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TETRAHEDRON: *ASYMMETRY*

Diastereoselective photodeconjugation of chiral α,β-unsaturated esters

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Abstract—Chiral alcohols available in both enantiomeric forms have been tested for the diastereoselective photochemical deconjugation of 2,4-dimethylpentenoic acid esters. (*R*)-Pantolactone afforded selectively the (2*R*)-β,γ-unsaturated ester in good yield and high d.e. (89%), while analogous use of (*S*)-pantolactone gave the (2*S*)-stereoisomer with similar selectivity. © 2001 Elsevier Science Ltd. All rights reserved.

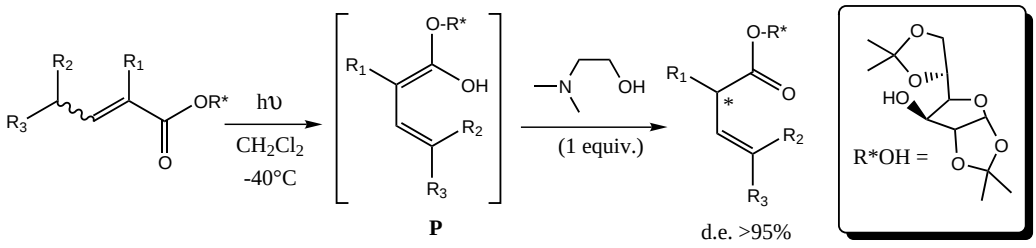
1. Introduction

Some years ago, we reported a useful and highly diastereoselective procedure to prepare α-substituted β,γ-unsaturated esters from α,β-unsaturated isomers under UV activation. We found that diacetone D-glucose (R*OH) was an effective chiral auxiliary for this photochemical transformation[1a] and the reaction was, therefore, applied to the synthesis of a number of natural products.[2]

The success of this method was based on the stereoselective protonation of a prochiral photodienol intermediate. In the case of diacetone D-glucose derivatives, the 5,6-isopropylidene group shielded one face of the dienol intermediate **P** and, therefore, protonation by an achiral β-aminoalcohol took place at the less hindered face[1] (Scheme 1). Because diacetone L-glucose is not readily available,[3] this diastereoselective method was not to date able to afford compounds with the opposite configuration at C(2). In order to find a cheap and efficient chiral compound to answer to this purpose, we tested the optically active and commercially available alcohols **2a**–**2d**. These compounds were esterified with 2,4-dimethyl-2-pentenoic acid **1** by the standard DCC esterification procedure,[4] which furnished substrates **3a**–**3d** in moderate to good yields (Scheme 2).

Irradiation of the conjugated esters was performed at –40°C in the presence of (achiral) 2-(*N*,*N*-dimethylamino)ethan-1-ol. The reaction was efficient with esters **3a**–**3c** and furnished esters **4a**–**4c** in yields of >80% (Table 1). In contrast, compound **3d** slowly degraded after a long irradiation period, which could be connected to the presence of the sulfonamide functionality which is cleaved under photochemical activation.[5]

The diastereoselectivities were difficult to estimate directly for esters **4a** and **4b**. In contrast, the d.e. for **4c** was easily measured from the ^{1}H NMR spectrum of the crude compound and determined as 88%. However, the diastereoselectivities for **4a** and **4b** could be readily



Scheme 1.

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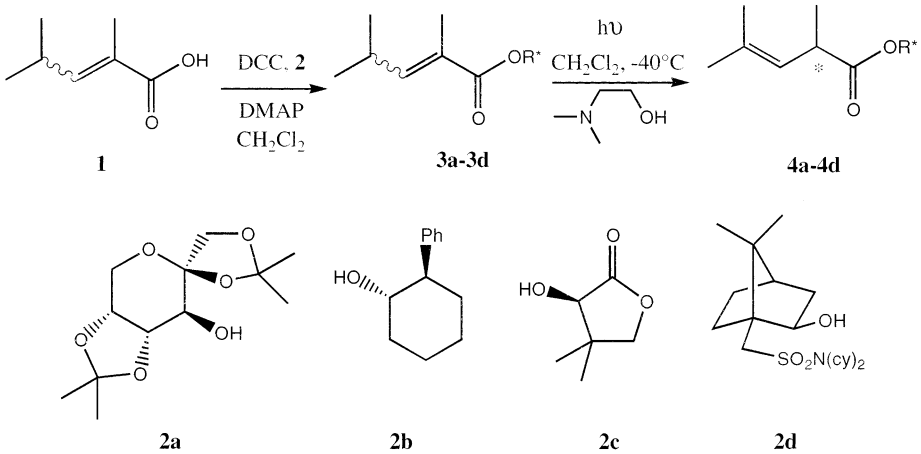


Scheme 2.

