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Synthesis of optically active (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one

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Abstract—Bicyclo[2.2.2]octanone is an important building block for the synthesis of bioactive compounds and natural products. Herein, we present a new synthetic route for the formation of (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one derivatives via a catalytic asymmetric Michael reaction in high stereoselectivity and yields.

1. Introduction

Optically active derivatives with a bicyclo[2.2.2]octane framework are important building blocks for the construction of molecules for mimicking bioactive compounds and have been successfully employed in regio- and stereocontrolled transformations towards natural products.[1–4] Our initial intention was to synthesize compounds with a bicyclo[2.2.2]oct-5-en-2-one backbone based on substituted cyclohex-2-en-1-ones as starting material for photochemical conversions via the oxa-di-π-methane rearrangement.[5,6] Since our synthetic route involves the addition of malonates to cyclohex-2-en-1-ones, which is achieved by a catalytic asymmetric reaction on a scale of up to 100 g, we implemented this asymmetric step in our synthesis, thus providing an enantiomeric excess (>99% ee) of optically active bicyclo[2.2.2]octanone derivatives.[7–13]

2. Results and discussion

The asymmetric 1,4-addition of dimethyl malonate to cyclohex-2-en-1-one is well documented in the literature.[14–17] Among various additives for this addition reaction, the use of a chiral binaphthol **3** based catalyst combines high product yield and an enantiomeric excess of more than 90% on a multigram scale. The addition of dimethyl malonate **2** to **1** employing the chiral catalyst **4** yielded **5** in 92% (Scheme 1).

As previously reported, we also added powdered molecular sieves (MS) 4 Å to the reaction medium.[14–16] In contrast to the MS beads 4 Å,[18] powdered MS 4 Å greatly improved the catalytic asymmetric Michael addition.[14]

The optical purity of **5** was higher than 99% and was determined via its ketalization with D-(−)-2,3-butanediol (>99% ee, Fluka); only one diastereoisomer was detected by ^{1}H and ^{13}C NMR spectroscopy (the chemical shifts of the two diastereomers are different; see the Experimental) and gas chromatography [a mixture of two diastereomers gave two peaks, whereas the (*R*)-enantiomer **6** is only one peak]. The absolute configuration of **5** was confirmed by X-ray crystal structure analysis (Fig. 1).[19]

The following decarboxylation reaction[20] of **5** using LiI·$3H_2O$ and acetalization of **7** produced **8** in an overall yield of 69%. The reduction to alcohol **9** and reoxidation yielded aldehyde **10** in acceptable 65% yield. This two-step procedure is favoured over the direct reduction employing reagents such as DIBAH, which yielded **10** in only 30%. Treatment of **10** with phosphoric acid gave bicyclic compound (−)-**11** via an intramolecular aldol type cyclization in 38% yield (Scheme 2).[19]

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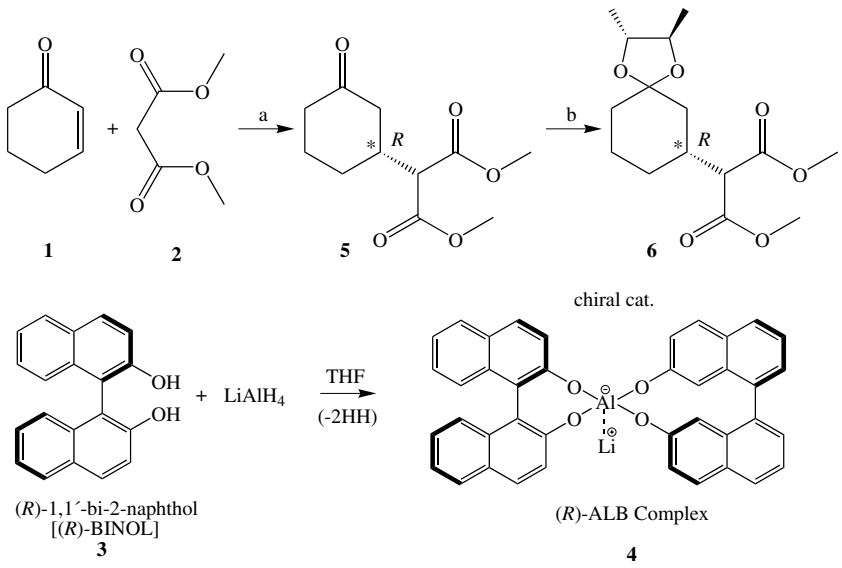


Scheme 1. Reagents and conditions: (a) 0.1 M (*R*)-ALB in THF (1.0 mol %) (**4**), KO-*t*-Bu (0.9 equiv to ALB) in THF (0.25 M), MS 4 Å, rt, 72 h, 92% (>99% ee); (b) (2*R*,3*R*)-(−)-butanediol (>99% ee), *p*-TsOH, PhH, reflux 2 h, 96%.

