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Efficient Total Synthesis of 12-oxo-PDA and OPC-8:0

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Although the supply of 12-oxo-PDA (**1**) and OPC-8:0 (**2**), the metabolites in the linolenic acid cascade leading to *epi*-jasmonic acid, is in demand for biological investigations, the previous syntheses of these metabolites suffer from low efficiency. Recently, we established a reaction to install an alkyl group onto the ring of cyclopentene monoacetate **4** by using a reagent system consisting of RMgCl (3 equiv) and CuCN (cat). The reaction was applied to $ClMg(CH_2)_8OTBDPS$ (**11**) with modification by which the quantity of **11** could be reduced to 2 equiv without decreasing efficiency. The product **12** obtained in 88% yield with 92% regioselectivity was successfully transformed into the key iodolactone **17** in good yield, from which 12-oxo-PDA (**1**) and OPC-8:0 (**2**) were synthesized as described in Schemes 3 and 5 through construction of the cis side chain by Wittig reaction. Note that the Wittig reaction proceeded with high cis selectivity of >95%, which is higher than in similar cases reported previously. Synthesis of the 13-isomers of **1** and **2** was also accomplished. With these compounds in hand, the epimerization speed of **1** and **2** was investigated to rule out overestimation of the finding in the literature that **1** and **2** change to the 13-epimers easily. Instead, we observed that the compounds are quite stable at room temperature for an extended period of days under slightly acidic and neutral conditions.

Introduction

Linolenic acid in plants is transformed into *epi*-jasmonic acid through 12-oxo-*cis*-10,15-phytodienoic acid (12-oxo-PDA). As illustrated in Figure 1, 12-oxo-PDA, the first product possessing the five-membered ring, is converted into 8-[3-oxo-2-cis-{(*Z*)-2-pentenyl}cyclopentyl]-octanoic acid (OPC-8:0), which upon β-oxidation produces *epi*-jasmonic acid.[1,2] According to recent study,[3] *epi*-jasmonic acid is a powerful signal transducer in plants and is involved in triggering senescence and defense reactions. These findings have prompted investigation into the metabolites in the upper side of the cascade. Biological study of the metabolites is, however, still rudimentary, probably due to the difficulty in obtaining a sufficient quantity of the metabolites in chemically pure and enantiomerically enriched forms. In contrast to the syntheses of the methyl esters and their stereoisomers (epimers) in racemic forms,[4] only one asymmetric synthesis of 12-oxo-PDA had been reported[5a] before we started a project to develop the synthesis of these compounds. Recently, asymmetric synthesis of 12-oxo-PDA and OPC-8:0 has appeared.[5b] These syntheses involve steps with low product selectivity or a step for

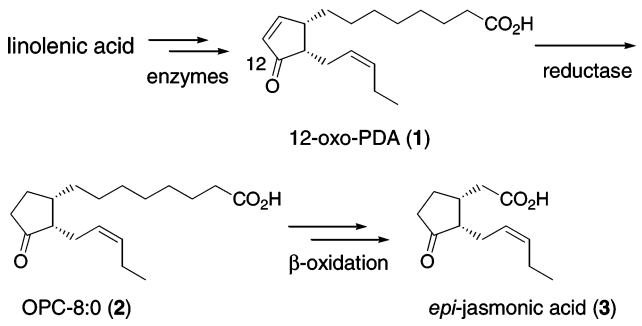

FIGURE 1. Metabolic pathway leading to *epi*-jasmonic acid.

* Corresponding author.

(1) (a) Zimmerman, D. C.; Feng, P. *Lipids* **1978**, *13*, 313−316. (b) Vick, B. A.; Zimmerman, D. C.; Weisleder, D. *Lipids* **1979**, *14*, 734−740. (c) Vick, B. A.; Zimmerman, D. C. *Plant Physiol.* **1979**, *63*, 490−494. (d) Baertschi, S. W.; Ingram, C. D.; Harris, T. M.; Brash, A. R. *Biochemistry* **1988**, *27*, 18−24. (e) Crombie, L.; Morgan, D. O. *J. Chem. Soc., Perkin Trans. 1* **1991**, 581−587. (f) Crombie, L.; Morgan, D. O. *J. Chem. Soc., Chem. Commun.* **1988**, 558−560. (g) Laudert, D.; Hennig, P.; Stelmach, B. A.; Müller, A.; Andert, L.; Weiler, E. W. *Anal. Biochem.* **1997**, *246*, 211−217. (h) Hamberg, M., Hughes, M. A. *Lipids* **1988**, *23*, 469−475. (i) Hamberg, M.; Miersch, O.; Sembdner, G. *Lipids* **1988**, *23*, 521−524.

(2) Vick, B. A.; Zimmerman, D. C. *Biochem. Biophys. Res. Commun.* **1983**, *111*, 470−477.

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(4) (a) Sakai, K.; Fujimoto, T.; Yamashita, M.; Kondo, K. *Tetrahedron Lett.* **1985**, *26*, 2089−2092. (b) Krüger, G.; Harde, C.; Bohlmann, F. *Tetrahedron Lett.* **1985**, *26*, 6027−6030. (c) Crombie, L.; Mistry, K. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1981−1991. (d) Schierle, K.; Hopke, J.; Niedt, M.-L.; Boland, W.; Steckhan, E. *Tetrahedron Lett.* **1996**, *48*, 8715−8718. (e) Toshima, H.; Nara, S.; Aramaki, H.; Ichihara, A.; Koda, Y.; Kikuta, Y. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1724−1728.

(5) (a) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008−6010. (b) Ernst, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4054−4056. (c) Overall yields and steps involved in the syntheses follow: 12-oxo-PDA (ref 5a), 4.9% and 8 steps from benzoquinone−cyclopentadiene adduct; 12-oxo-PDA (ref 5b), 6.5% and 11 steps from cyclopentenyl chloride; OPC-8:0 (ref 5b), synthesis of the methyl ester has just been announced.

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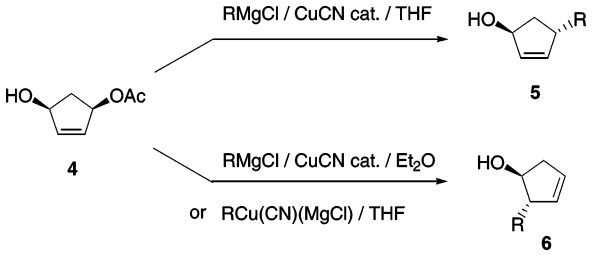
SCHEME 1. Examples of the Reagents for Selective Alkylation[a]



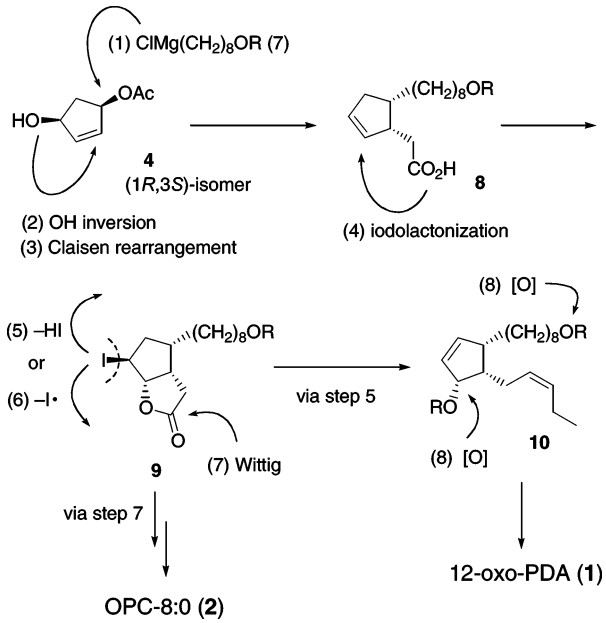
[a] Other reagents based on RMgX and CuCN also produce **5** or **6** selectively: see ref 8.

kinetic resolution, and purity of the final products is not described,[5c] thus demanding another synthetic method that provides these products more efficiently in a secure way.

