NMR spectrum of **4**.



(3)

OPC-6:0 (**4**)



(4)

28
(11-epimer of OPC-6:0)

3. Conclusion

We have secured the synthesis of Δ^2-OPC-8:0 (**3**) and OPC-6:0 (**4**). Consequently the specific function of OPC-8:0 will be elucidated by using Δ^2-OPC-8:0 (**3**). Moreover, a full metabolic study of linolenic acid will be carried out using these compounds synthesized previously,[10] here, and elsewhere.[25]

4. Experimental

4.1. General methods

Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 and 500 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ=0 ppm) and the center line of $CDCl_3$ triplet (δ=77.1 ppm) as internal standards, respectively. Purity of the title compounds was confirmed by elemental analysis in most of cases or by the spectral method (^1H NMR and ^{13}C NMR) in case the satisfactory results were not recorded.

4.2. Synthesis of the diol key intermediate 17

4.2.1. (4*S*,1*S*)-4-[6-{(*tert*-Butyldiphenylsilyl)oxy}hexyl]-2-cyclopenten-1-ol (6). To an ice-cold solution of (1*R*)-**1** (505 mg, 3.55 mmol, >99% ee) in THF (21 mL) was added *t*-BuMgCl (4.60 mL, 0.76 M in THF, 3.50 mmol) and the solution was stirred at 0 °C for 10 min to prepare the alkoxide of (1*R*)-**1**. To this solution was added CuCN (95 mg, 1.06 mmol) and a solution of $ClMg(CH_2)_6OTBDPS$ (10.2 mL, 0.70 M in THF, 7.14 mmol) at −18 °C. The resulting mixture was stirred for 4 h at −18 °C and diluted with saturated NH_4Cl and EtOAc. After being stirred vigorously at room temperature, the layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$), and concentrated to afford an oil, which was a mixture of **6**, regioisomer **24**, and $TBDPSO(CH_2)_6OH$. Ratio of **6** and **24** was 92:8 by ^1H NMR spectroscopy. The mixture was subjected to chromatography to collect fractions (1.86 g) consisting of **6** (1.22 g and 81% yield) and $TBDPSO(CH_2)_6OH$ (0.64 g) by ^1H NMR spectroscopy. This mixture was used for the next reaction without further purification: ^1H NMR (300 MHz, $CDCl_3$) (selected signals) δ 1.05 (s, 9H), 1.75 (ddd, *J*=14, 7, 5 Hz, 1H), 1.90 (ddd, *J*=14, 8, 3 Hz, 1H), 2.78–2.90 (m, 1H), 4.80–4.89 (m, 1H), 5.81 (dt, *J*=5.5, 2 Hz), 5.94 (ddd, *J*=5.5, 2, 1 Hz, 1H). Regioisomer **24**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.2–1.6 (m, 11H), 2.24 (d, *J*=17 Hz, 1H), 2.43–2.58 (m, 1H), 2.70 (ddq, *J*=17, 6, 2 Hz, 1H), 3.65 (t, *J*=6 Hz, 2H), 4.04–4.12 (br s, 1H), 5.62–5.72 (m, 2H), 7.33–7.46 (m, 6H), 7.63–7.70 (m, 4H).

4.2.2. (4*S*,1*R*)-4-[6-{(*tert*-Butyldiphenylsilyl)oxy}hexyl]-2-cyclopentenyl acetate (7). To a solution of the above mixture, Ph_3P (2.60 g, 9.91 mmol), and AcOH (0.71 mL, 12 mmol) in toluene (17 mL) was added DIAD (2.09 mL, 10.1 mmol) at −78 °C. The mixture was stirred for 5 h at −78 °C and poured into saturated $NaHCO_3$ and hexane with vigorous stirring. The layers were separated, and the aqueous layer was extracted with hexane twice. The combined extracts were dried ($MgSO_4$) and concentrated to