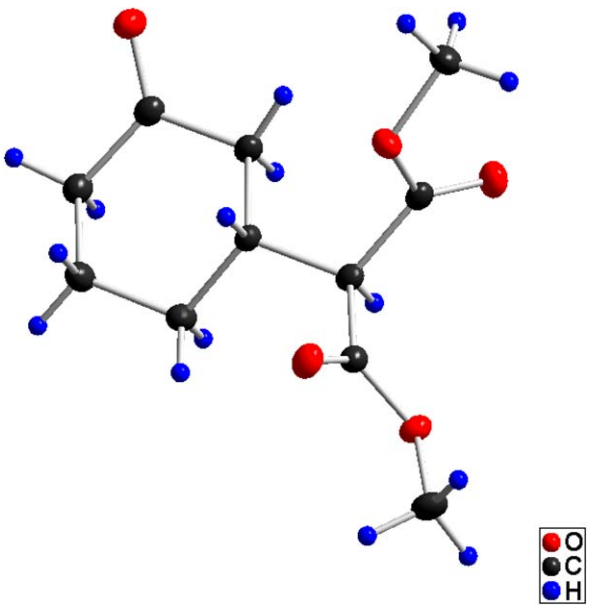


Figure 1. X-ray crystal structure analysis of **5**.

The *endo*-epimer[11,21] was the only product isolated, deduced from the available IR- and NMR-spectroscopic data (1D and 2D spectra including NOESY experiment[21]) and the melting point[11,21] of (−)-**11**. Fortunately, the relative *endo*-configuration of (−)-**11** was confirmed by an X-ray crystal structure analysis (Fig. 2).[19]

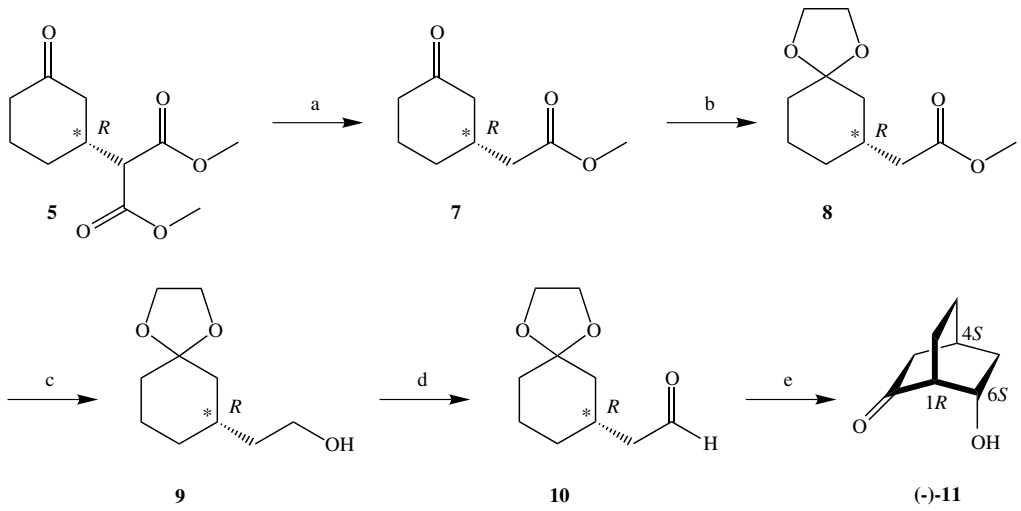
Comparison with similarly formed bicyclo[2.2.2]-octenones[22] and the experimental data (see the Experimental) led us to assume that (−)-**11** has the (1*R*,4*S*,6*S*)-configuration.[10,11] Since none of the reactions presented in Scheme 2 causes isomerization at the stereogenic centre, the enantiomeric purity of (−)-**11** should be the same as that of compound **5**. In addition to recent reports by other groups regarding synthesis and transformations of enantiomerically pure bicyclo[2.2.2]octane systems,[1,4,10,11,23–25] we consider our strategy a useful supplement in this area.

3. Conclusion

In conclusion we have presented a new synthetic strategy for the construction of optically active (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one (−)-**11**. Thereby, the necessary stereochemical information was introduced in the first step of the reaction sequence by an asymmetric catalytic 1,4-addition of dimethyl malonate to cyclohex-2-en-1-one. This reaction can easily be carried out on a multigram scale. The experimental and literature data (see the Experimental for compounds **5** and **7**–**9**) have proven the high stereoselectivity (>99% ee) of the proposed synthetic approach. By simply employing the optical antipode of the catalyst, that is, (*S*)-binaphthol in the synthesis of the catalyst, the corresponding (*S*)-enantiomer of **5** should be easily accessible as well, emphasizing the flexibility of this reaction sequence.

