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Total synthesis of E_1 and E_2 isoprostanes by diastereoselective protonation

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Abstract—A short total synthesis of the E-type isoprostanes has been achieved using a two-component coupling process combined with a diastereoselective protonation under *reagent control*. Mild cleavage of the silyl protective groups with cat. $BiBr_3$ or HF/Py followed by enzymatic hydrolysis of the methyl ester afforded the free E-type isoprostanes.

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 two side chains.[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 have been described.[6] Recent reports have shown that the E-type isoprostanes are potent vasoconstrictors at low nanomolar concentrations.[7]

The E-type isoprostanes are rather unstable and tend to epimerize to the thermodynamically more stable *trans* isomers. It has been reported that they can undergo further elimination to the A-type in either basic or acidic medium.[8] In order to evaluate the biological and pharmacological properties of these natural compounds,[9] it is necessary to obtain sufficient quantities by chemical synthesis.[10]

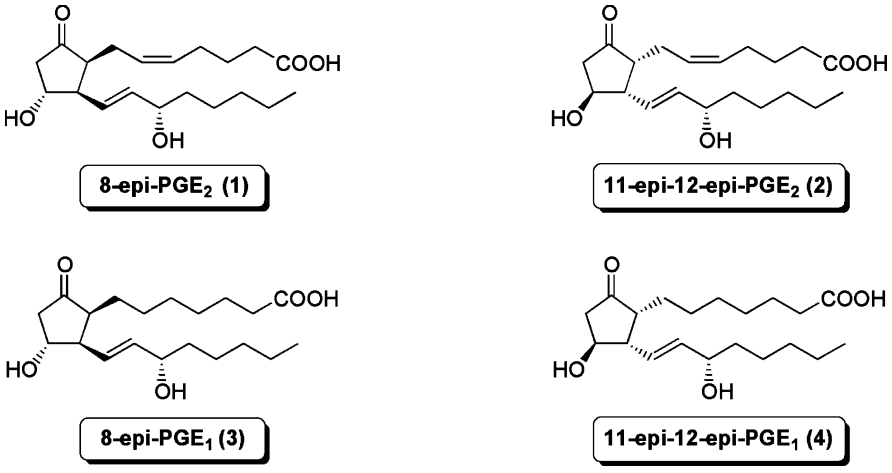

Figure 1.

Keywords: isoprostanes; protonation; enolates; cuprate; enzyme reactions.

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8-*epi*-Prostaglandin E_1 was isolated in the bioconversion of all-*cis*-8,11,14-eicosatrienoic acid in low yield.[11] 8-*epi*-Prostaglandin E_1 in racemic form was obtained as a by-product in the synthesis of prostaglandins E_1.[12,13]

A synthesis of racemic 8-*epi*-prostaglandin E_1 and E_2 has been reported by Sakai et al.[14] So far only the methyl ester of 8-*epi*-prostaglandin E_2 has been obtained in optical active form by Taber et al. using as the key step a Rh(II)-catalyzed cyclization of α-diazo ketones.[15] A stereoselective synthesis of free acid E-type isoprostanes (Fig. 1) has not yet been reported.[16]

The two-component coupling process, developed independently by Sih et al.,[17] Alvarez et al.[18] and Fried et al.,[19] is typically used for the synthesis of the natural prostaglandins and their analogs[20] having the α- and ω-side chains in the thermodynamically more stable *trans* configuration. We recently reported that this process combined with a diastereoselective protonation under *reagent control* afforded the products of kinetic control, the protected isoprostanes, with the *cis* configuration of the two side chains.[21]

In this communication we wish to report the successful application of this methodology towards a short total synthesis of the E-type isoprostanes (Fig. 2). The chiral key intermediates used in the conjugated addition were easily available on large scale as previously described (Scheme 1).[22–27]

