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Controlled syntheses of 12-oxo-PDA and its 13-epimer

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Abstract—Stereoselective synthesis of 12-oxo-PDA starting with (1*R*,3*S*)-cyclopenten-1,3-diol monoacetate is accomplished. Key transformations are copper-catalyzed installation of the C(1)–C(8) chain onto the cyclopentene ring and construction of the C(14)–C(18) chain. Similarly, 13-*epi*-12-oxo-PDA was synthesized, and its $[\alpha]_D$ was used to confirm the purity of 12-oxo-PDA (>95%) obtained by ^{1}H NMR spectroscopy. In addition, stability of 12-oxo-PDA was investigated to eliminate possibility of epimerization to the 13-epimer.

The plant metabolism of linolenic acid produces *epi*-jasmonic acid through 12-oxo-phytodienoic acid (12-oxo-PDA),[1] cyclopentanoic acid (OPC-8:0), and two β-oxidation products (OPC-6:0, OPC-4:0) (Fig. 1).[2] A significant role of this cascade in the regulation of process in plant physiology has been unveiled partially and is summarized in the reviews.[3] To support the biological study by supplying the natural acids as well as their analogues, synthesis of these metabolites has received attention. Among the metabolites, *epi*-jasmonic acid has been a synthetic target of active investigation,[4] while only few syntheses of the other acids are reported.[5] Although there is a structural similarity between *epi*-jasmonic acid and the other metabolites, difficulty would be encountered when the methods developed for *epi*-jasmonic acid synthesis are applied to synthesis of the other metabolites because of the specificity of the methods.

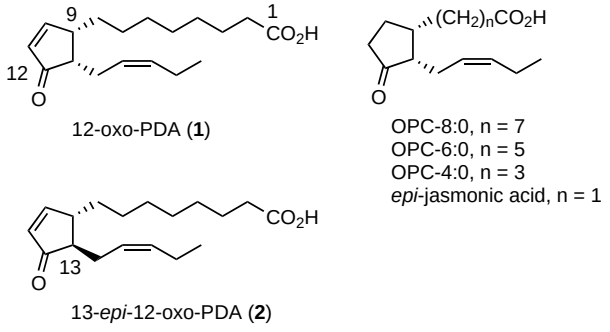
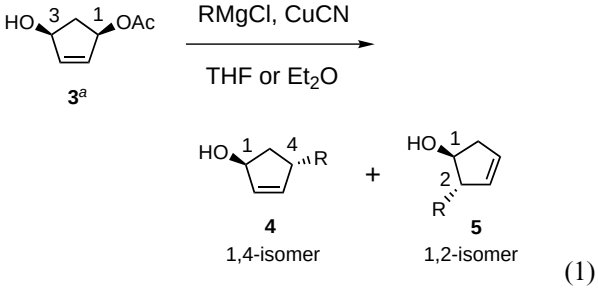


Figure 1. Metabolites of linolenic acid via the lipoxygenase pathway.



(1)

[a] (1*R*)-enantiomer is shown.

Recently, we reported a reaction of acetate **3** and the reagent derived from RMgCl and CuCN to afford either 1,4-isomer **4** or 1,2-isomer **5** with high regioselectivity (Eq. (1)).[6] This selectivity is controlled by the ratio of RMgCl/CuCN and the solvent used (THF or Et_2O). Thus, a reasonable approach to 12-oxo-PDA (**1**) is installation of one of the alkyl chains on the cyclopentene ring by using this reaction and the other chain by another method taking advantage of the allylic moiety on the ring. This idea was realized by a sequence of reactions illustrated in Scheme 1. In a similar manner, the 13-epimer of **1** (i.e. **2**) was synthesized stereoselectively and used to secure the purity of **1**. In addition, stability of **1** was studied briefly.

In order to prepare the key intermediate **7** in our synthesis (Scheme 1) by using the reaction shown in Eq. (1), a Grignard reagent derived from 8-chlorooctan-1-ol through protection of the hydroxyl group is required.

Keywords: asymmetric synthesis; 12-oxo-PDA; cyclopenten-1,3-diol monoacetate; copper catalyst; coupling reaction.