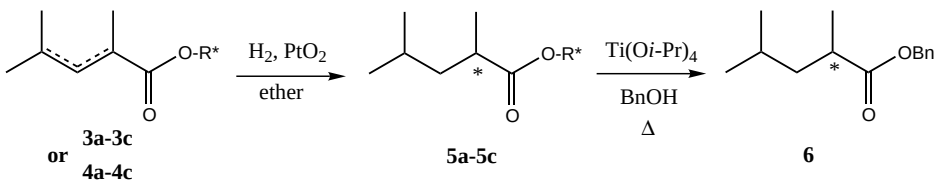
Table 1. Preparation and irradiation of esters **3**

Alcohol **2**	Ester **3**	Yield (%) (*E*)/(*Z*)	Ester **4**	Yield (%)	D.e. (%)
2a	**3a**	85 (55/45)	**4a**	81	85[a]
2b	**3b**	77 (65/35)	**4b**	81	83[a]
2c	**3c**	48 (72/28)	**4c**	82	88
2d	**3d**	30 (7/3)	**4d**	33	67

[a] D.e. measured on saturated ester **5**.

determined after reduction of the isolated C=C bond by hydrogenation over PtO_2 and a d.e. of 85% for **5a** and 83% for **5b** were established. The absolute configuration of the new stereogenic center was unambiguously determined by a free racemization transesterification process[6] of esters **5a**–**5c** with benzyl alcohol to the same ester **6** (Scheme 3). By simple comparison of the specific rotation of **6** with literature data,[1a] we were able to establish the absolute configuration of the newly created stereogenic center (it should be noted that conjugated esters **3a**–**3c** were also directly reduced to compounds **5a**–**5c** without significant levels of induction) (Table 2).

By using the three chiral alcohols **2a**–**2c**, we obtained the same (*R*)-configuration, already observed with the diacetone D-glucose moiety. Fortunately, among these three alcohols, the presence of a single stereogenic center in **2c** allows easy preparation of the enantiomeric form (*S*)-**2c**. Recent published procedures[7,8] based on a Mitsunobu reaction[9] can effectively furnish this compound. Therefore, the (2*S*)-deconjugated ester



Scheme 3.

Table 2. Access to chiral esters **5**

Substrate	Yield of **5** (%)	D.e. (%)	Benzyl ester **6**	Config.
3a	66	15		Not det.
4a	71	85	40% ($[\alpha]_D = -6.4$ (*c* 0.2, CH_2Cl_2))	(*R*)
3b	92	5		Not det.
4b	84	83	88% ($[\alpha]_D = -6.6$ (*c* 0.9, CH_2Cl_2))	(*R*)
3c	85	4		Not det.
4c	95	89	75% ($[\alpha]_D = -8.0$ (*c* 0.7, CH_2Cl_2))	(*R*)

(*S*)-**4c** can be prepared by simple switching of one pantolactone enantiomer for the other as detailed in Scheme 4.

2. Conclusion

In summary, new chiral alkoxy groups have been successfully tested for the diastereoselective photodeconjugation of 2,4-dimethyl-2-pentenoate esters. Of the alcohols studied the pantolactonyl group is the most suitable alcohol to obtain both (*S*)- and (*R*)-α-alkylated acid derivatives with high selectivity.

3. Experimental

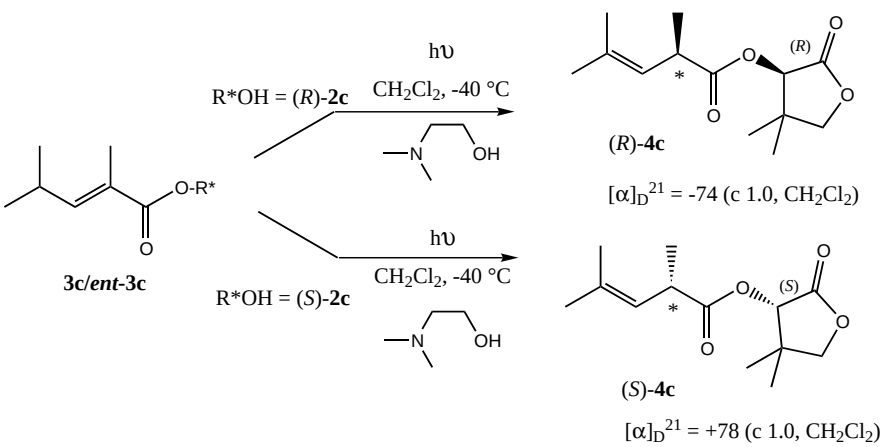
^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker AM 300 or DRX 500 instrument. FT-IR were recorded on a Perkin–Elmer Spectrum One. Optical rotations were measured on a Perkin–Elmer 343 polarimeter. Mass spectra were obtained on a Finigan-MAT 95 XL instrument. Flash chromatography was performed on silica gel 60 (40–63 mesh).

