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First Stereoselective Synthesis of (1*R*,2*R*,4*R*)- and (1*S*,2*R*,4*S*)-2-Substituted-1-azabicyclo[2.2.1]heptanes

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The first stereoselective synthesis of two diastereomeric 1-azabicyclo[2.2.1]heptanes substituted at the 2-position from an easily accessible (*R*)-2-substituted-4-piperidone is reported. The synthetic route involves the asymmetric one-carbon homologation of a chiral ketone followed by an intramolecular S_N2-type cyclisation and led to target compounds in high overall yield by using a simple procedure in which purification of the intermediate compounds is not required.

Introduction

The synthesis and the biological activity of compounds containing the 1-azabicyclo[2.2.1]heptane scaffold is documented by more than 350 publications.[1] Depending on the substitution pattern of the 1-azabicyclo[2.2.1]heptane, different activities have been reported, and many of these compounds have been used in the treatment of central nervous system disorders. Among the 1-azabicyclo[2.2.1]heptane derivatives, those with a substituent at C^2 are of relevance, because they have shown high affinity for histamine, opioid, muscarinic and nicotinic cholinergic receptors.[2] This behaviour is important in the treatment of diseases such as Alzheimer's dementia, schizophrenia, anxiety, attention-deficit hyperactivity disorder, depression, obesity, allergy, drug addiction and chronic pain. Moreover, 2-substituted-1-azabicyclo[2.2.1]heptanes have a close structural resemblance to cinchona alkaloids, so these compounds could behave as chiral ligands or organocatalysts for catalytic asymmetric transformations. In this regard, these new compounds feature a basic centre, which is a stereogenic nitrogen atom with a defined configuration.

Versatile stereocontrolled routes to 2-substituted-1-azabicyclo[2.2.1]heptanes are of interest due to the important properties of this class of compounds. In this context, several methods for the preparation of racemic products have been reported.[2,3] Our interest is focused on the development of the first asymmetric synthesis of this azabicyclic scaffold.

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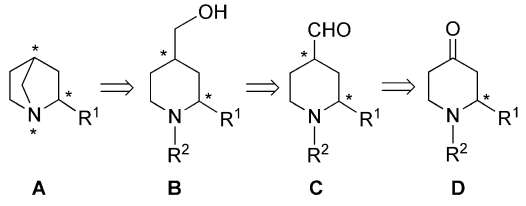
Results and Discussion

On the basis of our experience with the use of diastereoselective aza-Diels–Alder reactions to obtain enantiomerically pure 2-alkyl-4-piperidone derivatives,[4] we envisaged that these heterocyclic compounds could be useful starting materials for the stereoselective synthesis of 2-alkyl-1-azabicyclo[2.2.1]heptanes **A**. We reasoned that target compound **A** could be obtained from alcohol **B** by an intramolecular S_N2-type cyclisation. Straightforward reduction of aldehyde **C** would give primary alcohol **B**, and aldehyde **C** can be synthesised by asymmetric one-carbon homologation from 4-piperidone **D** (Scheme 1).

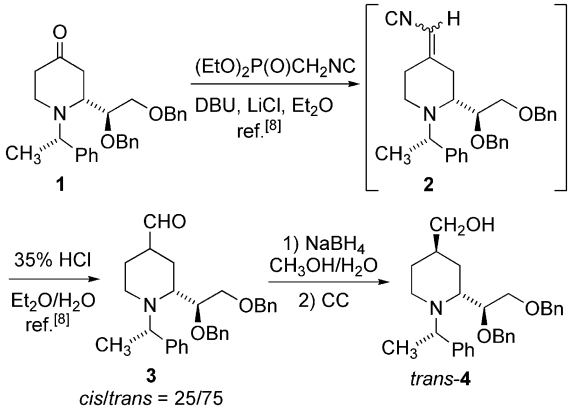


Scheme 1. Retrosynthetic analysis.

