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Synthesis of anti-Alzheimer (*R*)-arundic acid

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Abstract—The asymmetric synthesis of the anti-Alzheimer agent (*R*)-arundic acid has been performed via a diastereoselective photodeconjugation reaction as the key-step. The synthetic approach involves a readily available chiral auxiliary, diacetone-D-glucose, and allows access to either enantiomer as illustrated by the synthesis of (*S*)-arundic acid. Both enantiomers were obtained in 88% ee using the same chiral auxiliary.

1. Introduction

Alzheimer's disease is a neurodegenerative disorder of the central nervous system characterised by a progressive loss of memory and cognition, emotional disturbance and personality changes. This disease is the major cause of dementia among the elderly population and is associated with a deficiency in the cholinergic neurotransmission. Acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) currently represent the best palliative treatment, by temporary improvement of the cognitive function (Fig. 1).[1]

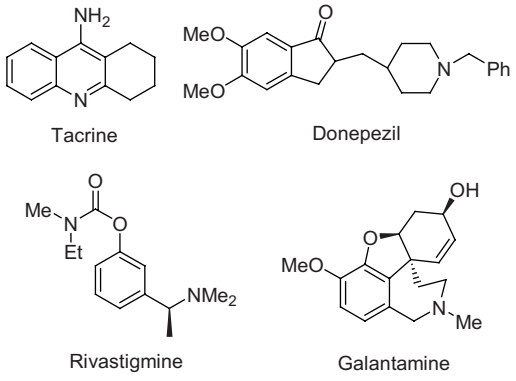

Figure 1. Acetylcholinesterase inhibitors.

Research into fighting this ever-growing disease is directed towards both the synthesis of analogues of this class of inhibitor[2] and the development of new therapeutic agents, such as secretase inhibitors, antioxidants or neuroprotective agents.[3] One novel emerging compound is (*R*)-arundic acid (Fig. 2), a neuroprotective agent, which modulates astrocyte activation by inhibiting the enhanced astrocytic synthesis of S-100β, responsible for inducing neuronal death.[4] This candidate is currently undergoing clinical studies and therefore has been prepared on a large scale by diastereoselective alkylation of a chiral sulfonamide derived from Oppolzer's camphorsultam.[5] However, the high cost of this auxiliary and the problems encountered with its recycling represent major drawbacks. An alternative chiral auxiliary derived from (*S*)-phenylethylamine was also developed but gave (*R*)-arundic acid with only moderate diastereoselectivity.[6]

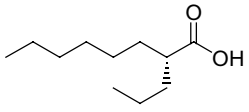

Figure 2. (*R*)-Arundic acid.

A few years ago, we reported high diastereoselectivities during the photodeconjugation of α,β-unsaturated esters into α-substituted β,γ-unsaturated isomers using diacetone-D-glucose as a chiral auxiliary (Scheme 1).[7] Under UV irradiation, conjugated esters undergo a *E*/*Z* isomerisation followed by a 1,5-sigmatropic hydrogen shift leading to a prochiral photodienol. The intermediate

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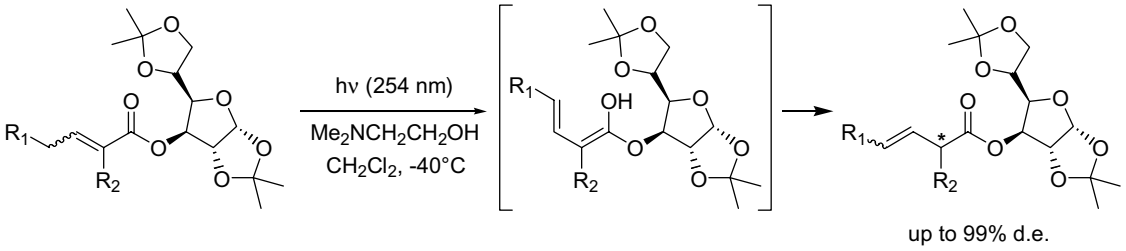


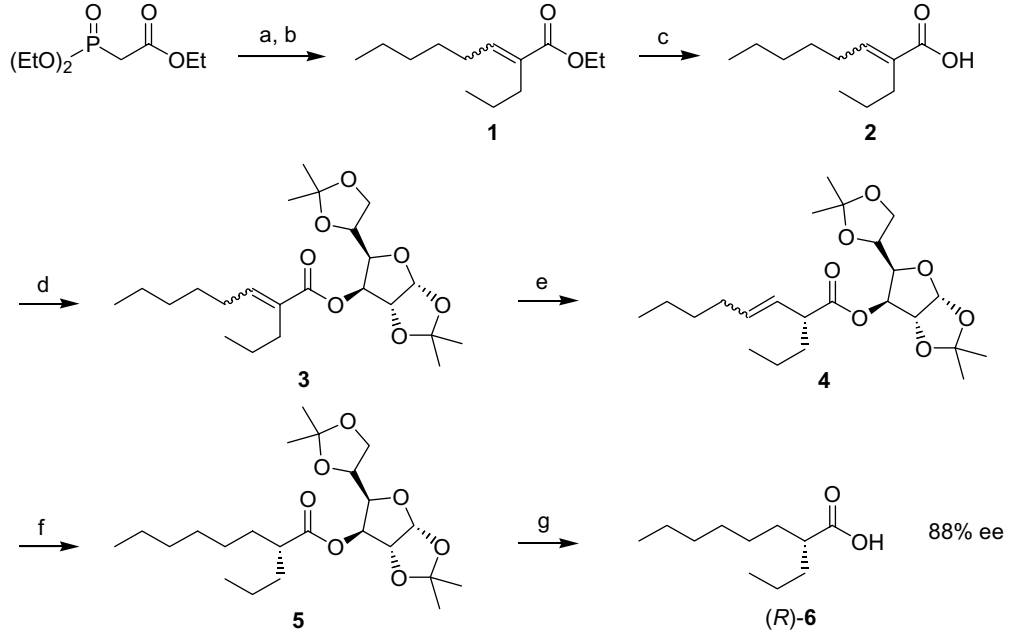
Scheme 1. Diastereoselective photodeconjugation.

photodienol is subsequently protonated in an asymmetric manner[8] by an aminoalcohol already present in the medium. The aminoalcohol can be used in catalytic amounts while the reaction can be viewed as an asymmetric organocatalytic process.[9] This reaction was successfully applied by us to the synthesis of (*R*)-lavandulol[10] and zaragozic acid C side chain[11] while Bach and co-workers used this strategy with a new chiral auxiliary for the synthesis of furanocembranoides.[12]

We report herein the diastereoselective synthesis of (*R*)-arundic acid by photodeconjugation of α,β-unsaturated esters derived from diacetone-D-glucose, a cheap and readily available chiral auxiliary. The synthesis of the (*S*)-enantiomer was also achieved using the same methodology.

