Synthesis of Δ^2-OPC-8:0 and OPC-6:0

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Received 12 July 2004

Abstract: Δ^2-OPC-8:0 (**6**), designed as a β-oxidation-insensitive analogue, was synthesized starting with 4-cyclopentene-1,3-diol monoacetate (**5**) in a stereocontrolled manner. The C(3)–C(8) moiety was first attached to the cyclopentene ring by using the Cu-catalyzed S_N2-type reaction with TBDPSO$(CH_2)_6$MgCl and was later converted into the full side chain by Wittig reaction. In addition, OPC-6:0 (**3**) was synthesized.

Key words: allylations, asymmetric synthesis, copper, cuprates, stereoselective synthesis

The linolenic acid cascade in plants leading to *epi*-jasmonic acid produces 12-oxophytodienoic acid (12-oxo-PDA) as the first metabolite possessing a five-membered ring, which is further transformed into 3-oxo-2-*cis*-(pent-2*Z*-enyl)cyclopentyloctanoic acid (OPC-8:0) by the reductase (Figure 1).[1,2] Subsequently, β-oxidation follows three times to produce sequentially OPC-6:0, OPC-4:0, and finally *epi*-jasmonic acid. It has become clear that *epi*-jasmonic acid is the key compound in the development, physiology, and defense of plants. These findings have suggested a biological function of the upper metabolites in the cascade. Indeed, tendril coiling response,[3] induction of secondary metabolites,[4] up-regulation of several genes,[5] and expression of the specific genes[6] have been reported for 12-oxo-PDA. However, a biological profile of OPC-n:0 (n = 8, 6, 4) has not been studied, probably because of unavailability of these compounds in chemically pure form and in sufficient quantity.[7,8] A biological approach to these metabolites seems to suffer from low product selectivity and efficiency, because of the fairly fast β-oxidation of OPC-n:0 to its daughter OPC.[9]

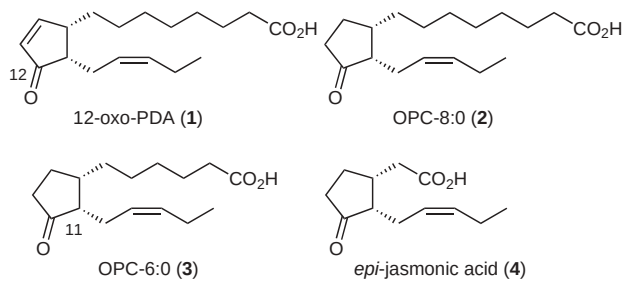


Figure 1 Some metabolites of linolenic acid.

SYNLETT 2004, No. 14, pp 2582–2584
Advanced online publication: 20.10.2004
DOI: 10.1055/s-2004-834794; Art ID: U20004ST

The two side chains on the five-membered ring of these metabolites are oriented *cis* fashion, which restricts compatibility of reactions to be used for synthesis due to thermodynamic instability. Consequently, the synthetic methodologies developed for the prostaglandins which are based on the enolate chemistry would be inadequately applicable to synthesis of these metabolites.[10] Recently, our group developed copper-catalyzed installation of an alkyl chain onto 4-cyclopentene-1,3-diol monoacetate (**5**)[11] and the reaction was successfully applied to synthesis of 12-oxo-PDA and OPC-8:0 in an enolate-free manner.[12] Herein, we report synthesis of Δ^2-OPC-8:0 (**6**) as a β-oxidation-insensitive analogue by analogy of the Δ^2-prostaglandins[13] (Figure 2). The analogue would be useful for evaluation of OPC-8:0 (**2**).[14] In addition, we describe the first synthesis and characterization of OPC-6:0 (**3**).