The addition of a one-carbon unit to a ketone to homologate it to a new carbonyl derivative is an important transformation that chemists have approached in different ways. Strategies using epoxides, vinyl heteroatoms, nitriles, ketals, alcohols or alkenes as intermediates have all been developed.[5] In this context, it has been reported[6] that ketones and aldehydes react through a Wadsworth–Emmons olefination by using diethyl isocyanomethylphosphonate to give α,β-unsaturated isocyanides and that hydrolysis of isocyanides under acidic conditions affords the corresponding homologated aldehydes.[7] This strategy has shown to be appropriate to homologate sterically hindered ketones, cyclic ketones, enolisable ketones and several aliphatic and aromatic aldehydes. Recently, we reported[8] the first asymmet-

ric version of this synthetic methodology, which consists of Wadsworth–Emmons olefination of (*R*)-2-[(*S*)-1,2-bis(benzyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-4-piperidone (**1**) with an excess amount of diethyl isocyanomethylphosphonate (5 equiv.) under the reaction conditions described by Masamune and Roush[9] and subsequent hydrolysis of intermediate α,β-unsaturated isocyanide **2** with HCl at room temperature in a two-phase system (diethyl ether/water). Under these conditions, aldehyde **3** was obtained as a thermodynamically unstable 25:75 mixture of *cis* and *trans* diastereoisomers,[10] in which *trans*-**3** was the major compound.

Next, the obtained 25:75 diastereomeric mixture of *cis* and *trans* aldehyde **3** was dissolved in 4:1 MeOH/H_2O and immediately reduced by using $NaBH_4$ to yield alcohol **4** as a 25:75 mixture of *cis* and *trans* diastereoisomers[10] (Scheme 2). After easy separation by column chromatography (CC), *cis*-**4** and *trans*-**4** were obtained in 17 and 59% yield, respectively, from starting piperidone **1**.



Scheme 2. Asymmetric homologation of chiral piperidone **1**.

It is worth mentioning that the use of water as cosolvent in the reduction step is essential to avoid the formation of compound **5** as a byproduct (Figure 1). Compound **5** is probably derived from intermolecular reductive amination of aldehyde **3** with diethyl aminomethylphosphonate generated through acidic hydrolysis of the diethyl isocyanomethylphosphonate reagent used in high excess.

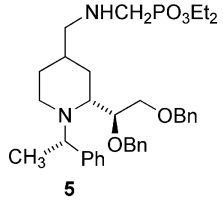
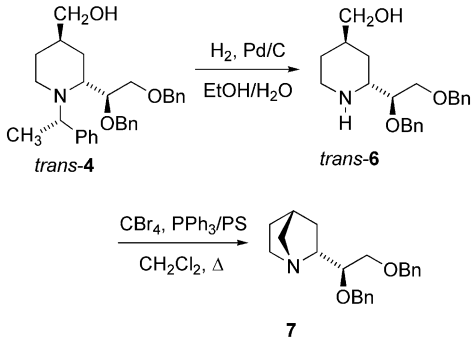


Figure 1. Structure of byproduct **5**.

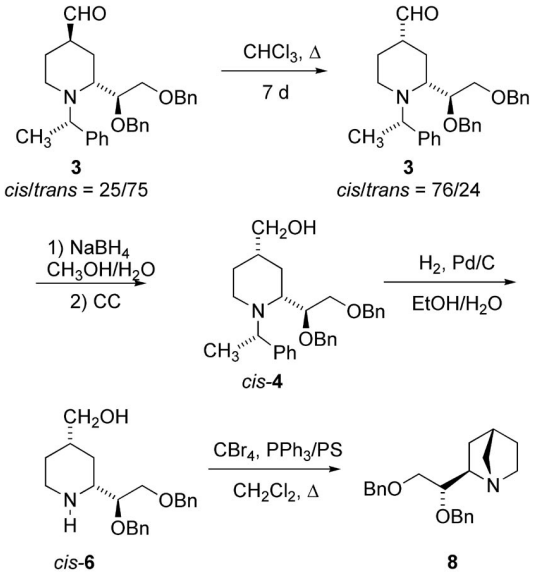
Conversion of *trans*-**4** into desired 1-azabicyclo[2.2.1]-heptane scaffold **7** was performed as follows. *N*-Debenzylation of *trans*-**4** by using palladium on carbon as a catalyst gave piperidine *trans*-**6** in 83% yield. It is noteworthy that the use of water as cosolvent proved to be essential for the success of the hydrogenolysis process, as in the absence of water the starting material was recovered unaltered. Substitution of the hydroxy group by bromine in compound *trans*-**6** with the use of a mixture of CBr_4 and Ph_3P/PS and subsequent intramolecular S_N2-type cyclisation gave **7** in quantitative yield (two steps, one pot). In this way, **7** was obtained in 49% overall yield from piperidone **1** by using a simple six-step procedure in which most of the intermediate compounds did not require purification. The whole sequence for the synthesis of **7** is shown in Scheme 3.