The two-component coupling process of the chiral intermediates **10** and **12** followed by a diastereoselective protonation[28] with methyl acetoacetate as a chelating proton donor[29] gave directly the protected E_2 isoprostane **13** with 92% *cis*-selectivity[30] in 54% isolated yield (Scheme 1).[31,32] Under the same conditions **11** was converted to **14** with 82% *cis*-selectivity (Scheme 1).[30]

Attention was next turned to the cleavage of the TBS protective groups avoiding epimerization to the thermodynamically more stable *trans* isomer. Bajwa et al. introduced bismuth bromide in catalytic amounts in wet acetonitrile as a mild and effective deprotection method of alkyl *t*-butyldimethylsilyl ethers.[33] Using slightly higher amounts of bismuth bromide (30%) a smooth deprotection of both TBS groups was observed to give **15** in 62% isolated yield. A faster reaction was achieved using HF/Py in THF at rt to give **15** in 78% isolated yield (Scheme 2).[32] In both cases no epimerization was observed.

The hydrolysis of esters of the E-type prostaglandins has been accomplished by lipases and esterases.[22,26] The fact that isoprostanes are formed in vivo in esterified phospholipids and are released by lipases suggested the use of an enzymatic ester cleavage at neutral pH to obtain the E-type isoprostanes. Compound **15** was treated with porcine pancreatic lipase (type II EC 3.1.1.3, Sigma) in THF/H_2O at rt affording crystalline 8-*epi*-PGE_2 (**1**) in 50% yield after extractive isolation with ethyl acetate and flash chromatography. Under the same conditions **14** was converted to 11-*epi*-12-*epi*-PGE_2 (**2**) (Scheme 2).[32]

In a similar manner starting from **17** and **18**[21] 8-*epi*-PGE_1 (**3**) and 11-*epi*-12-*epi*-PGE_1 (**4**) were obtained respectively (Scheme 3).[32]

Compounds **1**, **2**, **3**, **4** have been identified in vivo.[9,34,35] 8-*epi*-PGE_1 (**3**) was identical in all aspects with an authentic sample (Cayman Chemical Company, Ann Arbor, MI).