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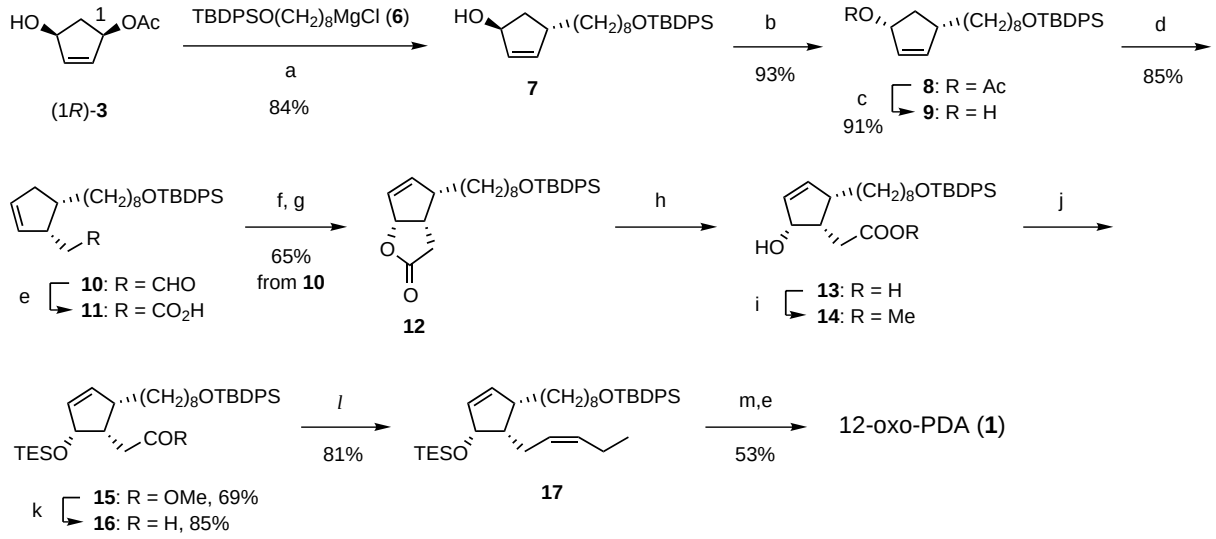
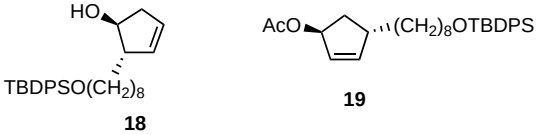
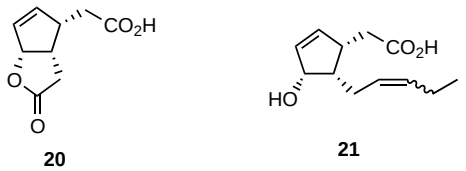


Scheme 1. Synthesis of 12-oxo-PDA (**1**). *Reagents and conditions*: (a) **6**, CuCN (15 mol%), THF, −18°C; (b) AcOH, DEAD, PPh_3, toluene, −78 to −60°C; (c) MeLi (3 equiv.), Et_2O, 0°C; (d) CH_2=CHOEt, $Hg(OAc)_2$ (0.5 equiv.), benzene, 170°C, 60 h; (e) CrO_3, H_2SO_4, acetone; (f) I_2 (2 equiv.), KI (6 equiv.), 0.5N $NaHCO_3$ (3 equiv.), rt, 13 h; (g) DBU (2.5 equiv.), THF; (h) LiOH, MeOH/H_2O/THF (1:1:3); (i) CH_2N_2; (j) TESCl, imidazole; (k) DIBAL, CH_2Cl_2, −78°C; (l) $[Ph_3PPr]^+Br^-$, $NaN(TMS)_2$, THF/DMF (9:1), 0°C to rt; (m) TBAF, 4 Å MS, 55°C.

Among common protecting groups we tested,[7] *t*-$BuPh_2Si$ group (TBDPS) showed excellent stability throughout the synthesis. The Grignard reagent, $ClMg(CH_2)_8OTBDPS$ (**6**), was prepared from $Cl(CH_2)_8OTBDPS$ and Mg in THF, and subjected to the CuCN-catalyzed reaction with (1*R*)-**3**[8] of >99% ee (checked by MTPA ester) to furnish **7** as a major product in 84% yield. The ratio of **7** and the corresponding 1,2-isomer **18**[9] was 97:3 by ^1H NMR spectroscopy (300 MHz, $CDCl_3$): **7**, δ 5.79–5.84 (m, 1H) and 5.93–5.98 (m, 1H); **18**, δ 5.64–5.77 (m, 2H). After separation of the regioisomer **18**, the hydroxyl group of **7** was inverted by the Mitsunobu reaction[10] to afford acetate **8** with a 98:2 ratio of **8** and the *trans* isomer **19**[11] by ^1H NMR spectroscopy: **8**, δ 2.42–2.66 (m, 2H); **19**, δ 2.78–2.92 (m, 1H). In contrast to the case of a related cyclopentenol,[12] formation of the regioisomeric acetate was not observed by TLC and ^1H NMR spectroscopy. Acetate **8** was hydrolyzed, and the resulting alcohol **9** was submitted to the Claisen rearrangement using CH_2=CHOEt and $Hg(OAc)_2$ as a catalyst. Although reaction temperature of 140°C is sufficient for the rearrangement of a related compound,[13] higher temperature of 170°C for 60 h was necessary for alcohol **9** to furnish the corresponding aldehyde **10** in 85% yield. Jones reagent was used for oxidation of **10** to acid **11**, and iodolactonization of **11** followed by elimination of HI from the resulting iodolactone under the given conditions afforded lactone **12** in 65% yield from aldehyde **10**.



