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First total synthesis of the E type I phytoprostanes

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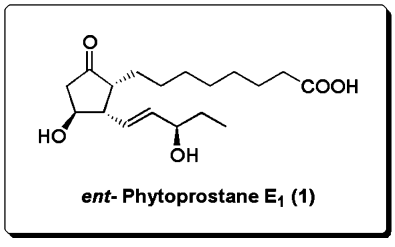
Abstract—The first total synthesis of two E type I phytoprostanes from furan, azelaic acid monomethyl ester and *rac*-1,2-epoxybutane is described. The key features of our synthetic strategy encompass an enzymatic kinetic resolution of a hydroxycyclopentenone, a Co-salen hydrolytic kinetic resolution of a terminal epoxide and a tandem conjugate addition/diastereoselective protonation sequence to construct the protected phytoprostanes. Mild cleavage of the silyl protective groups followed by enzymatic ester hydrolysis afforded the free E-type phytoprostanes.

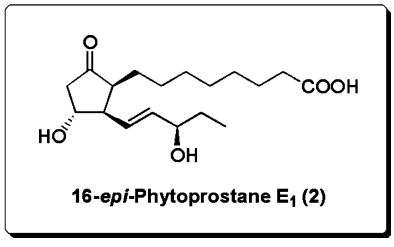
In 1990 Roberts et al. reported that phospholipid-bound arachidonic acid is converted in vivo by a free radical oxidation to isoprostanes with a *cis*-arrangement of the two side chains.[1,2] These products are isomeric to the cyclooxygenase-derived prostaglandins.[3–5] Since the discovery of the isoprostanes there has been a growing interest in the total synthesis of these molecules.[6–8] Recently the A and J type isoprostanes have been synthesized.[9,10] Subsequent investigations showed that other polyunsaturated fatty acids undergo similar transformations.[11,12] In higher plants arachidonic acid is generally absent and the most abundant polyunsaturated fatty acid is α-linolenic acid. This fatty acid is transformed in vivo, via autooxidation, to the phytoprostanes.[13–15] Their amounts increase dramatically after the drying of plant materials. Humans are exposed to high amounts, especially during the pollen season. Due to their structural similarity with isoprostanes, the phytoprostanes could cause tissue irritation and contribute to allergic reactions in humans. On the other hand they could interfere with isoprostanes at the receptor level.

The first synthesis of *ent*-phytoprostane F_1 and its 16 epimer has been recently described by Durand et al.[16] The E-type phytoprostanes 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.[17] In order to test the biological activities of the different phytoprostanes sufficient quantities can only be obtained by chemical synthesis. In this communication we wish to report the first total synthesis of the E type I phytoprostanes **1** and **2** (Fig. 1), which have been identified in vivo.[17]

We recently reported that the two-component coupling process, developed by Sih et al.[18] for the synthesis of prostaglandins, combined with an in situ diastereoselective protonation with chelating proton donors under



***ent*- Phytoprostane E_1 (1)**



16-*epi*-Phytoprostane E_1 (2)

Figure 1.

Keywords: phytoprostanes; hydrolytic kinetic resolution; protonation; Takai reaction; enzyme reactions.
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reagent control, gave a rapid entry to the isoprostanes.[19,20] Application of this methodology to the synthesis of the phytoprostanes is illustrated in the retrosynthetic analysis (Fig. 2). The chiral center at C-12 is introduced via an enzymatic kinetic resolution and at C-16 via a salen-Co catalyzed hydrolytic kinetic resolution (Fig. 2).