2. Results and discussion

Based on our preliminary work,[7] we envisioned that arundic acid with an (*R*)-configuration could be obtained from diacetone-D-glucosyl α,β-unsaturated ester **3** bearing a propyl chain at the α-position (Scheme 2). This precursor ester was synthesised in four steps from commercially available triethylphosphonoacetate. Alkylation of triethylphosphonoacetate with propyl bromide followed by a Wittig–Horner reaction[13] between the resulting propyl phosphonoacetate and hexanal gave ethyl ester **1**. Saponification of **1** with potassium hydroxide in aqueous ethanol led to acid **2** along with a small amount of deconjugated acid, the formation of which could not be avoided even at room temperature. Acid **2** was esterified with diacetone-D-glucose under DCC-activation[14] to yield α,β-unsaturated ester **3** in 52% overall yield. Under UV irradiation, diacetone-D-glucosyl ester **3** underwent a diastereoselective photoisomerisation to give a 72/28 mixture of *E*- and *Z*-isomers of deconjugated ester **4** in 97% yield. Neither the diastereoselectivity of the process nor the absolute configuration of the C-2 carbon could be determined at this stage. The mixture of alkenes **4** was quantitatively hydrogenated over PtO_2 to give **5** as one major diastereoisomer. Removal of the chiral auxiliary was performed under nonracemising Evans' conditions[15] ($LiOH{\cdot}H_2O/H_2O_2$) to give (*R*)-arundic acid in 88% ee,[16] albeit in a modest 44% yield. The (*R*)-configuration was confirmed by the comparison of the sign of the

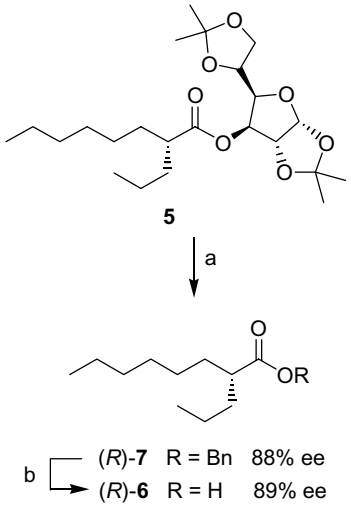


Scheme 2. Synthesis of (*R*)-arundic acid **6**. Reagents and conditions: (a) (i) KO*t*-Bu, (ii) propyl bromide, NaI, DMSO, 65 °C; (b) (i) NaH, (ii) hexanal, THF, 0 °C to rt, 72% over two steps; (c) KOH, H_2O/EtOH, 80 °C, 92%; (d) diacetone-D-glucose, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 79%; (e) *hv* (254 nm), *N,N*-dimethylaminoalcohol, CH_2Cl_2, −40 °C, 97%; (f) H_2, PtO_2, Et_2O, rt, quantitative; (g) $LiOH{\cdot}H_2O$, H_2O_2 30%, rt, 44%.

specific rotation ($[\alpha]_D$ value) with the literature value.[17]

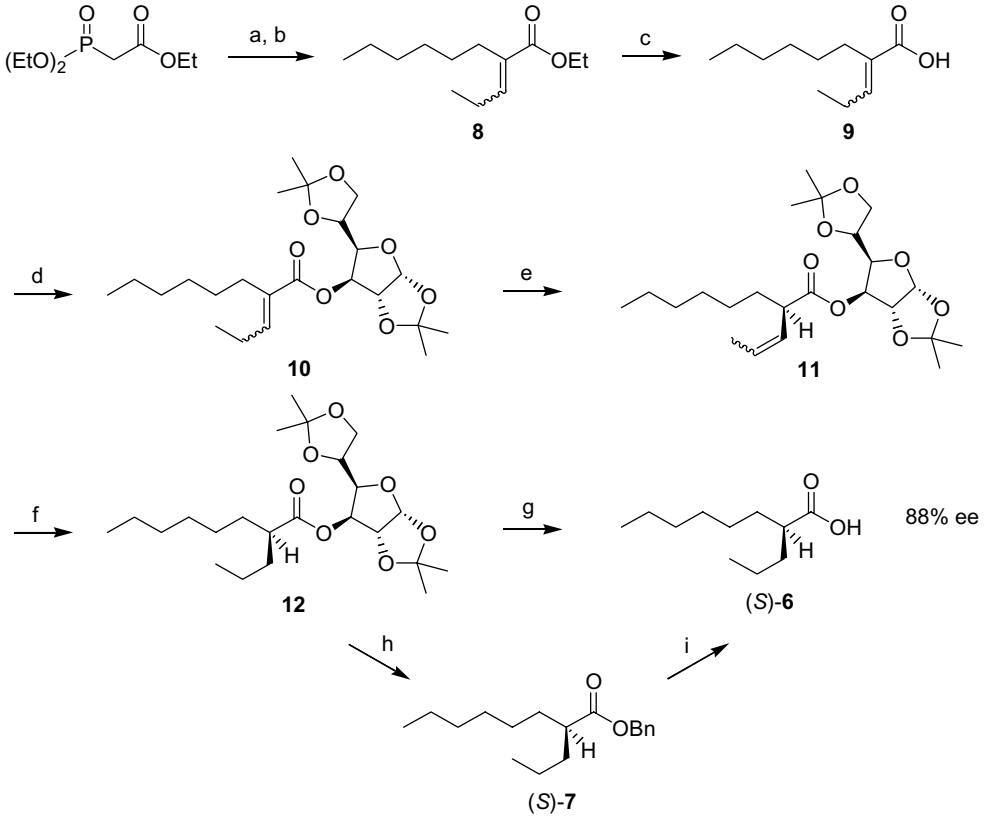
The poor yield obtained in the last step of this synthesis of (*R*)-arundic acid led us to consider an alternative approach to the final molecule from ester **5**. Thus, **5** was transesterified in high yield with benzyl alcohol in the presence of Ti(O*i*-Pr)$_4$ as catalyst according to Seebach's method[18] (Scheme 3). No epimerisation of C(2) of **5** nor racemisation of (*R*)-**6** occurred, as confirmed by the 88% enantiomeric excess of benzyl ester (*R*)-**7** (determined by chiral HPLC). The target acid was finally released by hydrogenolysis of (*R*)-**7** without loss of enantioselectivity (89% ee). This two-step sequence afforded (*R*)-arundic acid from ester **5** in 92% overall yield.

