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Total synthesis of isoprostanes via the two-component coupling process

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Abstract—A short total synthesis of isoprostanes has been achieved using a two-component coupling process combined with a diastereoselective protonation under *reagent control*. The F_1-isoprostanes were easily obtained by stereoselective reduction of the C-9 keto group.

In 1990 Roberts et al. reported that phospholipid-bound arachidonic acid is converted in vivo by a free radical oxidation to isoprostanes with a *cis*-arrangement of the 8- and 12-side chain.[1] Subsequent investigations showed that other polyunsaturated fatty acids undergo similar transformations.[2,3] The levels of isoprostanes measured in biological fluids were significantly higher than the enzymatically produced prostaglandins. These metabolites are established markers of oxidative stress in several diseases including Alzheimer's disease.[4,5] The release of isoprostanes during kidney failure and severe liver diseases has been reported,[6] but there is little known about their biological activities. In the interest of evaluating the biological and pharmacological properties of these compounds it is necessary to obtain sufficient quantities by chemical synthesis.

Several approaches towards isoprostanes have been reported in the literature. Corey et al. described a biomimetic route to the 8-*epi*-$PGF_{2\alpha}$ from arachidonic acid;[7] Larock et al. used a Pd promoted intermolecular coupling of three different alkenes to 12-*epi*-$PGF_{2\alpha}$.[8] A chiral pool strategy combined with a free radical cyclization to the all-*cis*-Corey lactone was reported by Rokach et al.[9,10] and modified by Durand[11] and Mulzer;[12] the side chains were introduced by a Wittig and an Emmons–Horner reaction. The Corey lactone has also been transformed to 12-*epi*-$PGF_{2\alpha}$.[13] Another general approach was developed by Taber et al. using as the key step a Rh II catalyzed cyclization of α-diazo ketones.[14]

It was our goal to develop a short general route that allowed the synthesis of all epimeric forms of isoprostanes. The two-component coupling process, typically used for the synthesis of the natural prostaglandins,[15] would be ideal if the outcome of the relative configuration of both side chains could be controlled. Due to their *cis* 2,3-disubstituted cyclopentanone structure the isoprostanes could be accessible by diastereoselective protonation of chiral enolates with chelating proton sources under *reagent control*.[16] Studies by Krause et al. revealed that five-membered ring enolates are the most difficult substrates to use.[17]

In this communication we wish to report the successful application of the two-component coupling process towards a short total synthesis of isoprostanes (Fig. 1). The chiral key intermediates used in the conjugated addition were easily available on a large scale as previously described (Scheme 1).[18–22]

The two-component coupling process of the chiral intermediates **8** and **10** followed by a diastereoselective protonation gave directly the protected isoprostane **11** (Scheme 1). Under the same conditions **9** was converted to **12** (Scheme 1).

The evaluation of different chelating proton donors for the diastereoselective protonation is summarized in Table 1. Methyl acetoacetate[23] (entry 8, Table 1) gave the desired protected isoprostane **11** with 82% *cis*-selectivity in 68% isolated yield.[24] The salicylates (entries 5 and 6, Table 1), introduced by Krause,[16] gave **11** with 46% and 63% selectivity, respectively.

Keywords: isoprostanes; protonation; enolates; stereoselectivity; cuprate.