give a residue, which was purified by chromatography (hexane/EtOAc) to furnish *cis*-acetate **7** exclusively (1.26 g, 77% from (1*R*)-**1**): $[\alpha]_D^{24}$ −3 (*c* 1.19, $CHCl_3$); IR (neat) 1735, 1242, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.20–1.62 (m, 11H), 2.03 (s, 3H), 2.45–2.63 (m, 2H), 3.65 (t, *J*=6.5 Hz, 2H), 5.57–5.66 (m, 1H), 5.75 (dt, *J*=6, 2 Hz, 1H), 5.99 (d, *J*=5.5 Hz, 1H), 7.32–7.45 (m, 6H), 7.59–7.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 21.5, 25.8, 27.0, 27.8, 29.5, 32.6, 36.4, 36.7, 44.4, 64.0, 80.0, 127.6, 128.8, 129.6, 134.2, 135.7, 141.2, 171.1. Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 74.85; H, 8.74.

4.2.3. (4*S*,1*R*)-4-[6-{(*tert*-Butyldiphenylsilyl)oxy}hexyl]-2-cyclopenten-1-ol (8). To an ice-cold solution of acetate **7** (1.81 g, 3.89 mmol) in THF (16 mL), MeOH (8 mL), and H_2O (4 mL) was added $LiOH\cdot H_2O$ (898 mg, 21.4 mmol). The mixture was stirred at room temperature overnight and diluted with saturated NH_4Cl and EtOAc with stirring at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc two times. The combined extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to give alcohol **8** (1.57 g, 95%): $[\alpha]_D^{28}$ –12 (*c* 1.11, $CHCl_3$); IR (neat) 3319, 1112, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.17–1.65 (m, 12H), 2.44–2.60 (m, 2H), 3.65 (t, *J*=6.5 Hz, 2H), 4.75–4.87 (m, 1H), 5.77 (dt, *J*=5.5, 2 Hz, 1H), 5.88 (d, *J*=5.5 Hz, 1H), 7.30–7.50 (m, 6H), 7.62–7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.8, 27.0, 27.9, 29.5, 32.6, 36.9, 40.6, 44.5, 64.0, 77.5, 127.7, 129.6, 133.0, 134.2, 135.7, 139.1. Anal. Calcd for $C_{27}H_{38}O_2Si$: C, 76.72; H, 9.06. Found: C, 76.68; H, 9.19.

4.2.4. (1*S*,2*S*)-2-([6-{(*tert*-Butyldiphenylsilyl)oxy}hexyl]-4-cyclopentenyl)ethanal (9). A sealed glass tube containing alcohol **8** (917 mg, 2.17 mmol), $Hg(OAc)_2$ (162 mg, 0.508 mmol), ethyl vinyl ether (2.4 mL, 25 mmol), and benzene (5 mL) was immersed in an oil bath set at 190 °C. After 70 h at 180–190 °C, the solution was cooled to room temperature and transferred with benzene to a flask containing K_2CO_3 (701 mg, 5.07 mmol). The mixture was stirred for 30 min and filtered through a pad of Celite with EtOAc. The filtrate was concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to give aldehyde **9** (944 mg, 97%): $[\alpha]_D^{25}$ –45 (*c* 1.39, $CHCl_3$); IR (neat) 1726, 1112, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.18–1.61 (m, 10H), 1.94 (dd, *J*=15, 9 Hz, 1H), 2.23 (ddd, *J*=16, 9, 2 Hz, 1H), 2.28–2.33 (m, 1H), 2.39 (dd, *J*=15, 8 Hz, 1H), 2.49 (ddd, *J*=16, 5, 2 Hz, 1H), 3.00–3.12 (m, 1H), 3.65 (t, *J*=6.5 Hz, 2H), 5.77 (s, 2H), 7.32–7.46 (m, 6H), 7.63–7.75 (m, 4H), 9.79 (t, *J*=2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.8, 26.9, 28.7, 29.6, 30.7, 32.6, 37.2, 41.3, 41.6, 44.6, 64.0, 127.6, 129.6, 131.2, 134.1, 134.2, 135.6, 202.9. Anal. Calcd for $C_{29}H_{40}O_2Si$: C, 77.62; H, 8.99. Found: C, 77.54; H, 9.07.