The racemic hydroxycyclopentenone **7** was conveniently obtained from furan (**3**) and commercial available azelaic monomethyl ester (**4**) as outlined in Scheme 1. The half ester **4** is converted to the mixed anhydride and reacted with **3** in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ to give the ketoester **5** (77%). Sodium borohydride reduction in methanol at 0°C furnished the hydroxy ester **6** in quantitative yield, which was rearranged to **7** in H_2O at reflux followed by treatment with a catalytic amount of chloral in the presence of triethylamine (70%).[21–23]

The synthesis of the optical pure iodovinyl side chain **13** is outlined in Scheme 2. The Jacobsen hydrolytic kinetic resolution of (±)-1,2-epoxybutane (**8**) with water in the presence of 0.0015 equivalents of S,S-salen-Co catalyst **9** without solvent gave diol **10** with 99% ee in 47% yield (94% theoretical) after distillation.[24] Conversion to the di-TES-ether **11** (75%),[25] followed by chemoselective oxidation with $CrO_3{\cdot}2Py$ gave TES-aldehyde **12**,[23,26] that was subjected to Takai olefination.[27] Treatment with CHI_3 and $CrCl_2$ in THF at room temperature furnished the desired *trans*-vinyl iodide **13** (65%).[23] A small amount of the *cis* isomer was conveniently removed by flash chromatography.[28,29]

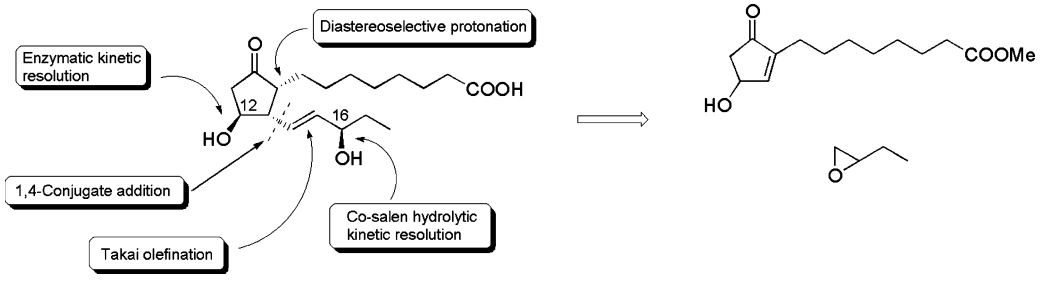
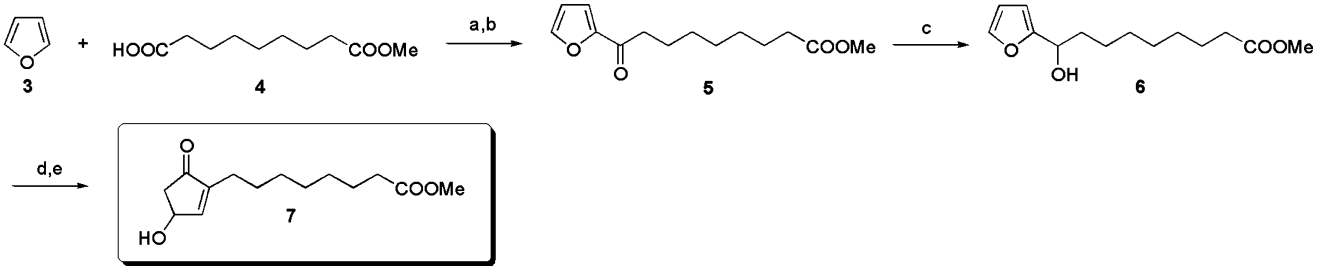
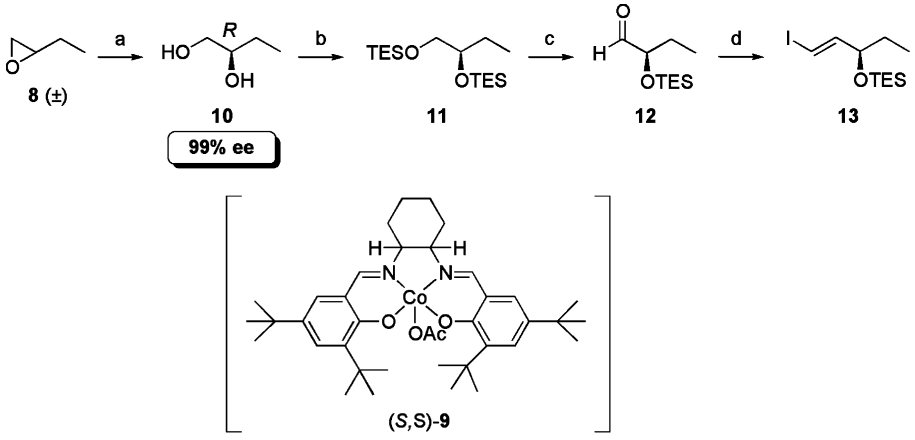


Figure 2.

