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Stereoselective synthesis of *syn*-α-methyl-β-hydroxy esters

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Abstract

Boron enolates of an ethyl ketone structurally related to erythrulose react with achiral aldehydes in a highly stereoselective fashion to yield 1,2-*syn*/1,3-*syn* stereoisomers. Oxidative cleavage of the aldol adducts yields enantiopure *O*-formylated *syn*-α-methyl-β-hydroxy esters, easily cleaved to the corresponding hydroxyl-free compounds. The aforementioned ketone behaves therefore as a chiral propionate enolate equivalent.

1. Introduction

Among the biologically active, naturally occurring molecules known to date, macrolide and polyether antibiotics have been the object of particular interest.[1] For the stereoselective synthesis of such molecules, a number of strategies have been developed, the aldol reaction being particularly worthy of mention.[2] In connection with our current interest in the development of erythrulose as a C_4 chiral building block,[3] we have recently described the formation of boron enolates of protected erythrulose derivatives and their subsequent addition to aldehydes.[4] We have subsequently shown that oxidative cleavage of these aldols yields selectively protected α,β-dihydroxy esters.[5] In the present communication, we show that the structurally related ethyl ketone (*R*)- or (*S*)-**1** (Scheme 1) behaves in the same way and provides aldols of general structure **2**, precursors in turn of α-methyl-β-hydroxy esters **3** via oxidative cleavage of bond a. Ketone **1** is thus a chiral equivalent of the d^2 synthon propionic acid enolate, a key chiral building block in the synthesis of natural polypropionates.[1] Furthermore, alternative functional manipulations of aldols **2** (e.g. cleavage of bond b or no C–C bond cleavage) should lead to polyhydroxy derivatives such as **4** or **5**, which constitute structural units present in natural macrolides and polyethers. Ketone **1** may thus be an equivalent of the hitherto undescribed d^3 and d^4 chirons depicted below.

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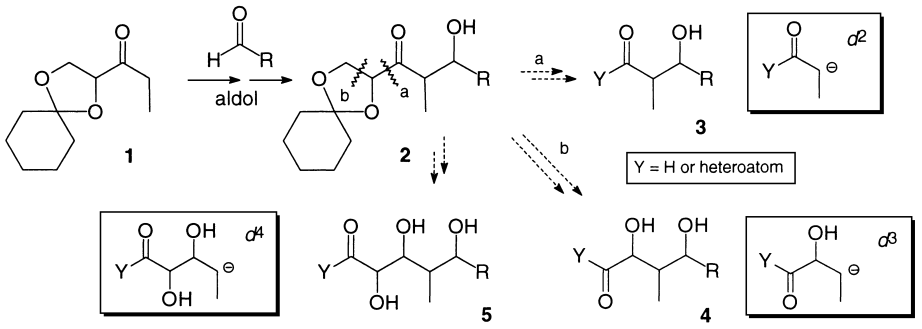
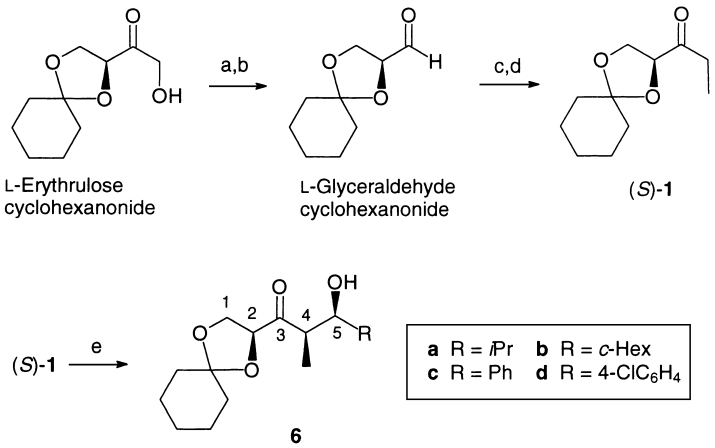


Scheme 1.

2. Results and discussion

Ethyl ketone (*S*)-**1** was prepared as shown in Scheme 2 from the corresponding L-erythrulose acetal.[6,7] Similarly to that observed in erythrulose acetals, (*S*)-**1** was amenable to transformation into boron enolates by means of Brown's dicyclohexylboron chloride (Chx_2BCl)/tertiary amine system.[8a] In contrast to the ketones above, however, (*S*)-**1** gave boron enolates also with Mukaiyama's $n Bu_2BOTf$/tertiary amine system.[8b] Aldol reactions promoted by either of these reagents led to the same *syn* aldol adducts **6** in good chemical yields as essentially single diastereoisomers (diastereomeric ratio, d.r. >95:5, as determined by ^1H and ^{13}C NMR). The sterically hindered pivaldehyde was the only aldehyde tested which did not react under the conditions described.[9]