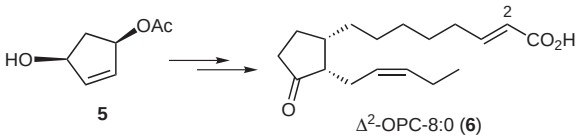
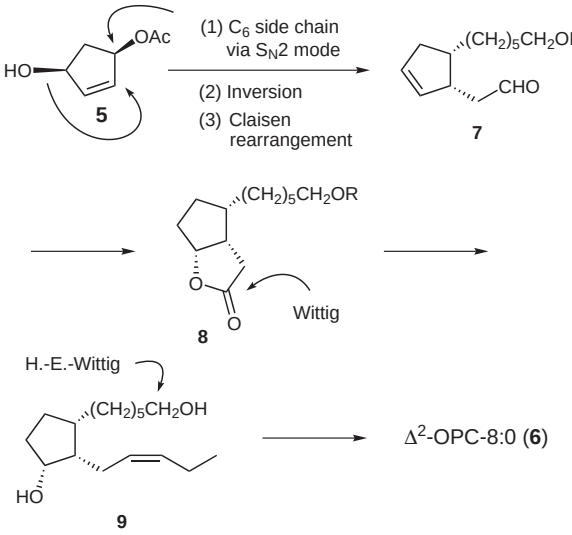


Figure 2 Target and starting compounds of the present study.

Our approach to Δ^2-OPC-8:0 (**6**) is summarized in Scheme 1. The key intermediate, diol **9**, possessing the two carbon shorter side chain [C(3)–C(8)] was prepared from **5** through aldehyde **7** and lactone **8**, and the full side chain was constructed by Horner–Emmons–Wittig reaction. The results of this investigation are delineated in Scheme 2.

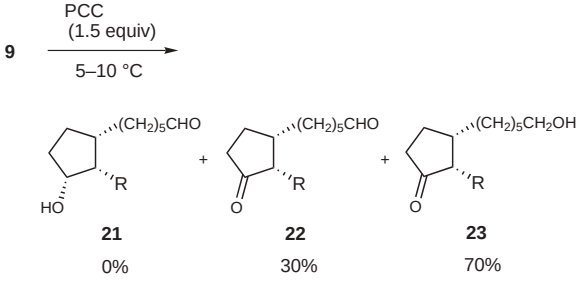
According to our protocol to execute the S_N2-type reaction, 3 equivalents of RMgCl was required with CuCN catalyst to complete the reaction with monoacetate **5**. To reduce the quantity (3 equivalents) of TBDPSO$(CH_2)_6$MgCl, the hydroxyl group of **5** (>99% ee), prepared by the literature method,[15] was initially quenched with 1 equivalent of *t*-BuMgCl at 0 °C. Subsequently, 2 equivalents of TBDPSO$(CH_2)_6$MgCl was added at –18 °C to produce **10** in 81% yield with 92% regioselectivity after 4 hours. Mitsunobu inversion with HOAc, DIAD, and PPh_3 in toluene at –78 °C followed by hydrolysis afforded the alcohol (structure not shown) in 83% yield (2 steps). Claisen rearrangement of the alcohol with CH_2=CHOEt at 180–190 °C for 3 days furnished aldehyde **11**, which was converted into acid **12** in 86% yield. Lactonization with KI_3 followed by reaction with Bu_3SnH under the radical conditions afforded lactone **13**, which is equal to the key intermediate **8** proposed in Scheme 1.



Scheme 1 Summary of Δ^2-OPC-8:0 synthesis.

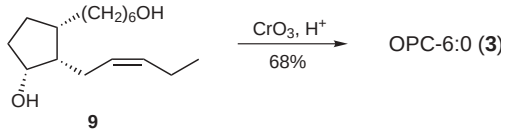
To complete the *cis*-pentenyl side chain, lactone **13** was hydrolyzed into hydroxyl acid, which upon esterification and silylation of the OH group afforded **14** in 80% yield. Reduction of ester **14** to aldehyde was followed by Wittig reaction with Ph_3P=CHEt to furnish *cis*-olefin **15**, which upon deprotection afforded the key diol **9** in quantitative yield.

In order to obtain aldehyde **21** for synthesis of Δ^2-OPC-8:0 (**6**), direct oxidation of diol **9** with PCC was attempted (Scheme 3). However, the oxidation produced a mixture of **22** and **23**. To avoid this result, we then studied a transformation shown in Scheme 2. Silylation of diol **9** with TBSCl afforded **16**, which upon exposure to PPTS in EtOH and CH_2Cl_2 (1:1) at 5–10 °C for 24 hours successfully afforded primary alcohol **17** in 89% yield.[16] PCC

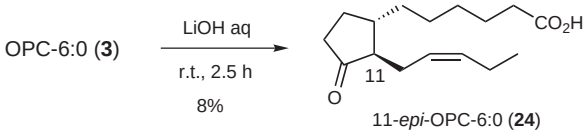


Scheme 3 Attempted oxidation of diol **9**, R = (*Z*)-CH_2CH=CHEt.