3.1. General procedure for esterification reactions

To a solution of 2,4-dimethyl-2-pentenoic acid **1** (0.628 g, 3.3 mmol) in methylene chloride (10 mL) was added DMAP (0.134 g, 1.1 mmol) followed by the chiral alcohol **2a**–**2d** (3.3 mmol). The reaction mixture was cooled to 0°C and a solution of dicyclohexylcarbodiimide (0.678 g, 3.3 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise. After stirring the mixture for 5 min at 0°C, the cooling bath was removed and the mixture stirred overnight at rt. Urea was filtered off and the solvent removed by evaporation under reduced pressure. Purification of the crude product by flash chromatography on silica (eluent: AcOEt/hexanes: 1/9) afforded ester **3**.

3.1.1. (1,2;4,5-Di-*O*-isopropyliden-α-D-fructopyranose-3-*O*-yl) 2,4-dimethyl-2-pentenoate 3a. Yield: 85% (*E*)/(*Z*)=55/45). Mp: 96°C. ^{1}H NMR ($CDCl_3$, 300 MHz): (*E*)-Isomer: δ 6.70 (dq, J=9.5 Hz, J=1.47 Hz, 1H), 5.21 (d, J=8.1 Hz, 1H), 4.40–4.30 (m, 1H), 4.28–4.21 (m, 1H), 4.20–4.05 (m, 2H), 3.95 (d, J=5.1 Hz, 1H), 3.80 (d, J=9.5 Hz, 1H), 2.64 (dh, J=9.5 Hz, J=6.6 Hz, 1H), 1.86 (d, J=1.5 Hz, 3H), 1.60 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 0.99 (d, J=6.6 Hz, 6H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 167.6 (C), 150.5 (CH), 124.7 (C), 111.9 (C), 109.5 (C), 75.1 (CH), 74.9 (CH), 73.7 (2CH), 71.6 (CH_2), 69.9 (CH), 27.9 (CH_3), 27.8 (CH), 26.0 (CH_3), 22.6 (CH_3), 21.8 (CH_3), 20.6 (CH_3), 12.2 ($2CH_3$). (*Z*)-Isomer: δ 5.78 (dq, J=10.3 Hz, J=1.5 Hz, 1H), 5.22 (d, J=8.1 Hz, 1H), 4.4–4.3 (m, 1H), 4.28–4.21 (m, 1H), 4.20–4.05 (m, 2H), 3.98 (d, J=5.1 Hz, 1H), 3.84 (d, J=9.5 Hz, 1H), 3.30 (dh, J=10.3 Hz, J=5.14 Hz, 1H), 1.91 (d, J=1.5 Hz, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.02 (d, J=5.1 Hz, 6H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 167.1 (C), 151.4 (CH), 124.0 (C), 112.0 (C), 103.9 (C), 75.1 (CH), 74.9 (CH), 73.7 (2CH), 69.9 (CH), 60.3 (CH_2), 28.8 (CH_3), 27.7 (CH), 26.0 (CH_3), 22.6 (CH_3), 21.8 (CH_3), 20.6 (CH_3), 12.2 ($2CH_3$). IR (*E*+*Z*): 2980, 2960, 2940, 2870, 1720, 1650, 1460, 1370 cm^{-1}. (*E*)-Isomer $[\alpha]_D^{21}=-115$ (*c* 1.0, CH_2Cl_2). (*Z*)-Isomer $[\alpha]_D^{21}=-98$ (*c* 0.1, CH_2Cl_2). MS: *m*/*z*: 371 (M+H$^+$), 313, 111. HRMS: $[C_{19}H_{30}O_7+H]^+$ requires: 371.20697. Found: 371.20705. UV (CH_2Cl_2): $\varepsilon_{238}=2400$.