The syntheses published for *epi*-jasmonic acid[6] and prostaglandins (PGs)[7] might be applicable to the synthesis of **1** and **2** due to the structural similarity. However, the synthesis reported by Crombie[4c] implies difficulty of this approach with respect to efficiency because some of the reactions in the syntheses of *epi*-jasmonic acid are specific for the acetic acid side chain (CH_2CO_2H). On the other hand, the two side chains in the linolenic acid metabolites and PGs are in cis and trans orientation, respectively. Moreover, the cis orientation is prone to cause epimerization at the carbon next to the carbonyl function, thus limiting methods which are compatible with the synthesis of the compounds in question.

Recently, we developed[8] a reagent based on RMgCl and CuCN for installation of an alkyl group on the cyclopentane ring of 2-cyclopentene-1,4-diol monoacetate (**4**) that is available easily by the established method[9] (Scheme 1). This reaction was applied to the synthesis of 12-oxo-PDA (**1**), which was published as a communication.[10] Later, the steps involved in the synthesis were modified to increase efficiency, and the intermediate was utilized for the synthesis of OPC-8:0 (**2**). The 13-epimers of **1** and **2** were also synthesized. Furthermore, with the compounds in hand, the stability of **1** and **2** toward epimerization was studied. Herein, we report results of these studies in detail.

SCHEME 2. Synthetic Plan for 12-oxo-PDA and OPC-8:0



Results and Discussion

Synthetic Plan. Our synthetic plan for 12-oxo-PDA (**1**) and OPC-8:0 (**2**) is illustrated in Scheme 2 featuring major transformations (steps 1−8). Alkylation of monoacetate **4** with a Grignard reagent **7** corresponding to the C(1)−C(8) chain is followed by [3,3]-sigmatropic rearrangement after inversion of the hydroxyl group to furnish acid **8**, which upon lactonization should produce the key iodo-lactone **9** (steps 1−4). Elimination of HI (step 5) and subsequent Wittig reaction (step 7) through lactol would afford cyclopentene **10**, which possesses the full structure of 12-oxo-PDA (**1**). On the other hand, reduction of the iodo-lactone **9** with Bu_3SnH (step 6) to afford the cyclopentane (structure not shown) followed by the same transformation as above would afford OPC-8:0 (**2**). Since this approach is designed to provide the C(12)-carbonyl function at the last stage, epimerization at the α carbon, if any, would be suppressed.

Synthesis of 12-oxo-PDA (Scheme 3). According to the procedure reported,[8] alkylation of monoacetate **4**[9a] (>99% ee) was conducted with 3 equiv of $ClMg(CH_2)_8$-OTBDPS (**11**)[11] in the presence of CuCN as a catalyst at −18 °C to afford the desired product **12** (1,4-isomer) with high regioselectivity over 1,2-isomer **25** (97:3)[12] in 84% isolated yield after chromatography on silica gel. Although the result with respect to the regio- and stereoselectivities and yield was excellent, use of 3 equiv of the reagent **11** might be a drawback of the synthesis.

(6) Recent syntheses: (a) Roth, G. J.; Kirschbaum, S.; Bestmann, H. J. *Synlett* **1997**, 618−620. (b) Stadtmüller, H.; Knochel, P. *Synlett* **1995**, 463−464. (c) Kitahara, T.; Nishi, T.; Mori, K. *Tetrahedron* **1991**, *47*, 6999−7006. (d) Helmchen, G.; Goeke, A.; Lauer, G.; Urmann, M.; Fries, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1024−1025. (e) Montforts, F.-P.; Gesing-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, *72*, 1852−1859.

(7) Reviews: (a) Kobayashi, Y. *Current Org. Chem.* **2003**, *7*, 133−147. (b) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533−1564. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229−9272. (d) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847−876. (e) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44−45. (f) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480−492.

(8) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881−5889.

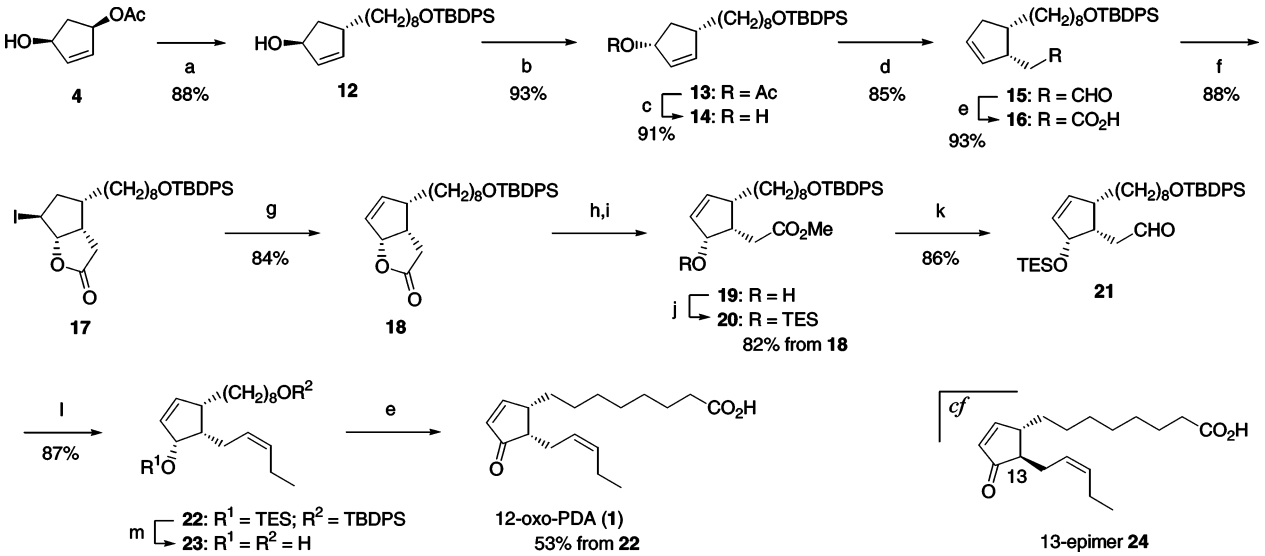
(9) (1*R*,3*S*)-**1**: (a) Sugai, T.; Mori, K. *Synthesis* **1988**, 19−22. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298−1299. (1*S*,3*R*)-**1**: (c) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875−5878. (d) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695−3696.

(10) Kobayashi, Y.; Matsuumi, M. *Tetrahedron Lett.* **2002**, *43*, 4361−4364.

(11) The THP protection was somewhat unstable during the preparation of the corresponding Grignard reagent in THF, while the *t*-$BuMe_2Si$ group was partially deprotected by Jones reagent.

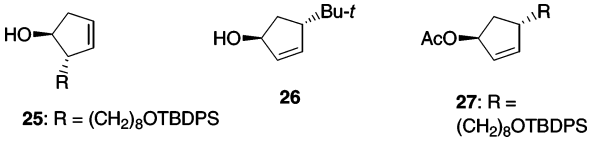
(12) The authentic 1,2-isomer **25** was prepared selectively by using the reagent derived from **11** (3 equiv) and CuCN (3.5 equiv) in THF at 0 °C for 5 h: IR (neat) 3349, 1112, 701 cm^{-1}; ^1H NMR δ 1.07 (s, 9 H), 1.2−1.5 (m, 12 H), 1.52−1.74 (m, 3 H), 2.26 (dm, *J* = 15 Hz, 1 H), 2.46−2.57 (br peak, 1 H), 2.71 (ddq, *J* = 15, 6.5, 2 Hz, 1 H), 3.67 (t, *J* = 6.5 Hz, 2 H), 4.05−4.16 (br peak, 1 H), 5.64−5.77 (m, 2 H), 7.35−7.50 (m, 6 H), 7.66−7.74 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.0, 27.9, 29.5, 29.7, 29.9, 32.7, 33.4, 41.8, 55.3, 64.1, 77.6, 127.49, 127.53, 129.4, 133.3, 134.1, 135.5.