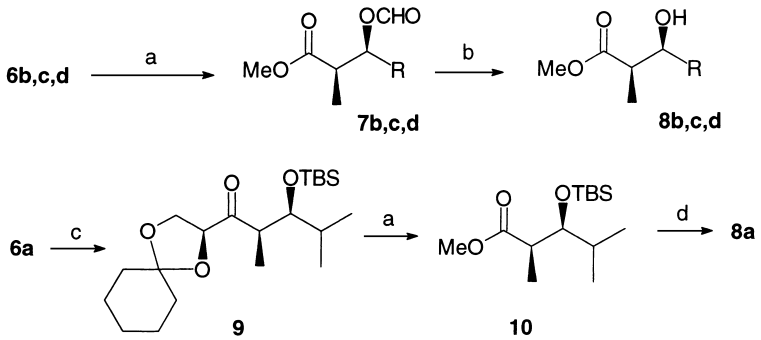


Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF; (b) $NaIO_4$/MeOH; (c) EtMgBr; (d) PCC/CH_2Cl_2, 45% overall; (e) L_2BX, Et_3N, Et_2O, –78°C, then RCHO, –78°C, 77–85%, d.r. >95:5 ($L_2BX = n Bu_2BOTf$ or Chx_2BCl)

The 2,4-*syn*/4,5-*syn* relative as well as the absolute configuration of aldol adducts **6** was assumed on the basis of the observations on structurally related erythrulose derivatives. The relatively small values of the coupling constants $J_{4,5}=2.9$–4.5 Hz supported this conclusion,[10] later confirmed as described below. We show here that ketone (*S*)-**1** behaves as an effective chiral equivalent of the d^2 propionic acid enolate synthon.

Suitable conditions for acetonide cleavage were adapted from our recent report.[5] Thus, compounds **6** were treated with periodic acid hydrate in ethyl acetate[11] under carefully controlled conditions (see Experimental). The acids formed were isolated as their methyl esters and assigned structure **7** (Scheme 3) on the basis of spectroscopic findings and the subsequent synthetic manipulations. Hydrolysis of the formyl group in **7** took place under mild basic conditions to yield the α-methyl-β-hydroxy esters **8**. A particular case was the formylated ester **7a** which, due to its volatility, was isolated in low yields. For this reason, aldol **6a** was silylated with *t*-butyldimethylsilyl triflate (TBSOTf) to **9**, which was then oxidatively cleaved to **10**. Desilylation of **10** afforded hydroxy ester **8a**. This compound, as well as its enantiomer and **8c**, has already been described.[10] Its physical and spectral properties are completely coincident with those found by us, therefore confirming our stereochemical assignment. Esters **8** should be amenable to conversion, via nucleophilic substitution of the hydroxyl group or other synthetic processes, into compounds of pharmacological interest such as, for example, β-amino acids.[12] Furthermore, since ketone (*R*)-**1** is also easily available through the corresponding D-glyceraldehyde derivative,[13] the preparation of compounds of the antipodal series is also feasible. Efforts in these directions are presently underway in our group.

The stereochemical outcome of the aldol reactions with ketone **1** is worth mentioning. Whether the reaction was promoted by Chx_2BCl or by $n Bu_2BOTf$, the same *syn* aldols **6** were obtained. This strongly suggests that *Z* enolates are key intermediates in both types of processes, which is expected for the latter reagent but not for the former.[14] Ethyl ketone **1** therefore shares the same stereochemical preferences displayed by erythrulose acetals, and perhaps for the same reasons.[4,15] Computational calculations by our group[16,17] support the idea that aldol adducts are formed through the *Z* boron enolate participating in a chair-like transition state of the Zimmerman–Traxler type.[18] The formation of a *Z* boron enolate with Chx_2BCl, rather than the expected *E* enolate, thus remains to be explained and is the object of current theoretical and experimental work in our group.[17]



Scheme 3. Reagents and conditions: (a) H_5IO_6, EtOAc, then CH_2N_2, 84–90%; (b) $KHCO_3$/MeOH, 82–85%; (c) TBSOTf, 2,6-lutidine, 79%; (d) HF, aq. MeCN, 80%

3. Experimental

3.1. General methods

NMR spectra were measured in $CDCl_3$ solution at 25°C (Varian Unity 500 and 400 NMR spectrometers). Mass spectra were run either by the electron impact (EIMS, 70 eV), chemical ionization (CIMS, CH_4) or fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 22°C. Commercial reagents (Aldrich or Fluka) were used as received. Hexane solutions of Chx_2BCl were generated by hydroboration of cyclohexene with monochloroborane as reported in the literature.[19] Reactions which required an inert atmosphere were performed under dry Ar in flame-dried glassware. Et_2O and THF were freshly distilled under Ar from sodium–benzophenone ketyl. Dichloromethane was distilled from P_2O_5 and stored over 4 Å molecular sieves. Tertiary amines were distilled from CaH_2. Column chromatography was performed on silica gel Süd-Chemie AG (60–200 μm) with the indicated eluent. All new compounds gave satisfactory combustion analyses (±0.4%).

