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Stereoselective cross aldol condensation of bicyclo[3.2.0]alkanones†

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A cross aldol reaction between [(*S*)-(−)] or [(*R*)-(+)]-benzyloxypropanal and silyl enol ethers derived from bicyclo[3.2.0]alkanones was carried out in the presence of $TiCl_4$, leading with total stereoselectivity to a 1 : 1 mixture of enantiomerically pure diastereomers isolated in 81% overall yield. Thus, 5 stereogenic centers could be created starting from one. Furthermore, an efficient access to an enantiomerically pure tricyclo[5.3.0.0^{2,6}]decane scaffold was possible *via* a 4 step reaction sequence.

Introduction

The aldol reaction is one of the most powerful methods for forming carbon–carbon bonds and for generating stereochemistry in a controlled fashion.[1] In this context, the condensation involving bicyclo[3.2.0]alkanone derivatives and aldehydes is poorly documented in the literature. Indeed, to the best of our knowledge, a unique report by Clark *et al.* showed that the addition of racemic aldehydes to the lithio enolate derived from bicyclo[3.2.0]heptanone afforded the corresponding aldol products.[2] On the other hand, it has also been mentioned that the boron enolate or the silyl enol ether derived from bicyclo[3.2.0]heptan-6-one led to the corresponding aldol product as a mixture of *syn–anti* products when benzaldehyde was added to the latter: however, no experimental details and no spectroscopic data are available to support these results.[3]

To the best of our knowledge, no cross-aldol reactions involving enantiomerically pure aldehydes and bicyclo[3.2.0]alkanones have been described in the literature. Being already involved in the reactivity of bicyclo[3.2.0]alkanone derivatives,[4] we became interested in the stereochemical outcome of the $TiCl_4$-mediated aldol reaction of enantiomerically pure benzyloxypropanal with silyl enol ethers derived from (±)-bicyclo-[3.2.0]alkanones.

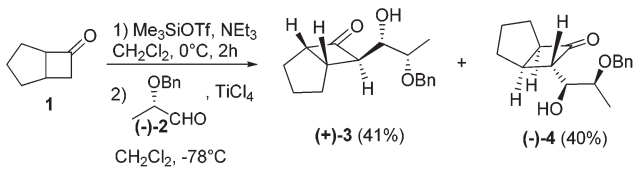
Herein, we report on a completely stereoselective cross-aldol condensation that takes place between the silyl enol ether derived from bicyclo[3.2.0]alkanone derivatives and [(*S*)-(−)] or [(*R*)-(+)]-benzyloxypropanal.

Results and discussion

The bicyclo[3.2.0]heptane skeleton represents not only a substructure of numerous natural products[5] but also a very useful building block for different purposes such as ring expansion and skeletal isomerization.[6] Therefore, the functionalization of such a scaffold is of importance.

In particular, cross aldol reactions between bicylo[3.2.0]-alkanones and an aldehyde could represent a powerful tool to access polyfunctionalized bicyclo[3.2.0]heptane skeletons. To this end, we examined the cross aldol reaction between [(*S*)-(−)]-benzyloxy propanal **(−)-2** and the silyl enol ether derived from racemic bicyclo[3.2.0]heptan-6-one **1**. When this reaction was carried out in the presence of $TiCl_4$, a 1 : 1 mixture of diastereomers **(+)-3** and **(−)-4** was isolated in 81% overall yield. A similar reaction was repeated with (*R*)-(+) benzyloxypropanal **(+)-2**, providing the corresponding enantiomers **(−)-3** and **(+)-4** as confirmed by the opposite optical rotation (Scheme 1). Cross aldol products were easily separable by silica gel chromatography.

The formation of two diastereomers **(+)-3** and **(−)-4** could be explained according to the following mechanism: first, the approach of aldehyde **2** takes place exclusively on the concave face of the trimethylsilyl enol ether derived from bicyclo[3.2.0]-heptanone **1**.



Scheme 1 Cross aldol condensation between bicyclo[3.2.0]heptan-6-one **1** and [(*S*)-(−)]-benzyloxy propanal **(−)-2**.