Previously, conversion of a closely related lactone **20** into olefin **21** was reported by Crombie,[5b] who used a sequence through reduction to γ-lactol followed by Wittig olefination. Though this protocol is surely applicable to our lactone **12**, the observed stereoselectivity in the Wittig reaction is only 80:20 for the *cis* and *trans* olefins,[14] which is probably insufficient for a biological study. Consequently, the free aldehyde **16**, which is not involved in the equilibrium with lactol, was chosen as a substrate for the Wittig reaction.



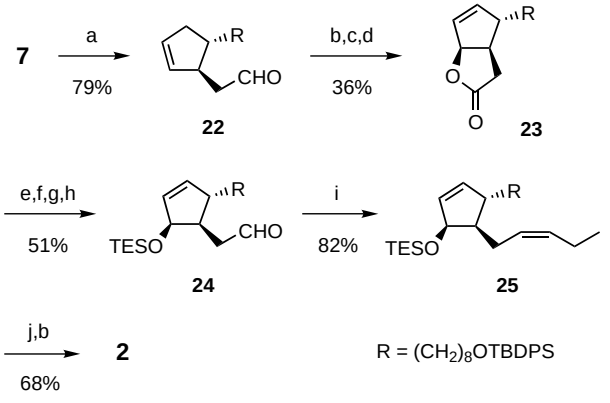
Lactone **12** was hydrolyzed, and the resulting acid **13**, after acidification, was extracted with Et_2O. Without concentration,[15] the solution was treated with CH_2N_2 to produce the hydroxyl methyl ester **14**, and protection of the hydroxyl group with TESCl furnished TES ether **15** in 69% yield from lactone **12**. Little contamination of lactone **12** was detected by TLC. Reduction of ester **15** with DIBAL at −78°C afforded the key aldehyde **16** in 85% yield. Wittig reaction of **16** with $[Ph_3PPr]^+Br^-$ was best carried out under the modified conditions of Santelli[16] using $NaN(TMS)_2$ in THF/DMF (9:1) to produce **17** in good yield with a 99:1 ratio of **17** (δ 4.50, dd, J = 5.7, 2.4 Hz, 1H in ^1H NMR (300 MHz, $CDCl_3$) spectrum) and the corresponding *trans* isomer (ca. δ 4.48). Note that use of *n*-BuLi as a base gave an 89:11 ratio of **17** and the *trans* isomer.

The remaining steps for the synthesis of **1** were deprotection of the two silyl groups and oxidation of the resulting alcohol. This transformation was accomplished easily under the conditions presented in Scheme 1.

The ^{1}H NMR spectrum of **1** thus synthesized was in good agreement with data reported,[1a] and showed >95% purity of **1** with <5% contamination of the thermodynamically more stable epimer **2**.[17] However, values of the specific rotation of **1** measured twice ($[\alpha]_D^{28}$ +127 (*c* 0.496, $CHCl_3$) and $[\alpha]_D^{29}$ +127 (*c* 0.198, $CHCl_3$)) were inconsistent with that reported[5a] ($[\alpha]_D^{25}$ +104.0 (*c* 9.5, $CHCl_3$)). It seemed likely that a large $[\alpha]_D$ of the epimer **2**, though less than 5% contamination in **1**, was responsible for the larger $[\alpha]_D$ of synthetic **1** we observed.