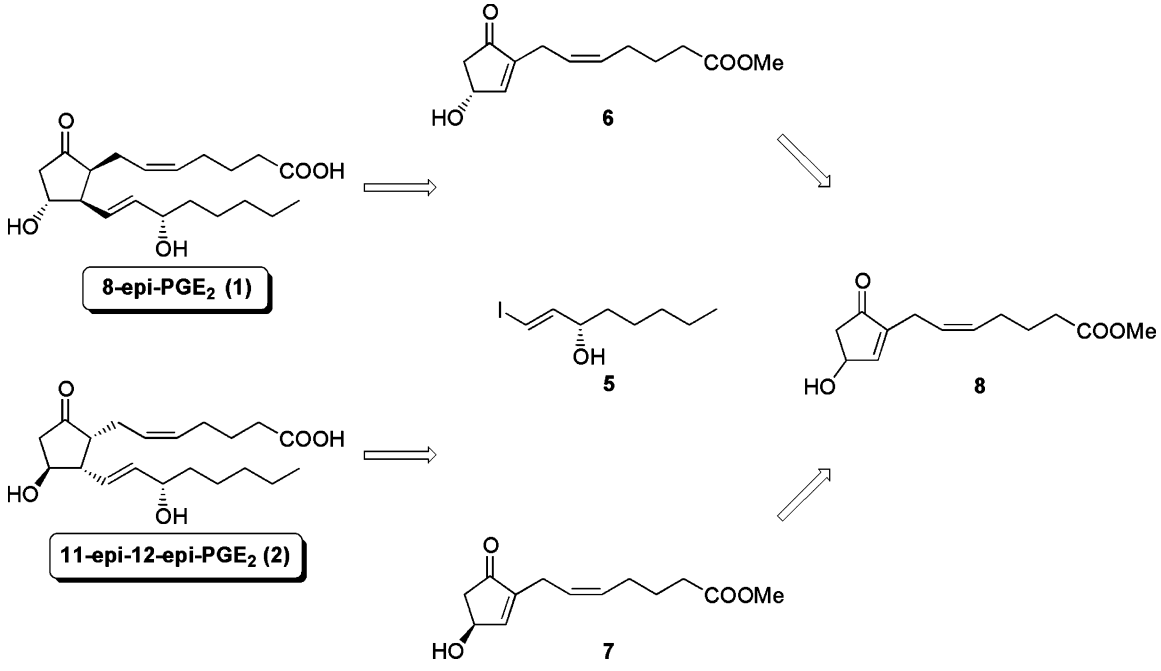
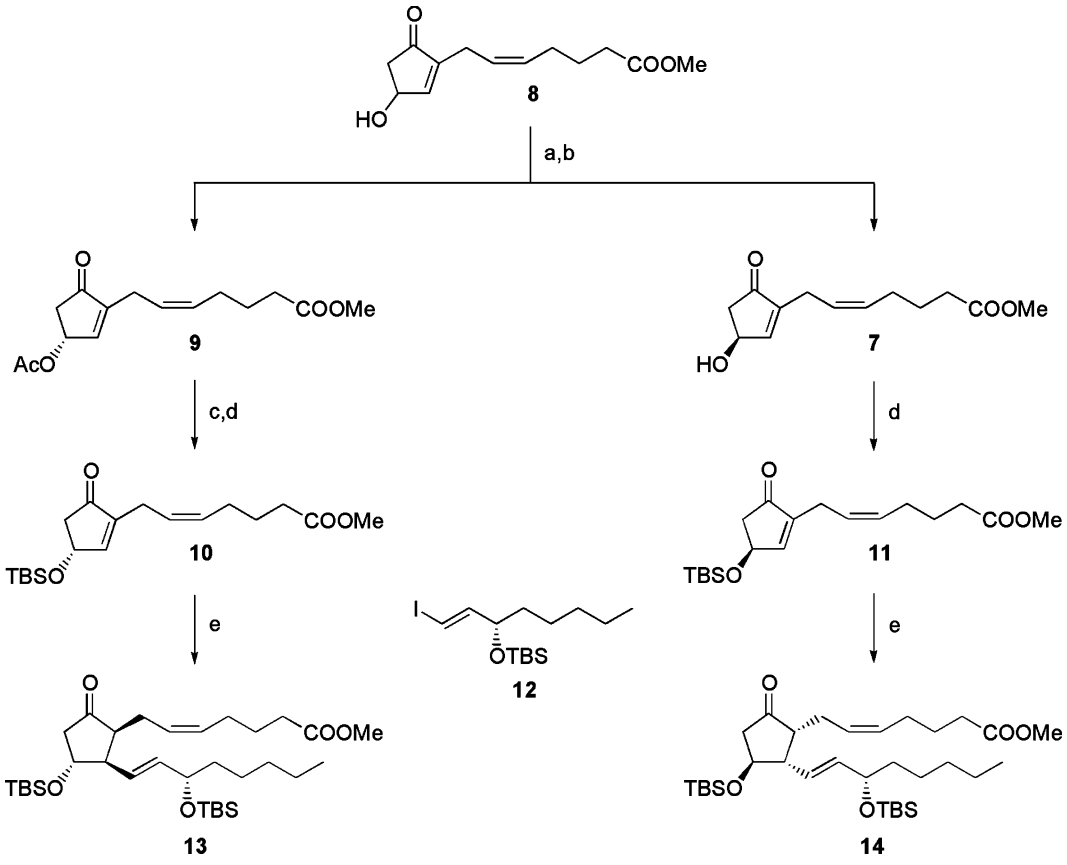
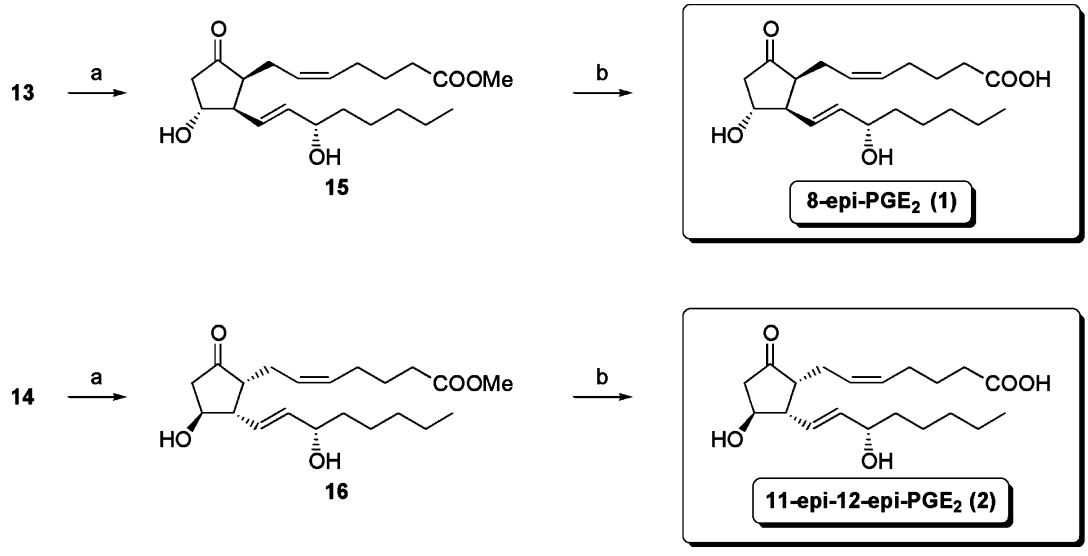