This methodology allows access to a large number of analogues as many derivatives of the precursor diacetone-D-glucosyl α,β-unsaturated ester can be prepared in four steps from triethylphosphonoacetate. Moreover, the configuration of the asymmetric centre can be predicted and therefore controlled by the position of the double bond on the starting diacetone-D-glucosyl α,β-unsaturated ester. Thus, whereas diacetone-D-glucosyl ester **3** gave (*R*)-arundic acid, its isomer **10** should lead to (*S*)-arundic acid (Scheme 4). The synthesis of (*S*)-arundic acid was therefore also achieved in order to both check this prediction and to illustrate the applicability of this synthetic approach.



Scheme 3. Alternative approach to (*R*)-**6**. Reagents and conditions: (a) BnOH, Ti(O*i*-Pr)$_4$, toluene, reflux, 97%; (b) H_2, Pd/C, MeOH, rt, 95%.

Chiral precursor ester **10** was synthesised in four steps from triethylphosphonoacetate. Alkylation of triethylphosphonoacetate with hexyl iodide followed by a Wittig–Horner reaction[13] between the resulting hexyl phosphonoacetate and propanal gave ethyl ester **8**. Saponification to acid **9** followed by esterification with diacetone-D-glucose under DCC-activation[14] afforded



Scheme 4. Synthesis of (*S*)-arundic acid **6**. Reagents and conditions: (a) (i) KO*t*-Bu, (ii) hexyl iodide, DMSO, 70 °C; (b) (i) NaH, (ii) propanal, THF, 0 °C to rt, 69% over two steps; (c) KOH, H_2O/EtOH, 80 °C, 85%; (d) diacetone-D-glucose, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 71%; (e) *hv* (254 nm), *N,N*-dimethylaminoalcohol, CH_2Cl_2, −40 °C, 78%; (f) H_2, PtO_2, Et_2O, rt, 96%; (g) LiOH·H_2O, H_2O_2 30%, rt, 49%; (h) BnOH, Ti(O*i*-Pr)$_4$, toluene, reflux, 92%; (i) H_2, Pd/C, MeOH, rt, 96%.

ester **10** in good yields. The diastereoselective photodeconjugation of α,β-unsaturated ester **10** gave a 76/24 mixture of the *E*- and *Z*-isomers of deconjugated ester **11** in 78% yield. The mixture of alkenes **11** was hydrogenated over PtO_2 to leave **12** as one major diastereoisomer. The synthesis of (*S*)-arundic acid was completed by the two previously reported methods: the direct saponification under mild conditions ($LiOH{\cdot}H_2O/H_2O_2$)[15] of ester **12** and the transesterification of **12** with benzyl alcohol followed by hydrogenolysis of the resulting benzyl ester (*S*)-**7**. In both cases, arundic acid of (*S*)-configuration was obtained in a high 88% ee.[16] Nevertheless, as for the (*R*)-isomer, direct saponification gave the acid in a modest 49% yield while the two-step sequence afforded the acid in 87% overall yield.

It is worth noting that both enantiomers of arundic acid were obtained with the chiral auxiliary (diacetone-D-glucose) and the same enantioselectivity, indicating that the substitution on the precursor α,β-unsaturated ester does not play a major role on the level of diastereoselectivity during the protonation step.

3. Conclusion

In conclusion, both enantiomers of arundic acid were synthesised in 88% ee using the same methodology and the same chiral auxiliary. The key-step involves a diastereoselective photodeconjugation of a chiral diacetone-D-glucosyl α,β-unsaturated ester with the configuration of the resulting asymmetric centre dependent on the initial position of the unsaturation. In addition to the low cost and large availability of the chiral inductor, the tunability of the method makes this approach suitable for the synthesis of various analogues of anti-Alzheimer (*R*)-arundic acid.

4. Experimental

Flash chromatography was performed on silica gel 60 (40–63 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker AM 300 or DRX 500 spectrometer. Mass spectra were obtained on a ThermoFinigan-MAT 95 XL instrument and LSIMS experiments were performed in a 3-nitrobenzylalcohol and sodium acetate matrix. Optical rotations were measured on a Perkin–Elmer 343 polarimeter. The ee values were determined by chiral HPLC using a Shimadzu pump (LC-10AS) and UV detector (SPD-6A).

4.1. Ethyl 2-propyloct-2-enoate 1

Potassium *tert*-butoxide (3.08 g, 27.5 mmol) was added at 0 °C to a stirred solution of ethyl (diethoxyphosphoryl)acetate (5 mL, 25 mmol) in DMSO (25 mL). After complete dissolution of potassium *tert*-butoxide, 1-bromopropane (3.2 mL, 35 mmol) and sodium iodide (4.12 g, 27.5 mmol) were added. The mixture was stirred at 65 °C for 4 h, then poured into saturated NH_4Cl solution and extracted with diethyl ether. The organic layers were washed with a saturated solution of sodium thiosulfate, dried over $MgSO_4$ and concentrated to give ethyl 2-(diethoxyphosphoryl)pentanoate as a pale yellow oil (5.86 g). The crude product (5.57 g) was dissolved in THF (5 mL) and added to a stirred suspension of NaH (60% in oil, 920 mg, 23 mmol) in THF (20 mL) at 0 °C. After 1 h, a solution of hexanal (2.10 g, 21 mmol) in THF (3 mL) was added at 0 °C. The mixture was allowed to warm up to rt overnight, then quenched with water and extracted with diethyl ether. The organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 2/98) to yield compound **1** (3.20 g, 15 mmol, 72%) as a mixture of *E*- and *Z*-isomers (*E*/*Z* = 51/49). ^1H NMR: *E*-isomer: δ 6.75 (t, J = 7.5 Hz, 1H, HC=C), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 2.30–2.12 (m, 4H, CH_2–CH=C and CH_2–C–CO_2Et), 1.50–1.20 (m, 8H, $4\times CH_2$), 1.30 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 0.92 (t, J = 7.3 Hz, 3H, CH_3), 0.90 (t, J = 7.3 Hz, 3H, CH_3); *Z*-isomer: δ 5.83 (t, J = 7.4 Hz, 1H, HC=C), 4.20 (q, J = 7.2 Hz, 2H, OCH_2), 2.39 (br q, J = 7.3 Hz, 2H, CH_2–CH=C), 2.30–2.12 (m, 2H, CH_2–C–CO_2Et), 1.50–1.20 (m, 8H, $4\times CH_2$), 1.31 (t, J = 7.2 Hz, 3H, CH_3CH_2O), 0.91 (t, J = 6.8 Hz, 3H, CH_3), 0.89 (t, J = 6.5 Hz, 3H, CH_3). ^{13}C NMR: *E*-isomer: δ 168.4, 142.9, 132.5, 60.5, 36.9, 31.9, 28.9, 28.8 (2C), 22.8, 14.5, 14.2 (2C); *Z*-isomer: δ 168.6, 141.7, 132.3, 60.2, 36.9, 31.8, 29.8, 29.5, 22.8, 22.5, 14.5, 14.3, 13.8. MS (CI): m/z (%) = 213 ($M+H^+$, 100), 185 (15), 85 (73), 69 (37).