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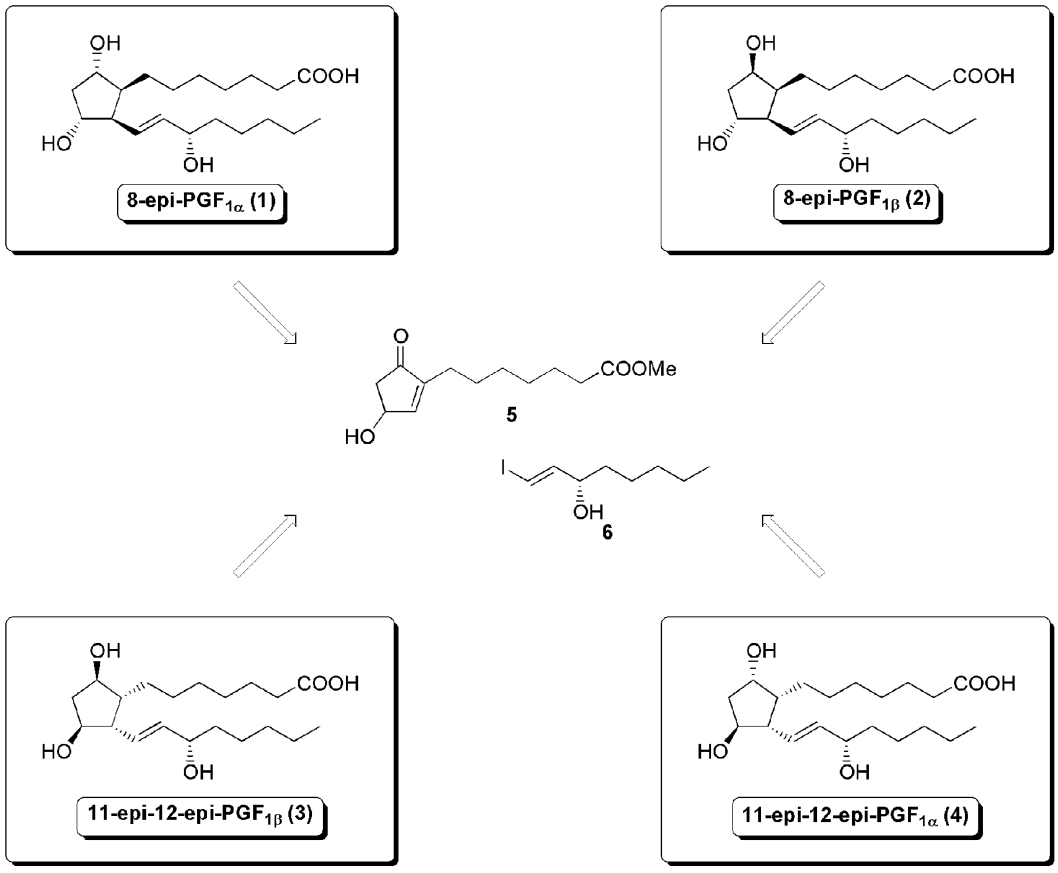
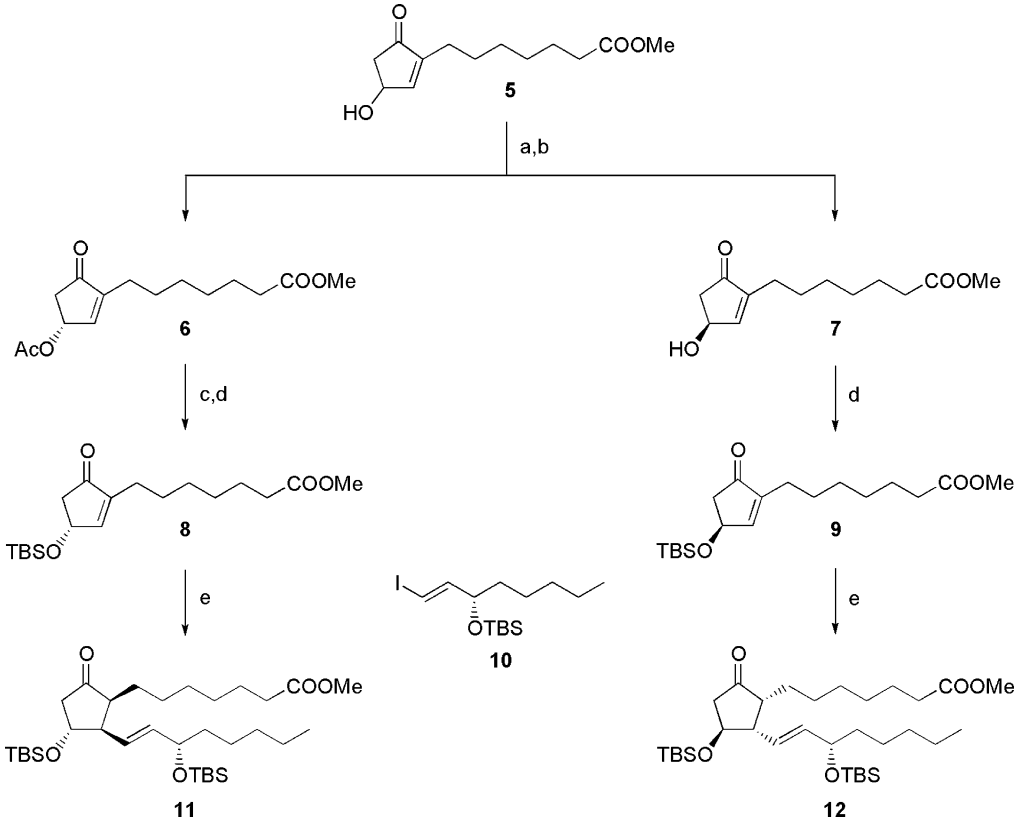
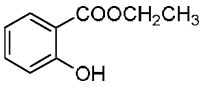
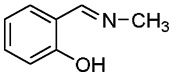