SCHEME 3. Synthesis of 12-oxo-PDA (1)[a]



[a] Reagents and conditions: (a) $ClMg(CH_2)_8OTBDPS$ (**11**) (2 equiv), *t*-BuMgCl (1 equiv), CuCN (30 mol %), THF, −18 °C; (b) AcOH, DEAD, PPh_3, toluene, −78 to −60 °C; (c) MeLi (3 equiv), Et_2O, 0 °C; (d) CH_2=CHOEt, $Hg(OAc)_2$ (0.5 equiv), benzene, 170 °C, 61 h; (e) CrO_3, H_2SO_4, acetone; (f) I_2 (2 equiv), KI (6 equiv), $NaHCO_3$ (3 equiv), THF/H_2O; (g) DBU (2.6 equiv), THF; (h) LiOH, MeOH/H_2O/THF (1:1:3); (i) CH_2N_2; (j) TESCl, imidazole; (k) DIBAL (1.3 equiv), CH_2Cl_2, −78 °C; (l) $[Ph_3PPr]^+Br^-$, $NaN(TMS)_2$, THF/DMF (12:1), 0 °C to room temperature; (m) TBAF, 4A MS, 55 °C.

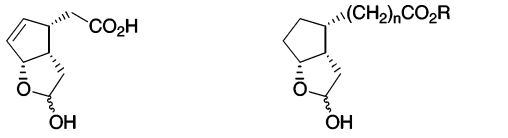
Attempted reactions with a reduced quantity of **11** (2.1−2.5 equiv) at −18 °C and 0 °C to room temperature were incomplete in all cases, thus recovering monoacetate **4** in ca. 20−40% yields. Since 1 equiv of the reagent is apparently consumed by the OH group of **4** to generate the alkoxide, the reagent for the alkoxide formation was replaced by *t*-BuMgCl (1 equiv, room temperature, 30 min). Subsequently, 2 equiv of **11** was submitted to the reaction under otherwise the same reaction conditions to provide **12** in 88% isolated yield with 92% regioselectivity and the perfect stereoselectivity. Thus, isolated yield was increased with the decreased use of the reagent. No compound derived from *t*-BuMgCl (i.e., **26**) was



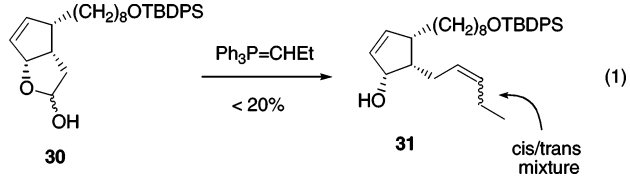
produced.[13]

Mitsunobu inversion[14] of **12** gave cis acetate **13** in 93% yield with high stereoselectivity (**13**: **27**[15] = 98:2). Toluene at < −60 °C was the indispensable solvent for attaining the high stereoselectivity, since THF, the standard solvent, afforded a few % lower selectivity, and higher temperatures resulted in contamination of the SN2′ product (structure not shown).[16] A mixture of acetate **13** and the isomer **27** (2%) was hydrolyzed and the resulting alcohols were separated by chromatography to afford alcohol **14** in 91% yield. Claisen rearrangement of **14** at 170 °C[17] was followed by Jones oxidation to furnish acid **16**, which upon iodo-lactonization produced iodo-lactone **17** in 70% yield from **14**. The lactone **17** thus synthesized is the key intermediate **9** proposed in Scheme 2. The next step with DBU in THF furnished lactone **18** in 84% yield.

Since the purity of the final product is important for biological study, literature regarding the Wittig reaction of lactols possessing similar structures was investigated to obtain the following information that lactol **28** affords



the corresponding cis olefin with 80:20 selectivity,[4c,18] and that the selectivity for the saturated lactoles **29** ranges from ca. 80% to >95% according to the reaction conditions. To apply the selective protocol for **29**,[6e] lactone **18** was first reduced to lactol **30** with DIBAL, and Wittig reaction of **30** was carried out under the conditions reported for the >95% selectivity ($[Ph_3PCH_2Et]^+Br^-$, $NaN(TMS)_2$, THF). However, the reaction, in our hand, was slow and the product was a mixture of cis and trans olefins **31** in <20% yield (eq 1).



We then investigated a route through a free aldehyde. To gain preliminary information for high cis selectivity,

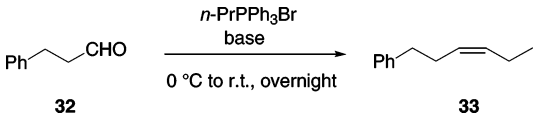
(13) However, use of *t*-BuMgCl (2 equiv) and the reagent **11** (1 equiv) produced a mixture of **12**, 1,2-isomer **25**, and *t*-Bu-products (i.e., **26** and its 1,2-isomer).

(14) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(15) The authentic stereoisomer **27** was prepared from **12** by the standard method (Ac_2O, pyridine, rt): IR (neat) 1734, 1241, 1112 cm^{-1}; ^1H NMR δ 1.05 (s, 9 H), 1.16−1.68 (m, 14 H), 1.80 (ddd, J = 14, 7, 5 Hz, 1 H), 1.94−2.05 (m, 1 H), 2.02 (s, 3 H), 2.78−2.92 (br s, 1 H), 3.65 (t, J = 7 Hz, 2 H), 5.64−5.72 (m, 1 H), 5.79 (dt, J = 6, 2 Hz, 1 H), 6.06 (dd, J = 6, 2 Hz, 1 H), 7.29−7.49 (m, 6 H), 7.67 (dd, J = 8, 2 Hz, 4 H).

(16) Hodgson, D. M.; Gibbs, A. R. *Synlett* **1997**, 657−658.

TABLE 1. A Model of the Wittig Reaction



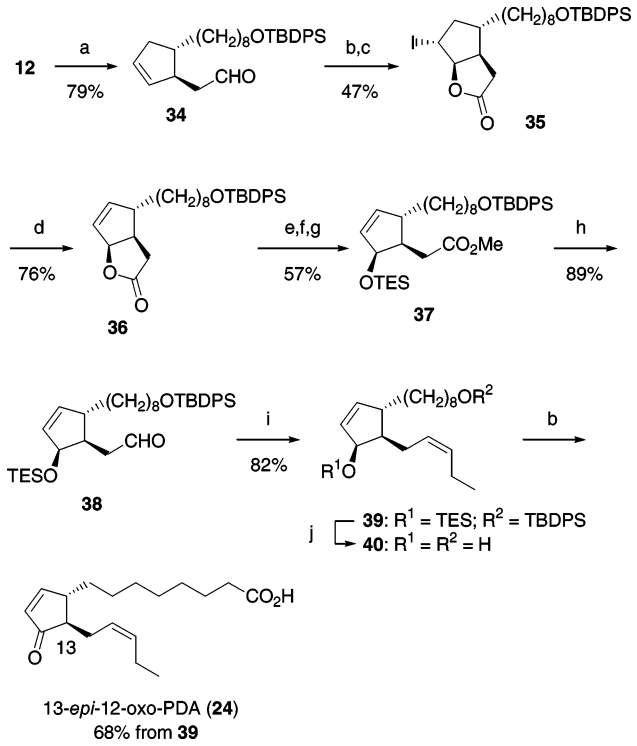
entry	base	solvent	yield, %[a]
1	*n*-BuLi	THF	57[b]
2	$NaN(TMS)_2$	THF	41
3	$NaN(TMS)_2$	THF + HMPA (12:1)	60
4	$NaN(TMS)_2$	THF + DMF (12:1)	74
5	$KN(TMS)_2$	THF + HMPA (12:1)	69
6	$KN(TMS)_2$	THF + DMF (12:1)	70

[a] Isolated yields. [b] A mixture of cis/trans olefins.

the Wittig reaction of a model aldehyde **32** and $[Ph_3PCH_2Et]^+Br^-$ was studied briefly with convenient bases. As summarized in Table 1, amides such as $NaN(TMS)_2$ and $KN(TMS)_2$ according to Bestmann[19] produced cis olefin **33** exclusively in varying yields (entries 2−6), and the highest yield was recorded in a THF/DMF mixture (entry 4). With this result in mind, lactone **18** was converted into aldehyde **21** in 71% yield from **18** by a sequence of conventional reactions through **20**.[20] Wittig reaction under the conditions of entry 4 was successful to afford cis olefin **22** in 87% yield with 99% cis selectivity by ^{1}H NMR spectroscopy.[21] As expected from the model study (Table 1, entry 1), *n*-BuLi as a base resulted in a lower selectivity of 89%.