4.2. 2-Propyloct-2-enoic acid 2

To a solution of ester **1** (530 mg, 2.5 mmol) in ethanol (4 mL) was added a solution of potassium hydroxide (420 mg, 7.5 mmol) in water (1 mL). The mixture was refluxed for 3 h. Water (20 mL) and diethyl ether (20 mL) were added and the two phases separated. The aqueous phase was acidified to pH = 1 with a 1 M HCl solution and extracted three times with diethyl ether. The organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 7/93) to afford acid **2** (424 mg, 2.3 mmol, 92%) as a colourless oil. ^1H NMR: *E*-isomer: δ 6.92 (t, J = 7.5 Hz, 1H, HC=C), 2.32–2.15 (m, 4H, CH_2–CH=C and CH_2–C–CO_2H), 1.55–1.25 (m, 8H, $4\times CH_2$), 0.92 (t, J = 7.3 Hz, 3H, CH_3), 0.90 (t, J = 7.3 Hz, 3H, CH_3); *Z*-isomer: δ 6.02 (t, J = 7.5 Hz, 1H, HC=C), 2.49 (q, J = 7.5 Hz, 2H, CH_2–CH=C), 2.32–2.15 (m, 2H, CH_2–C–CO_2H), 1.55–1.25 (m, 8H, $4\times CH_2$), 0.90 (t, J = 7.3 Hz, 3H, CH_3), 0.89 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR: *E*-isomer: δ 174.4, 146.2, 132.0, 36.8, 31.9, 29.1, 28.8, 28.7, 22.8, 14.3 (2C); *Z*-isomer: δ 174.6, 146.4, 131.2, 36.8, 31.9, 30.1, 29.5, 22.9, 22.7, 14.3, 13.9. MS (CI): m/z (%) = 185 ($M+H^+$, 100), 167 (10).

4.3. (1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl) 2-propyloct-2-enoate 3

To a solution of acid **2** (157 mg, 0.85 mmol, *E*/*Z*, 38/62) in dichloromethane (2 mL) at 0 °C was added 1,2:5,6-diisopropylidene-D-glucose (245 mg, 0.94 mmol) and 4-dimethylaminopyridine (11 mg, 0.085 mmol). A solution

of dicyclohexylcarbodiimide (194 mg, 0.94 mmol) in dichloromethane (1 mL) was then added dropwise. The mixture was allowed to warm up to rt and stirred overnight. The white precipitate was filtered off and the solvent evaporated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 5/95) to yield ester **3** (288 mg, 0.68 mmol, 79%, *E*/*Z*, 90/10) as a colourless oil. ^{1}H NMR: *E*-isomer: δ 6.77 (br t, J = 7.5 Hz, 1H, HC=C), 5.88 (d, J = 3.7 Hz, 1H, O–CH–O), 5.28 (d, J = 2.3 Hz, 1H, CH–O–C=O), 4.52 (d, J = 3.7 Hz, 1H, C*H*–CH(O)$_2$), 4.28–4.18 (m, 2H, O–C*H*–C*H*–CH$_2$O), 4.13–4.06 (m, 1H, 1/2 ABX, OC*H*$_A$H$_B$), 4.04–3.98 (m, 1H, 1/2 ABX, OCH$_A$*H*$_B$), 2.28 (td, J = 7.1, 1.9 Hz, 2H, CH$_2$–C–CO$_2$), 2.19 (br q, J = 7.5 Hz, 2H, C*H*$_2$–CH=C), 1.54 (s, 3H, CH$_3$C(O)$_2$), 1.42 (s, 3H, CH$_3$C(O)$_2$), 1.31 (s, 6H, 2 × CH$_3$C(O)$_2$), 1.50–1.20 (m, 8H, 4 × CH$_2$), 0.90 (t, J = 7.1 Hz, 3H, CH$_3$), 0.89 (t, J = 6.8 Hz, 3H, CH$_3$); [*Z*-isomer: δ 5.73 (t, J = 7.3 Hz, 1H, HC=C)]. ^{13}C NMR *E*-isomer: δ 166.9, 144.6, 131.9, 112.4, 109.5, 105.3, 83.6, 80.4, 76.4, 72.8, 67.6, 31.8, 28.9, 28.8, 28.7, 27.0, 26.9, 26.4, 25.4, 22.7 (2C), 14.2 (2C). MS (LSIMS): *m*/*z* (%) = 449 (M+Na$^+$, 20), 411 (50), 369 (65), 266 (16), 167 (100), 101 (51). HRMS calcd for $C_{23}H_{38}O_7Na^+$: 449.2515. Found: 449.2516.