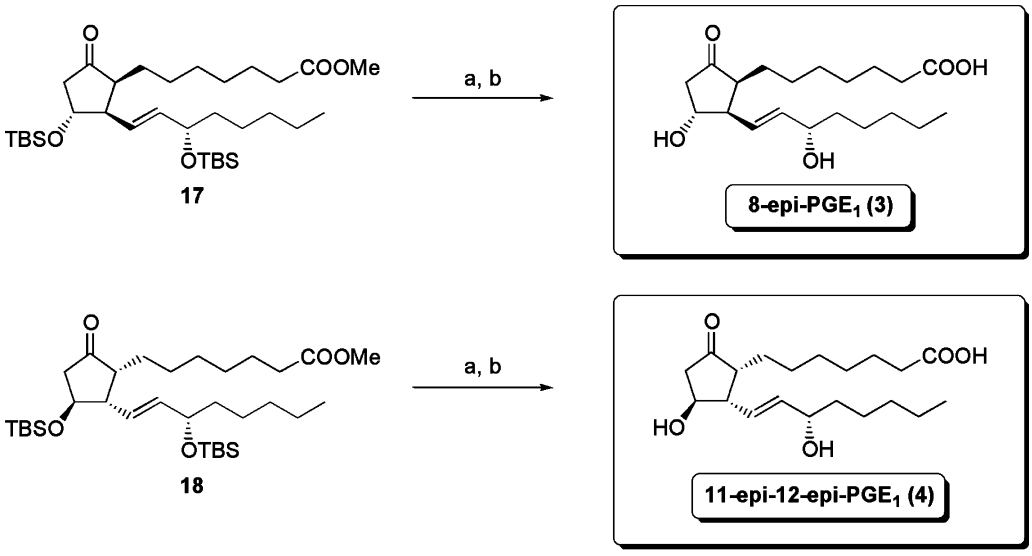
Figure 2.



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; (e) **12**, *n*-BuLi, CuCN, MeLi, Et_2O, −78°C/methyl acetoacetate, Et_2O, −78°C→rt, CH_3COOH.



Scheme 2. *Reagents and conditions*: (a) HF/Py, THF, 0°C→rt, (or $BiBr_3$ 30%, CH_3CN, cat. H_2O, rt); (b) lipase (PPL), NaCl, $CaCl_2$, H_2O/THF.