3.1.2. (1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl 2,4-dimethyl-2-pentenoate 3b. Yield: 77%; (*E*)/(*Z*)=65/35. (*E*)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 6,24 (dq, J=9.5 Hz, J=1.5 Hz, 1H), 4.92 (dt, J=10.3 Hz, J=4.4 Hz, 1H), 2.74 (dt, J=10.8 Hz, J=3.7 Hz, 1H), 2.48 (dh, J=9.5 Hz, J=6.6 Hz, 1H), 1.60 (d, J=1.5 Hz, 3H), 2.4–2.1 (m, 2H), 2.00–1.70 (m, 2H), 1.70–1.30 (m, 4H), 0.93 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 167.9 (C), 148.3 (CH), 143.3 (C), 128.8 (C), 128.14 (2CH), 127.5 (2CH), 126.2 (CH), 76.6 (CH), 50.0 (CH), 33.5 (CH_2), 32.3 (CH_2), 27.6 (CH_3), 25.9 (CH_2), 24.8 (CH_2), 21.8 (CH), 12.0 ($2CH_3$). IR: 2930, 2860, 1710, 1650, 1450, 1250, 1160, 1090, 750, 700 cm^{-1}. $[\alpha]_D^{21}=-66$ (0.1, $CHCl_3$). (*Z*)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 5.43 (dq, J=9.5 Hz, J=1.5 Hz, 1H), 5.07 (dt, J=10.3 Hz, J=4.4 Hz, 1H), 2.80–2.60 (m, 2H), 1.60 (d, J=1.5 Hz, 3H), 2.40–1.00 (m, 8H),



Scheme 4.

0.81 (d, $J=6.6$ Hz, 3H), 0.77 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 167.9 (C), 147.5 (CH), 143.3 (C), 128.8 (C), 128.7 (2CH), 127.9 (2CH), 125.5 (CH), 74.3 (CH), 53.2 (CH), 34.4 (CH_2), 33.3 (CH_2), 27.7 (CH_3), 26.0 (CH_2), 25.0 (CH_2), 21.8 (CH), 12.0 ($2CH_3$). IR: 2930, 2860, 1720, 1650, 1450, 1230, 1160, 700 cm^{-1}. $[\alpha]_D^{21}=-22$ (c 1.0, CH_2Cl_2). UV (CH_2Cl_2): $\varepsilon_{236}=2350$. MS (E)+(Z): m/z: 288 (M+H$^+$), 158, 111, 91, 83. HRMS: $[C_{19}H_{27}O_2]^+$ requires: 287.20110. Found: 287.20125.

3.1.3. (*3R*)-(−)-(4,4−Dimethyl-2-oxotetrahydrofuran-3-yl) 2,4-dimethyl-2-pentenoate 3c. Yield: 48%; (Z)/(E)= 28/72. (E)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (dq, $J=9.5$ Hz, $J=1.5$ Hz, 1H), 5.44 (s, 1H), 4.08 (d, $J=8.8$ Hz, 1H), 4.05 (d, $J=8.8$ Hz, 1H), 2.68 (dh, $J=9.6$ Hz, $J=1.5$ Hz, 1H), 1.89 (d, $J=1.5$ Hz, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.05 (d, $J=1.5$ Hz, 3H), 1.03 ($J=1.5$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 173.9 (C), 172.1 (C), 134.7 (C), 122.8 (CH), 76.0 (CH_2), 74.6 (CH), 40.0 (C), 38.6 (CH_3), 25.4 (CH), 22.8 (CH_3), 19.6 (CH_3), 18.0 (CH_3), 17.9 (CH_3). (Z)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (dq, $J=10.0$ Hz, $J=1.5$ Hz, 1H), 5.46 (s, 1H), 4.07 (s, 1H), 4.06 (s, 1H), 3.30 (dh, $J=10.0$ Hz, $J=1.5$ Hz, 1H), 1.94 (d, $J=1.5$ Hz, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.02 (d, $J=1.5$ Hz, 3H), 1.00 ($J=1.5$ Hz, 3H). IR: 2970, 2930, 2870, 1790, 1720, 1650, 1470, 1370, 1240, 1150, 1100 cm^{-1}. UV (CH_2Cl_2): $\varepsilon_{238}=2460$. (E)-Isomer $[\alpha]_D^{21}=+6$ (c 1.0, CH_2Cl_2). (Z)-Isomer $[\alpha]_D^{21}=+7$ (c 0.1, CH_2Cl_2). MS: m/z: 240 (M$^{+\bullet}$+1), 128, 111, 83. HRMS $[C_{13}H_{20}O_4]^+$ requires: 240.13615. Found: 240.13618.