4.2.5. (1*S*,2*S*)-2-([6-{(*tert*-Butyldiphenylsilyl)oxy}hexyl]-4-cyclopentenyl)acetic acid (10). To an ice-cold solution of aldehyde **9** (1.18 g, 2.63 mmol) in acetone (26 mL) was added Jones reagent (4 M solution) slowly until the color of the reagent persisted (ca. 0.7 mL). After 10 min of stirring at the same temperature, 2-propanol was added to destroy the excess reagent. The resulting mixture was filtered through a pad of Celite with Et_2O. The filtrate was washed with brine three times to make the aqueous solution slightly acidic (pH 4). The aqueous layer was extracted with EtOAc three times. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexane/EtOAc) to afford acid **10** (1.09 g, 90%): $[\alpha]_D^{26}$ –43 (*c* 0.394, $CHCl_3$); IR (neat) 3100, 1707, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.20–1.62 (m, 10H), 1.80–1.93 (m, 1H), 2.02 (dd, *J*=15, 10 Hz, 1H), 2.12–2.32 (m, 2H), 2.37 (dd, *J*=15, 5.5 Hz, 1H), 2.86–3.09 (m, 1H), 3.58 (t, *J*=6.5 Hz, 2H), 5.66–5.88 (m, 2H), 7.19–7.44 (m, 6H), 7.52–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.9, 27.0, 28.8, 29.7, 30.4, 32.7, 34.8, 37.2, 41.5, 43.3, 64.1, 127.6, 129.5, 131.2, 134.1, 134.3, 135.6, 179.5. Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 74.83; H, 8.90.

4.2.6. Iodo-lactone 11. To an ice-cold solution of acid **10** (1.74 g, 3.74 mmol) in Et_2O (13 mL) and THF (13 mL) was added $NaHCO_3$ (989 mg, 11.8 mmol) dissolved in H_2O (24 mL) and the mixture was stirred for 30 min. Then an aqueous solution of I_2 (1.99 g, 7.84 mmol) and KI (3.91 g, 23.6 mmol) in H_2O (12 mL) was added. The resulting dark brown mixture was stirred at room temperature for 16 h under the dark and poured into aqueous $Na_2S_2O_3$ with vigorous stirring. The mixture was extracted with EtOAc three times. The combined extracts were dried ($MgSO_4$) and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to furnish **11** (1.90 g, 86%): $[\alpha]_D^{23}$ +2 (*c* 1.2, $CHCl_3$); IR (neat) 1787, 1166, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.22–1.42 (m, 7H), 1.48–1.72 (m, 4H), 2.09 (dd, *J*=15, 6 Hz, 1H), 2.49 (dd, *J*=18, 4 Hz, 1H), 2.59 (dd, *J*=18, 10 Hz, 1H), 2.58–2.73 (m, 1H), 3.05–3.16 (m, 1H), 3.66 (t, *J*=6.5 Hz, 2H), 4.46 (d, *J*=5 Hz, 1H), 5.27 (d, *J*=6 Hz, 1H), 7.32–7.50 (m, 6H), 7.64–7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.8, 27.0, 28.4, 28.5, 28.9, 29.6, 30.1, 32.6, 39.0, 40.3, 40.5, 64.0, 92.8, 127.6, 129.5, 134.1, 135.5, 176.4. Anal. Calcd for $C_{29}H_{39}O_3Si$: C, 58.97; H, 6.66. Found: C, 58.98; H, 6.77.

4.2.7. Lactone 12. To a solution of iodo-lactone **11** (165 mg, 0.279 mmol) in benzene (0.9 mL) were added Bu_3SnH (0.23 mL, 0.86 mmol) and AIBN (5 mg, 0.03 mmol). After 1 h of reflux, the reaction was quenched by addition of NaF (59 mg, 1.41 mmol). The slurry was stirred at room temperature for 30 min, and filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and a residue was purified by chromatography (hexane/EtOAc) to afford **12** (126 mg, 97%): $[\alpha]_D^{24}$ –5.7 (*c* 0.53, $CHCl_3$); IR (neat) 1771, 1111, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.10–1.36 (m, 8H), 1.42–2.20 (m, 7H), 2.35 (dd, *J*=19, 6 Hz, 1H), 2.42 (dd, *J*=19, 10 Hz, 1H), 2.78–2.92 (m, 1H), 3.58 (t, *J*=6 Hz, 2H), 4.95 (t, *J*=6 Hz, 1H), 7.33–7.43 (m, 6H), 7.63–7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.7, 26.9, 28.5, 28.7, 28.9, 29.5, 30.6, 32.5, 33.1, 40.5, 42.8, 63.9, 86.2, 127.6, 129.6, 134.2, 135.6, 178.1. Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 75.03; H, 8.72.