4.4. (*R*)-(1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl) 2-propyloct-3-enoate 4

To a solution of ester **3** (141 mg, 0.33 mmol) in dichloromethane (35 mL) was added *N*,*N*-dimethylethanolamine (30 mg, 0.33 mmol). The mixture was transferred into quartz tubes (10 mm diameter) and deoxygenated with nitrogen for 5 min. The tubes were placed around a quartz tube in which a short wavelength OSRAM lamp was introduced. The irradiation was carried out at −40 °C and monitored by TLC. After 6 h, the solvent was evaporated and the crude product purified by flash chromatography (ethyl acetate/petroleum ether, 5/95) to yield compound **4** (136 mg, 0.32 mmol, 97%) as a mixture of diastereoisomers in a 28/72 ratio of *E*- and *Z*-isomers. ^{1}H NMR: major isomer: δ 5.86 (d, J = 3.7 Hz, 1H, O–CH–O), 5.61–5.48 (m, 1H, CH=C), 5.45–5.28 (m, 1H, CH=C), 5.26 (d, J = 1.5 Hz, 1H, CH–O–C=O), 4.40 (d, J = 3.7 Hz, 1H, C*H*–CH(O)$_2$), 4.25–4.15 (m, 2H, O–C*H*–C*H*–CH$_2$O), 4.13–4.05 (m, 1H, 1/2 ABX, OC*H*$_A$H$_B$), 4.03–3.95 (m, 1H, 1/2 ABX, OCH$_A$*H*$_B$), 2.98 (br q, J = 7.5 Hz, 1H, CH–C=O), 2.10–1.95 (m, 2H, C*H*$_2$–CH=C), 1.80–1.65 (m, 2H, C*H*$_2$–CH–C=O), 1.52 (s, 3H, CH$_3$C(O)$_2$), 1.40 (s, 3H, CH$_3$C(O)$_2$), 1.30 (s, 3H, CH$_3$C(O)$_2$), 1.29 (s, 3H, CH$_3$C(O)$_2$), 1.50–1.20 (m, 6H, 3 × CH$_2$), 0.90 (t, J = 7.1 Hz, 3H, CH$_3$), 0.89 (t, J = 7.3 Hz, 3H, CH$_3$); [minor isomer: δ 3.35 (br q, J = 7.1 Hz, 1H, CH–C=O)]. ^{13}C NMR major isomer: δ 173.3, 134.2, 127.4, 112.6, 109.5, 105.4, 83.6, 80.4, 76.0, 72.5, 67.6, 49.5, 34.7, 32.4, 31.6, 27.0 (2C), 26.5, 25.5, 22.4, 20.5, 14.1, 14.0; [minor isomer: δ 173.1, 133.4, 127.0, 80.5, 67.7, 44.3, 35.1, 31.9, 27.5, 25.4, 22.5, 20.4, 14.2]. MS (LSIMS): *m*/*z* (%) = 449 (M+Na$^+$, 22), 411 (46), 369 (100), 139 (38), 101 (53). HRMS calcd for $C_{23}H_{38}O_7Na^+$: 449.2515. Found: 449.2516.

4.5. (*R*)-(1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl) 2-propyloctanoate 5

A solution of ester **4** (106 mg, 0.25 mmol) in diethyl ether (3 mL) was hydrogenated over PtO_2 (balloon, 1 atm) for 12 h. The crude mixture was filtered through a short plug of silica and eluted with ethyl acetate/petroleum ether 5/95 to give compound **5** (107 mg, 0.25 mmol, quantitative). $[\alpha]_D^{20} = -28.0$ (*c* 1.23, CH_2Cl_2). ^{1}H NMR: δ 5.86 (d, J = 3.6 Hz, 1H, O–CH–O), 5.29 (d, J = 2.1 Hz, 1H, CH–O–C=O), 4.43 (d, J = 3.6 Hz, 1H, C*H*–CH(O)$_2$), 4.26–4.16 (m, 2H, O–C*H*–C*H*–CH$_2$O), 4.16–4.08 (m, 1H, 1/2 ABX, OC*H*$_A$H$_B$), 4.05–3.98 (m, 1H, 1/2 ABX, OCH$_A$*H*$_B$), 2.38 (tt, J = 8.9, 5.3 Hz, 1H, CH–C=O), 1.53 (s, 3H, CH$_3$C(O)$_2$), 1.41 (s, 3H, CH$_3$C(O)$_2$), 1.32 (s, 3H, CH$_3$C(O)$_2$), 1.30 (s, 3H, CH$_3$C(O)$_2$), 1.70–1.20 (m, 14H, 7 × CH$_2$), 0.91 (t, J = 7.2 Hz, 3H, CH$_3$), 0.88 (t, J = 6.8 Hz, 3H, CH$_3$). ^{13}C NMR: δ 175.2, 112.6, 109.6, 105.4, 83.8, 80.4, 75.9, 72.6, 67.8, 46.0, 34.9, 32.8, 31.9, 29.5, 27.5, 27.1 (2C), 26.5, 25.4, 22.9, 20.9, 14.3 (2C). MS (LSIMS): *m*/*z* (%) = 451 (M+Na$^+$, 44), 413 (56), 371 (100), 176 (50), 147 (68), 109 (90). HRMS calcd for $C_{23}H_{40}O_7Na^+$: 541.2672. Found: 541.2671.

4.6. (*R*)-Arundic acid 6

4.6.1. Saponification of 5. To a solution of ester **5** (89 mg, 208 μmol) dissolved in methanol (2 mL) and cooled to 0 °C was added hydrogen peroxide (35% in water, 81 mg, 0.83 mmol). An aqueous solution of lithium hydroxide monohydrate (1 M, 18 mg, 0.42 mmol) was then added dropwise. The cold bath was then allowed to warm up. After 6 h, a saturated solution of aqueous sodium hydrogen carbonate (10 mL) was added and the mixture extracted with dichloromethane (3 × 3 mL). The aqueous phase was acidified to pH 1 with 1 M HCl, the excess hydrogen peroxide quenched with aqueous sodium sulfite (2 M) and extraction was carried out with ethyl acetate (3 × 10 mL). The organic phases were dried over $MgSO_4$ and concentrated. The crude acid was purified by flash chromatography (ethyl acetate/petroleum ether, 10/90) to give (*R*)-**6** as a colourless oil (17 mg, 91 μmol, 44%). 88% ee (ee determined after conversion into the corresponding phenacyl ester (phenacyl bromide, Et_3N, CH_2Cl_2), Chiralcel OJ-H, heptane/isopropanol 99/1, 0.5 mL/min, 254 nm, 22.6 min (*S*) and 26.5 min (*R*)). $[\alpha]_D^{20} = -5.4$ (*c* 0.24, CH_2Cl_2), lit.[5a] $[\alpha]_D^{20} = -6.1$ (*c* 2.00, EtOH) for (*R*)-arundic acid. ^{1}H NMR: δ 2.37 (tt, J = 8.7, 5.3 Hz, 1H, CH–C=O), 1.70–1.55 (m, 2H, 2 × C*H*–CH–C=O), 1.55–1.20 (m, 12H, 2 × C*H*–CH–C=O and 5 × CH$_2$), 0.91 (t, J = 7.2 Hz, 3H, CH$_3$), 0.88 (t, J = 7.0 Hz, 3H, CH$_3$). ^{13}C NMR: δ 183.3, 45.7, 34.7, 32.5, 32.0, 29.6, 27.7, 22.9, 20.9, 14.4, 14.3.