Scheme 3. Synthesis of compound **7**.

Upon standing, *trans*-**3** slowly epimerised to the thermodynamically more-stable *cis*-**3**. Thus, when crude aldehyde **3** (*cis*/*trans* = 25:75) was dissolved in chloroform and the resulting solution was heated under reflux for 7 d, the initial diastereomeric ratio progressively evolved to reach a constant value of 76:24 in favour of the *cis* diastereoisomer. It is of note that the epimerisation rate increased upon heating, but not under basic conditions. The resulting diastereomeric mixture was subsequently reduced with the use of $NaBH_4$ to give alcohol **4** as a 76:24 mixture of *cis* and *trans* diastereoisomers, from which alcohols *cis*-**4** and *trans*-**4** were isolated by column chromatography in 48 and 26% yield, respectively, from starting piperidone **1**. Conversion of *cis*-**4** into 1-azabicyclo[2.2.1]heptane **8** was performed by following the same route as before (Scheme 3). *N*-Debenzylation of *cis*-**4** by using palladium on carbon as a catalyst and water as a cosolvent gave *cis*-**6** in 79% yield. Substitution of the hydroxy group by bromine followed by intramolecular S_N2-type cyclisation gave **8** in quantitative yield (two steps, one pot). Compound **8** was obtained in 38% overall yield from piperidone **1** by using a simple seven-step procedure in which most of the intermediate compounds did not require purification. The complete sequence for the synthesis of **8** is shown in Scheme 4.

Following complete assignment of the ^1H NMR resonances with the aid of 2D NMR spectroscopic studies (COSY, HSQC, HMBC) the *cis* and *trans* configurations of compounds *cis*-**4** and *trans*-**4** were unequivocally determined by 2D NOESY experiments. NOE crosspeaks observed between H^a (δ = 2.61–2.67 ppm, m) and H^c (δ = 1.25–1.33 ppm, m) in compound *cis*-**4** are consistent with a *cis* relative configuration for this compound (Figure 2). The assignment of the *trans* configuration to the diastereomeric compound *trans*-**4** is consistent with the observation of NOE crosspeaks between H^a (δ = 3.14–3.20 ppm, m) and the methylene groups at C^4 (δ = 3.28 ppm, dd; δ =



Scheme 4. Synthesis of compound **8**.

3.31 ppm, dd) as well as between H^c (δ = 1.67–1.77 ppm, m) and the methine proton of substituent at C^2 (δ = 3.91–3.97 ppm, m) (Figure 2).

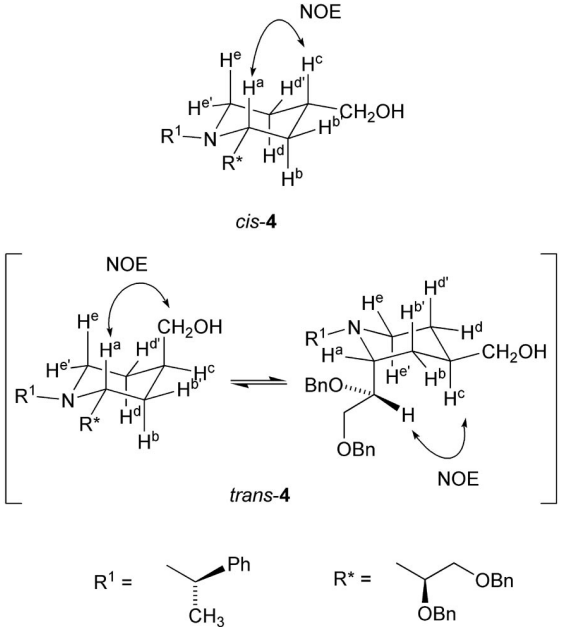


Figure 2. Determination of the relative configuration of compounds *cis*-**4** and *trans*-**4** by 2D NOESY experiments.