Deprotection of TBDPS and TES groups of **22** with Bu_4NF was followed by Jones oxidation to furnish 12-oxo-PDA (**1**) in 53% yield.[22] The ^{1}H NMR spectrum of synthetic **1** agreed with data reported for **1**[1d] and showed <5% contamination of the epimer at C(13) with respect to the side chains (i.e., **24**).[23−25] The ^{13}C NMR spectrum also supported the structure and purity. In the following paragraphs, the synthesis of trans isomer **24** and the stability of **1** are presented.

SCHEME 4. Synthesis of 13-*epi*-12-oxo-PDA (24)[a]



[a] Reagents and conditions: (a) CH_2=CHOEt, $Hg(OAc)_2$ (cat.), benzene, 170 °C, 64 h; (b) CrO_3, H_2SO_4, acetone; (c) I_2, KI, $NaHCO_3$, rt, 17 h; (d) DBU, THF; (e) LiOH, MeOH/H_2O/THF (1:1:3); (f) CH_2N_2; (g) TESCl, imidazole; (h) DIBAL, −78 °C; (i) $[Ph_3PPr]^+Br^-$, $NaN(TMS)_2$, THF/DMF (13:1), 0 °C to room temperature; (j) TBAF, 4A MS, 55 °C.

Synthesis of 13-*epi*-12-oxo-PDA. To study the structure and activity relation of 12-oxo-PDA (**1**), the 13-epimer **24** which is thermodynamically more stable than **1** is indispensable. As summarized in Scheme 4, the sequence of Scheme 3 was successfully repeated without the Mitsunobu inversion. Thus, Claisen rearrangement of **12** followed by further transformation afforded lactone **36**, which was converted to aldehyde **38** without any trouble. Wittig reaction provided cis olefin **39**, which upon deprotection and subsequent Jones oxidation furnished the 13-epimer **24** ($[\alpha]^{25}_D$ +93 (*c* 0.176, $CHCl_3$)). The ^{1}H NMR spectrum of **24** thus synthesized showed no contamination of **1**, and is consistent with the reported data.[1d] The ^{13}C NMR spectrum provided additional evidence for the structure.

Synthesis of OPC-8:0 and the 13-Epimer. As mentioned in the Introduction, reductive elimination of iodide **17** in Scheme 3 is the first step leading to OPC-8:0 (**2**), which was conducted by using Bu_3SnH and AIBN (Scheme 5). Lactone **41**, produced in 94% yield, was transformed to ester **42**, which upon reduction with DIBAL furnished aldehyde **43** in 58% yield from **41** (4 steps). Wittig reaction of **43** provided the cis olefin **44** exclusively, which upon deprotection and Jones oxidation afforded OPC-8:0 (**2**) in 71% yield from **43** (3 steps). The ^{1}H NMR and ^{13}C NMR spectra of **2** thus synthesized supported the structure.

The structure of OPC-8:0 (**2**) was also confirmed by transformation to the known methyl ester **46** in 67% yield from diol **45** (Scheme 6). The ^{1}H NMR and ^{13}C NMR

(17) (a) Nara, M.; Terashima, S.; Yamada, S. *Tetrahedron* **1980**, *36*, 3161−3170. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun*. **1986**, 1298−1299.

(18) A similar rather low stereoselectivity was reported: Takahashi, K.; Sato, H.; Mikami, K.; Nakai, T. *Chem. Lett*. **1989**, 247−250.

(19) (a) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber*. **1976**, *109*, 1694−1700. (b) Viala, J.; Santelli, M. *Synthesis* **1988**, 395−397.

(20) Although the steps to afford **20** were prone to produce back lactone **18**, esterification of the acid after extraction without concentration, use of a somewhat shorter column to isolate **19**, and TES protection immediately after the isolation are recommended to obtain reproducible results.

(21) Diagnostic signals in ^{1}H NMR (300 MHz, $CDCl_3$) for cis olefin **22**, δ 4.50 (dd, J = 5.7, 2.4 Hz, 1 H), and for the trans isomer, δ ca. 4.48 (probably dd, 1 H).

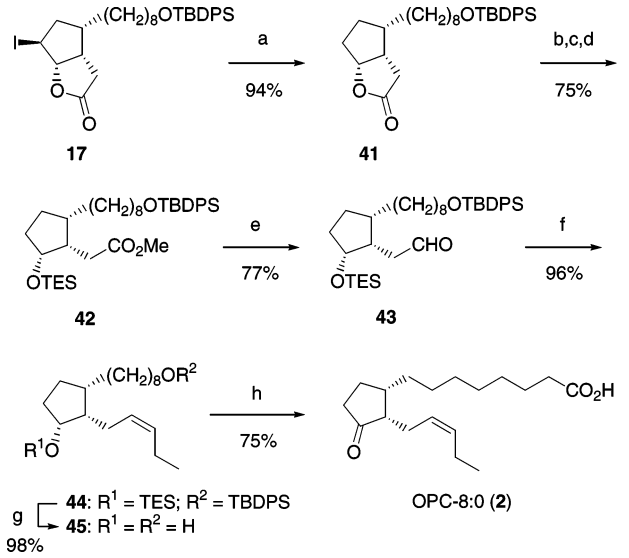
(22) Although the specific rotations of synthetic **1** measured twice ($[\alpha]^{28}_D$ +127 (*c* 0.496, $CHCl_3$) and $[\alpha]^{29}_D$ +127 (*c* 0.198, $CHCl_3$)) were different from the data reported ($[\alpha]^{25}_D$ +104.0 (*c* 9.5, $CHCl_3$)),[5a] we are confident that our value is definitely correct on the basis of the purity and the identity mentioned in the text.

(23) High cis stereochemistry of >95% in terms of the two side chains has been attained in the later syntheses of 12-oxo-PDA (**1**) repeated several times in our laboratory.

(24) Since the stability of **1** under the almost neutral conditions is established as described in the latter part of the text, it is likely that the strongly acidic conditions for Jones oxidation to produce **1** and subsequent purification by silica gel chromatography brought about epimerization of **1**, but to a small extent (<5%).

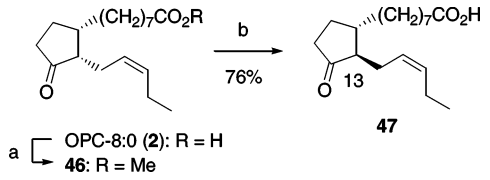
(25) The following signals in the ^{1}H NMR (300 MHz) spectra were used for the calculation: **1**, δ 6.19 (dd, J = 6, 1.5 Hz), 7.74 (dd, J = 6, 3 Hz, 1 H); **24**, δ 6.13 (dd, J = 6, 2 Hz, 1 H), 7.61 (dd, J = 6, 2.5 Hz, 1 H).

SCHEME 5. Synthesis of OPC-8:0 (2)[a]



[a] Reagents and conditions: (a) Bu_3SnH, AIBN; (b) LiOH, MeOH/H_2O/THF; (c) CH_2N_2; (d) TESCl, imidazole; (e) DIBAL, −78 °C; (f) $[Ph_3PPr]^+Br^-$, $NaN(TMS)_2$, THF/DMF (12:1), 0 °C to room temperature; (g) TBAF, 4A MS, 60−65 °C; (h) CrO_3, H_2SO_4, acetone.

SCHEME 6. Synthesis of 13-*epi*-OPC-8:0 (47)[a]



[a] Reagents and conditions: (a) CH_2N_2; (b) LiOH, MeOH/H_2O/THF.

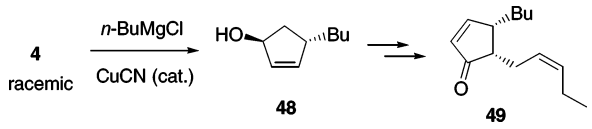
spectra of **46** were consistent with the data reported.[4c] The methyl ester **46** was then submitted to hydrolysis with LiOH, which, as expected, triggered epimerization at C(13) to furnish 13-*epi*-OPC-8:0 (**47**), which was found by NMR spectroscopy to be likewise identical with the data reported.[4e]

We then examined these spectra to find signals which are characteristic of **2** and its isomer **47** to determine the purity of **2**. Although the absence of **47** was apparent from the partially resolved ^1H NMR signals, calculation of the molar ratio from these signals was difficult, while the ^{13}C NMR spectra allowed estimation of ca. >97% purity for OPC-8:0 (**2**).