4.6.2. Hydrogenolysis of (*R*)-7. A solution of ester (*R*)-**7** (62 mg, 0.22 mmol) in methanol (6 mL) was hydrogenated over Pd/C 10% (10% w/w, 6 mg, H_2 balloon, 1 atm) for 3 h. The solvent was then evaporated and the residue purified by flash chromatography (ethyl acetate/petroleum ether, 8/92) to give compound (*R*)-**6** (39 mg, 0.21 mmol, 95%). 89% ee (ee determined after

conversion into the corresponding phenacyl ester (phenacyl bromide, Et_3N, CH_2Cl_2), Chiralcel OJ-H, heptane/isopropanol 99/1, 0.5 mL/min, 254 nm, 22.6 min (*S*) and 26.5 min (*R*)). $[\alpha]_D^{20} = -5.4$ (*c* 0.39, CH_2Cl_2), lit.[5a] $[\alpha]_D^{20} = -6.1$ (*c* 2.00, EtOH) for (*R*)-arundic acid.

4.7. (*R*)-Benzyl 2-propyloctanoate 7

To a solution of ester **5** (112 mg, 0.26 mmol) in toluene (5 mL) under nitrogen was added freshly distilled benzyl alcohol (270 μL, 2.6 mmol) and $Ti(Oi\text{-}Pr)_4$ (120 μL, 0.39 mmol). The mixture was refluxed for 6 h. After cooling, the residue was purified by flash chromatography (diethyl ether/petroleum ether, 2/98) to give (*R*)-**7** as a colourless oil (70 mg, 0.25 mmol, 97%). 88% ee (Chiralcel OJ-H, heptane, 0.5 mL/min, 254 nm, 13.0 min (*R*) and 14.0 min (*S*)). $[\alpha]_D^{20} = -1.2$ (*c* 0.69, CH_2Cl_2). ^{1}H NMR: δ 7.40–7.30 (m, 5H, 5 × CH arom), 5.14 (d, J = 12.7 Hz, 1/2 AB, OCH_AH_B), 5.10 (d, J = 12.7 Hz, 1/2 AB, OCH_AH_B), 2.40 (tt, J = 8.9, 5.3 Hz, 1H, CH–C=O), 1.70–1.55 (m, 2H, 2 × C*H*–CH–C=O), 1.50–1.35 (m, 2H, 2 × C*H*–CH–C=O), 1.35–1.15 (m, 10H, 5 × CH_2), 0.88 (t, J = 7.1 Hz, 3H, CH_3), 0.86 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR: δ 176.7, 136.6, 128.8 (2C), 128.4 (2C), 128.3, 66.1, 45.8, 35.0, 32.8, 32.0, 29.5, 27.7, 22.9, 20.9, 14.4, 14.3. MS (CI): *m*/*z* (%) = 277 ($M+H^+$, 22), 91 (100). HRMS calcd for $C_{18}H_{22}O_2H^+$: 277.2167. Found: 277.2167.

4.8. Ethyl 2-(propylidene)octanoate 8

Potassium *tert*-butoxide (3.08 g, 27.5 mmol) was added at 0 °C to a stirred solution of ethyl (diethoxyphosphoryl)acetate (5 mL, 25 mmol) in DMSO (25 mL). After complete dissolution of potassium *tert*-butoxide, 1-iodohexane (4.1 mL, 27.5 mmol) was added. The mixture was stirred at 70 °C for 2.5 h, then poured into saturated NH_4Cl solution and extracted with diethyl ether. The organic layers were washed with a saturated solution of sodium thiosulfate, dried over $MgSO_4$ and concentrated to give ethyl 2-(diethoxyphosphoryl)octanoate as a pale yellow oil (7.67 g). The crude product (7.34 g) was dissolved in THF (7 mL) and added to a stirred suspension of NaH (60% in oil, 1.04 g, 26 mmol) in THF (20 mL) at 0 °C. After 1 h, a solution of propanal (1.38 g, 23.8 mmol) in THF (3 mL) was added at 0 °C. The mixture was allowed to warm up to rt overnight, then quenched with water and extracted with diethyl ether. The organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 2/98) to yield compound **8** (3.50 g, 16.5 mmol, 69%) as a mixture of *E*- and *Z*-isomers (*E*/*Z* = 54/46). ^{1}H NMR: *E*-isomer: δ 6.71 (t, J = 7.5 Hz, 1H, HC=C), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 2.30–2.10 (m, 4H, C*H*$_2$–CH=C and C*H*$_2$–C–CO_2Et), 1.50–1.20 (m, 8H, 4 × CH_2), 1.31 (t, J = 7.1 Hz, 3H, C*H*$_3$$CH_2O$), 1.05 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 7.0 Hz, 3H, CH_3); *Z*-isomer: δ 5.81 (br t, J = 7.3 Hz, 1H, HC=C), 4.20 (q, J = 7.2 Hz, 2H, OCH_2), 2.39 (quint, J = 7.5 Hz, 2H, C*H*$_2$–CH=C), 2.30–2.10 (m, 2H, C*H*$_2$–C–CO_2Et), 1.50–1.20 (m, 8H, 4 × CH_2), 1.32 (t, J = 7.1 Hz, 3H, C*H*$_3$$CH_2O$), 1.01 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR *E*-isomer: δ 168.4, 143.9, 132.5, 60.5, 34.8, 32.0, 29.7, 29.5, 27.0, 22.1, 14.5, 14.3, 13.7; *Z*-isomer: δ 168.7, 142.8, 132.2, 60.2, 34.8, 31.9, 29.3, 29.1, 23.2, 22.9, 14.5, 14.3 (2C).