Conclusions

In summary, we have developed the first diastereoselective synthesis of (1*R*,2*R*,4*R*)- and (1*S*,2*R*,4*S*)-2-substituted-1-azabicyclo[2.2.1]heptanes **10** and **11** from piperidone **1**. The products were obtained in enantiomerically pure form with very high overall yield, 49 and 38%, respectively. This synthesis represents another example of the utility of piperidone **1** as a versatile chiral starting material.[8,11]

Experimental Section

General Methods: All reagents were of analytical grade and were used as obtained from commercial sources with the exception of anhydrous lithium chloride, which was dried under vacuum at 140 °C overnight before use. Reactions were carried out by using anhydrous solvents with the exception of chloroform, methanol and ethanol. Whenever possible, the reactions were monitored by thin-layer chromatography (TLC). TLC was performed on precoated silica-gel polyester plates, and the products were visualised by using UV light (254 nm) and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed with silica gel (60 Å, 35–70 μm). Microanalyses were determined by using a Perkin-Elmen 2400 CHNS elemental analyser. Melting points were determined in open capillaries with a Gallenkamp apparatus and are uncorrected. FTIR spectra of oils were recorded as thin films on NaCl plates and those of solids were recorded as KBr pellets with a Thermo Nicolet Avatar 360 FTIR spectrometer; $\tilde{\nu}$ values are given for the main absorption bands. Optical rotations were measured with a Jasco P-1020 polarimeter at λ = 589 nm and 25 °C in a cell with 10 cm path length. NMR spectra were acquired with a Bruker AV-400 spectrometer or a Bruker AV-500 spectrometer operating at 400 or 500 MHz for ^{1}H NMR and 100 or 125 MHz for ^{13}C NMR by using a 5-mm probe. The chemical shifts were referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; q, quartet; m, multiplet; dd, doublet of doublets; dq, doublet of quartets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dddq, doublet of doublet of doublet of quartets; ddddd, doublet of doublet of doublet of doublet of doublets; br. s, broad singlet; br. d, broad doublet; br. dd, broad doublet of doublets. NOESY spectra were acquired in the phase-sensitive mode with gradient pulses in the mixing time as 2048 × 256 hipercomplex files with 8 transients for 256 time increments. An optimised mixing time of 750 ms was used and processing was carried out by using a sine-bell squared function shifted by π/2 and a states-TPPI method. Special precautions such as degassing of the sample were not taken. High-resolution mass spectra were recorded with a Bruker Daltonics MicroToF-Q instrument from methanolic solutions by using the positive electrospray ionisation mode (ESI+).

(2*R*,4*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-4-hydroxymethyl-1-[(*S*)-1-phenylethyl]piperidine (*trans*-4): $NaBH_4$ (76 mg, 2.0 mmol) was added to a solution of the 25:75 mixture of *cis*-**3**/*trans*-**3** (914 mg, 2.0 mmol) obtained as described previously[8] in CH_3OH/H_2O (4:1, 5 mL). After vigorously stirring for 2 h at room temperature, the reaction mixture was evaporated under reduced pressure. The obtained crude was solved in Et_2O (50 mL), treated with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/hexanes, 1:1; then EtOAc/EtOH, 4:1) of the obtained crude obtained allowed the isolation of 542 mg (59%) of pure *trans*-**4**. Oil. $[\alpha]_D^{25}$ = –21.6 (*c* = 1.00, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3388 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.16 (m, 1 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 1.34 (br. dd, *J* = 13.1, 3.5 Hz, 1 H), 1.43–1.49 (m, 2 H), 1.67–1.77 (m, 1 H), 2.51–2.62 (m, 2 H), 2.71 (br. s, 1 H), 3.14–3.20 (m, 1 H), 3.28 (dd, *J* = 10.8, 6.4 Hz, 1 H), 3.31 (dd, *J* = 10.8, 6.5 Hz, 1 H), 3.51 (dd, *J* = 10.6, 5.3 Hz, 1 H), 3.62 (dd, *J* = 10.6, 2.9 Hz, 1 H), 3.91–3.97 (m, 1 H), 3.98 (q, *J* = 6.5 Hz, 1 H), 4.43 (s, 2 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 7.06–7.36 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 26.5, 28.0, 34.4, 42.6, 54.3, 59.7, 67.6, 71.6, 72.7,