Fig. 1.



Scheme 1. *Reagents and conditions:* (a) lipase (PPL), vinyl acetate; (b) chromatographic separation; (c) 0.5 M guanidine, MeOH, 0°C; (d) TBSCl, imidazole, Et_3N, DMF, 84%; (e) **10**, *n*-BuLi, CuCN, MeLi, Et_2O, −78°C/methyl acetoacetate, Et_2O, −78°C→rt, CH_3COOH, 68%.

Table 1. Ratio *cis*/*trans* obtained in the diastereoselective protonation using different proton donors (ether, −78°C)

Entry	Proton donors	Ratio *cis*:*trans*[a]
1	CH_3–COOH	<1:>99
2	CF_3–CO–CH_2–$COOCH_2$–CH_3	3:97
3	CH_3–CO–CH_2–CO–CH_3	3:97
4	CF_3–CO–CH_2–CO–CH_3	5:95
5		46:54
6		63:37
7	CH_3–CO–CH_2–$COOCH_2$–CH_3	65:35
8	**CH_3–CO–CH_2–$COOCH_3$**	**82:18**

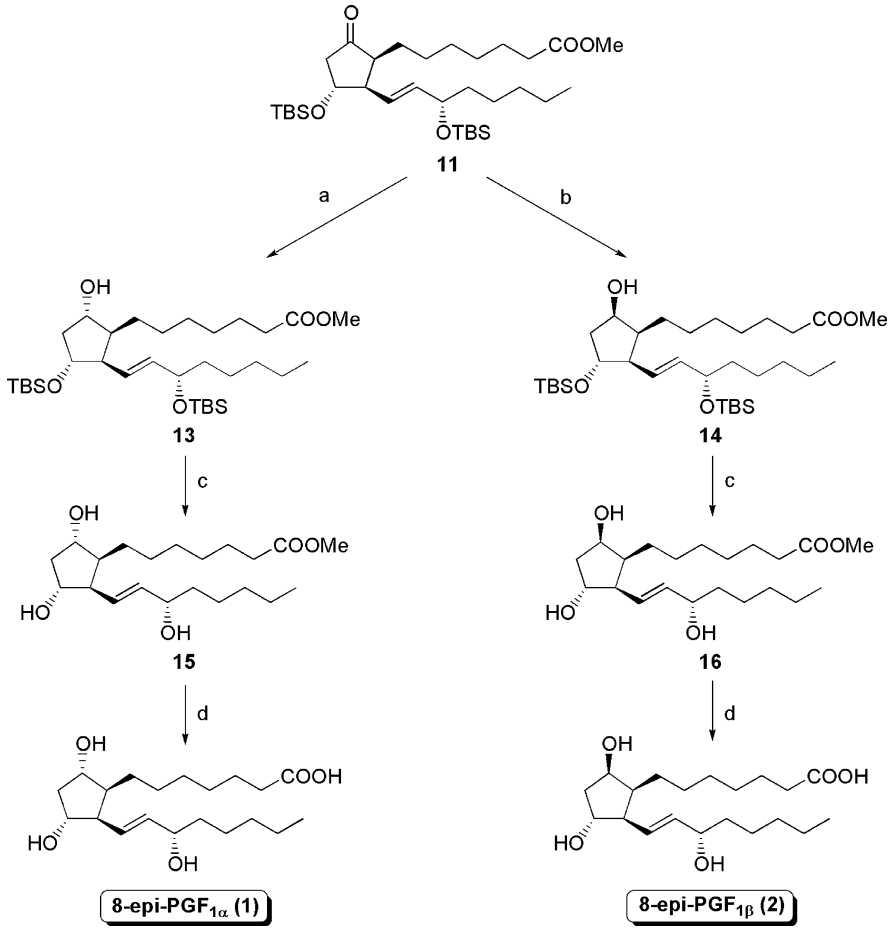
[a] The ratios were determined by HPLC [column: Hypersil-ODS, mobile phase: gradient MeOH/CH3CN/H2O, λ = 210 nm.]