Scheme 3. *Reagents and conditions*: (a) HF/Py, THF, 0°C→rt, (or $BiBr_3$ 30%, CH_3CN, cat. H_2O, rt); (b) lipase (PPL), NaCl, $CaCl_2$, H_2O/THF.

In conclusion, we have developed a practical synthesis of isoprostanes of the E-type 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.

Acknowledgements

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30. The ratios were determined by HPLC [column: Nucleosil 100 Silica 5 μm, mobile phase: Hexane/*i*-PrOH (99.75:0.25) $\lambda = 214$ nm].
31. To a −78°C solution of **12** (0.69 g, 1.87 mmol) in diethyl ether (3 ml), in a flame dried flask under argon, was added a 1.6 M solution of *n*-butyllithium in hexane (1.3 ml, 2.01 mmol) and stirred at −78°C for 2 h. Copper(I) cyanide (0.17 g, 1.87 mmol) was placed in a second flame dried flask and suspended in diethyl ether (6 ml). The mixture was cooled at −78°C and a 1.4 M solution of methyllithium in diethyl ether (1.4 ml, 1.90 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 **10** (0.33 g, 0.94 mmol) in diethyl ether (2 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 (1.4 ml, 13.0 mmol) in diethyl ether (25 ml) which was kept at −78 C. The mixture was slowly warmed to room temperature and acetic acid (0.55 ml, 9.61 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 **13**. 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 0.30 g (54%) of **13**.
32. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J = 15.3$, 6.3 Hz, 1H), 5.4–5.3 (m, 2H), 5.1 (dd, $J = 15.3$, 10.2 Hz, 1H), 4.2 (m, 1H), 4.0 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.7–2.6 (m, 1H), 2.5–2.4 (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), 2.0 (m, 2H), 1.9–1.7 (m, 1H), 1.7–1.6 (quint., $J = 7.5$ Hz, 2H), 1.6–1.2 (m, 8H), 0.9 (m, 21H), 0.1–0.0 (4s, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 217.57, 173.99, 138.15, 129.92, 127.79, 125.59, 73.18, 72.73, 51.81, 51.34, 50.22, 45.28, 38.21, 33.37, 31.66, 26.65, 25.74 (3C), 25.65 (3C), 24.72, 24.66, 22.81, 22.49, 18.09, 17.91, 13.86, −4.44, −4.79, −4.95, −5.04. $[\alpha]_D^{25} = +49$ (*c* 1.05, $CHCl_3$). Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.3 Hz, 1H), 5.4–5.3 (m, 2H), 5.3 (dd, $J = 15.3$, 10.2 Hz, 1H), 4.3 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.9 (m, 1H), 2.7 (m, 1H), 2.5 (dd, $J = 19.2$, 5.7 Hz, 1H), 2.4–2.2 (m, 2H), 2.3 (t, $J = 7.3$ Hz, 2H), 2.1–1.9 (m, 3H), 1.7–1.6 (quint., $J = 7.3$ Hz, 2H), 1.5–1.2 (m, 8H), 0.9–0.8 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 216.99, 174.34, 137.59, 130.11, 127.63, 126.67, 72.36, 71.99, 51.50, 51.39, 50.65, 44.79, 37.23, 33.32, 31.60, 26.61, 24.97, 24.56, 23.21, 22.47, 13.87. $[\alpha]_D^{25} = +60.5$ (*c* 0.67, $CHCl_3$) (lit.[14] $[\alpha]_D = +40.9$ (*c* 0.00075, MeOH). Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.3 Hz, 1H), 5.4–5.3 (m, 2H), 5.3 (dd, $J = 15.3$, 9.6 Hz, 1H), 4.3 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.9 (m, 1H), 2.7 (m, 1H), 2.5 (dd, $J = 19.5$, 5.7 Hz, 1H), 2.5–2.3 (m, 2H), 2.3 (t, $J = 7.3$ Hz, 2H), 2.1–1.9 (m, 3H), 1.7–1.6 (m, 2H), 1.6–1.2 (m, 8H), 0.9–0.8 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 216.55, 174.35, 137.85, 130.10, 127.84, 126.42, 72.33, 72.18, 51.44, 51.26, 50.64, 44.78, 37.30, 33.35, 31.62, 26.68, 25.00, 24.61, 23.13, 22.46, 13.82. $[\alpha]_D^{25} = -56$ (*c* 0.69, $CHCl_3$). Compound **1**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.6 Hz, 1H), 5.5–5.3 (m, 2H), 5.3 (dd, $J = 15.3$, 9.9 Hz, 1H), 4.3–4.2 (m, 1H), 4.0 (m, 1H), 3.0 (m, 1H), 2.7–2.6 (m, 1H), 2.6–2.5 (dd, $J = 19.2$, 5.7 Hz, 1H), 2.5–2.3 (m, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.3–2.2 (m, 1H), 2.1–1.9 (m, 3H), 1.7–1.6 (quint., $J = 7.5$ Hz, 2H), 1.6–1.2 (m, 8H), 0.9 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 219.70, 177.49, 138.66, 131.12, 129.11, 128.23, 73.32, 72.85, 52.45, 51.74, 45.49, 38.40, 34.34, 32.91, 27.76, 26.17, 25.93, 24.22, 23.64, 14.29. $[\alpha]_D^{25} = +87$ (*c* 0.057, MeOH). Compound **2**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.0 Hz, 1H), 5.5–5.3 (m, 2H), 5.3 (dd, $J = 15.3$, 9.6 Hz, 1H), 4.3–4.2 (m, 1H), 4.0 (m, 1H), 3.0 (m, 1H), 2.7–2.6 (m, 1H), 2.6–2.5 (dd, $J = 19.2$, 5.7 Hz, 1H), 2.5–2.3 (m, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.2 (m, 1H), 2.1–1.9 (m, 3H), 1.7–1.6 (quint., $J = 7.5$ Hz, 2H), 1.6–1.2 (m, 8H), 0.9 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 219.67, 177.68, 138.61, 131.14, 129.19, 127.75, 73.08, 72.86, 52.26, 51.89, 45.54, 38.42, 34.45, 32.89, 27.75, 26.20, 25.99, 24.16, 23.61, 14.26. $[\alpha]_D^{25} = -69$ (*c* 0.13, MeOH). Compound **3**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.6 (dd, $J = 15.3$, 6.9 Hz, 1H), 5.3–5.2 (dd, $J = 15.3$, 10.5 Hz, 1H), 4.3–4.2 (m, 1H), 4.0–3.9 (m, 1H), 3.0 (m, 1H), 2.7–2.5 (m, 1H), 2.6–2.5 (dd, $J = 19.2$, 5.4 Hz, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.2 (m, 1H), 1.7–1.1 (m, 18H), 0.9 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 220.66, 177.81, 138.47, 128.55, 73.54, 72.93, 52.69, 50.98, 45.51, 38.40, 34.98, 32.94, 30.38, 30.10, 28.30, 26.25, 26.21, 26.05, 23.69, 14.34. $[\alpha]_D^{25} = +88$ (*c* 0.33, MeOH). Compound **4**: ^{1}H NMR (CD_3OD, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.0 Hz, 1H), 5.3 (dd, $J = 15.3$, 9.9 Hz, 1H), 4.2 (m, 1H), 4.0 (m, 1H), 3.0 (m, 1H), 2.7–2.5 (m, 1H), 2.5 (dd, $J = 19.2$, 5.4 Hz, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.3–2.1 (m, 1H), 1.7–1.2 (m, 18H), 0.9 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 220.76, 178.00, 138.42, 127.46, 72.99, 72.88, 52.46, 51.10, 45.56, 38.46, 35.06, 32.94, 30.32, 30.10, 28.34, 26.16, 26.11, 26.09, 23.67, 14.32. $[\alpha]_D^{25} = -78$ (*c* 0.095, MeOH).
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