4. Experimental

Chiral catalyst (*R*)-aluminium-lithium-bis-(binaphthoxid)-complex [(*R*)-ALB] was prepared according to the literature procedure.[14] All solvents used were of analytically pure quality or purified by distillation from potassium and $LiAlH_4$ under an argon atmosphere immediately before use in all reactions. Commercial (*R*)-1,1′-bi-2-naphthol [(*R*)-BINOL, >99% ee, Fluka], dimethylmalonate (Fluka) and cyclohex-2-en-1-one (Fluka), (2*R*,3*R*)-(−)-butanediol (>99% ee, Fluka), $LiAlH_4$ (Merck-Schuchardt), potassium *tert*-butylate (Merck), *p*-toluene-sulfonacid monohydrate (Aldrich), lithium iodate trihydrate (Fluka), ethylene glycol (Fluka), oxalic acid dichloride (Aldrich) were used as provided. NMR spectra were measured on a



5 7 8 9 10 (-)-11

Scheme 2. Reagents and conditions: (a) LiI·3H_2O, DMSO, 52%; (b) ethylene glycol, *p*-TsOH, PhH, reflux 2 h, 95%; (c) $LiAlH_4$, Et_2O, 86%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 85%; (e) H_3PO_4, THF/water, reflux 2 h, 38%.

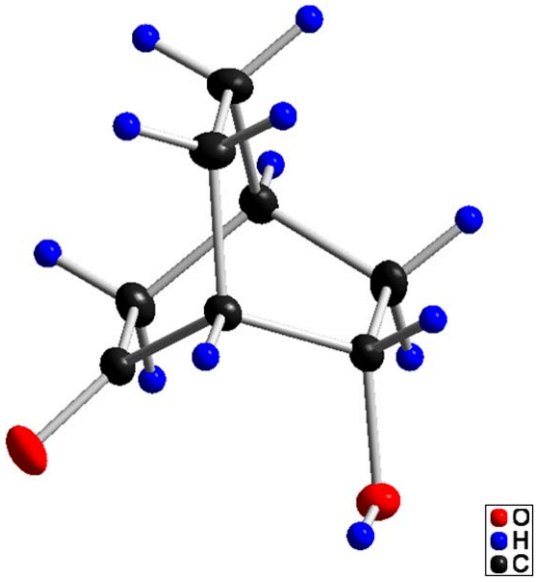


Figure 2. X-ray crystal structure analysis of (−)-**11**.

Bruker DRX 500 (^{1}H NMR: $\delta = 500.13$ MHz; ^{13}C NMR: $\delta = 125.77$ MHz) instrument in $CDCl_3$ with $CHCl_3$ as reference (for ^{1}H: $\delta = 7.26$ ppm; for ^{13}C: $\delta = 77.0$ ppm) or DMSO-d_6 (for ^{1}H: $\delta = 2.49$ ppm; for ^{13}C: $\delta = 39.7$ ppm). Infrared spectra (IR) were recorded on a Perkin–Elmer 841 Infrared Spectrophotometer or a Matson Genesis Series ATT FT-IR spectrometer. Specific rotations were measured on a Perkin–Elmer 341 polarimeter at the sodium D line. Melting points were measured in an open capillary tube on a Büchi B-540 instrument and are uncorrected (to 100 ± 0.3 °C, to 250 ± 0.5 °C, to 400 ± 0.8 °C). Elemental analyses were carried out on a Perkin–Elmer 240 instrument. High-resolution mass spectra (HRMS) were recorded on a Micromass VG Autospec X (Vacuum Generators, Manchester) with EI in positive ion mode. GC/MS were recorded on a Shimadzu GC 17A/MSQP 5050A equipped with a Hewlett–Packard 5MS capillary column (25.0 m, 0.20 mm, 0.33 μm); software Class 5000 V 2.0 and LabSolutions GCMSolution V 1.02 (Schimadzu); carrier gas helium (pressure 0.95 bar). GC analysis was carried out using Shimadzu GC-17A/ver. 3 (FID detector and Class VP 4.2 software) equipped with HP-5MS (Hewlett–Packard) capillary column (25.0 m, 0.20 mm, 0.33 μm). HPLC was performed on a silica gel column (Macherey & Nagel Nucleosil 100-7, 250 × 21 mm and 50 × 21; flow 10 mL min^{-1}) with use of a Merck-Hitachi pump (L-6250) and a Merck-Hitachi UV–vis-detector (L-7420). Analytical thin-layer chromatography (TLC) was carried out on silica gel thick plates (Alugram®, 0.20 mm) with fluorescent indicator SIL G/UV_{254} (Macherey & Nagel). Column chromatography was carried out on silica gel MN-60 (40–60 μm Macherey & Nagel).

4.1. Preparation of (*R*)-AlLibis(binaphthoxide) [(*R*)-ALB] complex in THF solution 4[14,15]

To a suspension of fresh $LiAlH_4$ (powder, 189.8 mg, 5.0 mmol) in 20 mL of dry THF, (*R*)-BINOL (2.864 g, 10.0 mmol) in dry THF (20 mL, plus 5 mL × 2) was slowly added via cannula and a septum at 0 °C. After being stirred at the same temperature under an argon atmosphere for 30 min and then at room temperature for an additional 70 min, the resulting white mixture was kept standing without stirring overnight (22 h). The resulting solution was used as 0.1 M (*R*)-ALB-complex in THF.