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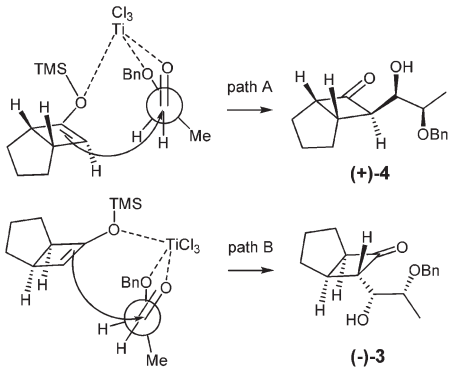


Fig. 1 The Cram chelate model.

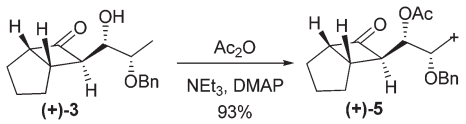
On the other hand, the exclusive formation of two diastereoisomers can be explained by the Cram chelate model:[7] indeed, titanium chelates not only the two oxygens of the benzyloxypropanal, but also the oxygen of the trimethylsilyl enol ether derived from bicyclo[3.2.0]heptanone **1**. Therefore, only two pathways are possible, leading to only two of eight possible enantiomerically pure diastereomers with complete stereoselectivity (Fig. 1).

This reaction also constitutes a resolution of the racemic bicyclo[3.2.0]heptan-6-one.

The absolute configuration of compound (+)-**3** was unambiguously confirmed by X-ray crystallographic analysis of the acetate **5**, which was readily obtained by treatment of (+)-**3** with acetic anhydride in the presence of NEt_3 and DMAP (Scheme 2, Fig. 2).[8]

This reaction was extended to the silyl enol ether derived from 7-methylbicyclo[3.2.0]heptan-6-one **6**, giving readily the two ketols (+)-**7** and (−)-**8**. Equally, the reaction took place with complete stereoselectivity (Scheme 3).

Thus, the aldol reaction promoted by $TiCl_4$ induced a double induction process where the two enantiomers of the racemic ketone react with total stereoselectivity with the chiral aldehyde. It turned out that the configuration of the newly formed stereogenic center was controlled by the configuration



Scheme 2 Synthesis of acetate **(+)-5**.

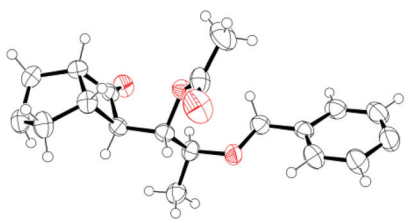
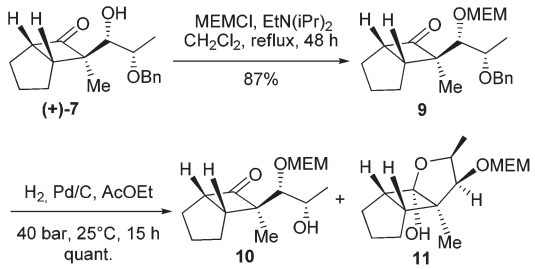


Fig. 2 X-ray structure of compound **5**.



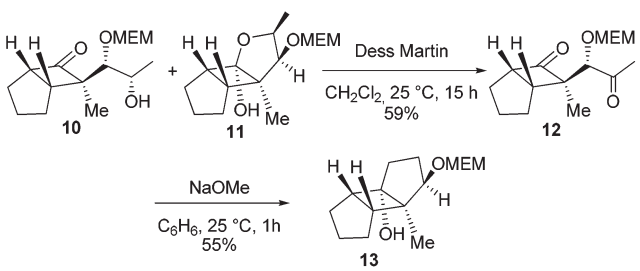
Scheme 3 Cross aldol condensation between 7-methylbicyclo[3.2.0]heptan-6-one **6** and **(−)-2**.

of the aldehyde and, in this way, 5 stereogenic centers could be created starting from one. These results are in accordance with cross aldol reactions previously reported by our group.[9]