3.2. (2S)-1,2-O-Cyclohexylidene-1,2-dihydroxypentan-3-one (S)-**1** (The following procedure can be scaled up ten times without noticeable changes in the yields.)

A solution of 3,4-*O*-cyclohexylidene-L-erythrulose[6] (2 g, ca. 10 mmol) in dry THF (100 mL) was added dropwise under Ar to a cooled suspension (0°C) of $LiAlH_4$ (380 mg, 10 mmol) in the same solvent (50 mL). The mixture was then stirred for 4 h at room temperature. After recooling to 0°C, the excess of reducing agent was destroyed by careful addition of water (3 mL), 5% aq. NaOH (15 mL) and again water (20 mL). The mixture was then stirred for a further 30 min, filtered through Celite and concentrated in vacuo. This furnished an oil which was submitted without purification to oxidative cleavage with $NaIO_4$.

A solution of $NaIO_4$ (3.9 g, 18.2 mmol) in water (25 mL) was added dropwise at room temperature to a solution of the crude product above in MeOH (40 mL). After stirring for 1 h, the mixture was concentrated in vacuo to dryness, the residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. This gave crude cyclohexylidene glyceraldehyde as a colourless oil, which was used directly in the next step.

The product obtained above was dissolved in dry Et_2O (25 mL), cooled to 0°C and treated dropwise under Ar with EtMgBr (6.7 mL of a 3 M solution in Et_2O, ca. 20 mmol). After stirring for 1 h at the same temperature, the reaction was quenched with satd. aq. NH_4Cl (1 mL) and poured onto brine. The mixture was extracted with EtOAc, and the organic layer was dried on anhydrous Na_2SO_4 and evaporated in vacuo to afford a colourless oil, which was used as such in the last step.

The crude mixture of epimeric alcohols obtained in the previous step was dissolved in dry CH_2Cl_2 (10 mL) and treated at room temperature under Ar with NaOAc (1.5 g, 18.3 mmol) and PCC (3.2 g, 14.8 mmol). The reaction mixture was stirred overnight at room temperature and then filtered. The residue was evaporated in vacuo and chromatographed on silica gel (hexane EtOAc, 9:1) to yield (*S*)-**1** (891 mg, 45% overall yield from 3,4-*O*-cyclohexylidene-L-erythrulose): oil, $[\alpha]_D$ –62 ($CHCl_3$, *c* 3.1); IR ν_{max} cm^{-1}: 3019, 2941, 1716 (ketone C=O), 1450, 1370, 1216, 1161, 1110, 1095, 1042, 924, 763; EIMS, *m*/*z* (rel. int.) 198.1248 M^+ (11), 155 (66), 141 (100), 81 (22), 57 (38). Calcd for $C_{11}H_{18}O_3$, M = 198.1256; ^1H NMR (500 MHz): δ 4.42 (1H, *dd*, J = 7.5, 6 Hz, H-2), 4.18 (1H, *dd*, J = 8.5, 7.5 Hz, H-1_a), 3.97 (1H, *dd*, J = 8.5, 6 Hz, H-1_b), 2.64 (2H, *q*, J = 7

Hz, H-4), 1.75–1.40 (10H, *m*, cyclohexane protons), 1.05 (3H, *t*, J = 7 Hz, H-5); ^{13}C NMR (125 MHz): δ 211.7 (C-3), 111.5 (acetal Cq), 79.9 (C-2), 66.2 (C-1), 35.7, 34.5, 31.8, 25.1, 23.9, 23.7 (cyclohexane ring carbons+C-4), 7.0 (C-5).

3.3. General procedure for aldol additions of ketone (S)-*1*

Reactions were performed under an inert atmosphere: to a stirred solution of Chx_2BCl (1.8 mL of a 1 M hexane solution, 1.8 mmol) and Et_3N (278 μL, 2 mmol) in anhydrous Et_2O (6 mL) at –78°C was added (*S*)-**1** (198 mg, ca. 1 mmol) in anhydrous ether (6 mL). A solution of the aldehyde (4 mmol) in ether (6 mL) was then added, and the reaction mixture was stirred at –78°C for 2 h. The mixture was then heated to 0°C and treated with pH 7 phosphate buffer (6 mL) and MeOH (6 mL), followed by a 30% aq. H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was poured into satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried on anhydrous Na_2SO_4. Solvent removal in vacuo and column chromatography of the residue on silica gel (hexane:Et_2O, 9:1, then 4:1) afforded the aldol addition product **6** as essentially one diastereoisomer. Chemical yields: **6a** (85%), **6b** (80%), **6c** (77%), **6d** (85%). When Chx_2BCl was replaced by nBu$_2$BOTf, analogous results were observed.