4.2. (*R*)-Dimethyl 2-(3-oxocyclohexyl)malonate 5 (100 g scale reaction using 1.0 mol % of the (*R*)-ALB-KO-*t*-Bu catalyst)[14]

KO-*t*-Bu (483 mg) in 17 mL dry THF (0.253 M; 4.3 mmol), 66.0 g dimethyl malonate **2** (57.1 mL; 0.50 mol) and 48.1 g cyclohex-2-en-1-one **1** (0.50 mol) were successively added to a mixture of (*R*)-ALB-complex **4** (in dry THF, 0.05 M; 100 mL, 5.0 mmol) and 10 g freshly opened powdered molecular sieves 4 Å (Fluka catalog No. 69836). After being stirred for 72 h at room temperature, the reaction

mixture was diluted with 100 mL ethyl acetate and filtered over Celite® 545 to remove the molecular sieves. The filtrate was washed with 40 mL of 0.1 M hydrochloric acid and extracted with 2×40 mL ethyl acetate. The combined organic layers were washed with 2×10 mL saturated $NaHCO_3$ solution, brine (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by repeated recrystallization (toluene/*n*-hexane 1:1, 100 mL) to afford a combined yield of pure **5** (81.1 g). The remaining mother liquor was concentrated and again purified by repeated recrystallization (toluene/*n*-hexane 1:1, 40 mL) to give a combined yield of pure **5** (11.3 g) after filtration, which spontaneously recrystallized. The remaining mother liquor was again concentrated yielding a residue, which was then purified by alumina flash chromatography (acetone/*n*-hexane 1:6) to give another 12.9 g of pure **5**. The combined yield of **5** was 105.3 g (0.46 mol; 92%; >99% ee). Most of the (*R*)-BINOL was recovered during chromatography as a fraction eluted after the main product **5**; mp 56.5–57.5 °C; $[\alpha]_D^{28} = +3.6$ (*c* 2.28, $CHCl_3$) and $[\alpha]_D^{28} = +3.3$ (*c* 1.00, $CHCl_3$) {lit.[15,17] for **5**: $[\alpha]_D^{28} = +3.75$ (*c* 2.28, $CHCl_3$); mp 54.5–55.5 °C; >99% ee}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.47$ (ddd, $J = 3.6/12.8/24.3$ Hz, 1H), 1.66 (tddd, $J = 4.4/12.5/12.5/12.5$ Hz, 1H), 1.89–1.95 (m, 1H), 2.05 (ddd, $J = 3.4/6.6/13.7$ Hz, 1H), 2.20–2.27 (m, 2H), 2.35–2.40 (m, 1H), 2.42 (td, $J = 2.2/4.2$ Hz, 1H), 2.51 (ddd, $J = 3.8/8.1/19.9$ Hz, 1H), 3.31 (d, $J = 8.0$ Hz, 1H, 1′-H), 3.72 (s, 3H, O–CH_3), 3.73 (s, 3H, O–CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.5$ (CH_2, C-5), 28.8 (CH_2, C-4), 38.1 (CH, C-3), 40.9 (CH_2, C-6), 45.1 (CH_2, C-2), 52.6 ($2CH_3$, O–*C*H_3), 56.6 (CH, C-1′), 168.1 (Cq, *C*O_2CH_3), 168.2 (Cq, *C*O_2CH_3), 209.5 (Cq, C-1); IR (KBr): $\tilde{\nu} = 3472$, 2960, 2873, 1737, 1435, 1258, 1157, 1105, 1062, 1017, 950, 929, 870, 795, 751 cm^{-1}; MS *m*/*z* (relative intensity): 228 (2), 197 (13), 168 (23), 165 (13), 157 (18), 153 (25), 141 (11), 137 (11), 136 (25), 133 (11), 132 (34), 101 (38), 100 (25), 99 (11), 98 (10), 97 (100), 96 (66), 95 (12), 81 (19), 79 (10), 74 (18), 69 (39), 68 (65), 67 (19), 59 (45), 55 (33), 53 (14), 42 (35), 41 (49).