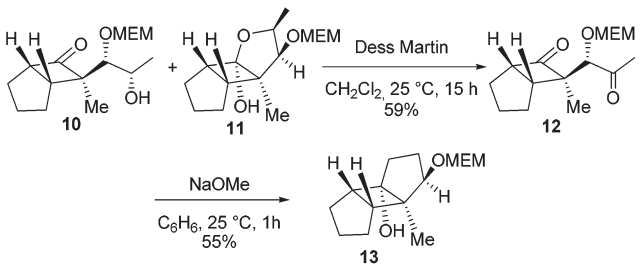
Having compound (+)-**7** in hand, the latter could be considered as a precursor of a 1,4-diketone that could undergo an intramolecular condensation to afford a tricyclo[5.3.0.0^{2,6}]-decane ring system. Indeed, this scaffold is prevalent in numerous natural products and could be considered as a formal precursor of hydroazulene ring systems *via* ring opening reactions.[11]

For that purpose, the hydroxyl group of compound **7** was protected as a MEM ether to afford **9** using standard conditions. After hydrogenolysis of the benzyl ether, a 2 : 1 mixture of two inseparable compounds was obtained: the hydroxy derivative **10** and the lactol derivative **11** resulting from an intramolecular nucleophilic addition of the hydroxyl group to the cyclobutanone (Scheme 4).

Finally, a Dess–Martin oxidation[10] of this mixture provided the desired 1,4-diketone **12** which, after treatment with sodium methoxide, led to the desired tricyclo[5.3.0.0^{2,6}]decane scaffold **13** (Scheme 5).



Scheme 4 Synthesis of compounds **10** and **11**.



Scheme 5 Synthesis of tricyclo[5.3.0.0^{2,6}]decane **13**.

In summary, a cross aldol reaction between [(*S*)-(−)] or [(*R*)-(+)]-benzyloxypropanal and silyl enol ethers derived from bicylo[3.2.0]alkanones allowed the resolution of the bicyclic system and constitutes a good way to introduce concomitantly 3 stereogenic centers and allow access to a key intermediate for the synthesis of tricyclic skeletons. The aldol compounds provided an enantiomerically enriched tricyclo[5.3.0.0^{2,6}]-decane substructure in a four step sequence, providing possible entry to natural compounds possessing the same structural platform.[11]

Experimental section

General information

Reactions were carried out under a positive pressure of argon with magnetic stirring and using degassed solvents in oven-dried glassware. Et_2O and THF were distilled from Na/benzophenone. Thin-layer chromatography (TLC) was carried out on silica gel plates Merck $60F_{254}$ and the spots were visualized under a UV lamp (254 or 365 nm) and/or sprayed with a solution of vanillin (25 g) in EtOH–H_2SO_4 (98 : 2; 1 L) or with phosphomolybdic acid followed by heating on a hot plate. For column chromatography, silica gel (Merck, Si60, 40–60 μm) was used. Melting points (m.p.) were measured on a hot plate Stuart Scientific SMP 3 apparatus. ^{1}H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 75 or 125 MHz on a Bruker AC-300 or ARX-500 using the signal of the residual nondeuterated solvent as the internal reference. Significant ^{1}H NMR spectroscopic data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constants J in hertz, the number of protons. The ratios of compounds indicated below were calculated from the NMR integrations. IR spectra were recorded as CCl_4 solutions on a Perkin Elmer IR-881 spectrometer. Microanalyses were carried out by the Service Commun d'Analyses du CNRS, Institut de Chimie-Strasbourg.

Cross aldol reaction general procedure

(a) Formation of the silyl enol ether. To a solution of bicyclo[3.2.0]alkanone (1 equiv.) in anhydrous dichloromethane (~30 mL/1 mmol) at 0 °C were added successively triethylamine (2.5 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.3 equiv.). The reaction mixture was stirred under an argon atmosphere at 0 °C for 2 h and then concentrated to afford the crude enoxysilane.

(b) Formation of the aldehyde–$TiCl_4$ complex. To a solution of (*S*)-2-(benzyloxy)propanal (1.2 equiv.) in anhydrous dichloromethane (~10 mL/10 mmol) at −78 °C was added a titanium chloride solution (1 M in dichloromethane, 1.2 equiv.) and the solution was stirred for 10 minutes.