3.1.4. (−)-1-[(Dicyclohexylsulfonamoyl)-methyl]-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl 2,4-dimethyl-2-pentenoate 3d. Yield: 30%; (E)/(Z)=7/3. (E)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, $J=9.5$ Hz, 1H), 4.09 (dd, $J=7.3$ Hz, $J=4.4$ Hz, 1H), 3.40–3.20 (m, 3H), 2.69 (s, 1H), 2.64 (s, 1H), 2.00–1.50 (m, 27H), 1.50–1.20 (m, 4H), 1.20–1.00 (m, 8H), 0.80 (s, 3H). (Z)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (d, $J=9.5$ Hz, 1H), 4.09 (dd, $J=7.3$ Hz, $J=4.4$ Hz, 1H), 2.69 (s, 1H), 2.64 (s, 1H), 2.8–2.5 (m, 1H), 2.00–1.50 (m, 27H), 1.50–1.20 (m, 4H), 1.20–1.00 (m, 8H), 0.80 (s, 3H). UV (CH_2Cl_2): $\varepsilon_{238}=2320$. MS: m/z: 507, 464, 397, 380, 327, 245, 181, 138, 111. (E)-Isomer $[\alpha]_D^{21}=-25$ (c 1.0, CH_2Cl_2). (Z)-Isomer $[\alpha]_D^{21}=-0.4$ (c 1.0, CH_2Cl_2). HRMS $[C_{29}H_{49}NO_4S]^+$ requires: 507.33823. Found: 507.33869.

3.2. General procedure for irradiation of α,β-unsaturated esters

To a solution of the ester **3** (10 mmol) in methylene chloride (100 mL) was added *N*,*N*-dimethylethanolamine. The resulting solution first deoxygenated by a stream of nitrogen for 10 min was poured into 12 mm diameter quartz tubes which were fitted with septa and placed around a transparent quartz Dewar equipped with a short wavelength OSRAM lamp ($\lambda=254$ nm). The irradiation was carried out at −40°C. After total disappearance of the starting material (thin-layer chromatography control), the solvent was removed by concentration. The deconjugated ester was purified by flash chromatography (eluent: AcOEt/petrol ether: 5/95).

3.2.1. (1,2;4,5-Di-*O*-isopropyliden-α-D-fructopyranose-3-*O*-yl) 2,4-dimethyl-3-pentenoate 4a. Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (d, $J=8.8$ Hz, 1H), 5.10 (d, $J=7.3$ Hz, 1H), 4.30–4.18 (m, 2H), 4.13–4.07 (m, 2H), 3.93 (d, $J=9.5$ Hz, 1H), 3.76 (d, $J=8.8$ Hz, 1H), 3.38 (dq, $J=8.8$ Hz and 6.6 Hz, 1H), 1.70 (s, 3H), 1.65 (s, 3H), 1.54 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.26 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 174.8 (C), 134.4 (C), 123.3 (CH), 111.8 (C), 109.5 (C), 103.7 (C) 74.8 (CH), 73.6 (CH), 71.6 (CH_2), 71.6 (CH_2), 69.9 (CH), 39.1 (CH), 27.7 (CH_3), 26.3 (CH_3), 26.3 (CH_3), 26.0 (CH_3), 25.6 (CH_3), 18.2 (CH_3), 18.0 (CH_3). MS m/z: 371 (M$^{+\bullet}$+1), 313. $[\alpha]_D^{21}=-17$ (c 1.0, CH_2Cl_2). UV (CH_2Cl_2): $\varepsilon_{232}=1690$. HRMS: $[C_{19}H_{30}O_7+H]^+$ requires: 371.20697. Found: 371.20696.

3.2.2. (1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl 2,4-dimethylpent-3-enoate 4b. Yield: 81%. Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 4.97 (dt, $J=11.0$ Hz, $J=4.4$ Hz, 1H), 4.74 (dh, $J=8.8$ Hz, $J=1.5$ Hz, 1H), 3.02 (dq, $J=8.8$ Hz, $J=6.6$ Hz, 1H), 2.67 (dt, $J=11.0$ Hz, $J=3.7$ Hz, 1H), 1.53 (s, 3H), 1.37 (d, $J=1.5$ Hz, 3H), 2.2–1.7 (m, 4H), 1.7–1.3 (m, 4H), 0.92 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 174.4 (C), 143.0 (C), 133.3 (C), 128.0 (CH), 127.3 (2CH), 126.0 (2CH), 123.6 (CH), 75.2 (CH), 49.7 (CH), 38.8 (CH), 34.1 (CH_2), 32.1 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 24.6 (CH_2), 17.5 (CH_3), 17.4 (CH_3). Minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 4.97 (dt, $J=11.0$ Hz, $J=4.4$ Hz, 1H), 4.74 (dh, $J=8.8$ Hz, $J=1.5$ Hz, 1H), 3.02 (dq, $J=11.0$ Hz, $J=6.6$ Hz, 1H), 2.67 (dt, $J=11.0$ Hz, $J=3.7$ Hz, 1H), 1.53 (s, 3H), 1.37 (d, $J=1.5$ Hz, 3H), 2.2–1.7 (m, 4H), 1.7–1.3 (m, 4H), 0.89 (d, $J=6.6$ Hz, 3H). IR: 2930, 2860, 1730, 1450, 1170, 700 cm^{-1}. MS: m/z: 286 (M$^{+\bullet}$), 175, 158, 111, 91, 83. $[\alpha]_D^{21}=-11$ (c 1.0, CH_2Cl_2). HRMS: $[C_{19}H_{26}O_2+H]^+$ requires: 287.20115. Found: 287.20111.