4.3. (*R*)-2-(2,3-Dimethyl-1,4-dioxaspiro[4,5]dec-7-yl)-dimethylmalonate 6

For determining the enantiomeric excess of the former reaction (2*R*,3*R*)-(−)-butanediol (0.6 mL, 0.66 mmol, >99% ee, Fluka), a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) and 0.5 g molecular sieve 4 Å were added to a solution of 150 mg (0.60 mmol) of the adduct **5** in 5 mL benzene. After refluxing the solution for 2 h, 10 mL of saturated $NaHCO_3$ solution was added and the mixture was extracted with 3×10 mL diethyl ether. The combined organic phase was dried over $MgSO_4$ and purified by HPLC (EtOAc/cyclohexane 90:10) yielding 190 mg (96%) of pure product as a yellowish oil after removal of the solvent by Kugelrohr distillation (0.02 mbar/5 h). The same procedure was used for the racemic mixture; $[\alpha]_D^{28} = -12.9$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.03$ (dtd, $J = 3.6/12.2/18.4$ Hz, 1H), 1.19 (d, $J = 5.7$ Hz, 3H, CH_3), 1.21 (d, $J = 5.6$ Hz, 3H, CH_3), 1.32 (t, $J = 12.4$ Hz, 1H), 1.43 (ddt, $J = 4.9/12.5/13.4$ Hz, 1H), 1.57 (ttd, $J = 3.2/12.5/12.5$ Hz, 1H), 1.62–1.66 (m, 1H), 1.67–1.78 (m, 3H), 2.42 (ddd, $J = 3.5/11.9/23.9$ Hz, 1H), 3.24 (d, $J = 8.5$ Hz, 1H, 1′-H), 3.55–3.62 (m, 2H, O–C*H*), 3.69 (s, 3H, O–CH_3), 3.71 (s, 3H, O–CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 16.78$ (CH_3), 17.03 (CH_3), 22.32 (CH_2), 29.02 (CH_2), 35.67 (CH, C-3), 36.68 (CH_2), 39.96 (CH_2), 52.31 ($2 \times CH_3$, O–*C*H_3), 57.01 (CH, C-1′), 78.04 ($2 \times$ CH, O–*C*H), 107.60 (Cq, C-1), 168.84 (Cq, *C*O_2CH_3), 168.94 (Cq, *C*O_2CH_3).

Racemate: ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 16.78$ (CH_3), 16.96 (CH_3), 17.03 (CH_3), 17.08 (CH_3), 22.32 (CH_2), 22.64 (CH_2), 29.01 (CH_2), 29.07 (CH_2), 35.27 (CH), 35.70 (CH), 35.76 (CH_2), 36.68 (CH_2), 39.96 (CH_2), 40.89 (CH_2), 52.28 ($2CH_3$, O–*C*H_3), 52.31 ($2CH_3$, O–*C*H_3), 57.01 (CH, C-1′), 57.10 (CH, C-1′), 77.84 (CH, O–*C*H), 78.04 (2CH, O–*C*H), 78.24 (CH, O–*C*H), 107.60 (Cq), 107.66 (Cq), 168.80 (Cq), 168.83 (Cq, *C*O_2CH_3), 168.91 (Cq, *C*O_2CH_3), 168.94 (Cq, *C*O_2CH_3); IR (neat): $\tilde{\nu} = 2360$, 2341, 1734, 1635, 1456, 1437, 1261, 1151, 1095, 1024, 796 cm^{-1}; MS *m*/*z* (relative intensity): 300 (5), 257 (5), 241 (7), 197 (6), 170 (11), 169 (94), 165 (4), 153 (10), 141 (8), 128 (9), 127 (70), 125 (16), 124 (28), 115 (9), 114 (47), 97 (60), 96 (16), 81 (12), 79 (16), 69 (32), 67 (14), 59 (19), 55 (100), 53 (8), 43 (35), 42 (13), 41 (37), 39 (7); HRMS (EI): *m*/*z* calcd for $C_{15}H_{24}O_6$ 300.1573, found 300.1571, deviation 0.24 ppm.

4.4. (*R*)-Methyl 2-(3-oxocyclohexyl)acetate 7

(*R*)-Dimethyl 2-(3-oxocyclohexyl)-malonate **5** (80.0 g, 0.350 mol) and LiI·$3H_2O$ (60.0 g, 0.318 mol) in 500 mL DMSO were heated for 25 min at 180 °C in a 1000 mL round bottomed flask equipped with a reflux condenser (CO_2 production). After cooling to room temperature, the reaction mixture was diluted with 400 mL water and portioned into two parts of 500 mL, each extracted with 3×150 mL diethyl ether. The combined organic phase was washed with 2×100 mL brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified first by vacuum distillation (bp 86–89 °C/0.032 mbar), and secondly by Kugelrohr distillation (0.020 mbar/75 °C for 1 h) yielding 31.9 g (52%) of a colourless oil; $[\alpha]_D^{28} = +8.9$ (*c* 1.00, $CHCl_3$) {lit.[26] for (*S*)-isomer: $[\alpha]_D^{25} = -8.7$ (*c* 0.96, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.37$ (dddd, $J = 3.6/10.4/12.0/23.8$ Hz, 1H), 1.60–1.70 (m, 1H), 1.87–1.93 (m, 1H), 1.97–2.04 (m, 1H), 2.05 (ddd, $J = 1.3/11.3/14.0$ Hz, 1H), 2.17–2.37 (m, 5H), 2.41 (tddt, $J = 3.9/4.0/14.0/3.9$ Hz, 1H), 3.64 (s, 3H, O–CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.7$ (CH_2), 30.8 (CH_2), 35.5 (CH, C-1′), 40.7 (CH_2), 41.0 (CH_2), 47.4 (CH_2), 51.6 (CH_3, O–*C*H_3), 172.1 (Cq, *C*O_2CH_3), 210.4 (Cq, C-1); IR (neat): $\tilde{\nu} = 3460$, 2957, 2001, 1736, 1438, 1347, 1315, 1225, 1157, 1098, 1059, 1037, 998, 955, 911, 868, 851, 753, 704 cm^{-1}; MS *m*/*z* (relative intensity): 171 (5), 170 (17), 139 (10), 127, (10), 110 (19), 99 (33), 98 (10), 97 (100), 96 (20), 95 (32), 82 (20), 79 (8), 74 (26), 71 (8), 69 (20), 68 (19), 67 (18), 59 (35), 55 (71), 53 (13), 43 (23), 42 (30), 41 (71), 39 (28).