Chemical Stability of 12-oxo-PDA and OPC-8:0. Through the syntheses of **1** and **2** we were aware that these compounds are fairly stable. However, epimerization of 12-oxo-PDA (**1**) and OPC-8:0 (**2**) at C(13) has been reported to be an easy process under acidic and basic conditions.[1b,d,e,h,i] To avoid overestimation of the literature information, the epimerization rate of **1** and **2** was briefly studied by using NMR.

Preliminarily, a model compound **49** was synthesized in a similar way to 12-oxo-PDA (**1**) through **48** (Scheme 7). Commercial $CDCl_3$ with a trace of DCl[26] and $CDCl_3$ free of DCl[27] were used as solvents for ^1H NMR measurement at 300 MHz. Solutions of **49** in these solvents were left at room temperature with monitoring of the olefinic protons attached to the ring carbons (δ 6.17 (dd, J = 6, 1.5 Hz) and 7.75 (dd, J = 6, 3 Hz)). Even after 40 days, no epimerization was detected, thus establishing that **49** is quite stable under slightly acidic and neutral conditions. In a similar manner, the olefinic protons of 12-oxo-PDA (**1**) in commercial $CDCl_3$ were monitored for 26 days at room temperature to observe no epimerization of **1** to **24** under these conditions.

SCHEME 7. Synthesis of Model Compound for 12-oxo-PDA



Stability of OPC-8:0 (**2**) in commercial $CDCl_3$ at room temperature was also studied, in this case by monitoring the ^{13}C NMR signals of the C(15)−C(16) olefinic carbons at 75 MHz. No change after 39 days was confirmed. The sample was then exposed to K_2CO_3 in the NMR tube. Epimerization started at such a rate that the ratio of **2** and the 13-epimer **47** was 96:4 after 12 h, 87:13 after 3 days, and 53:47 after 16 days.

Conclusion

The synthesis of 12-oxo-PDA (**1**) and OPC-8:0 (**2**) was accomplished both in 14 steps and in 14% and 20% overall yields, respectively, from readily available monoacetate **4**. The key steps are regioselective installation of the C(1)−C(8) side chain on the five-membered ring of **4** and stereoselective Wittig reaction to furnish the C(15)−C(16) cis side chain, thus furnishing high overall efficiency. High purity of the final products are secured by the synthesis, for the first time. In addition, these compounds were found to be quite stable at room temperature. No epimerization at C(13) takes place. Careful handling of these compounds is no longer necessary.

Experimental Section[28]

(4*S*,1*S*)-4-[8-{(*tert*-Butyldiphenylsilyl)oxy}octyl]-2-cyclopenten-1-ol (12). Original procedure: To a slurry of CuCN (48 mg, 0.54 mmol) in THF (10 mL) was added $TBDPSO(CH_2)_8MgCl$ (20 mL, 0.53 M in THF, 10.6 mmol) slowly at −18 °C. After 20 min of stirring at −18 °C, acetate **4**[9a] (500 mg, 3.52 mmol, >99% ee by ^1H NMR spectroscopy of the MTPA ester) in THF (2 mL) was added dropwise. Reaction was carried out at the same temperature for 3 h and quenched by addition of saturated NH_4Cl and 28% NH_4OH with vigorous stirring. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried and concentrated to afford an oil, which was a 97:3 mixture of **12** and **25** by ^1H NMR spectroscopy. The mixture was purified by chromatography (hexane/EtOAc) to give 1,4-isomer **12** (1.33 g, 84%): $[\alpha]^{31}_D$ −62 (*c* 0.826, $CHCl_3$); IR (neat) 3337, 1112, 701 cm^{-1}; ^1H NMR δ 1.05 (s, 9 H), 1.14−1.47 (m, 13 H), 1.49−1.61

(26) DCl-catalyzed isomerization of the cis double bond in the conjugated triene of leukotriene B_4: Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem*. **1990**, *55*, 5324−5335.

(27) Conveniently prepared by passing commercial $CDCl_3$ through a pad of basic Al_2O_3 before use.

(28) The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$. Routinely, organic extracts were dried over $MgSO_4$ and concentrated by using a rotary evaporator to afford residues, which were purified by chromatography on silica gel. Synthesis of 13-*epi*-12-oxo-PDA (**24**) was presented in the Supporting Information.

(m, 2 H), 1.76 (ddd, J = 14, 7, 5 Hz, 1 H), 1.91 (ddd, J = 14, 7, 3 Hz, 1 H), 2.77−2.92 (m, 1 H), 3.65 (t, J = 6 Hz, 2 H), 4.81−4.91 (br peak, 1 H), 5.81 (dt, J = 6, 2 Hz, 1 H), 5.95 (ddd, J = 6, 2.5, 1 Hz, 1 H), 7.28−7.50 (m, 6 H), 7.58−7.76 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.1, 28.1, 29.5, 29.7, 29.9, 32.7, 36.1, 40.8, 44.2, 64.1, 77.3, 127.5, 129.5, 132.3, 134.2, 135.6, 140.4. Anal. Calcd for $C_{29}H_{42}O_2Si$: C, 77.28; H, 9.39. Found: C, 77.26; H, 9.79.

Modified procedure with *t*-BuMgCl: To an ice-cold solution of acetate **4** (809 mg, 5.69 mmol) in THF (8 mL) was added *t*-BuMgCl (7.10 mL, 0.80 M in THF, 5.68 mmol) and the solution was stirred at 0 °C for 30 min to prepare the alkoxide of **4**. In another flask were placed CuCN (153 mg, 1.71 mmol) and THF (20 mL). To this slurry was added a THF solution of $ClMg(CH_2)_8OTBDPS$ (15.9 mL, 0.72 M, 11.4 mmol) at −18 °C. The mixture was stirred for 20 min at −18 °C and then the above alkoxide was injected. Reaction was run at −18 °C for 2 h and quenched by addition of 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 and concentrated to afford an oil, which was a 92:8 mixture of **12** and **25**[12] by ^{1}H NMR spectroscopy. The oil was applied to chromatography to furnish **12** (2.26 g, 88%).

(4*S*,1*R*)-4-[8-{(*tert*-Butyldiphenylsilyl)oxy}octyl]-2-cyclopentenyl Acetate (13). To a solution of alcohol **12** (100 mg, 0.222 mmol), Ph_3P (110 mg, 0.421 mmol), and AcOH (0.025 mL, 0.44 mmol) in toluene (2.2 mL) was added DEAD (0.073 mL, 0.44 mmol) at −78 °C. The mixture was allowed to warm to −60 °C over 2 h and diluted with 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 and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to furnish a 98:2 mixture of cis acetate **13** and the trans isomer[15] (102 mg, 93%) by ^{1}H NMR spectroscopy: $[\alpha]_D$ +5.0 (c 0.894, $CHCl_3$); IR (neat) 1733, 1242, 1112 cm^{-1}; ^{1}H NMR δ 1.05 (s, 9 H), 1.19−1.62 (m, 15 H), 2.03 (s, 3 H), 2.44−2.67 (m, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 5.57−5.65 (m, 1 H), 5.76 (dt, J = 6, 2 Hz, 1 H), 5.96−6.05 (m, 1 H), 7.32−7.48 (m, 6 H), 7.62−7.76 (m, 4 H); ^{13}C NMR δ 19.4, 21.5, 25.9, 27.0, 28.0, 29.5, 29.7, 29.8, 32.7, 36.5, 36.8, 44.4, 64.1, 80.0, 127.5, 128.7, 129.5, 134.2, 135.5, 141.1, 170.9. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56; H, 9.00. Found: C, 75.34; H, 9.16.

(4*S*,1*R*)-4-[8-{(*tert*-Butyldiphenylsilyl)oxy}octyl]-2-cyclopenten-1-ol (14). To an ice-cold solution of acetate **13** (307 mg, 0.623 mmol, cis:trans = 98:2) in Et_2O (6.5 mL) was added MeLi (1.30 mL, 1.4 M in Et_2O, 1.82 mmol) slowly. The resulting solution was stirred at 0 °C for 40 min, and diluted with saturated NH_4Cl and EtOAc with stirring. The layers were separated, and the aqueous layer was extracted with EtOAc three times. The combined extracts were dried and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to give cis alcohol **14** (255 mg, 91%): $[\alpha]^{31}_D$ −12 (c 1.26, $CHCl_3$); IR (neat) 3361, 1113, 701 cm^{-1}; ^{1}H NMR δ 1.06 (s, 9 H), 1.15−1.66 (m, 16 H), 2.42−2.60 (m, 2 H), 3.66 (t, J = 6.5 Hz, 2 H), 4.72−4.90 (br peak, 1 H), 5.78 (dt, J = 6, 2 Hz, 1 H), 5.90 (dm, J = 6 Hz, 1 H), 7.30−7.50 (m, 6 H), 7.64−7.72 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.0, 28.0, 29.5, 29.7, 29.9, 32.7, 37.0, 40.7, 44.6, 64.1, 77.5, 127.5, 129.5, 132.8, 134.1, 135.5, 139.0.