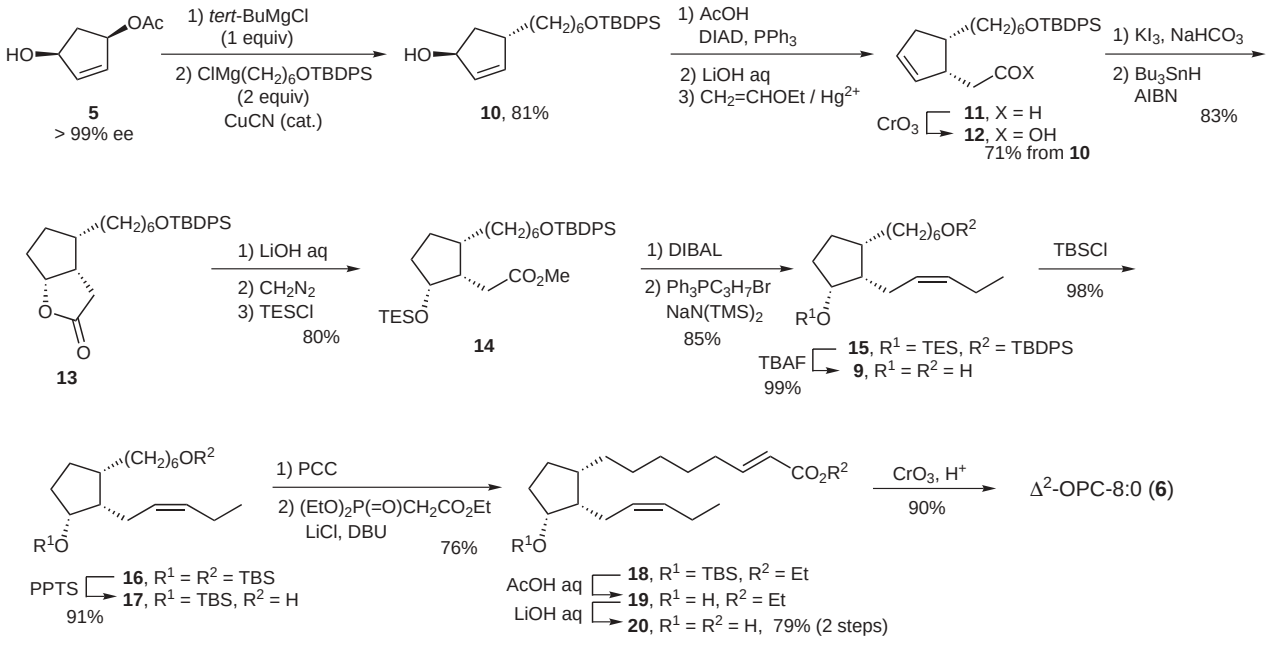
oxidation of **17** followed by Horner–Emmons–Wittig reaction under the Masamune conditions afforded the α,β-unsaturated ester **18**. Desilylation of **18** followed by hydrolysis of the resulting alcohol **19** gave hydroxyl acid **20** in 79% yield from **18**. Finally, Jones oxidation furnished Δ^2-OPC-8:0 (**6**) in 90% yield. Analytical data: IR (neat): 3196, 1738, 1699 cm^{-1}. ^1H NMR: δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.1–2.4 (m, 20 H), 5.36–5.46 (m, 2 H), 5.83 (d, *J* = 16 Hz, 1 H), 6.98–7.13 (dt, *J* = 16, 7 Hz, 1 H).[17]



Equation 1



Equation 2



Scheme 2 Synthesis of Δ^2-OPC-8:0.