4.5. (*R*)-Methyl 2-(1,4-dioxaspiro[4.5]dec-7-yl)acetate 8

To a solution of 28.0 g (0.165 mol) (*R*)-methyl 2-(3-oxocyclohexyl)acetate **7**, 26.0 g (0.419 mol) of dry ethylene

glycol and 10 g molecular sieves 4 Å in a 100 mL of dry benzene was added a catalytic amount of *p*-TsOH (0.016 mol) and the mixture was stirred at reflux under argon atmosphere for 2 h. After cooling to room temperature, the reaction was carefully diluted with 100 mL of water and extracted with 4×200 mL diethylether. The combined organic layer was washed with 50 mL water, 50 mL saturated $NaHCO_3$ solution, dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 20:80) yielding 33.6 g (95%) of a colourless oil, $R_f = 0.48$; $[\alpha]_D^{28} = +3.1$ (*c* 1.00, $CHCl_3$) {lit.[27] for **7**: $[\alpha]_D^{25} = +3.0$ (*c* 0.14, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.83$ (ddd, $J = 3.4/12.8/24.4$ Hz, 1H), 1.11 (t, $J = 12.5$ Hz, 1H), 1.26–1.33 (m, 1H), 1.37–1.47 (m, 1H), 1.56–1.62 (m, 3H), 1.66 (ddd, $J = 2.0/3.8/12.8$ Hz, 1H), 1.92–2.02 (m, 1H), 2.10–2.12 (m, 2H), 3.53 (s, 3H, O–C*H*$_3$), 3.79–3.82 (m, 4H, O–C*H*$_2$C*H*$_2$–O); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 22.6$ (CH_2), 31.20 (CH_2), 32.4 (CH, C-1′), 34.4 (CH_2), 40.9 (CH_2), 41.0 (CH_2), 51.1 (CH_3, O–*C*H$_3$), 64.0 (CH_2, O–CH$_2$*C*H$_2$–O), 64.1 (CH_2, O–*C*H$_2$CH$_2$–O), 108.5 (Cq, C-1), 172.7 (Cq, *C*O$_2$CH$_3$); IR (neat): $\tilde{\nu} = 3518$, 2946, 2677, 2006, 1738, 1435, 1354, 1335, 1283, 1171, 1095, 1046, 1014, 948, 930, 908, 845, 769, 684 cm^{-1}; MS *m*/*z* (relative intensity): 214 (4), 183 (8), 171 (19), 141 (42) 113 (16), 100 (11), 99 (100), 95 (8), 86 (37), 55 (26), 43 (10), 42 (15), 41 (25), 39 (6).

4.6. (*R*)-2-(1,4-Dioxaspiro[4.5]dec-7-yl)-1-ethanol 9[27]

A solution of 26.0 g (0.121 mol) (*R*)-methyl 2-(1,4-dioxaspiro[4.5]dec-7-yl)acetate **8** in 35 mL dry diethyl ether was added dropwise to a suspension of 5.53 g (0.146 mol) $LiAlH_4$ in 250 mL of dry diethylether under an argon atmosphere. After complete addition, the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and water was carefully added until a white solid precipitated and hydrogen evolution was completed (140 mL). The diethyl ether was decanted and the white solid washed with 3×200 mL methyl-*tert*-butyl ether (MTBE). The combined organic layers were washed with 2×50 mL saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 50:50) yielding 19.5 g (86%) of a colourless oil, $R_f = 0.46$; $[\alpha]_D^{28} = +3.3$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.87$ (ddd, $J = 2.4/12.5/25.1$ Hz, 1H), 1.19 (t, $J = 12.6$ Hz, 1H), 1.35–1.53 (m, 5H), 1.67–1.75 (m, 4H), 1.75–1.77 (m, 1H, O*H*), 3.66 (dt, $J = 1.4/6.9$ Hz, 2H, 2′-H), 3.88–3.93 (m, 4H, O–C*H*$_2$C*H*$_2$–O); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 23.1$ (CH_2), 31.8 (CH_2), 32.2 (CH, C-3), 34.7 (CH_2), 39.7 (CH_2) 41.7 (CH_2), 60.7 (*C*H$_2$–OH), 64.1 (O–*C*H$_2$), 64.3 (O–*C*H$_2$), 109.2 (Cq); IR (neat): $\tilde{\nu} = 3434$, 2935, 1719, 1648, 1476, 1448, 1353, 1278, 1235, 1153, 1074, 947, 924, 897, 874, 845, 813, 763, 682 cm^{-1}; MS *m*/*z* (relative intensity): 186 (5), 144 (3), 143 (48), 141 (55), 113 (15), 100 (13), 99 (100), 86 (31), 55 (35), 43 (16), 42 (21), 41 (39), 39 (6); Elemental analysis calcd (%) for $C_{10}H_{18}O_3$ (186.248): C 64.49, H 9.74; found: C 64.29, H 10.26.