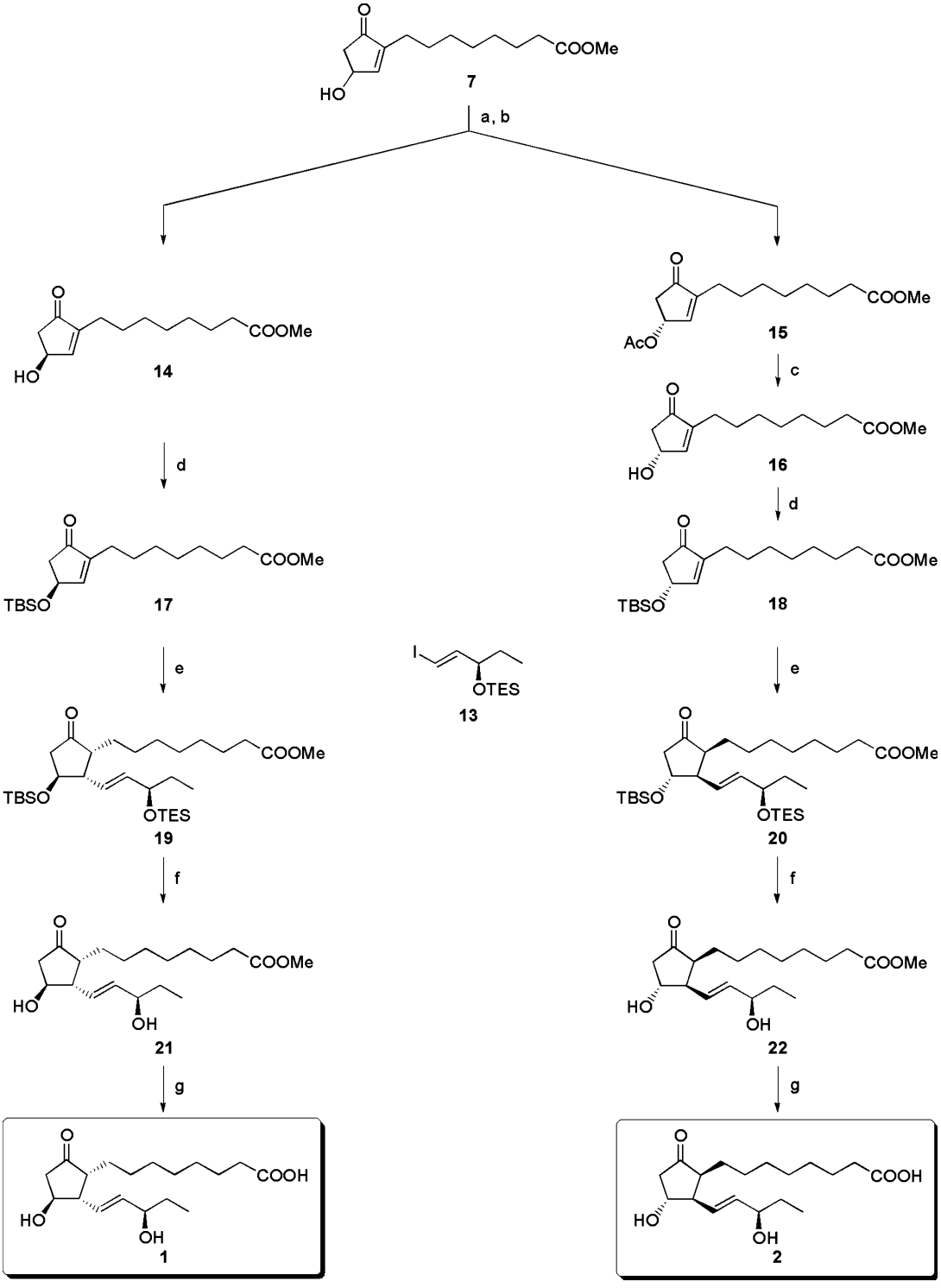


Scheme 1. *Reagents and conditions:* (a) $ClCH_2COCl$, Et_3N, CCl_4, 0°C to rt; (b) cat. $BF_3{\cdot}Et_2O$, CCl_4; (c) $NaBH_4$, MeOH, 0°C; (d) H_2O, reflux; (e) chloral, Et_3N, toluene, rt.



Scheme 2. *Reagents and conditions:* (a) (S,S)-(salen)Co(III)(OAc) catalyst (**9**), H_2O, 0°C to rt; (b) TESCl, imidazole, Et_3N, DMF, 0°C to rt; (c) $CrO_3{\cdot}2Py$, CH_2Cl_2, 0°C to rt.; (d) $CrCl_2$, CHI_3, THF, rt.

Rac-**7** can be easily converted into chiral intermediate **14** (97% ee) and **15** (99% ee) with lipase in vinyl acetate (Scheme 3).[30,31] The two-component coupling process of the chiral hydroxycyclopentenone **17** and **13** followed by a diastereoselective protonation provided the protected phytoprostane E **19** with 82% *cis*-selectivity in 53% isolated yield.[20,32] Similar reaction of **18** with **13** gave **20** with 72% *cis*-selectivity (Scheme 3).[32] Desilylation of **19** and **20** with HF/Py in THF at 0°C to rt gave the methyl esters **21** and **22** in 90% and 80% yield respectively (Scheme 3).[23] Under these conditions neither epimerization nor elimination was observed. The final enzymatic hydrolysis of **21** and **22** with lipase afforded the pure phytoprostanes **1** (66% yield) and **2** (81% yield) respectively (Scheme 3).[23,33]



Scheme 3. *Reagents and conditions:* (a) lipase (PPL), vinyl acetate; (b) chromatographic separation; (c) 0.5 M guanidine, MeOH, 0°C; (d) TBSCl, DMAP, Et_3N, CH_2Cl_2; (e) **13**, *n*-BuLi, CuCN, MeLi, Et_2O, −78°C to −40°C/methyl acetoacetate, Et_2O, −78°C to rt, CH_3COOH; (f) HF/Py, THF, 0°C to rt; (g) lipase (PPL), NaCl, $CaCl_2$, H_2O/THF.

In conclusion, we have developed a practical synthesis of phytoprostanes of the E-type. Our approach integrates highly effective kinetic resolutions to generate the two key chiral blocks and a straightforward coupling reaction to construct the phytoprostane skeleton. The extension of this methodology towards other natural products will be reported in due course.