4.9. 2-(Propylidene)octanoic acid 9

To a solution of ester **8** (554 mg, 2.6 mmol) in ethanol (4 mL) was added a solution of potassium hydroxide (700 mg, 12.5 mmol) in water (1 mL). The mixture was refluxed for 3 h. Water (20 mL) and diethyl ether (20 mL) were added and the two phases separated. The aqueous phase was acidified to pH = 1 with a 1 N HCl solution and extracted three times with diethyl ether. The organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 7/93) to afford acid **9** (409 mg, 2.2 mmol, 85%) as a colourless oil. ^{1}H NMR: *E*-isomer: δ 6.88 (t, J = 7.5 Hz, 1H, HC=C), 2.35–2.15 (m, 4H, C*H*$_2$–CH=C and C*H*$_2$–C–CO_2H), 1.50–1.20 (m, 8H, 4 × CH_2), 1.06 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 7.1 Hz, 3H, CH_3); *Z*-isomer: δ 6.00 (t, J = 7.5 Hz, 1H, HC=C), 2.50 (quint, J = 7.5 Hz, 2H, C*H*$_2$–CH=C), 2.35–2.15 (m, 2H, C*H*$_2$–C–CO_2H), 1.50–1.20 (m, 8H, 4 × CH_2), 1.03 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR *E*-isomer: δ 174.4, 146.9, 131.8, 34.7, 32.0, 29.7, 29.6, 26.7, 22.4, 14.3, 14.5; *Z*-isomer: δ 174.6, 147.2, 131.2, 34.7, 32.0, 29.6, 29.2, 23.5, 23.0, 14.3, 13.5. MS (CI): *m*/*z* (%) = 185 ($M+H^+$, 100), 167 (10).

4.10. (1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl)-2-(propylidene)octanoate 10

To a solution of dicyclohexylcarbodiimide (928 mg, 4.5 mmol) in dichloromethane (20 mL) was added a solution of acid **9** (553 mg, 3.0 mmol, *E*/*Z*, 67/33) in dichloromethane (1 mL). The mixture was cooled down to 0 °C and stirred for 30 min. A solution of 1,2:5,6-diisopropylidene-D-glucose (1.56 g, 6.0 mmol) and 4-dimethylaminopyridine (183 mg, 1.5 mmol) was then added and the resulting mixture allowed to warm up to rt and stirred overnight. The white precipitate was filtered off and the solvent evaporated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 5/95) to yield ester **10** (910 mg, 2.1 mmol, 71%, *E*/*Z*, 76/24) as a colourless oil. ^{1}H NMR: *E*-isomer: δ 6.74 (t, J = 7.5 Hz, 1H, HC=C), 5.88 (d, J = 3.6 Hz, 1H, O–CH–O), 5.29 (d, J = 2.0 Hz, 1H, CH–O–C=O), 4.52 (d, J = 3.6 Hz, 1H, C*H*–$CH(O)_2$), 4.30–4.20 (m, 2H, O–C*H*–C*H*–CH_2O), 4.15–4.05 (m, 1H, 1/2 ABX, OCH_AH_B), 4.04–3.95 (m, 1H, 1/2 ABX, OCH_AH_B), 2.35–2.05 (m, 4H, CH_2–C–CO_2 and C*H*$_2$–CH=C), 1.53 (s, 3H, $CH_3C(O)_2$), 1.41 (s, 3H, $CH_3C(O)_2$), 1.31 (s, 6H, 2 × $CH_3C(O)_2$), 1.50–1.20 (m, 8H, 4 × CH_2), 1.05 (t, J = 7.5 Hz, 3H, CH_3), 0.88 (t, J = 7.1 Hz, 3H, CH_3); [*Z*-isomer: δ 5.72 (t, J = 7.3 Hz, 1H, HC=C), 1.02 (t, J = 7.5 Hz, 3H, CH_3)]. ^{13}C NMR *E*-isomer: δ 166.7, 145.4, 131.7, 112.3, 109.4, 105.2, 83.5, 80.2, 76.3, 72.7, 67.4, 31.8, 29.4 (2C), 26.9 (2C), 26.3, 25.3, 22.7 (2C), 22.1, 14.2, 13.4. MS (LSIMS): *m*/*z*

(%) = 449 ($M+Na^+$, 16), 427 (17), 411 (29), 369 (100), 167 (89), 137 (47), 101 (29). HRMS calcd for $C_{23}H_{38}O_7Na^+$: 449.2515. Found: 449.2515.

4.11. (*S*)-(1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl) 2-(1-propenyl)octanoate 11

To a solution of ester **10** (188 mg, 0.44 mmol) in dichloromethane (45 mL) was added *N,N*-dimethylethanolamine (39 mg, 0.44 mmol). The mixture was transferred into quartz tubes (10 mm diameter) and deoxygenated with nitrogen for 5 min. The tubes were placed around a quartz tube in which a short wavelength OSRAM lamp was introduced. The irradiation was carried out at −40 °C and monitored by TLC. After 6 h, the solvent was evaporated and the crude product purified by flash chromatography (ethyl acetate/petroleum ether, 5/95) to yield compound **11** (146 mg, 0.34 mmol, 78%) as a mixture of diastereoisomers in a 26/74 ratio of *E*- and *Z*-isomers. ^{1}H NMR: major isomer: δ 5.87 (d, J = 3.7 Hz, 1H, O–CH–O), 5.65–5.50 (m, 1H, CH=C), 5.45–5.28 (m, 1H, CH=C), 5.27 (d, J = 1.9 Hz, 1H, CH–O–C=O), 4.43 (d, J = 3.7 Hz, 1H, C*H*–CH(O)$_2$), 4.24–4.14 (m, 2H, O–C*H*–C*H*–CH$_2$O), 4.12–4.05 (m, 1H, 1/2 ABX, OCH_AH$_B$), 4.02–3.95 (m, 1H, 1/2 ABX, OCH$_A H_B$), 2.96 (br q, J = 7.5 Hz, 1H, CH–C=O), 1.67 (dd, J = 6.4, 1.5 Hz, 3H, CH_3–CH=C), 1.52 (s, 3H, CH$_3$C(O)$_2$), 1.40 (s, 3H, CH$_3$C(O)$_2$), 1.30 (s, 3H, CH$_3$C(O)$_2$), 1.29 (s, 3H, CH$_3$C(O)$_2$), 1.80–1.20 (10H, m, 5 × CH$_2$), 0.87 (t, J = 6.8 Hz, 3H, CH$_3$); [minor isomer: δ 3.35 (br q, J = 7.5 Hz, 1H, CH–C=O)]. ^{13}C NMR major isomer: δ 173.3, 128.7 (2C), 112.6, 109.5, 105.4, 83.6, 80.4, 76.0, 72.5, 67.6, 49.6, 32.6, 31.9, 29.3, 27.3, 27.0 (2C), 26.5, 25.4, 22.8, 18.1, 14.3; [minor isomer: δ 173.2, 128.2, 127.5, 76.1, 44.1, 32.8, 13.4]. MS (LSIMS): m/z (%) = 449 ($M+Na^+$, 16), 411 (49), 369 (57), 266 (16), 167 (100), 101 (48). HRMS calcd for $C_{23}H_{38}O_7Na^+$: 449.2515. Found: 449.2516.