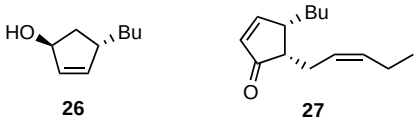
Since the specific rotation of **2** was not reported, a method to obtain **2** was investigated. Epimerization of **1** would be a more convenient method than a total synthesis.[18] Although, the methyl ester of **1** has been subjected to the epimerization,[1b,19] that of **1** to **2** is not reported. In addition, the yield of the 13-epimer (methyl ester of **2**), the product ratio after the epimerization, and the details of the reaction conditions are not presented. Consequently, it seemed a better way for us to follow the sequence of reactions shown in Scheme 1 without conducting the Mitsunobu reaction in this case. Although the yields were not optimized, **2** was synthesized stereoselectively as depicted in Scheme 2. In contrast to our assumption, observed $[\alpha]_D$ of **2** ($[\alpha]_D^{25}$ +93 (*c* 0.176, $CHCl_3$)) was smaller than that of **1**. Taking together this result and the >95% purity of **1** measured by ^{1}H NMR spectroscopy, the $[\alpha]_D$ of **1** is revised herewith to the value of +127 mentioned above.

Examined next was the stability of **1**. Preliminarily, a model compound **27** was synthesized in racemic form from cyclopentene **26** in a similar manner to Scheme 1,



Scheme 2. Synthesis of 13-*epi*-12-oxo-PDA (**2**). *Reagents and conditions*: (a) CH_2=CHOEt, $Hg(OAc)_2$ (0.5 equiv.), benzene, 170°C, 65 h; (b) CrO_3, H_2SO_4, acetone; (c) I_2 (2 equiv.), KI (6 equiv.), 0.5N $NaHCO_3$ (3 equiv.), rt, 17 h; (d) DBU (2.5 equiv.), THF; (e) LiOH, MeOH/H_2O/THF (1:1:3); (f) CH_2N_2; (g) TESCl, imidazole; (h) DIBAL, CH_2Cl_2, −78°C; (i) $[Ph_3PPr]^+Br^-$, $NaN(TMS)_2$, THF/DMF (9:1), 0°C to rt; (j) TBAF, 4 Å MS.

and **26**, in turn, was prepared from racemic **1** and BuMgCl according to Eq. (1).



26 **27**

Two solutions of **26** in $CDCl_3$ in NMR tubes were prepared. Commercial $CDCl_3$ was used without any purification in one tube (slightly acidic conditions due to the presence of DCl[20]), while DCl-free[21] $CDCl_3$ was added into the other tube (neutral conditions). The solutions were left on a bench at room temperature, and the diagnostic olefin protons in the ^{1}H NMR spectra[17] were monitored. During 1 month, no change was detected. A possibility of the DCl-assisted epimerization was thus eliminated. In a similar manner, a solution of synthetic **1** in commercial $CDCl_3$ was left at room temperature for 1 month, and the stable nature of **1** under these conditions was thus established.[22]

In conclusion, synthesis of 12-oxo-PDA (**1**) and the 13-epimer of **1** (i.e. **2**) is achieved. One of the key reactions in the present synthesis is the installation of the C(1)–C(8) chain, which was accomplished by the reaction shown in Eq. (1). This reaction is applicable to a number of alkylmagnesium chloride, and thence, other metabolites and analogues thereof as well as other cyclopentanoids possessing two side chains with the *cis* relationship would be synthesized by the present method.

Acknowledgements

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9. The regioisomer **18** was synthesized from **3** regioselectively by using the reagent derived from **6** (3 equiv.) and CuCN (3.5 equiv.) in THF at 0°C for 5 h.
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11. Authentic **19** was prepared from **7** by the standard acetylation (Ac$_2$O, pyridine).
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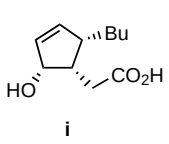
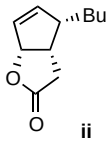
15. Concentration of an extract containing a model carboxylic acid **i** furnished lactonization to **ii**. The present operation described in the text reproducibly furnished **14** and, after the silylation, **15** in good yield.



i



ii

16. Viala, J.; Santelli, M. *Synthesis* **1988**, 395–397.
17. Diagnostic signals in the ^{1}H NMR (300 MHz, CDCl$_3$) spectra of **1** and **2** are protons at C(11) and C(10): **1**, δ 6.19 (dd, $J=6$, 1.5 Hz, 1H), 7.74 (dd, $J=6$, 3 Hz, 1H); **2**, δ 6.13 (dd, $J=6$, 2 Hz, 1H), 7.61 (dd, $J=6$, 2.5 Hz, 1H).
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21. Conveniently prepared by passing commercial CDCl$_3$ through a pad of basic Al$_2$O$_3$ before use.
22. Since the stability of **1** under the almost neutral conditions is established, it might be likely that the strongly acidic conditions of Jones oxidation to produce **1** and subsequent purification by silica gel chromatography brought about epimerization of **1**, but to a small extent (<5%).