(c) Cross aldol reaction. The crude enoxysilane was dissolved in anhydrous dichloromethane (1 mmol/1 mL) and the resulting solution was added dropwise at −78 °C to the titanium complex. The reaction mixture was stirred at −78 °C for 1.5 h and hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (10 mL/1 mmol). The aqueous layer was extracted with CH_2Cl_2 (10 mL/1 mmol) and Et_2O (10 mL/1 mmol). The combined organic extracts were washed with brine (10 mL/1 mmol), dried over Na_2SO_4 and concentrated. Purification of the resulting residue by chromatography on a silica gel column with petroleum ether–AcOEt (80 : 20) as an eluent provided the desired compounds.

Bicyclo[3.2.0]heptanones (+)-(3) and (−)-(4)

Bicyclo[3.2.0]heptan-6-one **1**: 1.583 g (14.37 mmol); NEt_3: 5.01 mL (35.93 mmol); Me_3SiOTf: 3.38 mL (18.68 mmol); (*S*)-2-(benzyloxy)propanal **(−)-2**: 2.831 g (17.24 mmol); $TiCl_4$ 1 M in CH_2Cl_2: 17.30 mL (17.24 mmol). Purification by column chromatography afforded compounds **(+)-3** and **(−)-4**.

(1*R*,5*S*,7*R*)-7-((1*S*,2*S*)-2-(benzyloxy)-1-hydroxypropyl)bicyclo-[3.2.0]heptan-6-one (+)-(3). Colorless oil, yield: 1.633 g (41%); $[\alpha]_D^{20}$ +70 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1775, 3573 cm^{-1}; ^{1}NMR (300 MHz, $CDCl_3$) δ 7.27–7.38 (m, 5 H), δ_A = 4.44, δ_B = 4.66 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 62.9 Hz, 2 H), 3.74 (t, J = 6.3 Hz, 1 H), 3.70 (q, J = 5.7 Hz, 1 H), 3.47 (td, J = 8.0, 2.8 Hz, 1 H), 2.90 (q large, J = 6.0 Hz, 1 H), 2.84 (sl, 1 H), 2.77 (td, J = 4.7, 3.3 Hz, 1 H), 1.49–2.10 (m, 6 H), 1.21 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.1, 138.3, 128.6, 128.0, 127.9, 76.5, 74.5, 71.3, 65.4, 62.9, 33.5, 32.6, 29.6, 25.5, 15.6; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_3$ $[M + Na]^+$: 297.3445; found: 297.3451.

(1*S*,5*R*,7*S*)-7-((1*S*,2*S*)-2-(benzyloxy)-1-hydroxypropyl)bicyclo-[3.2.0]heptan-6-one (−)-(4). Colorless oil, yield: 1.595 g (40%); $[\alpha]_D^{20}$ −50 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1768, 3573 cm^{-1}; ^{1}NMR (300 MHz, $CDCl_3$) δ 7.26–7.40 (m, 5 H), δ_A = 4.47, δ_B = 4.66 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 58.3 Hz, 2 H), 3.76 (q, J = 5.4 Hz, 1 H), 3.63 (q, J = 6.1 Hz, 1 H), 3.47 (d, J = 5.0 Hz, 1 H), 2.97 (td, J = 7.2, 4.9 Hz, 1 H), 2.81 (td, J = 5.0, 3.4 Hz, 1 H), 2.10–1.90 (m, 6 H), 2.53 (d, J = 5.0 Hz, 1 H), 1.19 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 138.3, 128.6, 128.0, 127.9, 76.3, 73.1, 71.3, 66.4, 63.3, 33.0, 32.1, 29.6, 25.5, 15.9; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_3$ $[M + Na]^+$: 297.3445; found: 297.3490.