3.2.3. (*3R*)-(−)-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl) 2,4-dimethyl-3-pentenoate 4c. Yield: 82% (d.e.=87.5% according to ^{1}H NMR). Major diastereoisomer (2*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (s, 1H), 5.19 (dtt, $J=9.5$ Hz, $J=1.5$ Hz and 1.5 Hz, 1H), 4.04 (d, $J=8.8$ Hz, 1H), 4.01 (d, $J=8.8$ Hz, 1H), 3.46 (dq, $J=9.6$ Hz, $J=6.6$ Hz, 1H), 1.73 (d, $J=1.5$ Hz, 3H), 1.67 (d, $J=1.5$ Hz, 3H), 1.29 (d, $J=6.6$ Hz, 3H), 1.19 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 174.0 (C), 172.2 (C), 134.8 (C), 122.8 (CH), 76.0 (CH_2), 74.6 (CH), 40.1 (C), 38.6 (CH), 25.5 (CH_3), 22.9 (CH_3), 19.7 (CH_3), 18.1 (CH_3), 18.0 (CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 174.0 (C), 172.2 (C), 134.8 (C), 122.8 (CH), 76.0 (CH_2), 74.6 (CH), 40.1 (C), 38.6 (CH), 25.5 (CH_3), 22.9 (CH_3), 19.7 (CH_3), 18.1 (CH_3), 18.0 (CH_3). Minor diastereoisomer (2*S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (s, 1H), 5.19 (dtt, $J=9.5$ Hz, $J=1.5$ Hz and 1.5 Hz, 1H), 4.04 (d, $J=8.8$ Hz, 1H), 4.01 (d, $J=8.8$ Hz, 1H), 3.46 (dq, $J=9.6$ Hz, $J=6.6$ Hz, 1H), 1.73 (d,

$J=1.5$ Hz, 3H), 1.70 (d, $J=1.5$ Hz, 3H), 1.29 (d, $J=6.6$ Hz, 3H), 1.19 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 174.0 (C), 172.2 (C), 134.8 (C), 123.2 (CH), 76.0 (CH_2), 74.6 (CH), 40.1 (C), 38.5 (CH), 25.5 (CH_3), 22.8 (CH_3), 19.5 (CH_3), 18.1 (CH_3), 17.4 (CH_3). IR: 2970, 2930, 2880, 1790, 1750, 1460, 1380, 1150, 1090 cm^{-1}. MS (m/z): 240 ($M^{+\bullet}$), 110, 83. UV (CH_2Cl_2): $\varepsilon_{229}=890$. $[\alpha]_D^{21}=-74$ (c 1.0, CH_2Cl_2). HRMS: $[C_{12}H_{20}O_3]^+$ requires: 241.14398. Found: 241.14359.

3.2.4. (–)-1-[(Dicyclohexylsulfonamoyl)-methyl]-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl,2,4-dimethylpent-3-enoate 4d.

Yield: 33% (d.e. = 67%).

Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (d, $J=8.8$ Hz, 1H), 4.89 (dd, $J=8.1$ Hz, $J=3.7$ Hz, 1H), 3.40–3.10 (m, 3H), 2.67 (d, $J=5.9$ Hz, 1H), 2.63 (d, $J=5.9$ Hz, 1H), 1.71 (s, 3H), 1.62 (s, 3H), 2.00–1.50 (m, 21H), 1.50–1.00 (m, 9H), 0.98 (s, 3H), 0.88 (s, 3H). Minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (d, $J=8.8$ Hz, 1H), 4.89 (dd, $J=8.1$ Hz, $J=3.7$ Hz, 1H), 4.20–4.00 (m, 1H), 3.40–3.10 (m, 2H), 2.67 (d, $J=5.9$ Hz, 1H), 2.63 (d, $J=5.9$ Hz, 1H), 1.71 (s, 3H), 1.62 (s, 3H), 2.00–1.50 (m, 21H), 1.50–1.00 (m, 9H), 0.98 (s, 3H), 0.88 s, 3H). IR: 3520, 2930, 2860, 1730, 1650, 1450, 1330, 1170, 1140, 1050 cm^{-1}. MS: m/z: 507 ($M^{+\bullet}$+1), 380, 327, 246, 181, 135, 83. HRMS: $[C_{29}H_{49}NO_4S+H]^+$ requires: 508.34605. Found: 508.34628.