Acknowledgements

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23. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.1 (m, 1H), 4.9 (m, 1H), 3.6 (s, 3H), 2.8 (dd, $J=18.6$, 6.0 Hz, 1H), 2.4–2.2 (dd, $J=18.6$, 2.1 Hz, 1H), 2.3 (t, $J=7.6$ Hz, 2H), 2.2–2.1 (m, 2H), 1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.4–1.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 206.50, 174.54, 155.97, 148.15, 68.46, 51.39, 44.79, 33.91, 28.90, 28.80, 28.73, 27.18, 24.69, 24.25. Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6 (d, $J=1.8$ Hz, 1H), 3.9 (m, 1H), 1.8–1.6 (m, 2H), 1.0 (t, $J=8.1$ Hz, 9H), 0.9 (t, $J=7.5$ Hz, 3H), 0.6 (q, $J=8.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 204.67, 78.49, 25.88, 8.82, 6.41 (3C), 4.63 (3C). Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.5 (dd, $J=14.4$, 6.0 Hz, 1H), 6.2 (dd, $J=14.4$, 1.2 Hz, 1H), 4.0 (m, 1H), 1.5 (m, 2H), 0.9 (t, $J=7.8$ Hz, 9H), 0.9–0.8 (t, $J=7.5$ Hz, 3H), 0.6 (q, $J=7.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 149.21, 76.28, 75.65, 30.39, 9.04, 6.61 (3C), 4.83 (3C). $[\alpha]_D^{25}=+37.9$ (c 1.1, CH_2Cl_2). Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.0 (m, 1H), 4.9 (m, 1H), 3.6 (s, 3H), 2.7 (dd, $J=18.3$, 6.0 Hz, 1H), 2.3 (t, $J=7.5$ Hz, 2H), 2.3–2.2 (dd, $J=18.3$, 2.1 Hz, 1H), 2.2–2.1 (m, 2H), 1.6 (m, 2H), 1.5–1.4 (m, 2H), 1.4–1.2 (m, 6H), 0.9 (s, 9H), 0.1 (s, 3H), 0.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 206.35, 174.32, 156.63, 147.27, 68.98, 51.36, 45.48, 33.99, 29.10, 28.93, 28.87, 27.27, 25.72 (3C), 24.81, 24.35, 18.05, −4.77 (2C). $[\alpha]_D^{25}=+13.8$ (c 1.7, $CHCl_3$). Compound **19**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.0$, 6.9 Hz, 1H), 5.1–5.0 (ddd, $J=15.0$, 10.2, 0.6 Hz, 1H), 4.2 (m, 1H), 3.9 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.6 (m, 1H), 2.4 (dd, $J=19.2$, 5.1 Hz, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 2.2 (br. d, $J=19.2$ Hz, 1H), 1.8–1.0 (m, 14H), 0.9 (t, $J=7.8$ Hz, 9H), 0.8 (s, 9H), 0.8 (t, $J=7.5$ Hz, 3H), 0.5 (q, $J=7.8$ Hz, 6H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 218.45, 174.25, 137.62, 126.16, 74.55, 72.83, 52.08, 51.28, 49.66, 45.42, 33.99, 31.18, 29.31, 29.03, 29.01, 27.21, 25.65 (3C), 24.90, 24.82, 17.89, 9.38, 6.70 (3C), 4.91 (3C), −4.95, −5.05. $[\alpha]_D^{25}=-50.7$ (c 1.6, $CHCl_3$). Compound **20**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.3$, 6.3 Hz, 1H), 5.2–5.1 (ddd, $J=15.3$, 9.9, 0.9 Hz, 1H), 4.2–4.1 (m, 1H), 4.0–3.9 (m, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.6 (m, 1H), 2.4–2.3 (dd, $J=18.6$, 5.1 Hz, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 2.2 (br. d, $J=18.6$ Hz, 1H), 1.7–1.0 (m, 14H), 0.9 (t, $J=7.8$ Hz, 9H), 0.9 (s, 9H), 0.8 (t, $J=7.5$ Hz, 3H), 0.5 (q, $J=7.8$ Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 218.25, 174.22, 137.41, 126.03, 73.98, 73.31, 51.98, 51.25, 49.95, 45.51, 34.03, 31.18, 29.35, 29.09, 29.07, 27.50, 25.68 (3C), 24.99, 24.87, 17.92, 9.28, 6.70 (3C), 4.94 (3C), −4.89, −4.97. $[\alpha]_D^{25}=+53.5$ (c 1.1, $CHCl_3$). Compound **21**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6 (dd, $J=15.3$, 7.2 Hz, 1H), 5.3–5.2 (dd, $J=15.3$, 10.2 Hz, 1H), 4.3 (m, 1H), 4.0–3.9 (m, 1H), 3.6 (s, 3H), 3.1 (br. s, 1H), 2.9 (m, 1H), 2.6 (m, 1H), 2.5 (dd, $J=19.2$, 5.7 Hz, 1H), 2.3 (br. s, 1H), 2.3–2.2 (m, 1H), 2.3–2.2 (t, $J=7.5$ Hz, 2H), 1.7–1.0 (m, 14H), 0.9–0.8 (t, $J=7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 217.65, 174.41, 136.96, 127.51, 74.00, 72.04, 51.68, 51.32, 50.16, 44.85, 33.96, 30.18, 29.16, 28.90, 28.87, 27.18, 25.14, 24.75, 9.41.