(1*S*,2*S*)-2-([8-{(*tert*-Butyldiphenylsilyl)oxy}octyl]-4-cyclopentenyl)ethanal (15). A sealed glass tube containing cis alcohol **14** (174 mg, 0.386 mmol), $Hg(OAc)_2$ (62 mg, 0.19 mmol), ethyl vinyl ether (0.56 mL, 5.82 mmol), and benzene (2 mL) was immersed in an oil bath set at 170 °C for 61 h. The solution was cooled to room temperature and transferred to a flask containing K_2CO_3 (92 mg, 0.67 mmol) with benzene. After 30 min of stirring, the resulting mixture was filtered through a pad of Celite with EtOAc and the filtrate was concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to give aldehyde **15** (156 mg, 85%): $[\alpha]^{27}_D$ −44 (c 1.06, $CHCl_3$); IR (neat) 1726, 1111, 701 cm^{-1}; ^{1}H NMR δ 1.05 (s, 9 H), 1.17−1.64 (m, 14 H), 1.88−2.02 (m, 1 H), 2.16−2.59 (m, 4 H), 3.01−3.14 (m, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 5.77 (s, 2 H), 7.32−7.46 (m, 6 H), 7.62−7.73 (m, 4 H), 9.79 (t, J = 2 Hz, 1 H); ^{13}C NMR δ 19.4, 25.9, 27.0, 28.9, 29.5, 29.8, 30.0, 30.9, 32.7, 37.3, 41.5, 41.7, 44.7, 64.1, 127.5, 129.5, 131.1, 134.0, 134.2, 135.5, 202.8.

(1*S*,2*S*)-2-([8-{(*tert*-Butyldiphenylsilyl)oxy}octyl]-4-cyclopentenyl)acetic Acid (16). To an ice-cold solution of aldehyde **15** (937 mg, 1.97 mmol) in acetone (19 mL) was added Jones reagent (4 M solution) slowly until the color of the reagent persisted. After 30 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 solution slightly acidic (pH 4), dried, and concentrated. The residue was purified by chromatography (hexane/EtOAc) to afford acid **16** (901 mg, 93%): IR (neat) 3110, 1704, 1111 cm^{-1}; ^{1}H NMR δ 1.06 (s, 9 H), 1.16−1.45 (m, 12 H), 1.50−1.62 (m, 2 H), 1.88−2.55 (m, 5 H), 2.94−3.08 (m, 1 H), 3.66 (t, J = 6.5 Hz, 2 H), 5.75−5.86 (m, 1 H), 7.33−7.51 (m, 6 H), 7.68 (dd, J = 7, 2 Hz, 4 H), 9−13 (br peak, 1 H); ^{13}C NMR δ 19.4, 25.9, 27.1, 28.9, 29.5, 29.7, 30.0, 30.5, 32.7, 34.7, 37.2, 41.5, 43.3, 64.1, 127.6, 129.5, 131.3, 134.2, 134.3, 135.6, 179.1. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56; H, 9.00. Found: C, 75.58; H, 9.01.

Iodo-lactone 17. To an ice-cold solution of acid **16** (168 mg, 0.341 mmol) in Et_2O (3.5 mL) and THF (3.5 mL) was added $NaHCO_3$ (89 mg, 1.06 mmol) dissolved in H_2O (2 mL) and the mixture was stirred for 20 min. An aqueous solution of I_2 (179 mg, 0.705 mmol) and KI (350 mg, 2.11 mmol) in H_2O (1 mL) was then added. The resulting dark brown mixture was stirred at room temperature for 13 h in 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 and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to furnish **17** (186 mg, 88%): $[\alpha]^{27}_D$ +2 (c 1.25, $CHCl_3$); IR (neat) 1784, 1111, 702 cm^{-1}; ^{1}H NMR δ 1.05 (s, 9 H), 1.14−1.74 (m, 15 H), 2.09 (dd, J = 14, 6 Hz, 1 H), 2.43−2.76 (m, 3 H), 3.03−3.18 (m, 1 H), 3.66 (t, J = 6.5 Hz, 2 H), 4.45 (d, J = 5 Hz, 1 H), 5.26 (d, J = 7 Hz, 1 H), 7.28−7.52 (m, 6 H), 7.64−7.72 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.0, 28.4, 28.6, 28.9, 29.4, 29.6, 29.8, 30.2, 32.7, 39.0, 40.3, 40.5, 64.0, 92.8, 127.5, 129.5, 134.1, 135.5, 176.4.

Lactone 18. A solution of iodo-lactone **17** (331 mg, 0.535 mmol) and DBU (0.21 mL, 1.4 mmol) in THF (6 mL) was refluxed for 6 h, then diluted with EtOAc and saturated NH_4Cl at 0 °C with stirring. The layers were separated, and the aqueous layer was extracted with EtOAc three times. The combined extracts were dried and concentrated to leave an oil, which was purified by chromatography (hexane/EtOAc) to afford lactone **18** (220 mg, 84%): $[\alpha]^{26}_D$ −29 (c 0.88, $CHCl_3$); IR (neat) 1771, 1112, 702 cm^{-1}; ^{1}H NMR δ 1.05 (s, 9 H), 1.16−1.64 (m, 14 H), 2.36−2.55 (m, 2 H), 2.73−2.89 (m, 1 H), 3.11−3.27 (m, 1 H), 3.66 (t, J = 6.5 Hz, 2 H), 5.46 (dm, J = 8 Hz, 1 H), 5.82 (dm, J = 6 Hz, 1 H), 5.95 (dm, J = 6 Hz, 1 H), 7.29−7.50 (m, 6 H), 7.62−7.73 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.0, 28.3, 29.4, 29.5, 29.6, 29.7, 31.2, 32.7, 39.9, 46.5, 64.1, 89.1, 127.5, 128.1, 129.5, 134.1, 135.5, 140.0, 177.2. Anal. Calcd for $C_{31}H_{42}O_3Si$: C, 75.87; H, 8.63. Found: C, 75.95; H, 8.71.

Methyl Ester 20. A mixture of lactone **18** (374 mg, 0.763 mmol) and $LiOH\cdot H_2O$ (160 mg, 3.81 mmol) in THF (4.8 mL), MeOH (1.6 mL), and H_2O (1.6 mL) was stirred vigorously at room temperature for 1 h, immersed in an ice-salt (NaCl) mixture (<0 °C), and diluted with saturated NH_4Cl and Et_2O. The mixture was acidified to pH ca. 4 with 1 N HCl. The phases were separated and the aqueous layer was extracted with Et_2O. The extracts were combined, cooled to 0 °C, and treated with excess CH_2N_2 in Et_2O for 30 min. The solution was concentrated and the residue was passed through a short column of silica gel with use of Et_2O as an eluent to give methyl ester **19**.

A solution of the above methyl ester **19**, TESCl (0.26 mL, 1.55 mmol), and imidazole (130 mg, 1.91 mmol) in DMF (8 mL) was stirred at room temperature for 1 h, cooled to 0 °C, and diluted with hexane and saturated $NaHCO_3$ with vigorous stirring. The layers were separated, and the aqueous layer was extracted with hexane three times. The combined extracts were dried and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to afford silyl ether **20** (398 mg, 82% from lactone **18**): $[\alpha]^{29}_D$ −4.2 (*c* 0.836, $CHCl_3$); IR (neat) 1739, 1120, 701 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.93 (t, J = 8 Hz, 9 H), 1.05 (s, 9 H), 1.14−1.64 (m, 14 H), 2.31−2.64 (m, 4 H), 3.65 (t, J = 6.5 Hz, 2 H), 3.67 (s, 3 H), 4.62 (dd, J = 5, 2 Hz, 1 H), 5.80 (dm, J = 6 Hz, 1 H), 6.04 (dd, J = 6, 2 Hz, 1 H), 7.30−7.48 (m, 6 H), 7.61−7.75 (m, 4 H); ^{13}C NMR δ 5.2, 7.0, 19.4, 26.0, 27.0, 28.0, 29.5, 29.7, 30.0, 30.3, 32.5, 32.7, 42.4, 45.9, 51.4, 64.1, 76.4, 127.5, 129.4, 132.5, 134.2, 135.5, 139.1, 174.2. Anal. Calcd for $C_{38}H_{60}O_4Si_2$: C, 71.64; H, 9.49. Found: C, 71.22; H, 9.40.