3.4. (2S,4R,5S)-1,2-O-Cyclohexylidene-1,2,5-trihydroxy-4,6-dimethylheptan-3-one *6a*

Colourless needles, mp 65–66°C (hexane–CH_2Cl_2), $[\alpha]_D$ –60.5 ($CHCl_3$, *c* 1); IR ν_{max} cm^{-1}: 3450 (br, OH), 3055, 2941, 1709 (ketone C=O), 1421, 1266, 1096, 896, 739; EIMS, *m*/*z* (rel. int.) 270.1837 M$^+$ (5), 227 (5), 155 (20), 141 (100). Calcd for $C_{15}H_{26}O_4$, M = 270.1831; ^{1}H NMR (400 MHz): δ 4.52 (1H, *dd*, J = 7.8, 5.7 Hz, H-2), 4.17 (1H, *dd*, J = 8.6, 7.8 Hz, H-1$_a$), 3.98 (1H, *dd*, J = 8.6, 5.7 Hz, H-1$_b$), 3.64 (1H, *dd*, J = 8.2, 3 Hz, H-5), 3.31 (1H, *dq*, J = 7, 3 Hz, H-4), 2.30 (1H, *br s*, OH), 1.70–1.50 (9H, *m*, H-6+cyclohexane protons), 1.40 (2H, *m*, cyclohexane protons), 1.04 (3H, *d*, J = 7 Hz, *Me*-C$_4$), 1.00, 0.88 (2×3H, 2×*d*, J = 6.5 Hz, H-7/*Me*-C$_6$); ^{13}C NMR (100 MHz): δ 214.6 (C-3), 111.6 (acetal C$_q$), 79.2 (C-2), 76.2 (C-5), 66.3 (C-1), 43.8 (C-4), 35.6, 34.3, 25.0, 23.9, 23.7 (cyclohexane carbons), 31.2 (C-6), 19.1, 19.0 (C-7/*Me*-C$_6$), 8.4 (*Me*-C$_4$).

3.5. (2S,4R,5S)-1,2-O-Cyclohexylidene-1,2,5-trihydroxy-5-cyclohexyl-4-methylpentan-3-one *6b*

Oil, $[\alpha]_D$ –59.9 ($CHCl_3$, *c* 1); IR ν_{max} cm^{-1}: 3480 (br, OH), 2928, 2854, 1713 (ketone C=O), 1450, 1369, 1267, 1161, 1095, 923, 910, 736; CIMS, *m*/*z* (rel. int.) 293.2119 [M+H$^+$–H_2O] (60), 195 (90), 151 (100). Calcd for $C_{18}H_{31}O_4$–H_2O, M = 293.2117; ^{1}H NMR (500 MHz): δ 4.52 (1H, *dd*, J = 7.8, 5.7 Hz, H-2), 4.16 (1H, *dd*, J = 8.6, 7.8 Hz, H-1$_a$), 3.98 (1H, *dd*, J = 8.6, 5.7 Hz, H-1$_b$), 3.71 (1H, *dd*, J = 8.5, 2.9 Hz, H-5), 3.30 (1H, *dq*, J = 7, 2.9 Hz, H-4), 2.02 (1H, *br d*, J = 13 Hz, cyclohexane proton), 1.80–1.50 (12H, *m*, cyclohexane protons), 1.40–1.10 (7H, *m*, H-6+cyclohexane protons), 1.04 (3H, *d*, J = 7 Hz, *Me*-C$_4$), 1.00 (2H, *m*, cyclohexane protons); ^{13}C NMR (125 MHz): δ 214.5 (C-3), 111.6 (acetal C$_q$), 79.2 (C-2), 74.9 (C-5), 66.3 (C-1), 43.5 (C-4), 40.6 (C-6), 35.6, 34.4, 29.3, 29.1, 26.3, 26.0, 25.8, 25.0, 23.9, 23.8 (cyclohexane carbons), 8.3 (*Me*-C$_4$).