73.3, 78.2, 126.4, 127.2, 127.3, 127.5, 127.6, 127.7, 128.0, 128.2, 128.3, 138.3, 139.0, 146.9 ppm. HRMS (ESI+): calcd. for $C_{30}H_{38}NO_3$ [M + H]$^+$ 460.2846; found 460.2846.

(2*R*,4*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-4-hydroxymethyl-1-[(*S*)-1-phenylethyl]piperidine (*cis*-4): $NaBH_4$ (76 mg, 2.0 mmol) was added to a solution of the 76:24 mixture of *cis*-**3**/*trans*-**3** (914 mg, 2.0 mmol) obtained as described previously[8] in CH_3OH/H_2O (4:1, 5 mL). After vigorously stirring for 2 h at room temperature the reaction mixture was evaporated under reduced pressure. The obtained crude was dissolved in Et_2O (50 mL), treated with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (EtOAc/hexanes, 1:1; then EtOAc/EtOH, 4:1) of the obtained crude obtained allowed the isolation of 440 mg (48%) of pure *cis*-**4**. Oil. $[\alpha]_D^{25}$ = +10.4 (*c* = 1.25, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3354 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69–0.87 (m, 2 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.25–1.33 (m, 1 H), 1.38 (br. d, *J* = 13.0 Hz, 1 H), 1.56 (br. s, 1 H), 1.92 (ddd, *J* = 11.1, 11.1, 2.2 Hz, 1 H), 1.98 (br. d, *J* = 13.0 Hz, 1 H), 2.31 (ddd, *J* = 11.1, 3.1, 3.1 Hz, 1 H), 2.61–2.67 (m, 1 H), 3.25 (dd, *J* = 10.5, 6.4 Hz, 1 H), 3.31 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.59 (dd, *J* = 10.6, 7.8 Hz, 1 H), 3.96 (br. d, *J* = 10.6 Hz, 1 H), 4.00 (q, *J* = 6.8 Hz, 1 H), 4.01–4.08 (m, 1 H), 4.40 (d, *J* = 12.2 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.73 (d, *J* = 12.0 Hz, 1 H), 7.02–7.35 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 28.9, 29.1, 39.2, 44.6, 53.6, 58.8, 67.7, 71.1, 72.6, 73.4, 77.7, 126.2, 127.4, 127.4, 127.4, 127.5, 127.7, 127.8, 128.2, 128.3, 138.3, 138.8, 143.7 ppm. HRMS (ESI+): calcd. for $C_{30}H_{38}NO_3$ [M + H]$^+$ 460.2846; found 460.2854.