Table 2. Reduction of the keto group at C-9 of compound **11** using different reducing agents

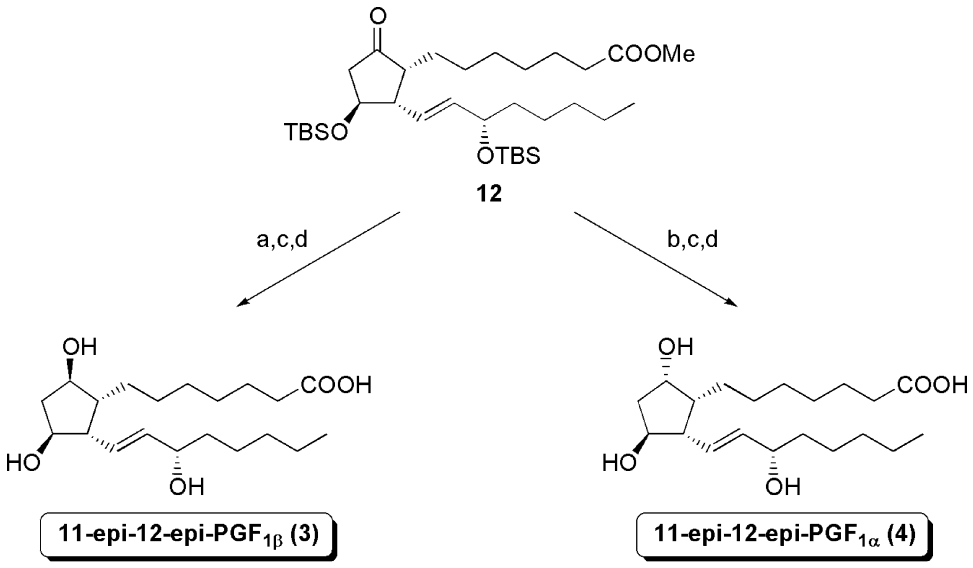
Entry	Reducing agent	Solvent	Temperature (°C)	Ratio α:β[a]
1	L-Selectride®	THF	−78	<1:>99
2	$NaBH_4/CeCl_3$	MeOH	0	79:21
3	$NaBH_4$	MeOH	0	83:17
4	$Me_2S{\cdot}BH_3$	THF	−20	84:16
5	$NaBH_4/CeCl_3$	MeOH	−65	88:12
6	$LiBH_4$	THF	−40	93:7

[a] The ratios were determined by HPLC [Column: Hypersil-ODS, mobile phase: gradient CH_3CN/H_2O, $\lambda = 210$ nm].

The synthesis of the 8-*epi*-PGF_1 series from the E-type intermediates required the stereoselective reduction of the 9-keto group. The results obtained with different reducing agents are shown in Table 2. As described for the natural prostaglandins reduction of the C-9 keto group of **11** with L-Selectride® gave **14** with a β-stereoselectivity >99% (entry 1, Table 2),[25] whereas lithium borohydride in THF at −40°C produced **13** with 93% α-stereoselectivity (entry 6, Table 2).[26,27] Removal of the silyl protective groups from **13** and **14** with HF/Py, followed by alkaline hydrolysis gave 8-*epi*-prostaglandin $F_{1\alpha}$ (**1**)[28] and 8-*epi*-prostaglandin $F_{1\beta}$ (**2**), respectively (Scheme 2), which were identical in all aspects with an authentic sample (Cayman Chemical Company, Ann Arbor, MI).[29] Compounds **1** and **2** have been identified in humans.[30,31]



Scheme 2. *Reagents and conditions:* (a) $LiBH_4$, THF, −40°C, 62%; (b) L-Selectride®, THF, −78°C, 75%; (c) HF/Py, THF, 0°C→rt, 92%; (d) LiOH, THF/H_2O, 0°C→rt, 95%.