4.2.8. Methyl ester 14. To an ice-cold solution of lactone **12** (52 mg, 0.11 mmol) in THF (0.72 mL), MeOH (0.24 mL),

and H_2O (0.24 mL) was added $LiOH \cdot H_2O$ (24 mg, 0.57 mmol). The mixture was stirred at room temperature for 3 h, cooled to −18 °C, and diluted with saturated NH_4Cl. The resulting mixture was acidified to ca. pH 4 with 1 N HCl, and extracted with Et_2O three times. The extracts were dried ($MgSO_4$) at −18 °C and $MgSO_4$ was filtered out. The filtrate was treated with excess CH_2N_2 in Et_2O at −18 °C for 5 min. The solution was concentrated and the residue was passed through a short column of silica gel with Et_2O as an eluent to give the hydroxyl methyl ester **13** after evaporation.

To an ice-cold solution of the above ester **13** and imidazole (19 mg, 0.28 mmol) in DMF (1 mL) was added TESCl (0.038 mL, 0.23 mmol). The solution was stirred at room temperature for 14 h and diluted with saturated $NaHCO_3$ and hexane. The layers were separated, and the aqueous layer was extracted with hexane twice. The combined extracts were dried ($MgSO_4$) and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to afford silyl ester **14** (55 mg, 82% from lactone **12**) after chromatography (hexane/EtOAc): $[\alpha]_D^{23}$ +0.1 (*c* 1.98, $CHCl_3$); IR (neat) 1741, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (q, *J*=8 Hz, 6H), 0.93 (t, *J*=8 Hz, 9H), 1.04 (s, 9H), 1.08–1.93 (m, 15H), 2.20 (dd, *J*=15, 5.5 Hz, 1H), 2.32–2.44 (m, 1H), 2.46 (dd, *J*=15, 7.5 Hz, 1H), 3.64 (t, *J*=6.5 Hz, 2H), 3.65 (s, 3H), 4.17–4.24 (m, 1H), 7.33–7.43 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.9, 19.3, 25.9, 26.9, 28.1, 28.4, 29.5, 29.7, 31.7, 32.7, 32.8, 39.6, 43.8, 51.4, 64.1, 75.0, 127.6, 129.6, 134.3, 135.7, 174.9. Anal. Calcd for $C_{36}H_{58}O_4Si_2$: C, 70.77; H, 9.57. Found: C, 70.78; H, 9.53.

4.2.9. Aldehyde 15. To a solution of ester **14** (474 mg, 0.776 mmol) in CH_2Cl_2 (8 mL) was added DIBAL-H (1.0 mL, 0.94 M in hexane, 0.94 mmol) at −78 °C. The reaction was carried out at the same temperature for 1 h, and quenched with MeOH (0.40 mL, 9.9 mmol). After 10 min at −78 °C, a solution of H_2O (0.50 mL, 28 mmol) diluted with THF (0.50 mL) was added and the cooling bath was removed. The resulting mixture was stirred for 30 min and NaF (782 mg, 18.6 mmol) was added to it. After 30 min of vigorous stirring, the resulting mixture was filtered through a pad of Celite with EtOAc and the filtrate was concentrated to afford a residue, which was purified by chromatography (hexane/EtOAc) to give aldehyde **15** (415 mg, 92%): $[\alpha]_D^{26}$ −6 (*c* 0.53, $CHCl_3$); IR (neat) 1726, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, *J*=8 Hz, 6H), 0.94 (t, *J*=8 Hz, 9H), 1.06 (s, 9H), 1.1–2.0 (m, 15H), 2.13–2.27 (m, 1H), 2.43–2.60 (m, 2H), 3.66 (t, *J*=6.5 Hz, 2H), 4.19–4.29 (m, 1H), 7.34–7.48 (m, 6H), 7.64–7.75 (m, 4H), 9.82 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.8, 6.9, 19.3, 25.8, 26.9, 27.7, 28.3, 29.6, 31.9, 32.1, 32.6, 38.9, 39.4, 43.0, 64.0, 75.2, 127.6, 129.5, 134.2, 135.6, 203.5. Anal. Calcd for $C_{35}H_{56}O_3Si_2$: C, 72.36; H, 9.72. Found: C, 72.21; H, 9.73.