4.7. (*R*)-2-(1,4-Dioxaspiro[4.5]dec-7-yl)acetaldehyde 10

Dimethylsulfoxide (11.1 g, 142 mmol) in 32 mL dichloromethane was slowly added over a period of 15 min to a solution of 9.00 g (70.9 mmol) oxalyl chloride in 154 mL of dry dichloromethane under an argon atmosphere at −78 °C. Stirring was continued for 10 min at this temperature. Then, 12.0 g (64.4 mmol) of (*R*)-2-(1,4-dioxaspiro[4.5]dec-7-yl)-1-ethanol **9** in 50 mL dry dichloromethane was added over a period of 20 min and stirring continued for an additional 15 min. The mixture was quenched at −78 °C with 32.6 g (322 mmol) triethylamine in 10 mL dichloromethane and allowed to reach room temperature. After adding 160 mL water, the phases were separated and the aqueous phase was extracted with 2×100 mL dichloromethane. The combined organic phase was washed with 100 mL brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 80:20) yielding 10.1 g (85%) of a colourless oil, $R_f = 0.78$; $[\alpha]_D^{28} = +1.5$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.90$–0.99 (m, 1H), 1.24 (t, $J = 12.4$ Hz, 1H), 1.40 (dd, $J = 8.8/13.3$ Hz, 1H), 1.50–1.60 (m, 1H), 1.67–1.77 (m, 4H), 2.15–2.25 (m, 1H, 7-H), 2.30–2.33 (m, 2H, C*H*$_2$–CHO), 3.90–3.94 (m, 4H, O–C*H*$_2$C*H*$_2$–O), 9.72 (t, $J = 2.2$ Hz, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 22.9$ (CH_2), 30.4 (CH), 31.6 (CH_2), 34.6 (CH_2), 41.3 (CH_2), 50.5 (CH_2, *C*H$_2$–CHO), 64.2 (O–*C*H$_2$), 64.3 (O–*C*H$_2$), 108.7 (Cq), 202.2 (*C*HO); IR (neat): $\tilde{\nu} = 3446$, 2932, 1709, 1448, 1353, 1313, 1279, 1226, 1140, 1070, 1039, 948, 882, 845, 817, 766, 682 cm^{-1}; MS *m*/*z* (relative intensity): 184 (1), 141 (28), 113 (38), 99 (86), 96 (100), 87 (11), 69 (11), 55 (34), 43 (15), 42 (26), 41 (48), 39 (12); Elemental analysis calcd (%) for $C_{10}H_{16}O_3$ (184.232): C 65.19, H 8.75; found: C 64.93, H 8.32.

4.8. (1*R*,4*S*,6*S*)-6-Hydroxybicyclo[2.2.2]octan-2-one (−)-11

A solution of 7.00 g (38.0 mmol) of (*R*)-2-(1,4-dioxaspiro[4.5]dec-7-yl)acetaldehyde **10** and 74 mL of a mixture of 5 M phosphoric acid and THF (ratio 1:1) was heated at reflux for 4 h. After reaching room temperature, the solution was concentrated under reduced pressure, diluted with 30 mL water and extracted with 3×100 mL diethylether. The combined organic phase was washed with 100 mL of saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 60:40) yielding 2.01 g (38%, >99% ee) of a white solid, $R_f = 0.53$. The crude crystalline material was recrystallized from *n*-hexane/benzene 1:1 (12 mL) to give (−)-**11** as white crystals with mp = 197.4–199.8 °C; $[\alpha]_D^{21} = -5.2$ (*c* 1.00, $CHCl_3$) {lit.[10] for (−)-**11**: $[\alpha]_D^{22} = -6.5$ (*c* 1.00, $CHCl_3$); mp 161–162 °C; 95% ee}; NMR experiments: ^{1}H, H/H-COSY, NOESY, ^{13}C, DEPT, HMQC; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.46$–1.58 (m, 3H, 5-H and $2 \times$ 8-H), 1.69 (ddd, $J = 2.6/6.3/10.8$ Hz, 1H, 7-H), 1.77 (dddd, $J = 2.5/4.1/7.5/14.3$ Hz, 1H, 7-H), 2.11 (dddt, $J = 2.6/4.0/8.0/2.8$ Hz, 1H, 5-H), 2.15 (dt, $J = 9.7/2.7$ Hz, 1H, 3-H), 2.20 (t, $J = 2.9$ Hz, 1H, OH), 2.23 (td, $J = 6.0/3.0$ Hz, 1H, 4-H), 2.30 (dt, $J = 18.5/2.5$ Hz, 1H, 3-H), 2.42 (dd,