Scheme 3. *Reagents and conditions*: (a) $LiBH_4$, THF, −40°C; (b) L-Selectride®, THF, −78°C; (c) HF/Py, THF, 0°C→rt; (d) LiOH, THF/H_2O, 0°C→rt.

In a similar manner starting from intermediate **12**, 11-*epi*-12-*epi*-prostaglandin $F_{1\beta}$ (**3**) and 11-*epi*-12-*epi*-prostaglandin $F_{1\alpha}$ (**4**) were obtained (Scheme 3).

In conclusion we have developed a practical synthesis of isoprostanes via the tandem two-component coupling process and the diastereoselective protonation with chelating proton sources under *reagent control*. The extension of this methodology towards other natural products will be reported in due course.

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24. To a −78°C solution of **10** (1.0 g, 2.70 mmol) in diethyl ether (4 ml), in a flame dried flask under argon, was added a 1.6 M solution of *n*-butyllithium in hexane (1.8 ml, 2.90 mmol) and stirred at −78°C for 2 h. Copper(I)

cyanide (0.24 g, 2.70 mmol) was placed in a second flame dried flask and suspended in diethyl ether (8 ml). The mixture was cooled at −78°C and a 1.4 M solution of methyllithium in diethyl ether (2.0 ml, 2.74 mmol) was slowly added. After 20 min at 0°C the clear solution was cooled to −78°C and the previously prepared vinyllithium reagent was added via cannula. The reaction was slowly warmed to −30°C and kept at this temperature for 20 min. After cooling to −78°C compound **8** (0.48 g, 1.35 mmol) in diethyl ether (3 ml) was added. The reaction mixture was stirred at −78°C (20 min) and at −40°C (10 min) and cooled again to −78°C. The reaction was transferred into a solution of methyl acetoacetate (2 ml, 19.0 mmol) in diethyl ether (40 ml) which was kept at −78°C. The mixture was slowly warmed to room temperature and acetic acid (0.8 ml, 13.6 mmol) was added. The solution was filtered through a pad of celite and washed with a saturated solution of sodium bicarbonate and brine. Drying (Na_2SO_4) and evaporating under vacuo gave crude **11**. The excess of methyl acetoacetate was removed in high vacuo (0.1 mm) at room temperature. Purification by flash chromatography (silica gel, hexane:EtOAc 95:5) afforded 0.55 g (68%) of **11**.