4.2.10. Olefin 16. To an ice-cold suspension of *n*-propyltriphenylphosphonium bromide (861 mg, 2.23 mmol) in THF (1 mL) was added a solution of $NaN(TMS)_2$ (2.1 mL, 0.99 M in THF, 2.1 mmol). The mixture was stirred at room temperature for 40 min and cooled to 0 °C. A solution of aldehyde **15** (351 mg, 0.604 mmol) in THF (3 mL) was added. The mixture was stirred at room temperature overnight. Hexane and saturated NH_4Cl were added to the mixture at 0 °C with vigorous stirring. The layers were separated and aqueous layer was extracted with hexane twice. The combined extracts were dried ($MgSO_4$) and concentrated to leave a residue, which was purified by chromatography (hexane/EtOAc) to afford olefin **16** (363 mg, 99%): $[\alpha]_D^{25}$ +2.2 (*c* 0.368, $CHCl_3$); IR (neat) 1428, 1112, 740, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, *J*=8 Hz, 6H), 0.95 (t, *J*=8 Hz, 9H), 0.96 (t, *J*=7.5 Hz, 3H), 1.04 (s, 9H), 1.15–1.88 (m, 16H), 1.98–2.24 (m, 4H), 3.65 (t, *J*=6.5 Hz, 2H), 4.13 (q, *J*=5 Hz, 1H), 5.24–5.48 (m, 2H), 7.34–7.43 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 7.0, 14.4, 19.3, 20.8, 22.4, 25.9, 26.9, 28.5, 28.8, 29.8, 31.8, 32.7, 33.4, 39.9, 48.7, 64.1, 75.5, 127.6, 129.5, 129.9, 131.1, 134.3, 135.7. Anal. Calcd for $C_{38}H_{62}O_2Si_2$: C, 75.18; H, 10.29. Found: C, 75.38; H, 10.14.

4.2.11. Diol 17. To an ice-cold solution of olefin **16** (135 mg, 0.222 mmol) in THF (1 mL) was added Bu_4NF (1.1 mL, 1.0 M in THF, 1.1 mmol) slowly. The resulting solution was stirred at 65 °C for 1 h, cooled to 0 °C, and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The mixture was filtered through a pad of Celite with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$) and concentrated to leave a residue, which was purified by chromatography (hexane/EtOAc) to afford diol **17** (56 mg, 99%): $[\alpha]_D^{24}$ +12 (*c* 0.388, $CHCl_3$); IR (neat) 3350, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J*=7.5 Hz, 3H), 1.19–1.95 (m, 17H), 2.20–2.50 (m, 5H), 3.64 (t, *J*=6.5 Hz, 2H), 4.14–4.26 (m, 1H), 5.34–5.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 20.9, 22.8, 25.9, 28.9, 29.1, 29.8, 31.8, 32.9, 33.2, 40.1, 47.9, 63.1, 75.5, 128.7, 132.1. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.50; H, 11.80.