Next, the key diol **9** used above was subjected to Jones oxidation to afford OPC-6:0 (**3**) in 68% yield (Equation 1): $[\alpha]_D^{23}$ +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, 3 H), 1.18–1.48 (m, 8 H), 1.56–1.72 (m, 2 H), 1.76–2.42 (m, 10 H), 5.27–5.49 (m, 2 H). ^{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. In addition, **3** was exposed to aqueous LiOH for epimerization at C(11) (Equation 2). The 11-epimer of **3** (i.e., **24**) thus synthesized in 81% yield was identical with the racemic 11-epimer reported in the literature[8c] by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Purity of OPC-6:0 (**3**) was >95% by calculation of the peak heights at δ = 38.7 and 53.7 ppm for **3** and δ = 41.2 and 55.1 ppm for **24**, respectively, in the ^{13}C NMR spectrum of **3**.[18]

Acknowledgment

We thank Professor Hiroyuki Ohta of Tokyo Institute of Technology, Department of Biological Sciences for helpful information to start this project. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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(14) Synthesis of 3-oxa analogue of 13-*epi*-OPC-8:0 methyl ester (*trans* isomer) in racemic form was reported: see ref. 4a.

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(16) The conditions used here for the selective desilylation are also successful in other cases.

(17) Spectral data (^1H NMR at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$) and specific rotations of the intermediates. Lactone **13**: $[\alpha]_D^{24}$ –5.7 (*c* 0.53, $CHCl_3$). IR (neat): 1771, 1111 cm^{-1}. ^1H NMR: δ = 0.97 (s, 9 H), 1.10–1.36 (m, 10 H), 1.42–2.20 (m, 5 H), 2.35 (dd, *J* = 19, 6 Hz, 1 H), 2.42 (dd, *J* = 19, 10 Hz, 1 H), 2.78–2.92 (m, 1 H), 3.58 (t, *J* = 6 Hz, 2 H), 4.95 (t, *J* = 6 Hz, 1 H), 7.33– 7.43 (m, 6 H), 7.63–7.69 (m, 4 H). ^{13}C NMR: 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. Ester **14**: $[\alpha]_D^{23}$ +0.10 (*c* 1.98, $CHCl_3$). IR (neat): 1741, 1112 cm^{-1}. ^1H NMR: δ = 0.55 (q, *J* = 8 Hz, 6 H), 0.93 (t, *J* = 8 Hz, 9 H), 1.04 (s, 9 H), 1.08–1.93 (m, 15 H), 2.20 (dd, *J* = 15, 5.5 Hz, 1 H), 2.32–2.44 (m, 1 H), 2.46 (dd, *J* = 15, 7.5 Hz, 1 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 3.65 (s, 3 H), 4.17–4.24 (m, 1 H), 7.33–7.43 (m, 6 H), 7.64–7.70 (m, 4 H). ^{13}C NMR: 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. Olefin **15**: $[\alpha]_D^{25}$ +2.2 (*c* 0.368, $CHCl_3$). IR (neat): 1428, 1112, 701 cm^{-1}. ^1H NMR: δ = 0.56 (q, *J* = 8 Hz, 6 H), 0.95 (t, *J* = 8 Hz, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 1.04 (s, 9 H), 1.15–1.88 (m, 16 H), 1.98–2.24 (m, 4 H), 3.65 (t, *J* = 6.5 Hz, 2 H), 4.06–4.19 (m, 1 H), 5.24–5.48 (m, 2 H), 7.34–7.43 (m, 6 H), 7.64–7.70 (m, 4 H). ^{13}C NMR: 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. Diol **9**: $[\alpha]_D^{24}$ +12 (*c* 0.388, $CHCl_3$). IR (neat): 3350, 1056 cm^{-1}. ^1H NMR: δ = 0.98 (t, *J* = 7.5 Hz, 3 H), 1.19–1.95 (m, 17 H), 2.20–2.50 (m, 5 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 4.14–4.26 (m, 1 H), 5.34–5.49 (m, 2 H). ^{13}C NMR: 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. Hydroxyl acid **20**: IR (neat): 3410, 1699, 1652 cm^{-1}. ^1H NMR: δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.13–2.44 (m, 21 H), 4.15–4.25 (m, 1 H), 5.22–5.51 (m, 2 H), 5.82 (d, *J* = 16 Hz, 1 H), 6.98–7.13 (dt, *J* = 16, 7 Hz, 1 H). ^{13}C NMR: 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.

(18) Both **3** and **24** appeared on TLC with the same R_f value.