Aldehyde 21. To a solution of methyl ester **20** (320 mg, 0.503 mmol) in CH_2Cl_2 (5 mL) was added DIBAL (0.70 mL, 0.93 M in hexane, 0.651 mmol) slowly at −78 °C. Reaction was carried out at −78 °C for 1 h and quenched by addition of MeOH (0.26 mL, 6.5 mmol). After 10 min at −78 °C, H_2O (0.23 mL, 13 mmol) diluted with THF (0.23 mL) was added. The cooling bath was removed, NaF (547 mg, 13 mmol) was added to the solution, and the mixture was stirred vigorously for 30 min. The resulting mixture was filtered through a pad of Celite with EtOAc. Concentration of the filtrate gave a residue, which was purified by chromatography (hexane/EtOAc) to afford aldehyde **21** (263 mg, 86%): IR (neat) 1726, 1112, 701 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.05 (s, 9 H), 1.14−1.63 (m, 14 H), 2.38 (dd, J = 15, 4 Hz, 1 H), 2.48−2.59 (m, 1 H), 2.61−2.79 (m, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.68 (dm, J = 6 Hz, 1 H), 7.31−7.49 (m, 6 H), 7.63−7.73 (m, 4 H), 9.87 (t, J = 1 Hz, 1 H); ^{13}C NMR δ 5.2, 7.1, 19.4, 26.0, 27.0, 28.1, 29.5, 29.7, 30.0, 32.3, 32.7, 40.2, 41.7, 45.9, 64.1, 76.8, 127.5, 129.4, 132.6, 134.2, 135.6, 138.1, 202.8.

Olefin 22. To a suspension of *n*-propyltriphenylphosphonium bromide (720 mg, 1.87 mmol) in THF (3 mL) was added $NaN(TMS)_2$ (1.80 mL, 1.0 M in THF, 1.80 mmol) at 0 °C. The mixture was stirred at room temperature for 40 min and cooled to 0 °C before addition of DMF (0.54 mL, 6.97 mmol) and a solution of aldehyde **21** (263 mg, 0.434 mmol) in THF (2 mL). Reaction was carried out at room temperature for 1 h and quenched by addition of hexane and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with hexane three times. The combined extracts were dried and concentrated to give an oil. To remove PPh_3 residue, the oil was diluted with THF (4 mL) and treated with 35% H_2O_2 (0.49 mL, 5.6 mmol) at 0 °C for 30 min. Hexane and brine were added to the mixture and the layers were separated. The aqueous layer was extracted with hexane three times. The combined extracts were dried and concentrated to leave a residue, which was purified by chromatography (hexane/EtOAc) to afford olefin **22** (238 mg, 87%): $[\alpha]^{27}_D$ +1.2 (*c* 0.724, $CHCl_3$); IR (neat) 1112, 701 cm^{-1}; ^1H NMR δ 0.57 (q, J = 8 Hz, 6 H), 0.95 (q, J = 8 Hz, 9 H), 1.05 (s, 9 H), 0.86−1.62 (m, 17 H), 1.88−2.48 (m, 6 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.50 (dd, J = 6, 3 Hz, 1 H), 5.26−5.58 (m, 2 H), 5.78−5.92 (m, 1 H), 6.12 (dd, J = 6, 3 Hz, 1 H), 7.33−7.47 (m, 6 H), 7.64−7.72 (m, 4 H); ^{13}C NMR δ 5.4, 7.2, 14.5, 19.4, 21.0, 23.4, 26.0, 27.0, 28.2, 29.6, 29.8, 30.2, 32.6, 32.8, 46.2, 47.4, 64.1, 76.4, 127.5, 128.7, 129.5, 131.6, 132.7, 134.2, 135.6, 140.2. Anal. Calcd for $C_{40}H_{64}O_2Si_2$: C, 75.79; H, 10.23. Found: C, 75.88; H, 10.19.

Diol 23. A mixture of olefin **22** (245 mg, 0.387 mmol), Bu_4NF (1.93 mL, 1.0 M in THF, 1.93 mmol), 4A molecular sieves (128 mg), and THF (4 mL) was stirred at 55 °C for 1 h, cooled to 0 °C, and diluted with EtOAc and saturated NH_4Cl with stirring. The resulting mixture was filtered through a pad of Celite with EtOAc, and the filtrates were separated. The aqueous layer was extracted with EtOAc three times, and the combined extracts were dried and concentrated to give crude diol **23**, which was used for the next reaction without further purification. An analytically pure sample was obtained by chromatography: $[\alpha]^{25}_D$ +61 (*c* 0.89, $CHCl_3$); IR (neat) 3350, 1056 cm^{-1}; ^1H NMR δ 0.99 (t, J = 7.5 Hz, 3 H), 1.15−1.68 (m, 15 H), 1.96−2.53 (m, 7 H), 3.63 (t, J = 6.5 Hz, 2 H), 4.51 (dd, J = 6, 2 Hz, 2 H), 5.33−5.57 (m, 2 H), 5.96 (ddd, J = 6, 4, 2 Hz, 1 H), 6.23 (dd, J = 6, 3 Hz, 1 H); ^{13}C NMR δ 14.4, 20.9, 23.2, 25.9, 28.2, 29.5, 29.7, 30.0, 32.9, 33.7, 46.2, 46.3, 63.1, 76.7, 127.9, 132.0, 132.4, 141.7. Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.20; H, 11.19.

12-oxo-PDA (1). Jones reagent (4 M) was added to a solution of the above crude diol **23** in acetone (2.5 mL) at 0 °C until the color of the reagent persisted (17 drops). After 30 min at 0 °C, excess reagent was quenched by addition of 2-propanol, and the resulting mixture was filtered through a pad of Celite with Et_2O. The filtrate was washed with brine several times until the solution became slightly acidic (pH 4). The ethereal solution was dried ($MgSO_4$) and concentrated to give an oil, which was purified by chromatography (CH_2Cl_2/acetone) to give **1** (60 mg, 53% from olefin **22**). The ^1H NMR (300 MHz) spectrum for the major product (**1**) was consistent with the reported data (400 MHz),[1d] and a ratio of **1** and the epimer **24** was >95:<5 from the spectrum: $[\alpha]^{29}_D$ +127 (*c* 0.496, $CHCl_3$) (lit.[5a] $[\alpha]^{25}_D$ +104.0 (*c* 9.5, $CHCl_3$)); IR (neat) 3100, 1707 cm^{-1}; ^{13}C NMR δ 14.2, 20.9, 23.9, 24.8, 27.7, 29.1, 29.2, 29.7, 30.9, 34.1, 44.4, 50.0, 126.9, 132.4, 132.9, 167.2, 179.4, 210.9. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.81; H, 9.61.

Lactone 41. To a solution of iodo-lactone **17** (891 mg, 1.40 mmol) in benzene (5 mL) were added Bu_3SnH (1.13 mL, 4.31 mmol) and AIBN (23 mg, 0.14 mmol). After 1 h of reflux, the reaction was quenched by addition of NaF. 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 **41** (668 mg, 94%): $[\alpha]^{30}_D$ −6.5 (*c* 0.98, $CHCl_3$); IR (neat) 1772, 1111 cm^{-1}; ^1H NMR δ 1.05 (s, 9 H), 1.16−2.10 (m, 19 H), 2.38−2.57 (m, 2 H), 2.86−3.00 (m, 1 H), 3.66 (t, J = 6.5 Hz, 2 H), 5.03 (t, J = 6 Hz, 1 H), 7.32−7.48 (m, 6 H), 7.60−7.74 (m, 4 H); ^{13}C NMR δ 19.4, 25.9, 27.1, 28.7, 28.9, 29.1, 29.5, 29.7, 29.9, 30.8, 32.7, 33.2, 40.6, 42.9, 64.1, 86.2, 127.6, 129.5, 134.2, 135.6, 177.9. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56; H, 9.00. Found: C, 75.58; H, 9.17.