4.3. Synthesis of Δ^2-OPC-8:0

4.3.1. Olefin 18. To an ice-cold mixture of TBSCl (106 mg, 0.682 mmol) and imidazole (54 mg, 0.79 mmol) in DMF (1 mL) was added a solution of diol **17** (57 mg, 0.224 mmol) in DMF (1.3 mL). The resulting solution was stirred at room temperature overnight, and diluted with hexane and saturated NH_4Cl at 0 °C with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with hexane twice. The combined extracts were dried ($MgSO_4$) and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish disilyl ether **18** (106 mg, 98%): $[\alpha]_D^{27}$ −0.3 (*c* 0.59, $CHCl_3$); IR (neat) 1255, 1102, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.05 (s, 6H), 0.88 (s, 9H), 0.90 (s, 9H), 0.97 (t, *J*=7.5 Hz, 3H), 1.06–1.76 (m, 15H), 1.77–1.90 (m, 1H), 2.00–2.17 (m, 4H), 3.59 (t, *J*=7 Hz, 2H), 4.07–4.14 (m, 1H), 5.26–5.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.9, −4.4, 14.3, 18.1, 18.5, 20.8, 22.8, 25.9, 26.1, 28.8, 28.9, 29.8, 31.8, 33.0, 33.7, 39.8, 49.0, 63.5, 75.6, 129.6, 131.2.

4.3.2. Alcohol 19. A solution of olefin **18** (243 mg, 0.503 mmol) and PPTS (152 mg, 0.605 mmol) in EtOH (3 mL) and CH_2Cl_2 (3 mL) was stirred for 27 h at

5−10 °C, and diluted with saturated $NaHCO_3$ and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc twice. The combined organic portions were dried ($MgSO_4$) and concentrated under reduced pressure to obtain an oily residue, which was purified by chromatography (hexane/EtOAc) to afford alcohol **19** (168 mg, 91%): $[\alpha]_D^{23}$ 0 (*c* 0.52, $CHCl_3$); IR (neat) 3323, 1253, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 0.96 (t, *J*=7.5 Hz, 3H), 1.1–1.9 (m, 17H), 1.99–2.17 (m, 4H), 3.63 (t, *J*=7 Hz, 2H), 4.07–4.14 (m, 1H), 5.26–5.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.4, 14.3, 18.1, 20.8, 22.8, 25.8, 25.9, 28.7, 28.8, 29.8, 31.7, 32.9, 33.7, 39.7, 49.0, 63.2, 75.5, 129.6, 131.3.

4.3.3. Ethyl ester 21. To an ice-cold solution of alcohol **19** (30 mg, 0.081 mmol) in CH_2Cl_2 (1 mL) was added PCC (26 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite with hexane, and the filtrate was washed with brine three times. The combined extracts were dried ($MgSO_4$) and concentrated to give an oil, which was semi-purified by chromatography (hexane/EtOAc) to give aldehyde **20**.

To an ice-cold mixture of LiCl (5 mg, 0.12 mmol) in CH_3CN (0.2 mL) were added diethylphosphonoacetic acid ethyl ester (0.049 mL, 0.24 mmol), DBU (0.048 mL, 0.32 mmol) and a solution of above aldehyde **20** in CH_3CN (0.8 mL). The resulting solution was stirred at room temperature for 6 h, and diluted with hexane and saturated $NaHCO_3$ at 0 °C with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with hexane twice. The combined extracts were dried ($MgSO_4$) and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish ethyl ester **21** (27 mg, 77% from alcohol **19**): $[\alpha]_D^{21}$ 0 (*c* 0.38, $CHCl_3$); IR (neat) 1725, 1655, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.96 (t, *J*=7.5 Hz, 3H), 1.1–1.9 (m, 16H), 1.28 (t, *J*=7 Hz, 3H), 1.95–2.23 (m, 4H), 4.07–4.13 (m, 1H), 4.18 (q, *J*=7 Hz, 2H), 5.25–5.48 (m, 2H), 5.80 (dt, *J*=16, 1.5 Hz, 1H), 6.96 (dt, *J*=16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.4, 14.3, 14.6, 18.1, 20.8, 22.8, 25.9, 28.1, 28.5, 28.8, 29.5, 31.6, 32.3, 33.7, 39.7, 49.0, 60.2, 75.5, 121.2, 129.5, 131.3, 149.7, 166.9.