Bicyclo[3.2.0]heptanones (−)-3 and (+)-4

Bicyclo[3.2.0]heptan-6-one **1**: 0.300 g (2.72 mmol); NEt_3: 0.95 mL (6.81 mmol); Me_3SiOTf: 0.64 mL (3.54 mmol); (*R*)-2-(benzyloxy)propanal **(+)-2**: 0.537 g (3.27 mmol); $TiCl_4$ 1 M in CH_2Cl_2: 3.30 mL (3.27 mmol). Purification by column chromatography afforded compounds **(−)-3** and **(+)-4** as colorless oils.

(1*S*,5*R*,7*S*)-7-((1*R*,2*R*)-2-(benzyloxy)-1-hydroxypropyl)bicyclo-[3.2.0]heptan-6-one (−)-(3). Colorless oil, yield: 0.217 g (30%); $[\alpha]_D^{20}$ −71 (*c* 1.0, $CHCl_3$); ^{1}H NMR, ^{13}C NMR and IR data are identical to those reported for compound **(+)-3**; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_3$ $[M + Na]^+$: 297.3445; found: 297.3448.

(1*R*,5*S*,7*R*)-7-((1*R*,2*R*)-2-(benzyloxy)-1-hydroxypropyl)bicyclo-[3.2.0]heptan-6-one (+)-(4). Colorless oil, yield: 0.222 g (30%); $[\alpha]_D^{20}$ +49 (*c* 1.0, $CHCl_3$); ^{1}H NMR, ^{13}C NMR and IR data are identical to those reported for compound **(−)-4**; HRMS (ESI):

m/z [M + Na]$^+$ calcd for $C_{17}H_{22}NaO_3$ [M + Na]$^+$: 297.3445; found: 297.3478.

Methylbicyclo[3.2.0]heptanones (+7) and (−)-8

7-methylbicyclo[3.2.0]heptan-6-one **6**: 1.150 g (9.26 mmol); NEt_3: 3.23 mL (23.15 mmol); Me_3SiOTf: 2.18 mL (12.04 mmol); (*S*)-2-(benzyloxy)propanal **(−)-2**: 1.824 g (11.11 mmol); $TiCl_4$ 1 M in CH_2Cl_2: 11.15 mL (11.11 mmol). Purification by column chromatography afforded compounds **(+7)** and **(−)-8**.

(1*R*,5*S*,7*R*)-7-((1*S*,2*S*)-2-(benzyloxy)-1-hydroxypropyl)-7-methylbicyclo[3.2.0]heptan-6-one (+)-(7). Colorless oil, yield: 1.048 g (39%); $[\alpha]_D^{20}$ +56 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1764, 3560 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5 H), δ_A = 4.46, δ_B = 4.62 (AB, J_{AB} = 11.2 Hz, $\Delta\nu$ = 46.4 Hz, 2 H), 3.68 (qd, *J* = 6.2; 4.1 Hz, 1 H), 3.61 (t large, *J* = 8.1 Hz, 1 H), 3.51 (dd, *J* = 6.0; 4.0 Hz, 1 H), 2.87 (t large, *J* = 8.2 Hz, 1 H), 2.86 (d, *J* = 6.0, 1 H), 1.30–2.10 (m, 6 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 138.0, 128.6, 128.1, 127.9, 78.4, 74.5, 71.0, 67.7, 63.2, 38.0, 28.5, 27.2, 27.0, 17.8, 10.9; Anal. Calcd for $C_{18}H_{24}O_3$: C, 75.00; H, 8.39. Found: C, 74.69; H, 8.46; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$ [M + Na]$^+$: 311.1623; found: 311.1607.

(1*S*,5*R*,7*S*)-7-((1*S*,2*S*)-2-(benzyloxy)-1-hydroxypropyl)-7-methylbicyclo[3.2.0]heptan-6-one (−)-(8). Colorless oil, yield: 0.947 g (35%); $[\alpha]_D^{20}$ −59 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1766, 3560 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 5 H), δ_A = 4.42, δ_B = 4.65 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 68.1 Hz, 2 H), 3.71 (qd, *J* = 6.3; 3.2 Hz, 1 H), 3.60 (t large, *J* = 8.1 Hz, 1 H), 3.53 (dd, *J* = 7.4; 4.0 Hz, 1 H), 3.05 (t large, *J* = 8.1 Hz, 1 H), 2.79 (d, *J* = 7.3, 1 H), 1.30–2.10 (m, 6 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.6, 138.0, 128.6, 128.0, 127.9, 77.6, 74.1, 70.7, 67.8, 63.2, 37.7, 28.6, 27.4, 27.1, 16.9, 10.5; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$ [M + Na]$^+$: 311.1623; found: 311.1609.