3.6. (2S,4R,5R)-1,2-O-Cyclohexylidene-1,2,5-trihydroxy-4-methyl-5-phenylpentan-3-one *6c*

Oil, $[\alpha]_D$ –71.2 ($CHCl_3$, *c* 0.25); IR ν_{max} cm^{-1}: 3470 (br, OH), 3019, 2939, 1712 (ketone C=O), 1451, 1370, 1216, 1161, 1095, 923, 764; EIMS, *m*/*z* (rel. int.) 304.1670 M$^+$ (6), 141 (100). Calcd for

$C_{18}H_{24}O_4$, M = 304.1674; ^{1}H NMR (500 MHz): δ 7.35–7.20 (5H, *m*, aromatic), 5.12 (1H, *d*, J = 4.5 Hz, H-5), 4.35 (1H, *dd*, J = 7.5, 5 Hz, H-2), 4.07 (1H, *dd*, J = 8.5, 7.5 Hz, H-1$_a$), 3.85 (1H, *dd*, J = 8.5, 5 Hz, H-1$_b$), 3.40 (1H, *dq*, J = 4.5, 7 Hz, H-4), 1.70–1.50 (8H, *m*, cyclohexane protons), 1.40 (2H, *m*, cyclohexane protons), 1.03 (3H, *d*, J = 7 Hz, *Me*-C$_4$); ^{13}C NMR (125 MHz): δ 213.4 (C-3), 141.9, 128.2, 127.5, 126.0 (aromatic), 111.6 (acetal C$_q$), 79.4 (C-2), 73.3 (C-5), 65.8 (C-1), 48.9 (C-4), 35.6, 34.3, 24.9, 23.9, 23.7 (cyclohexane carbons), 10.0 (*Me*-C$_4$).

*3.7. (2*S*,4*R*,5*R*)-1,2-*O*-Cyclohexylidene-1,2,5-trihydroxy-4-methyl-5-(4-chlorophenyl)pentan-3-one* **6d**

Oil, $[\alpha]_D$ –63.1 ($CHCl_3$, *c* 0.25); IR ν_{max} cm^{-1}: 3470 (br, OH), 3019, 2936, 1714 (ketone C=O), 1491, 1450, 1370, 1161, 1092, 923, 847, 829; EIMS, *m*/*z* (rel. int.) 338.1281 M$^+$ (3), 141 (100). Calcd for $C_{18}H_{23}{}^{35}ClO_4$, M = 338.1285; ^{1}H NMR (500 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 5.12 (1H, *br d*, J = 4 Hz, H-5), 4.42 (1H, *dd*, J = 8, 5.5 Hz, H-2), 4.17 (1H, *dd*, J = 8.5, 8 Hz, H-1$_a$), 3.92 (1H, *dd*, J = 8.5, 5.5 Hz, H-1$_b$), 3.38 (1H, *dq*, J = 4, 7 Hz, H-4), 2.90 (1H, *br s*, OH), 1.70–1.50 (8H, *m*, cyclohexane protons), 1.40 (2H, *m*, cyclohexane protons), 1.02 (3H, *d*, J = 7 Hz, *Me*-C$_4$); ^{13}C NMR (125 MHz): δ 214.1 (C-3), 140.2, 133.3, 128.5, 127.5 (aromatic), 111.9 (acetal C$_q$), 79.5 (C-2), 72.6 (C-5), 66.3 (C-1), 48.3 (C-4), 35.7, 34.3, 25.0, 24.0, 23.7 (cyclohexane carbons), 9.7 (*Me*-C$_4$).

*3.8. (2*S*,4*R*,5*S*)-1,2-*O*-Cyclohexylidene-5-*O*-t-butyldimethylsilyl-1,2,5-trihydroxy-4,6-dimethylheptan-3-one* **9**

Compound **6a** (270 mg, ca. 1 mmol) was dissolved in dry CH_2Cl_2 (10 mL), cooled to 0°C and treated with 2,6-lutidine (350 μL, ca. 3 mmol) and TBSOTf (460 μL, ca. 2 mmol). After stirring for 2 h at room temperature, the reaction mixture was poured onto brine and extracted with CH_2Cl_2. The organic layer was then dried on anhydrous Na_2SO_4, filtered and evaporated in vacuo. Column chromatography of the residue on silica gel (hexane:Et_2O, 9:1) afforded **9** (303 mg, 79%): oil, $[\alpha]_D$ –79.5 ($CHCl_3$, *c* 0.5); IR ν_{max} cm^{-1}: 2935, 1713 (ketone C=O), 1463, 1252, 1094, 835, 774; EIMS, *m*/*z* (rel. int.) 384.2685 M$^+$ (1), 341 (7), 255 (32), 157 (100). Calcd for $C_{21}H_{40}O_4Si$, M = 384.2696; ^{1}H NMR (500 MHz): δ 4.51 (1H, *dd*, J = 7.7, 5.8 Hz, H-2), 4.17 (1H, *dd*, J = 8.5, 7.7 Hz, H-1$_a$), 3.98 (1H, *dd*, J = 8.5, 5.8 Hz, H-1$_b$), 3.89 (1H, *t*, J = 5 Hz, H-5), 3.33 (1H, *dq*, J = 5, 7 Hz, H-4), 1.75–1.55 (9H, *m*, H-6+cyclohexane protons), 1.40 (2H, *m*, cyclohexane protons), 1.06 (3H, *d*, J = 7 Hz, *Me*-C$_4$), 0.94, 0.89 (2×3H, 2×*d*, J = 6.5 Hz, H-7/*Me*-C$_6$), 0.90 (9H, *s*, SiC*Me*$_3$), 0.06, 0.00 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 213.2 (C-3), 111.4 (acetal C$_q$), 79.7 (C-2), 76.8 (C-5), 66.4 (C-1), 45.3 (C-4), 35.7, 34.4, 25.1, 23.9, 23.8 (cyclohexane carbons), 33.4 (C-6), 26.1 (SiC*Me*$_3$), 19.7, 18.2 (C-7/*Me*-C$_6$), 18.4 (Si*C*Me$_3$), 11.8 (*Me*-C$_4$), –3.8, –3.9 (Si*Me*$_2$).