4.3.4. Alcohol 22. A mixture of ethyl ester **21** (43 mg, 0.098 mmol) in THF (0.2 mL), H_2O (0.2 mL), and AcOH (0.6 mL) was stirred at 30 °C for 60 h, and diluted with EtOAc and saturated $NaHCO_3$ at 0 °C with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$) and concentrated to afford an oily residue, which was purified by chromatography (hexane/EtOAc) to furnish alcohol **22** (30 mg, 95%): $[\alpha]_D^{26}$ +13 (*c* 0.52, $CHCl_3$); IR (neat) 3490, 1722, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J*=7.5 Hz, 3H), 1.1–2.0 (m, 15H), 1.28 (t, *J*=7 Hz, 3H), 2.0–2.3 (m, 6H), 4.08–4.25 (m, 3H), 5.34–5.44 (m, 2H), 5.80 (d, *J*=16 Hz, 1H), 6.95 (dt, *J*=16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.33, 14.34, 20.8, 22.7, 28.1, 28.6, 29.0, 29.4, 31.7, 32.3, 33.2, 40.0, 47.9, 60.2, 75.4, 121.3, 128.7, 132.2, 149.5, 166.9.

4.3.5. Hydroxyl acid 23. To an ice-cold solution of alcohol **22** (16 mg, 0.0496 mmol) in THF (0.6 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH\cdot H_2O$ (10 mg, 0.24 mmol). The mixture was stirred at room temperature overnight and diluted with saturated NH_4Cl and EtOAc with stirring at room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was purified by chromatography (CH_2Cl_2/EtOAc) to give hydroxyl acid **23** (14 mg, 96%): $[\alpha]_D^{23}$ +13 (*c* 0.33, $CHCl_3$); IR (neat) 3410, 1699, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=7.5 Hz, 3H), 1.13–2.44 (m, 21H), 4.15–4.25 (m, 1H), 5.22–5.51 (m, 2H), 5.82 (d, *J*=16 Hz, 1H), 7.06 (dt, *J*=16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.8, 22.7, 28.0, 28.6, 29.0, 29.5, 31.7, 32.4, 33.1, 40.0, 47.8, 75.5, 120.8, 128.7, 132.3, 152.3, 171.8.

4.3.6. Δ^2-OPC-8:0 (3). To an ice-cold solution of the above hydroxyl acid **23** (28 mg, 0.095 mmol) in acetone (0.9 mL) was added Jones reagent (4 M solution) dropwise at 0 °C until the color of the reagent persisted (a few drops). After 10 min of stirring at 0 °C, *i*-PrOH was added to destroy the excess reagent. The mixture was filtered through a pad of Celite with EtOAc. The filtrate was washed with brine three times, dried ($MgSO_4$), and concentrated to give an oil, which was purified by chromatography (CH_2Cl_2/EtOAc) to give Δ^2-OPC-8:0 (**3**) (27 mg, 97%): $[\alpha]_D^{25}$ +51 (*c* 0.14, $CHCl_3$); IR (neat) 3196, 1738, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=7.5 Hz, 3H), 1.1–2.4 (m, 20H), 5.36–5.46 (m, 2H), 5.83 (d, *J*=16 Hz, 1H), 7.05 (dt, *J*=16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.7, 22.6, 24.9, 27.5, 27.9, 28.1, 29.3, 32.3, 35.4, 38.7, 53.7, 120.8, 126.2, 133.1, 152.2, 171.8, 220.3.

4.3.7. 13-Epimer 27. To an ice-cold solution of Δ^2-OPC-8:0 (**3**) (22 mg, 0.0752 mmol) in THF (0.6 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH\cdot H_2O$ (21 mg, 0.50 mmol). The mixture was stirred at room temperature for 2 h and diluted with saturated NH_4Cl and EtOAc with stirring. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was purified by chromatography (CH_2Cl_2/EtOAc) to give 13-epimer **27** (14 mg, 64%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=7.5 Hz, 3H), 1.2–2.4 (m, 20H), 5.19–5.48 (m, 2H), 5.83 (dt, *J*=16, 1.5 Hz, 1H), 7.07 (dt, *J*=16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 20.7, 25.5, 27.0, 27.1, 27.9, 29.4, 32.3, 34.7, 38.1, 41.2, 55.1, 120.6, 125.5, 133.6, 152.1, 170.8, 220.8.