(1*R*,5*S*,7*R*)-7-methyl-7-((3*S*,4*S*)-3-methyl-1-phenyl-2,5,7,10-tetraoxaundecan-4-yl) bicyclo[3.2.0]heptan-6-one (9). To a solution of compound **(+)-7** (0.100 g, 0.35 mmol) in anhydrous dichloromethane (5 mL) were added successively *N,N*-diisopropylethylamine (0.09 mL, 0.52 mmol) and 2-methoxyethoxymethyl chloride (0.06 mL, 0.52 mmol). The reaction mixture was stirred under reflux for 48 h and the same equivalents of reagents were added approximately every 12 h. After cooling and adding dichloromethane (10 mL) the resulting mixture was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and Et_2O (10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the resulting residue by chromatography on a silica gel column with petroleum ether–AcOEt (80 : 20) as an eluent afforded compound **9** (0.114 g, 87%). Colorless oil; $[\alpha]_D^{20}$ +65 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5 H), δ_A = 4.73, δ_B = 4.89 (syst AB, J_{AB} = 7.2 Hz, $\Delta\nu$ = 48.9 Hz, 2 H), δ_A = 4.46, δ_B = 4.58 (syst AB, J_{AB} = 11.6 Hz, $\Delta\nu$ = 34.4 Hz, 2 H), 3.65–3.78 (m, 3 H), 3.71 (d, *J* = 4.7 Hz, 1 H), 3.70 (t large, *J* = 8.1 Hz, 1 H), 3.48 (t, *J* = 4.6 Hz, 2 H), 3.36 (s, 3 H), 2.83 (t large, *J* = 8.3, 1 H), 1.30–2.05 (m, 6 H), 1.25 (d, *J* = 6.4 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 138.5, 128.4, 127.9, 127.6, 96.9, 83.8, 76.5, 71.8, 71.5, 67.9, 67.6, 62.9, 59.1, 38.7, 28.3, 27.1, 26.9, 17.3, 11.2; Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.19; H, 8.57. Found: C, 69.59; H, 8.41; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{32}NaO_5$ [M + Na]$^+$: 399.2147; found: 399.2186.

Compounds 10 and 11

Hydrogenolysis of compound **9** (0.120 g, 0.32 mmol) was carried out in ethyl acetate (10 mL) in the presence of 10% Pd/C (0.010 g) under hydrogen pressure (40 bar) for 15 h. After filtration and concentration *in vacuo*, the residue was purified by chromatography on silica gel with petroleum ether–AcOEt, 40 : 60, as an eluent, yielding a 1 : 2 mixture of inseparable compounds **10** and **11** (0.091 g, 100%). It was possible to determine the ^{1}H and ^{13}C chemical shifts for each compound. However, IR and elemental analyses are given for the mixture of compounds **10** and **11**. IR (CCl_4): 1758, 3360, 3600 cm^{-1}; Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.12; H, 9.19.

(1*R*,5*S*,7*R*)-7-((1*S*,2*S*)-2-hydroxy-1-((2-methoxyethoxy)methoxy)-propyl)-7-methylbicyclo[3.2.0]heptan-6-one (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ δ_A = 4.80, δ_B = 4.62 (AB, J_{AB} = 7.1 Hz, $\Delta\nu$ = 53.6 Hz, 2 H), 3.61–3.81 (m, 4 H), 3.51–3.57 (m, 2 H), 3.48 (d, *J* = 5.1 Hz, 1 H), 3.36 (s, 3 H), 2.78 (t, *J* = 8.2 Hz, 1 H), 2.65 (large d, *J* = 10.0 Hz, 1 H), 2.10–1.30 (m, 6 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5, 98.0, 88.0, 71.7, 68.4, 67.8, 67.6, 62.4, 59.1, 38.6, 28.6, 27.1, 26.9, 20.7, 14.4, 9.7.