3.9. Periodic acid cleavage of aldols **6**

The aldol (1 mmol) was dissolved in EtOAc (10 mL) and treated with H_5IO_6 (800 mg, ca. 3.5 mmol). After stirring at room temperature until consumption of **6** (ca. 2 h, *TLC monitoring*!), solid sodium thiosulfate (320 mg, ca. 2 mmol) was added. The reaction mixture was stirred for 5 min, filtered through Celite (the Celite was washed with an additional amount of EtOAc) and evaporated in vacuo. The oily residue was treated with ethereal diazomethane. Column chromatography on silica gel (hexane:Et_2O, 9:1) afforded **7**. Chemical yields: **7b** (84%), **7c** (90%), **7d** (86%). Oxidative cleavage of the silylated aldol **9** was performed under the same conditions to furnish **10** in 88% yield.

3.10. Methyl (2R,3S)-3-O-formyl-3-cyclohexyl-3-hydroxy-2-methylpropanoate **7b**

Oil, $[\alpha]_D$ –1 ($CHCl_3$, *c* 0.3); IR ν_{max} cm^{-1}: 3025, 2932, 2855, 1732 (ester C=O), 1450, 1168, 1076, 757; CIMS, *m/z* 183.1388 [M+H$^+$–HCOOH] (82), 151 (100). Calcd for $C_{12}H_{21}O_4$–HCOOH, M = 183.1385; ^{1}H NMR (500 MHz): δ 8.11 (1H, *s*, OCHO), 5.16 (1H, *dd*, J = 6.5, 5.5 Hz, H-3), 3.68 (3H, *s*, OMe), 2.80 (1H, *dq*, J = 5.5, 7 Hz, H-2), 1.80–1.50 (6H, *m*, cyclohexane protons), 1.30–1.00 (5H, *m*, cyclohexane protons), 1.18 (3H, *d*, J = 7 Hz, *Me*-C_2); ^{13}C NMR (125 MHz): δ 174.4 (C-1), 160.6 (*C*HO), 77.6 (C-3), 51.9 (OMe), 40.5 (C-2), 39.3 (C-4), 29.3, 28.3, 26.1, 25.9, 25.7 (cyclohexane carbons), 11.1 (*Me*-C_2).

3.11. Methyl (2R,3R)-3-O-formyl-3-hydroxy-2-methyl-3-phenylpropanoate **7c**

Oil, $[\alpha]_D$ +50.6 ($CHCl_3$, *c* 2.8); IR ν_{max} cm^{-1}: 1732 (br, ester C=O), 1455, 1263, 1161, 913, 760; EIMS, *m/z* (rel. int.) 222.0899 M$^+$ (20), 194 (11), 162 (22), 107 (100). Calcd for $C_{12}H_{14}O_4$, M = 222.0892; ^{1}H NMR (500 MHz): δ 8.09 (1H, *s*, OC*H*O), 7.35–7.25 (5H, *m*, aromatic), 6.18 (1H, *d*, J = 7 Hz, H-3), 3.55 (3H, *s*, OMe), 2.98 (1H, *quint*, J = 7 Hz, H-2), 1.23 (3H, *d*, J = 7 Hz, *Me*-C_2); ^{13}C NMR (125 MHz): δ 173.0 (C-1), 159.6 (*C*HO), 137.7, 128.2, 128.1, 126.4 (aromatic), 75.5 (C-3), 51.6 (OMe), 45.5 (C-2), 12.2 (*Me*-C_2).