4.4. Synthesis of OPC-6:0

4.4.1. OPC-6:0 (4). To an ice-cold solution of the above diol **17** (38 mg, 0.15 mmol) in acetone (1.5 mL) was added Jones reagent (4 M solution) dropwise at 0 °C until the color of the reagent persisted (a few drops). After 5 min of stirring at 0 °C, *i*-PrOH was added to destroy the excess reagent. The mixture was filtered through a pad of Celite with EtOAc. The filtrate was washed with H_2O three times, dried ($MgSO_4$), and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to give **4** (27 mg, 68%): $[\alpha]_D^{23}$ +43 (*c* 0.274, $CHCl_3$); IR (neat) 3080, 1738,

1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.5 Hz, 3H), 1.18–1.48 (m, 8H), 1.56–1.72 (m, 2H), 1.76–2.42 (m, 10H), 5.27–5.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.7, 22.6, 24.7, 24.8, 27.4, 28.0, 29.3, 33.9, 35.4, 38.7, 53.7, 126.2, 133.1, 179.2, 220.3.

4.4.2. 11-Epimer 28. To an ice-cold solution of OPC-6:0 (**4**) (27 mg, 0.10 mmol) in THF (0.6 mL), MeOH (0.2 mL), and H_2O (0.2 mL) was added $LiOH\cdot H_2O$ (21 mg, 0.50 mmol). The mixture was stirred at room temperature for 2.5 h and diluted with saturated NH_4Cl and EtOAc with stirring. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to give 11-epimer **28** (22 mg, 81%): ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.7, 24.8, 25.6, 26.9, 27.2, 29.4, 34.1, 34.6, 38.2, 41.2, 55.1, 125.4, 133.5, 179.6, 220.7. The ^1H NMR (300 MHz, $CDCl_3$) and the above ^{13}C NMR spectra of 11-epimer **28** were identical with the racemic 11-epimer reported in the literature.[9c]

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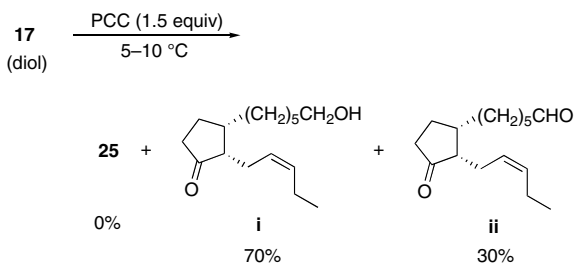
15. (a) Wakatsuka, H.; Kori, S.; Hayashi, M. *Prostaglandins* **1974**, *8*, 341–344; (b) Hirata, K.; Horie, T. *Cancer Chemother. Pharmacol.* **2003**, *51*, 216–220; (c) Gao, F.; Tomitori, H.; Igarashi, K.; Horie, T. *Life Sci.* **2002**, *72*, 669–676.
16. Synthesis of 3-oxa analogue of 13-*epi*-OPC-8:0 methyl ester (trans isomer) in racemic form was reported: see Ref. 4a.
17. Sugai, T.; Mori, K. *Synthesis* **1988**, 19–22.
18. The filtration was inevitably necessary step to remove the moisture involved in crude **13** in order to achieve the successful silylation.
19. Hydroxyl acid obtained by hydrolysis of lactone **12** and the hydroxyl ester **13** are highly prone to revert to **12**. The isolation and handling should be executed as fast as possible at low temperatures (preferably 0 °C or below) (see Section 4).
20. Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Organomet. Chem.* **1996**, *61*, 7452–7454.
21. PCC oxidation of **17** at 5–10 °C afforded the mixture of **i** and **ii**, while little **25** was obtained.



22. The conditions used here for the selective desilylation are also successful in other cases.
23. Blanchette, A. M.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sasaki, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
24. Although being thermodynamically less stable than the trans isomer, no epimerization took place during the Jones oxidation at the last stage and chromatography on silica gel. See Ref. 10 for stability of OPC-8:0.
25. We also accomplished synthesis of OPC-4:0.