Methyl Ester 42. According to the procedure for the synthesis of **20**, a mixture of lactone **41** (370 mg, 0.727 mmol) in THF (5.1 mL), MeOH (1.7 mL), and H_2O (1.7 mL) was stirred with $LiOH \cdot H_2O$ (178 mg, 4.24 mmol) at room temperature for 1 h, cooled to 0 °C, diluted with saturated NH_4Cl and Et_2O, acidified to pH ca. 4 with 1 N HCl, and extracted with Et_2O. The extracts were combined, cooled to 0 °C, and treated with CH_2N_2 to give the hydroxyl methyl ester after short-column chromatography by using Et_2O as an eluent.

A solution of the above ester, TESCl (0.28 mL, 1.69 mmol), and imidazole (144 mg, 2.12 mmol) in DMF (8 mL) was stirred at room temperature for 1 h to afford silyl ester **42** (358 mg, 75% from lactone **41**) after chromatography (hexane/EtOAc): $[\alpha]^{26}_D$ −0.5 (*c* 0.75, $CHCl_3$); IR (neat) 1740, 1112 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.05 (s, 9 H), 1.00−1.96 (m, 19 H), 2.21 (dd, J = 15, 6 Hz, 1 H), 2.33−2.44 (m, 1 H), 2.47 (dd, J = 15, 7.5 Hz, 1 H), 3.65 (s, 3 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.15−4.26 (m, 1 H), 7.28−7.48 (m, 6 H), 7.63−7.71 (m, 4 H); ^{13}C NMR δ 5.0, 7.0, 19.4, 26.0, 27.0, 28.2, 28.6, 29.5, 29.6, 29.8, 30.0, 31.8, 32.8, 32.9, 39.7, 43.9, 51.4, 64.1, 75.1, 127.5, 129.4, 134.2, 135.6, 174.6. Anal. Calcd for $C_{38}H_{62}O_4Si_2$: C, 71.42; H, 9.78. Found: C, 71.46; H, 9.94.

Olefin 44. According to the procedure for the synthesis of olefin **22**, ester **42** (84 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL) was submitted to reduction with DIBAL (0.17 mL, 0.93 M in hexane, 0.16 mmol) at −78 °C for 50 min to produce aldehyde **43** (61 mg, 77%) after chromatography (hexane/EtOAc): IR (neat) 1726, 1112 cm^{-1}; ^1H NMR δ 0.55 (q, J = 8 Hz, 6 H), 0.93 (t, J = 8 Hz, 9 H), 1.05 (s, 9 H), 1.13−2.26 (m, 20 H),

2.41−2.59 (m, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.18−4.28 (m, 1 H), 7.28−7.51 (m, 6 H), 7.56−7.78 (m, 4 H), 9.79−9.83 (m, 1 H); ^{13}C NMR δ 5.0, 7.0, 19.4, 26.0, 27.1, 27.8, 28.5, 29.5, 29.8, 29.9, 32.1, 32.2, 32.7, 38.9, 39.5, 43.1, 64.1, 75.2, 127.5, 129.5, 134.2, 135.6, 203.3.

The Wittig reaction of aldehyde **43** (244 mg, 0.402 mmol) in THF (1.6 mL) was carried out with *n*-propyltriphenylphosphonium bromide (573 mg, 1.49 mmol) and $NaN(TMS)_2$ (1.4 mL, 1.0 M in THF, 1.4 mmol) in THF (2.5 mL) and DMF (0.44 mL) at 0 °C and room temperature for 2 h to furnish olefin **44** (243 mg, 96%) after chromatography (hexane/EtOAc): $[\alpha]^{25}_D$ +3.4 (*c* 1.00, $CHCl_3$); IR (neat) 2931 cm^{-1}; ^{1}H NMR δ 0.57 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.05 (s, 9 H), 1.1−2.3 (m, 24 H), 3.66 (t, J = 6.5 Hz, 2 H), 4.06−4.25 (m, 1 H), 5.25−5.55 (m, 2 H), 7.28−7.51 (m, 6 H), 7.56−7.78 (m, 4 H); ^{13}C NMR δ 5.2, 7.1, 14.5, 19.4, 20.9, 22.6, 26.0, 27.1, 28.7, 28.9, 29.6, 29.9, 30.1, 31.9, 32.8, 33.6, 40.1, 48.9, 64.2, 75.6, 127.6, 129.5, 129.8, 131.0, 134.2, 135.6. Anal. Calcd for $C_{40}H_{66}O_2Si_2$: C, 75.64; H, 10.47. Found: C, 75.35; H, 10.21.

Alcohol 45. According to the procedure for the synthesis of diol **23**, silyl ether **44** (50 mg, 0.079 mmol) in THF (0.8 mL) was treated with Bu_4NF (0.40 mL, 1.0 M in THF, 0.40 mmol) and 4A molecular sieves (26 mg) in THF (0.8 mL) at 60−65 °C for 2 h to afford diol **45** (22 mg, 98%) after chromatography (hexane/EtOAc): $[\alpha]^{25}_D$ +17 (*c* 0.43, $CHCl_3$); IR (neat) 3370, 1057 cm^{-1}; ^{1}H NMR δ 0.98 (t, J = 7.5 Hz, 3 H), 1.1−2.3 (m, 26 H), 3.64 (t, J = 6.5 Hz), 4.08−4.30 (m, 1 H), 5.32−5.50 (m, 2 H); ^{13}C NMR δ 14.4, 20.9, 22.8, 25.9, 28.9, 29.1, 29.6, 29.8, 30.0, 31.9, 32.9, 33.2, 40.2, 47.9, 63.1, 75.5, 128.7, 132.1. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.50; H, 11.83.

OPC-8:0 (2). To an ice-cold solution of the above diol **45** (31 mg, 0.11 mmol) in acetone (1 mL) was added Jones reagent dropwise at 0 °C until the color of the reagent persisted. After 30 min of stirring at 0 °C, *i*-PrOH was added to destroy the excess reagent and purification of the product by chromatography gave **2** (24 mg, 75%): $[\alpha]^{32}_D$ +62 (*c* 0.13, $CHCl_3$); IR (neat) 3100, 1734, 1711 cm^{-1}; ^{1}H NMR δ 0.96 (t, J = 7.5 Hz, 3 H), 1.20−1.44 (m, 10 H), 1.56−1.70 (m, 2H), 1.78−1.94 (m, 2 H), 1.98−2.42 (m, 10 H), 5.27−5.52 (m, 2 H); ^{13}C NMR δ 14.4, 20.8, 22.7, 24.8, 25.0, 27.8, 28.2, 29.2, 29.3, 29.7, 34.1, 35.5, 38.8, 53.8, 126.1, 132.9, 179.2, 220.2. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.52; H, 10.02.

Methyl Ester of OPC-8:0 (46). Oxidation of diol **45** (44 mg, 0.156 mmol) with Jones reagent (0.12 mL, 4 M, 0.48 mmol) in acetone (1.5 mL) as described above produced crude OPC-8:0 (**2**), which without purification was treated with CH_2N_2 in Et_2O to furnish methyl ester **46** (32 mg, 67% from diol **45**). The ^{1}H NMR and ^{13}C NMR of **46** thus synthesized were identical with those reported in the literature.[4c]

13-*epi*-OPC-8:0 (47). A mixture of methyl ester **46** (32 mg, 0.104 mmol), $LiOH\cdot H_2O$ (23 mg, 0.55 mmol) in THF (0.66 mL), MeOH (0.22 mL), and H_2O (0.22 mL) was stirred vigorously at room temperature for 90 min to afford the 13-epimer **47** (23 mg, 76%). The ^{1}H NMR and ^{13}C NMR data for **47** thus synthesized were identical with the data reported in the literature.[4e]

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Supporting Information Available: ^{1}H NMR spectra of compounds **14**, **15**, **17**, **21**, **34**−**40**, **24**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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