3.12. Methyl (2R,3R)-3-O-formyl-3-hydroxy-2-methyl-3-(4-chlorophenyl)propanoate **7d**

Oil, $[\alpha]_D$ +61.5 ($CHCl_3$, *c* 1.7); IR ν_{max} cm^{-1}: 1735 (br, ester C=O), 1493, 1459, 1266, 1215, 1160, 1092, 1015, 822, 756; EIMS, *m/z* (rel. int.) 256.0503 M$^+$ (27), 196 (45), 141 (100), 88 (82). Calcd for $C_{12}H_{13}{}^{35}ClO_4$, M = 256.0502; ^{1}H NMR (500 MHz): δ 8.08 (1H, *s*, OC*H*O), 7.35–7.25 (4H, *m*, aromatic), 6.10 (1H, *d*, J = 7 Hz, H-3), 3.57 (3H, *s*, OMe), 2.93 (1H, *quint*, J = 7 Hz, H-2), 1.23 (3H, *d*, J = 7 Hz, *Me*-C_2); ^{13}C NMR (125 MHz): δ 173.0 (C-1), 159.7 (*C*HO), 136.5, 134.3, 128.7, 128.2 (aromatic), 75.2 (C-3), 51.9 (OMe), 45.6 (C-2), 12.7 (*Me*-C_2).

3.13. Methyl (2R,3S)-3-O-t-butyldimethylsilyl-3-hydroxy-2,4-dimethylpentanoate **10**

Oil, $[\alpha]_D$ –30.3 ($CHCl_3$, *c* 0.8); IR ν_{max} cm^{-1}: 1720 (ester C=O), 1463, 1257, 1113, 835, 773; EIMS, *m/z* (rel. int.) 259.1724 [M$^+$–Me] (4), 231 (22), 217 (100), 187 (24). Calcd for $C_{14}H_{30}O_3Si$–CH_3, M = 259.1729; ^{1}H NMR (500 MHz): δ 3.81 (1H, *t*, J = 5 Hz, H-3), 3.67 (3H, *s*, OMe), 2.60 (1H, *dq*, J = 5, 7.5 Hz, H-2), 1.70 (1H, *dqq*, J = 5, 7, 7 Hz, H-4), 1.15 (3H, *d*, J = 7.5 Hz, *Me*-C_2), 0.91, 0.89 (2×3H, 2×*d*, J = 7 Hz, H-5/*Me*-C_4), 0.90 (9H, *s*, SiC*Me*$_3$), 0.06, 0.00 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 176.1 (C-1), 77.8 (C-3), 51.5 (OMe), 43.1 (C-2), 33.1 (C-4), 26.1 (SiC*Me*$_3$), 19.3, 18.1 (C-5/*Me*-C_4), 18.4 (Si*C*Me$_3$), 12.4 (*Me*-C_2), –4.1, –4.2 (Si*Me*$_2$).

3.14. Alkaline deformylation of esters 7

The ester (1 mmol) was dissolved in dry MeOH (5 mL) and treated with solid $KHCO_3$ (110 mg, ca. 1.1 mmol). After stirring at room temperature for ca. 1 h (*TLC monitoring*!), the mixture was filtered and evaporated in vacuo. Column chromatography of the residue on silica gel (hexane:EtOAc, 4:1) afforded **8**. Chemical yields: **8b** (85%), **8c** (82%), **8d** (83%).

3.15. Desilylation of **10**

The silylated ester (137 mg, 0.5 mmol) was dissolved in acetonitrile (5 mL) and treated with 48% aqueous HF (180 μl, ca. 5 mmol). The reaction mixture was stirred at room temp. for 1 h, poured onto 5% aq. $NaHCO_3$ and worked up. Column chromatography of the residue on silica gel (hexane:EtOAc, 4:1) followed by bulb-to-bulb distillation provided ester **8a** (80%).

3.16. Methyl (2R,3S)-3-hydroxy-2,4-dimethylpentanoate **8a**

Oil, $[\alpha]_D$ +7.4 (CH_2Cl_2, *c* 0.2), lit.[10c] $[\alpha]_D$ +7.8 (CH_2Cl_2, *c* 0.2); IR ν_{max} cm^{-1}: 3500 (br, OH), 3019, 2930, 2854, 1728 (ester C=O), 1450, 1437, 1216; CIMS, *m*/*z* (rel. int.) 161.1170 [M+H$^+$] (12), 143 [M+H$^+$–H_2O] (100). Calcd for $C_8H_{17}O_3$, M = 161.1177; ^{1}H NMR (400 MHz): δ 3.65 (3H, *s*, OMe), 3.53 (1H, *dd*, J = 8, 3.8 Hz, H-3), 2.62 (1H, *dq*, J = 3.8, 7.1 Hz, H-2), 2.55 (1H, *br s*, OH), 1.61 (1H, *dqq*, J = 8, 6.5, 6.5 Hz, H-4), 1.13 (3H, *d*, J = 7.1 Hz, *Me*-C_2), 0.95, 0.83 (2×3H, 2×*d*, J = 6.5 Hz, *Me*-C_4/H-5); ^{13}C NMR (100 MHz): δ 176.9 (C-1), 76.8 (C-3), 51.8 (OMe), 41.8 (C-2), 30.6 (C-4), 19.1, 18.5 (C-5, *Me*-C_4), 10.2 (*Me*-C_2).