(2*R*,4*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-4-hydroxymethylpiperidine (*trans*-6): 10% Pd/C (92 mg) was added to a solution of *trans*-**4** (459 mg, 1.0 mmol) in absolute EtOH (15 mL) and water (2 mL), and the mixture was stirred at room temperature under an atmosphere of H_2 at atmospheric pressure for 24 h. After completion of the reaction, the mixture was filtered through Celite 545, and the Celite 545 was gently washed with EtOAc. The combined organic extract was concentrated in vacuo to afford 295 mg (83%) of pure *trans*-**6**. M.p. 88–90 °C. $[\alpha]_D^{25}$ = –17.9 (*c* = 1.32, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3298, 1642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.45 (m, 1 H), 1.41–1.52 (m, 2 H), 1.52–1.64 (m, 1 H), 1.69–1.80 (m, 1 H), 2.57–2.63 (m, 2 H), 2.83–2.91 (m, 1 H), 2.90 (br. s, 2 H), 3.37–3.47 (m, 2 H), 3.44–3.51 (m, 1 H), 3.47 (dd, *J* = 12.1, 4.3 Hz, 1 H), 3.60 (dd, *J* = 12.1, 4.9 Hz, 1 H), 4.42 (d, *J* = 12.1 Hz, 1 H), 4.42 (d, *J* = 11.3 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.68 (d, *J* = 11.3 Hz, 1 H), 7.14–7.30 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 28.8, 33.9, 40.7, 52.5, 64.5, 69.5, 72.6, 73.3, 79.5, 127.6 (×2), 127.7, 128.0, 128.3, 128.3, 137.9, 138.2 ppm. HRMS (ESI+): calcd. for $C_{22}H_{30}NO_3$ [M + H]$^+$ 356.2220; found 356.2229. $C_{22}H_{29}NO_3$ (355.47): calcd. C 74.33, H 8.22, N 3.94; found C 74.60, H 8.08, N 3.88.

(2*R*,4*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-4-hydroxymethylpiperidine (*cis*-6): 10% Pd/C (92 mg) was added to a solution of *cis*-**4** (459 mg, 1.0 mmol) in absolute EtOH (15 mL) and water (2 mL), and the mixture was stirred at room temperature under an atmosphere of H_2 at atmospheric pressure for 24 h. After completion of the reaction, the mixture was filtered through Celite 545, and the Celite 545 was gently washed with EtOAc. The combined organic extract was concentrated in vacuo to afford 280 mg (79%) of pure *cis*-**6**. M.p. 73–76 °C. $[\alpha]_D^{25}$ = –4.2 (*c* = 0.79, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (ddd, *J* = 12.1, 12.1, 12.1 Hz, 1 H), 1.05 (dddd, *J* = 11.5, 11.5, 11.5, 1.9 Hz, 1 H), 1.43–1.56 (m, 1 H), 1.54–1.65 (m, 2 H), 2.51 (br. dd, *J* = 11.5, 11.5 Hz, 1 H), 2.70 (br. s, 2 H), 2.63–2.72 (m, 1 H), 3.04 (br. d, *J* = 11.5 Hz, 1 H), 3.29–3.40 (m, 3 H), 3.50 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.64 (dd, *J* = 10.6, 3.1 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.44 (d, *J* = 11.2 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.66 (d, *J* = 11.2 Hz, 1 H), 7.16–7.30 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.0, 31.4, 38.8, 45.7, 57.1, 67.8, 69.4, 72.9, 73.3, 82.5, 127.6, 127.7, 127.9, 128.3, 128.3, 128.4, 138.1, 138.4 ppm. HRMS (ESI+): calcd. for $C_{22}H_{30}NO_3$ [M + H]$^+$ 356.2220; found 356.2223. $C_{22}H_{29}NO_3$ (355.47): calcd. C 74.33, H 8.22, N 3.94; found C 74.52, H 8.11, N 3.90.