3.3. General procedure for hydrogenation of α,β-unsaturated esters 3a–3c and deconjugated isomers 4a–4c

A solution of ester **3** or **4** (3 mmol) in ether (15 mL) was reduced over PtO_2 with hydrogen under 1 atm within 3 hours. After filtration over Celite and washing with ether, compound **5** (0.40 g, 0.92 mmol) was isolated as an oil and purified by flash chromatography (eluent: AcOEt/hexanes: 1/19).

3.3.1. (1,2;4,5-Di-*O*-isopropyliden-α-D-fructopyranose-3-*O*-yl) 2,4-dimethylpentanoate 5a.

From **3a**: Yield: 66% (d.e. = 15% according to ^{13}C NMR).
From **4a**: Yield: 71% (d.e. = 85% according to ^{13}C NMR).

Major diastereoisomer (2*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (d, $J=8.1$ Hz, 1H), 4.30–4.24 (m, 1H), 4.23–4.18 (m, 1H), 4.13–4.07 (m, 2H), 3.93 (d, $J=9.5$ Hz, 1H), 3.80 (d, $J=9.5$ Hz, 1H), 2.59 (tq, $J=7.4$ Hz, $J=6.6$ Hz, 1H), 1.70–1.55 (m, 2H), 1.53 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.30–1.10 (m, 1H), 1.18 (d, $J=6.6$ Hz, 3H), 0.92 (d, $J=6.6$ Hz, 3H), 0.87 (d, $J=5.9$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 176.5 (C), 111.8 (C), 109.5 (C), 103.8 (C) 74.8 (CH), 73.8 (CH), 71.8 (CH_2), 69.8 (CH), 60.5 (CH_2), 42.6 (CH_2), 37.6 (CH), 27.7 (CH_3), 26.4 (CH_3), 26.2 (CH_3), 26.2 (CH_3), 25.7 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 17.5 (CH_3). Minor diastereoisomer (2*S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (d, $J=7.4$ Hz, 1H), 4.30–4.24 (m, 1H), 4.23–4.18 (m, 1H), 4.13–4.07 (m, 2H), 3.93 (d, $J=9.5$ Hz, 1H), 3.80 (d, $J=9.5$ Hz, 1H), 2.59 (tq, $J=7.4$ Hz, $J=6.6$ Hz, 1H), 1.70–1.55 (m, 2H), 1.53 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.30–1.10 (m, 1H), 1.18 (d, $J=6.6$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 0.88 (d, $J=5.9$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 176.5 (C), 111.8 (C), 109.5 (C), 103.8 (C) 74.8 (CH), 73.8 (CH), 71.8 (CH_2), 69.8 (CH), 60.5 (CH_2), 42.7 (CH_2), 37.6 (CH), 27.7 (CH_3), 26.4 (CH_3), 26.2 (CH_3), 26.2 (CH_3), 25.7 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 17.3 (CH_3). IR: 2980, 2960, 2940, 2900, 1730, 1460, 1460, 1380, 1220, 1080 cm^{-1}. MS: m/z: 373 ($M^{+\bullet}$+1), 315. $[\alpha]_D^{21}=-13$ (c 1.0, CH_2Cl_2). HRMS: $[C_{19}H_{32}O_7+H]^+$ requires: 373.22262. Found: 373.22297.

3.3.2. (1*R*,2*S*)-*trans*-2-Phenyl-1-cyclohexyl 2,4-dimethylpentanoate 5b.

From **3b**: Yield: 92% (d.e. = 5%)
From **4b**: Yield: 84% (d.e. = 83%)

Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 4.99 (dt, $J=10.3$ Hz, $J=4.4$ Hz, 1H), 2.68 (dd, $J=11.8$ Hz, $J=3.7$ Hz, 1H), 2.64 (dd, $J=10.3$ Hz, $J=3.7$ Hz, 1H), 2.20 (tq, $J=6.6$ Hz, $J=2.2$ Hz, 1H), 2.20–2.10 (m, 1H), 2.00–1.70 (m, 3H), 1.70–1.00 (m, 6H), 0.86 (d, $J=7.3$ Hz, 3H), 0.65 (d, $J=6.6$ Hz, 3H), 0.60 (d, $J=6.6$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 176.2 (C), 143.1 (C), 128.1 (2CH), 127.5 (2CH), 126.2 (CH), 75.2 (CH), 49.9 (CH), 42.8 (CH_2), 37.5 (CH), 34.1 (CH_2), 32.2 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 24.6 (CH_2), 22.4 (CH), 22.0 (CH_3), 17.2 (CH_3). Minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 4.98 (dt, $J=10.3$ Hz, $J=4.4$ Hz, 1H), 2.68 (dd, $J=11.8$ Hz, $J=3.7$ Hz, 1H), 2.64 (dd, $J=10.3$ Hz, $J=3.7$ Hz, 1H), 2.20 (dq, $J=6.6$ Hz, $J=2.2$ Hz, 1H), 2.20–2.10 (m, 1H), 2.01–1.70 (m, 3H), 1.70–1.00 (m, 6H), 0.76 (d, $J=6.6$ Hz, 3H), 0.72 (d, $J=6.6$ Hz, 3H), 0.69 (d, $J=5.9$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 176.0 (C), 143.1 (C), 128.0 (2CH), 127.4 (2CH), 126.2 (CH), 75.1 (CH), 49.9 (CH), 42.5 (CH_2), 37.7 (CH), 34.0 (CH_2), 32.2 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 24.6 (CH_2), 22.6 (CH), 22.0 (CH_3), 17.4 (CH_3). IR: 2930, 2860, 1730, 1450, 1180, 730 cm^{-1}. $[\alpha]_D^{21}=-28$ (c 1.0, $CHCl_3$). MS: m/z: 289 ($M^{+\bullet}$+1), 159. HRMS: $[C_{19}H_{28}O_2+H]^+$ requires: 289.21675. Found: 289.21639.

3.3.3. (3*R*)-(–)-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl) 2,4-dimethylpentanoate 5c.

From **3c**: Yield: 85% (d.e. = 4%)
From **4c**: Yield: 95% (d.e. = 89%)

Major diastereoisomer (2*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 1H), 4.05 ($J=8.8$ Hz, 1H), 4.02 (d, $J=8.8$ Hz, 1H), 2.68 (tq, $J=6.6$ Hz, $J=6.6$ Hz, 1H), 2.80–2.60 (m, 2H), 1.22 (d, $J=6.6$ Hz, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 1.40–1.20 (m, 1H), 0.93 (d, $J=5.9$ Hz, 3H), 0.90 (d, $J=5.9$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 175.6 (C), 172.2 (C), 75.9 (CH_2), 74.4 (CH), 42.6 (CH_2), 40.0 (C), 37.3 (CH), 25.6 (CH), 22.8 (CH_3), 22.2 ($2CH_3$), 19.7 (CH_3), 17.4 (CH_3). Minor

diastereoisomer (2*S*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37 (s, 1H), 4.05 ($J=8.86$ Hz, 1H), 4.02 (d, $J=8.8$ Hz, 1H), 2.55 (tq, $J=6.6$ Hz, $J=6.6$ Hz, 1H), 2.80–2.60 (m, 2H), 1.22 (d, $J=6.6$ Hz, 3H), 1.20 (s, 3H), 1.12 (s, 3H), 1.40–1.20 (m, 1H), 0.92 (d, $J=5.9$ Hz, 3H), 0.89 (d, $J=5.9$ Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 175.6 (C), 172.2 (C), 75.9 (CH_2), 74.4 (CH), 42.7 (CH_2), 40.0 (C), 37.3 (CH), 25.8 (CH), 22.8 (CH_3), 22.3 ($2CH_3$), 19.8 (CH_3), 17.4 (CH_3). IR: 2960, 2940, 2880, 1800, 1750, 1470, 1380, 1150, 1100 cm^{-1}. MS: *m*/*z*: 243 ($M^{+\bullet}$+1), 113. HRMS: $[C_{12}H_{22}O_3+H]^+$ requires: 243.15963. Found: 243.16024. $[\alpha]_D^{21}=-11$ (*c* 1.0, CH_2Cl_2).

3.4. Transesterification[6] of esters 5 to compound 6

3.4.1. Benzyl 2,4-dimethylpentanoate[1a] 6. To a solution of ester **5** (0.60 mmol) in toluene (3 mL) was added benzyl alcohol (0.63 mL, 6.0 mmol) and titanium(IV) *iso*-propoxide (0.18 mL, 0.60 mmol). The resulting mixture was heated at 120°C until the starting material completed disappeared. After cooling to rt, the crude product was directly purified by flash chromatography (AcOEt/hexanes: 5/95), affording ester **6**.

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