Tricyclo derivative (11). ^{1}H NMR (300 MHz, $CDCl_3$) δ δ_A = 4.75, δ_B = 4.64 (AB, J_{AB} = 7.1 Hz, $\Delta\nu$ = 53.6 Hz, 2 H), 4.19 (qd, *J* = 6.4, 4.1 Hz, 1 H), 3.61–3.81 (m, 2 H), 3.79 (d, *J* = 4.0 Hz, 1 H), 3.54 (t, *J* = 4.7 Hz, 2 H), 3.38 (s, 3 H), 2.72 (s large, 1 H); 2.69 (t, *J* = 7.9 Hz, 1 H), 2.61 (t, *J* = 7.8 Hz, 1 H), 2.10–1.30 (m, 6 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.3, 95.2, 87.8, 76.5, 71.8, 67.4, 59.2, 52.7, 49.4, 34.1, 28.0, 27.0, 26.6, 14.5, 9.7.

(1*R*,5*S*,7*R*)-7-((*S*)-1-((2-methoxyethoxy)methoxy)-2-oxopropyl)-7-methylbicyclo[3.2.0]heptan-6-one (12)

To a solution of compound **10** + **11** (0.110 g, 0.384 mmol) in anhydrous dichloromethane (5 mL) at 0 °C was added Dess Martin Periodinane (0.212 g, 0.499 mmol). The reaction mixture was stirred for 2 hours at room temperature. Dess Martin Periodinane (0.212 g, 0.499 mmol) was added again. After an additional stirring of 15 hours the resulting mixture was quenched with a saturated solution of $Na_2S_2O_3$ (10 mL) and stirred for 5 minutes. The solution was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and Et_2O (10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the resulting residue by chromatography on a silica gel column with petroleum ether–AcOEt (70 : 30) as an eluent afforded compound **12** (0.064 g, 59%).

Colorless oil; $[\alpha]_D^{20}$ −12 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1715, 1772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2 H), 4.02 (s, 1 H), 3.64–3.79 (m, 3 H), 3.51 (t, J = 4.6 Hz, 2 H), 3.37 (s, 3 H), 2.93 (t, J = 8.3 Hz, 1 H), 2.20 (s, 3 H), 1.20–2.10 (m, 6 H), 0.93 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 209.0, 96.2, 86.8, 71.8, 68.3, 65.5, 63.5, 59.2, 38.5, 28.6, 27.6, 27.2, 27.1, 10.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_5$ $[M + Na]^+$: 307.1521; found: 307.1527.

Tricyclo[5.3.0.0^{2,6}]decane (13)

To a solution of compound **12** (0.049 g, 0.172 mmol) in benzene (4 mL) was added a solution of NaOMe (1 M in methanol, 0.86 mL). The reaction mixture was stirred at room temperature under an argon atmosphere for 1 hour. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and Et_2O (5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the resulting residue by chromatography on a silica gel column with petroleum ether–AcOEt, 60 : 40, as an eluent afforded compound **13** (0.027 g, 55%). Colorless oil; $[\alpha]_D^{20}$ −71 (*c* 1.0, $CHCl_3$); IR (CCl_4): ν_{max} 1757, 3471, 3606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ δ_A = 4.81, δ_B = 4.94 (syst AB, J_{AB} = 7.0 Hz, $\Delta\nu$ = 41.3 Hz, 2 H), 4.33 (d, J = 2.6 Hz, 1 H), 3.75–3.79 (m, 2 H), 3.53–3.57 (m, 2 H), 3.38 (s, 3 H), 2.77 (dd, J = 16.0; 2.7 Hz, 1 H), 2.33–2.53 (m, 3 H), 1.40–1.90 (m, 7 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 95.5, 86.5, 74.2, 71.8, 67.3, 59.2, 49.8, 49.0, 48.6, 35.2, 28.2, 28.1, 26.6, 13.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{24}NaO_5$ $[M + Na]^+$: 307.1521; found: 307.1519.

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