(1*R*,2*R*,4*R*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-1-azabicyclo[2.2.1]-heptane (7): CBr_4 (498 mg, 1.5 mmol) was added to a stirred solution of *trans*-**6** (178 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (20 mL), and the reaction mixture was cooled to 0 °C. Then, resin polystyrene-supported PPh_3 (3 mmol/g, 498 mg, 1.5 mmol) was added slowly, and the reaction mixture was stirred under reflux conditions for 8 h, filtered through Celite 545 and concentrated in vacuo. To a solution of the obtained crude in CH_2Cl_2 (15 mL) at 0 °C was added 1% aqueous NaOH solution (15 mL). After stirring at room temperature for 1 h the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was dried with anhydrous $MgSO_4$ and filtered and the solvents evaporated in vacuo to afford compound **7** in quantitative yield. Oil. $[\alpha]_D^{25}$ = –18.8 (*c* = 1.03, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1604, 1097, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64 (ddd, *J* = 8.0, 6.3, 1.6 Hz, 1 H), 0.85–0.94 (m, 1 H), 1.42 (ddddd, *J* = 15.2, 15.2, 11.2, 7.6, 4.1 Hz, 1 H), 1.55 (dddd, *J* = 14.8, 11.2, 7.8, 4.1 Hz, 1 H), 2.35 (dd, *J* = 9.4, 1.0 Hz, 1 H), 2.40 (dd, *J* = 4.1, 4.1 Hz, 1 H), 2.42 (br. d, *J* = 9.4 Hz, 1 H), 2.54 (ddd, *J* = 12.2, 11.9, 5.2 Hz, 1 H), 2.77 (ddddd, *J* = 12.2, 10.7, 7.5, 4.4, 2.2 Hz, 1 H), 3.02–3.11 (m, 1 H), 3.48 (ddd, *J* = 8.7, 5.4, 2.8 Hz, 1 H), 3.58 (dd, *J* = 10.5, 5.4 Hz, 1 H), 3.64 (dd, *J* = 10.5, 2.8 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.58 (d, *J* = 11.9 Hz, 1 H), 4.78 (d, *J* = 11.9 Hz, 1 H), 7.16–7.36 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 33.5, 37.7, 46.9, 61.4, 64.6, 72.2, 72.5, 73.4, 78.5, 127.3, 127.6, 127.6, 127.8, 128.2, 128.3, 138.2, 138.8 ppm. HRMS (ESI+): calcd. for $C_{22}H_{28}NO_2$ [M + H]$^+$ 338.2115; found 338.2101.

(1*S*,2*R*,4*S*)-2-[(*S*)-1,2-Bis(benzyloxy)ethyl]-1-azabicyclo[2.2.1]-heptane (8): CBr_4 (498 mg, 1.5 mmol) was added to a stirred solution of *cis*-**6** (178 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (20 mL), and the reaction mixture was cooled to 0 °C. Then, resin polystyrene-supported PPh_3 (3 mmol/g, 498 mg, 1.5 mmol) was added slowly, and the reaction mixture was stirred under reflux conditions for 8 h, filtered through Celite 545 and concentrated in vacuo. To a solution of the obtained crude in CH_2Cl_2 (15 mL) at 0 °C was added 1% aqueous NaOH solution (15 mL). After stirring at room temperature for 1 h the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was dried with anhydrous $MgSO_4$ and filtered and the solvents evaporated in vacuo to afford compound **8** in quantitative yield. Oil. $[\alpha]_D^{25}$ = –25.0 (*c* = 0.58, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1605, 1094, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.07 (m, 1 H), 1.12–1.20 (m, 1 H), 1.27–1.35 (m, 1 H), 1.49 (ddddd, *J* = 18.3, 15.2, 11.3, 7.2, 4.2 Hz, 1 H), 2.15 (br. d, *J* = 9.5 Hz, 1 H), 2.42 (br. dd, *J* = 3.9, 3.8 Hz, 1 H), 2.42–2.49 (m, 1 H), 2.54 (br. d, *J* = 9.5 Hz, 1 H), 2.66 (ddd, *J* = 7.0, 6.9, 6.8 Hz, 1 H), 2.78 (ddd, *J* = 11.4, 11.4, 5.7 Hz, 1 H), 3.23–3.30 (m, 1 H), 3.56 (dd, *J* = 10.2, 5.0 Hz, 1 H), 3.62 (dd, *J* = 10.2, 4.1 Hz, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.1 Hz, 1 H), 4.73 (d, *J* = 12.1 Hz, 1 H), 7.15–7.37 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2, 34.4, 36.8, 55.8, 57.5, 66.0, 71.0, 72.8, 73.4, 80.3, 127.2, 127.5, 127.6,

127.7, 128.1, 128.3, 138.3, 139.1 ppm. HRMS (ESI+): calcd. for $C_{22}H_{28}NO_2$ $[M + H]^+$ 338.2115; found 338.2118.

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