$[\alpha]_D^{25} = -66$ (c 1.0, $CHCl_3$). Compound **22**: ^1H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.6 (dd, $J = 15.3$, 6.0 Hz, 1H), 5.3 (ddd, $J = 15.3$, 9.6, 0.9 Hz, 1H), 4.3 (m, 1H), 4.0 (m, 1H), 3.6 (s, 3H), 3.0–2.9 (m, 1H), 2.6 (m, 1H), 2.5 (dd, $J = 19.2$, 5.7 Hz, 1H), 2.3–2.2 (m, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 1.7–1.1 (m, 14H), 0.9–0.8 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 217.87, 174.54, 136.91, 126.53, 73.40, 72.07, 51.39, 51.37, 50.08, 44.82, 33.94, 30.08, 29.13, 28.85 (2C), 27.13, 24.98, 24.71, 9.43. $[\alpha]_D^{25} = +67$ (c 0.58, $CHCl_3$). Compound **1**: ^1H NMR (CD_3OD, 300 MHz): δ 5.6 (ddd, $J = 15.3$, 6.9, 0.6 Hz, 1H), 5.3 (ddd, $J = 15.3$, 10.2, 0.9 Hz, 1H), 4.3–4.2 (m, 1H), 3.9 (m, 1H), 3.0 (m, 1H), 2.6 (m, 1H), 2.6–2.5 (dd, $J = 19.5$, 5.7 Hz, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.3–2.1 (m, 1H), 1.7–1.1 (m, 14H), 0.9 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 220.71, 177.80, 138.14, 128.64, 74.85, 72.95, 52.67, 50.98, 45.52, 34.90, 31.18, 30.47, 30.22, 30.13, 28.34, 26.24, 26.01, 10.06. $[\alpha]_D^{25} = -105$ (c 0.51, MeOH). Compound **2**: ^1H NMR (CD_3OD, 300 MHz): δ 5.7–5.6 (ddd, $J = 15.3$, 6.0, 0.6 Hz, 1H), 5.3 (ddd, $J = 15.3$, 9.9, 1.2 Hz, 1H), 4.2 (m, 1H), 4.0–3.9 (m, 1H), 3.0 (m, 1H), 2.6 (m, 1H), 2.5 (dd, $J = 19.2$, 5.4 Hz, 1H), 2.3–2.2 (t, $J = 7.5$ Hz, 2H), 2.1 (m, 1H), 1.7–1.1 (m, 14H), 0.9 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 220.74, 177.76, 138.07, 127.72, 74.22, 73.02, 52.50, 51.14, 45.56, 35.01, 31.19, 30.39, 30.16, 30.12, 28.41, 26.11, 26.02, 9.96. $[\alpha]_D^{25} = +83$ (c 0.37, MeOH).

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30. The enantiomeric excess was determined by Chiral-HPLC [column: Chiracel OD, mobile phase: hexane/*i*-PrOH (96:4) $\lambda = 210$ nm].
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32. The ratios were determined by HPLC [column: Nucleosil 100 Silica 5 μm, mobile phase: hexane/*i*-PrOH (99.6:0.4) $\lambda = 210$ nm].
33. To a suspension of porcine pancreatic lipase (PPL, Sigma, EC 3.1.13) (200 mg), NaCl (1.3 mg) and $CaCl_2$ (0.4 mg) in water (4 ml) was added **22** (35 mg, 0.103 mmol) in THF (1 ml). The reaction mixture was stirred for 24 h at room temperature to reach completion. After removing the enzyme by filtration through a pad of celite, the filtrate was layered with EtOAc, and solid $KHSO_4$ and NaCl were added. The aqueous phase was extracted several times with additional portions of EtOAc. Drying over Na_2SO_4 and evaporating afforded crude **2** that was purified by flash chromatography [silica gel, EtOAc] affording 27.2 mg (81%) of **2**.