$J = 3.8/6.4$ Hz, 1H, 1-H), 4.21 (ddd, $J = 2.5/3.9/9.0$ Hz, 1H, 6-H); ^{1}H NMR (DMSO-d_6, 500 MHz): $\delta = 1.36$–1.50 (m, 3H, 5-H and $2 \times$ 8-H), 1.56–1.66 (m, 2H, $2 \times$ 7-H), 2.00 (ddd, $J = 2.7/8.9/13.7$ Hz, 1H, 5-H), 2.06 (dd, $J = 2.5/14.6$ Hz, 1H, 3-H), 2.09 (td, $J = 2.4/2.5$ Hz, 1H, 3-H), 2.21 (dd, $J = 3.4/6.6$ Hz, 1H, 4-H), 3.30 (s, 1H, OH), 3.99 (ddd, $J = 2.8/3.3/9.2$ Hz, 1H, 6-H), 4.93 (d, $J = 3.14$ Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 19.9$ (CH_2, C-7), 23.6 (CH_2, C-8), 27.6 (CH, C-4), 36.1 (CH_2, C-5), 44.4 (CH_2, C-3), 50.7 (CH, C-1), 69.1 (CH, C-6), 215.5 (Cq, C-2); IR (KBr): $\tilde{\nu} = 3561$, 3427, 3286, 3214, 2952, 2861, 2844, 1718, 1450, 1400, 1326, 1294, 1220, 1091, 1043, 1008, 941, 883, 869, 839 cm^{-1}; MS *m/z* (relative intensity): 140 (6), 122 (14), 112 (8), 99 (4), 97 (14), 96 (8), 95 (11), 81 (20), 80 (100), 79 (31), 69 (12), 68 (11), 67 (14), 58 (11), 57 (17), 55 (41), 54 (16), 53 (12), 43 (20), 42 (15), 41 (38), 40 (8), 39 (25); Elemental analysis calcd (%) for $C_8H_{12}O_2$ (140.180): C 68.54, H 8.63; found: C 68.41, H 8.55.

Supplementary data

Supplementary data associated with 2D NMR experiments are available from the authors on request.

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References

1. Almqvist, F.; Frejd, T. *J. Org. Chem.* **1996**, *61*, 6947–6951.
2. Mori, K. *Synlett* **1995**, 1097–1109.
3. Paquette, L. A.; Tsui, H.-C. *Synlett* **1996**, 129–130.
4. Paquette, L. A.; Tsui, H.-C. *J. Org. Chem.* **1996**, *61*, 142–145.
5. Zimmermann, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065–3112.
6. Demuth, M.; Ritterskamp, P.; Weigt, E.; Schaffner, K. *J. Am. Chem. Soc.* **1984**, *106*, 2064–2071.
7. Waldmann, H.; Weigerding, M.; Dreisbach, C.; Wandrey, C. *Helv. Chim. Acta* **1994**, *77*, 2111–2116.
8. Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386–2388.
9. Seebach, D.; Jaeschke, G.; Yang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395–2396.
10. Almqvist, F.; Frejd, T. *Tetrahedron: Asymmetry* **1995**, *6*, 957–960.
11. Mori, K.; Nagano, E. *Biocatalysis* **1990**, *3*, 25–36.
12. Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, 1499.
13. Kazlauskas, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4953–4959.
14. Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547–7551.
15. Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 2585–2588.
16. Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845.
17. Ohshima, T.; Xu, Y.; Takita, R.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 9569–9588.
18. We found that the use of beads molecular sieves (MS) 4 Å yielded **5** in an enantiomer excess up to 18%.
19. CCDC-298971 **5** and CCDC-298972 (−)-**11** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
20. Krapcho, A. P. *Synthesis* **1982**, 805–822.
21. De Santis, B.; Iamiceli, A. L.; Bettolo, R. M.; Migneco, L. M.; Scarpelli, R. *Helv. Chim. Acta* **1998**, *81*, 2375–2387.
22. Maleczka, R. E., Jr.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 6538–6546.
23. Evans, D. A.; Golob, A. M.; Mandel, N. S.; Mandel, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 8170–8174.
24. Lightner, D. A.; Gawroñski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 5749–5754.
25. Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845–850.
26. Denmark, S. E.; Kim, J.-H. *J. Org. Chem.* **1995**, *60*, 7535–7547.
27. Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534–3538.