4.12. (*S*)-(1,2:5,6-Di-*O*-isopropyliden-α-D-glucofuranose-3-*O*-yl) 2-propyloctanoate 12

A solution of ester **11** (107 mg, 0.25 mmol) in diethyl ether (3 mL) was hydrogenated over PtO_2 (balloon, 1 atm) for 12 h. The crude mixture was filtered through a short plug of silica and eluted with ethyl acetate/petroleum ether 5/95 to give compound **12** (103 mg, 0.24 mmol, 96%). $[\alpha]_D^{20} = -23.0$ (c 1.45, CH_2Cl_2). ^{1}H NMR: δ 5.86 (d, J = 3.6 Hz, 1H, O–CH–O), 5.29 (d, J = 2.2 Hz, 1H, CH–O–C=O), 4.42 (d, J = 3.6 Hz, 1H, C*H*–CH(O)$_2$), 4.26–4.16 (m, 2H, O–C*H*–C*H*–CH$_2$O), 4.16–4.08 (m, 1H, 1/2 ABX, OCH_AH$_B$), 4.05–3.98 (m, 1H, 1/2 ABX, OCH$_A H_B$), 2.38 (tt, J = 9.1, 5.3 Hz, 1H, CH–C=O), 1.52 (s, 3H, CH$_3$C(O)$_2$), 1.40 (s, 3H, CH$_3$C(O)$_2$), 1.31 (s, 3H, CH$_3$C(O)$_2$), 1.30 (s, 3H, CH$_3$C(O)$_2$), 1.70–1.20 (m, 14H, 7 × CH$_2$), 0.89 (t, J = 7.3 Hz, 3H, CH$_3$), 0.87 (t, J = 6.8 Hz, 3H, CH$_3$). ^{13}C NMR: δ 175.2, 112.6, 109.6, 105.4, 83.7, 80.4, 75.8, 72.5, 67.8, 45.8, 34.9, 32.7, 31.9, 29.4, 27.7, 27.0 (2C), 26.5, 25.4, 22.8, 20.7, 14.3, 14.2. MS (LSIMS): m/z (%) = 451 ($M+Na^+$, 31), 413 (65), 371 (100), 169 (22), 101 (67). HRMS calcd for $C_{23}H_{40}O_7Na^+$: 451.2672. Found: 451.2675.

4.13. (*S*)-Arundic acid 6

4.13.1. Saponification of 12. To a solution of ester **12** (80 mg, 184 μmol) dissolved in methanol (2 mL) and cooled to 0 °C was added hydrogen peroxide (35% in water, 72 mg, 0.74 mmol). An aqueous solution of lithium hydroxide monohydrate (1 M, 16 mg, 0.37 mmol) was then added dropwise. The cold bath was allowed to warm up. After 6 h, a saturated solution of aqueous sodium hydrogen carbonate (10 mL) was added and the mixture was extracted with dichloromethane (3 × 3 mL). The aqueous phase was acidified to pH 1 with 1 M HCl, the excess hydrogen peroxide quenched with aqueous sodium sulfite (2 M) and extraction was carried out with ethyl acetate (3 × 10 mL). The organic phases were dried over $MgSO_4$ and concentrated. The crude acid was purified by flash chromatography (ethyl acetate/petroleum ether, 5/95) to give (*S*)-**6** as a colourless oil (17 mg, 91 μmol, 50%). 88% ee (ee determined after conversion into the corresponding phenacyl ester (phenacyl bromide, Et_3N, CH_2Cl_2), Chiralcel OJ-H, heptane/isopropanol 99/1, 0.5 mL/min, 254 nm, 22.6 min (*S*) and 26.5 min (*R*)). $[\alpha]_D^{20} = +5.5$ (c 0.20, CH_2Cl_2), lit.[5a] $[\alpha]_D^{20} = -6.1$ (c 2.00, EtOH) for (*R*)-arundic acid. ^{1}H NMR: δ 2.37 (tt, J = 8.7, 5.3 Hz, 1H, CH–C=O), 1.70–1.55 (m, 2H, 2 × C*H*–CH–C=O), 1.55–1.20 (m, 12H, 2 × C*H*–CH–C=O and 5 × CH$_2$), 0.91 (t, J = 7.2 Hz, 3H, CH$_3$), 0.88 (t, J = 7.0 Hz, 3H, CH$_3$). ^{13}C NMR: δ 183.3, 45.7, 34.7, 32.5, 32.0, 29.6, 27.7, 22.9, 20.9, 14.4, 14.3.

4.13.2. Hydrogenolysis of (*S*)-7. A solution of ester (*S*)-**7** (59 mg, 0.21 mmol) in methanol (6 mL) was hydrogenated over Pd/C 10% (10% w/w, 6 mg, H_2 balloon, 1 atm) for 6 h. The solvent was then evaporated and the residue purified by flash chromatography (ethyl acetate/petroleum ether, 8/92) to give compound (*S*)-**6** (38 mg, 0.20 mmol, 95%). 88% ee (ee determined after conversion into the corresponding phenacyl ester (phenacyl bromide, Et_3N, CH_2Cl_2), Chiralcel OJ-H, heptane/isopropanol 99/1, 0.5 mL/min, 254 nm, 22.6 min (*S*) and 26.5 min (*R*)). $[\alpha]_D^{20} = +5.5$ (c 0.38, CH_2Cl_2), lit.[5a] $[\alpha]_D^{20} = -6.1$ (c 2.00, EtOH) for (*R*)-arundic acid.

4.14. (*S*)-Benzyl 2-propyloctanoate 7

To a solution of ester **12** (111 mg, 0.26 mmol) in toluene (5 mL) under nitrogen were added freshly distilled benzyl alcohol (270 μL, 2.6 mmol) and Ti(O*i*-Pr)$_4$ (120 μ L, 0.39 mmol). The mixture was refluxed for 7 h. After cooling, the residue was purified by flash chromatography (diethyl ether/petroleum ether, 2/98) to give (*S*)-**7** as a colourless oil (66 mg, 0.24 mmol, 92%). 87% ee (Chiralcel OJ-H, heptane, 0.5 mL/min, 254 nm, 13.0 min (*R*) and 14.0 min (*S*)). $[\alpha]_D^{20} = +1.2$ (c 0.66, CH_2Cl_2). Spectroscopic data identical to (*R*)-**7**.

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