3.17. Methyl (2R,3S)-3-cyclohexyl-3-hydroxy-2-methylpropanoate **8b**

Oil, $[\alpha]_D$ –5.5 ($CHCl_3$, *c* 0.3); IR ν_{max} cm^{-1}: 3500 (br, OH), 2928, 2853, 1728 (ester C=O), 1450, 1262, 1204, 991, 757; CIMS, *m*/*z* 201.1488 [M+H$^+$] (8), 183 [M+H$^+$–H_2O] (100). Calcd for $C_{11}H_{21}O_3$, M = 201.1490; ^{1}H NMR (500 MHz): δ 3.71 (3H, *s*, OMe), 3.63 (1H, *dd*, J = 8.2, 3.3 Hz, H-3), 2.68 (1H, *dq*, J = 3.3, 7 Hz, H-2), 2.05 (1H, *br d*, J = 13 Hz, cyclohexane proton), 1.80–1.55 (4H, *m*, cyclohexane protons), 1.40–1.10 (4H, *m*, cyclohexane protons), 1.17 (3H, *d*, J = 7 Hz, *Me*-C_2), 1.00 (2H, *qd*, J = 13, 3 Hz, cyclohexane protons); ^{13}C NMR (125 MHz): δ 177.1 (C-1), 75.7 (C-3), 51.8 (OMe), 41.3 (C-2), 40.2 (cyclohexane CH), 29.1, 29.0, 26.4, 26.1, 25.9 (cyclohexane CH_2), 10.0 (*Me*-C_2).

3.18. Methyl (2R,3R)-3-hydroxy-2-methyl-3-phenylpropanoate **8c**

Oil, $[\alpha]_D$ +23.2 ($CHCl_3$, *c* 1), lit.[10b] $[\alpha]_D$ +23.1 ($CHCl_3$, *c* 1.5); IR ν_{max} cm^{-1}: 3450 (br, OH), 1721 (ester C=O), 1453, 1436, 1349, 1256, 1198, 1170, 1060, 1035, 900, 770, 745; EIMS, *m*/*z* (rel. int.) 194.0940 M$^+$ (12), 107 (88), 88 (100). Calcd for $C_{11}H_{14}O_3$, M = 194.0943; ^{1}H NMR (500 MHz): δ 7.35–7.25 (5H, *m*, aromatic), 5.12 (1H, *d*, J = 4 Hz, H-3), 3.68 (3H, *s*, OMe), 2.90 (1H, *br s*, OH), 2.80 (1H, *dq*, J = 4, 7 Hz, H-2), 1.14 (3H, *d*, J = 7 Hz, *Me*-C_2); ^{13}C NMR (125 MHz): δ 176.2 (C-1), 141.4, 128.2, 127.5, 126.0 (aromatic), 73.6 (C-3), 51.8 (OMe), 46.4 (C-2), 10.7 (*Me*-C_2).

3.19. Methyl (2R,3R)-3-hydroxy-2-methyl-3-(4-chlorophenyl)-propanoate **8d**

Oil, $[\alpha]_D$ +17.2 ($CHCl_3$, *c* 1.8); IR ν_{max} cm^{-1}: 3460 (br, OH), 1722 (br, ester C=O), 1493, 1458, 1437, 1349, 1201, 1091, 1063, 1014, 812; EIMS, *m*/*z* (rel. int.) 228.0561 M$^+$ (2), 141 (60), 88 (100). Calcd for $C_{11}H_{13}{}^{35}ClO_3$, M = 228.0553; ^{1}H NMR (500 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 5.04 (1H, *d*, J = 4.4 Hz, H-3), 3.66 (3H, *s*, OMe), 3.20 (1H, *br s*, OH), 2.74 (1H, *dq*, J = 4.4, 7 Hz, H-2), 1.10 (3H, *d*, J = 7 Hz, *Me*-C_2); ^{13}C NMR (125 MHz): δ 175.8 (C-1), 140.0, 133.1, 128.3, 127.3 (aromatic), 72.9 (C-3), 51.8 (OMe), 46.3 (C-2), 10.7 (*Me*-C_2).

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