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29. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.3$, 6.6 Hz, 1H), 5.1–5.0 (dd, $J=15.3$, 10.2 Hz, 1H), 4.2 (m, 1H), 4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.8 (m, 1H), 2.7–2.5 (m, 1H), 2.4 (dd, $J=18.9$, 5.1 Hz, 1H), 2.3 (t, $J=7.5$ Hz, 2H), 2.2 (br. d, $J=18.9$ Hz, 1H), 1.8–1.0 (m, 18H), 0.9 (m, 21H), 0.1–0.0 (4s, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 218.35, 174.24, 138.04, 125.92, 73.34, 72.96, 52.10, 51.25, 49.69, 45.41, 38.31, 33.98, 31.71, 29.13, 28.94, 27.15, 25.76 (3C), 25.67 (3C), 24.91, 24.83, 24.71, 22.49, 18.08, 17.90, 13.81, −4.45, −4.80, −4.95, −5.04. $[\alpha]_D^{25}$ +48 (*c* 1.4, $CHCl_3$). Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.3$, 6.3 Hz, 1H), 5.1 (ddd, $J=15.3$, 10.2, 0.9 Hz, 1H), 4.2–4.1 (m, 1H), 4.0 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.6 (m, 1H), 2.4 (dd, $J=18.9$, 5.1 Hz, 1H), 2.3 (t, $J=7.5$ Hz, 2H), 2.2 (br. d, $J=18.9$ Hz, 1H), 1.8–1.1 (m, 18H), 0.9 (m, 21H), 0.1–0.0 (4s, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 218.21, 174.18, 137.78, 125.80, 73.31, 72.95, 52.02, 51.31, 49.94, 45.52, 38.37, 34.07, 31.77, 29.21, 29.05, 27.42, 25.82 (3C), 25.73 (3C), 25.01, 24.94, 24.74, 22.56, 18.16, 17.98, 13.88, −4.46, −4.81 (2C), −4.90. $[\alpha]_D^{25}$ −49 (*c* 0.21, $CHCl_3$). Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5–5.4 (dd, $J=15.3$, 6.6 Hz, 1H), 5.2–5.1 (dd, $J=15.3$, 10.2 Hz, 1H), 4.1–3.9 (m, 2H), 3.8 (m, 1H), 3.6 (s, 3H), 2.7–2.6 (m, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 2.2–2.1 (m, 1H), 2.1 (m, 1H), 1.6 (m, 3H), 1.5–1.2 (m, 16H), 1.0–0.8 (m, 21H), 0.1–0.0 (4s, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.34, 136.48, 127.51, 78.42, 78.15, 73.49, 54.37, 51.31, 50.81, 43.14, 38.48, 34.04, 31.78, 29.61, 29.46, 29.07, 28.12, 25.81 (3C), 25.72 (3C), 24.90, 24.82, 22.55, 18.15, 17.90, 13.89, −4.38, −4.77, −4.83, −4.94. Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5 (dd, $J=15.3$, 9.9 Hz, 1H), 5.4 (dd, $J=15.3$, 6.6 Hz, 1H), 4.3 (m, 1H), 4.2–4.1 (m, 1H), 4.0 (m, 1H), 3.6 (s, 3H), 2.4 (m, 1H), 2.3 (t, $J=7.5$ Hz, 2H), 2.2–2.1 (m, 1H), 2.1–1.9 (m, 2H), 1.7–1.2 (m, 18H), 1.0–0.8 (m, 21H), 0.1–0.0 (br. s, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.25, 135.54, 130.33, 78.57, 74.56, 73.74, 54.89, 51.31, 46.03, 45.37, 38.72, 34.07, 31.87, 29.58, 29.12, 27.91, 25.91 (3C), 25.87 (3C), 25.79, 24.95, 24.91, 22.62, 18.19, 18.00, 13.93, −4.24, −4.61, −4.72, −4.76. Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.3$, 10.2 Hz, 1H), 5.5–5.4 (dd, $J=15.3$, 7.2 Hz, 1H), 4.4–4.2 (m, 2H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 2.5 (m, 1H), 2.3 (t, $J=7.5$ Hz, 2H), 2.2 (m, 1H), 2.2–2.1 (m, 1H), 2.0–1.8 (m, 1H), 1.8–1.2 (m, 18H), 0.9 (t, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.33, 135.08, 132.09, 78.13, 74.24, 73.08, 54.49, 51.33, 46.30, 44.23, 37.45, 34.00, 31.74, 29.44, 29.00, 27.85, 25.61, 25.08, 24.79, 22.55, 13.88. Compound **1**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.5–5.4 (dd, $J=15.3$, 6.6 Hz, 1H), 5.4 (dd, $J=15.3$, 9.3 Hz, 1H), 4.0–3.9 (m, 1H), 3.9 (m, 1H), 3.8 (m, 1H), 2.7–2.6 (m, 1H), 2.5–2.4 (m, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 2.0 (m, 1H), 1.7–1.2 (m, 19H), 0.9 (t, $J=6.6$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 177.74, 136.89, 130.84, 77.02, 76.71, 73.91, 54.25, 50.55, 43.75, 38.50, 34.94, 32.95, 30.63, 30.18, 29.85, 28.98, 26.23, 26.06, 23.65, 14.28. $[\alpha]_D^{25}$ +23 (*c* 0.075, MeOH). Compound **4**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.6 (dd, $J=15.3$, 10.2 Hz, 1H), 5.5–5.4 (dd, $J=15.3$, 6.6 Hz, 1H), 4.3–4.2 (m, 1H), 4.1–4.0 (m, 1H), 4.0–3.9 (m, 1H), 2.5–2.4 (m, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 2.2–2.1 (m, 1H), 2.1–2.0 (ddd, $J=14.4$, 6.9, 2.1 Hz, 1H), 1.9–1.8 (dt, $J=14.4$, 5.4 Hz, 1H), 1.7–1.2 (m, 18H), 0.9 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 177.91, 135.79, 132.71, 79.11, 74.77, 73.42, 55.28, 47.63, 44.89, 38.56, 35.02, 32.96, 30.67, 30.21, 29.22, 26.82, 26.22, 26.09, 23.61, 14.26. $[\alpha]_D^{25}$ +9 (*c* 0.078, MeOH).
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