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A Straightforward Synthesis of Enantiopure Bicyclic Azetidines

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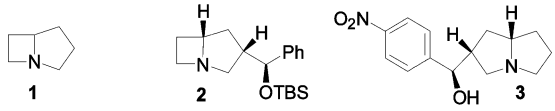
Enantiomerically pure 1-azabicyclo[3.2.0]heptane derivatives were synthesized in a straightforward manner from readily available chiral sources, namely, enantiomerically pure epoxides and L-proline. The key step of this synthesis relied on a diastereoselective intramolecular alkylation of a proline enolate, which led to an azetidine ring fused to a five-membered ring. These strained bicyclic nitrogen derivatives were found to be good precursors for the preparation of azepanes, after transformation into the corresponding ammonium trifluoromethanesulfonates followed by reaction with nucleophiles.

Introduction

The azabicyclo[3.2.0]heptane (**1**) skeleton, to the best of our knowledge, is not encountered in natural molecules, and reports describing the preparation of such strained heterocycles are also scarce. Synthetic strategies towards this ring system include photoaddition of olefins to iminium ions,[1] intramolecular carbolithiation of phenylthioalkenes with α-amino organolithium species,[2] direct ring closure of a four-membered ring by *N*-alkylation,[3] Pauson–Khand reaction of suitably functionalized azetidines,[4] and reduction of the corresponding thiolactams.[5] However, all these approaches suffer from major drawbacks such as low yield or a lack of generality, and straightforward access to enantiomerically pure derivatives of this bicyclic nitrogen heterocycle still needs to be discovered. Because of the strain in these compounds, the strong pyramidization of the amine moiety is expected to increase the accessibility of the lone pair of electrons on the nitrogen atom, which would thus enhance the nucleophilicity of the tertiary amine. Therefore, enantiomerically pure derivatives of **1** would be excellent candidates for organocatalytic processes involving nucleophilic attack of a tertiary amine in the catalytic cycle, such as ketene dimerization,[6] cyclopropanations mediated by ammonium ylides,[7] Baylis–Hillman reaction,[8] or kinetic resolution of alcohols involving acylation with acyl ammonium ions.[9] This idea was demonstrated by Barrett et al.[5] who reported that kinetics of the Baylis–Hillman reaction involving catalyst **2** was significantly enhanced relative to the same reaction catalyzed by pyrrolizidine **3**. However, difficulties encountered in the synthesis of **2** precluded further investigations. As part of our interest in the chemistry of azetidines,[10] we wish to present herein, a straightforward preparation of such bicyclic nitrogen heterocycles in a stereocontrolled way starting from readily available synthons from the chiral pool. By following a strategy developed in our group for the preparation of monocyclic azetidines, the key step in this synthesis relies on diastereoselective alkylation of an enolate generated from a proline derivative and involves the formation of the azetidine ring by anionic cyclization. We also demonstrate that these bicyclic nitrogen compounds are excellent precursors for functionalized azepanes after transformation into their ammonium trifluoromethanesulfonates followed by reaction with a nucleophile, which induces the cleavage of the endocyclic C–N bond.



Results

Synthesis of Azabicyclo[3.2.0]heptane Derivatives

Scheme 1 details our synthetic approach towards derivatives of **1**. Treatment of (*R*)-*O*-benzyl glycidol (**4**; 98% *ee*) with proline in basic media induced the regioselective opening of the epoxide ring to give an intermediate amino acid that was later transformed into methyl ester **5**. Chlorination of this compound by using Appel's reaction gave a mixture of isomeric chlorides **6** and **7** in a 1:4 ratio. This inseparable

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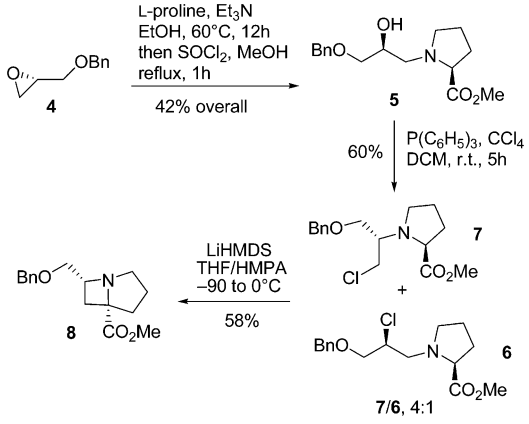
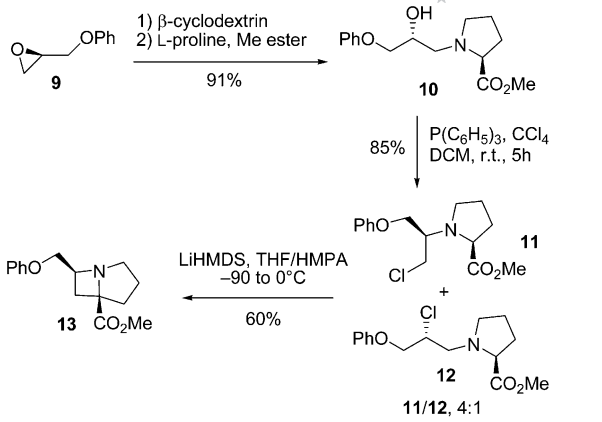
mixture was immediately subjected to anionic cyclization by treatment with LiHMDS in a mixture of THF/HMPA (10:1) to give compound **8**, which resulted from the intramolecular alkylation of the ester enolate by the primary chloride in **7**. This reaction did not consume secondary chloride **6**, which thus allowed facile purification of more polar **8** that was isolated in 58% yield (72% based on unreacted **7**). The enantiomeric purity of compound **8** was assessed as follows: compound *ent*-**8** was prepared following Scheme 1 starting from *ent*-**4** and D-proline. Examination of a mixture of **8** and *ent*-**8** by ^{1}H NMR spectroscopy in the presence of (*S*)-α-(trifluoromethyl)benzyl alcohol[13] showed resolved and separated signals for each enantiomer of the methyl ester. Compound **8** was found to be optically pure within the precision of the NMR (300 MHz) instrument.



Scheme 1. Synthesis of enantiomerically pure azabicyclo[3.2.0]heptane **8**.

In the case of *O*-aryl epoxides, nucleophilic opening by L-proline methyl ester could be efficiently promoted by β-cyclodextrin by following our previously published methodology.[11] Thus, the 1:1 β-CD complex of epoxide **9** (98% *ee*, with opposite absolute configuration to **4**) was treated with L-proline methyl ester to give proline derivative **10** in good yield. The same reaction sequence as in Scheme 1 was applied to this alcohol to furnish bicyclic compound **13** in 46% overall yield and with total diastereoselectivity (Scheme 2). The *cis* relative configuration of the substituents in this bicyclic azetidine was determined by X-ray analysis, and the structure is depicted in Figure 1.[12]

Two salient points of this efficient synthesis deserve comment. First, the formation of a mixture of chlorides is explained by the intervention of aziridinium ion **14**, which is kinetically opened at the less-substituted side to give **7** (or **11**) as the major chloride (Scheme 3, shown starting from **5**). The chlorination conditions used in this work were chosen in such a way as to minimize the amount of secondary chloride formed. Indeed, chlorination of **5** with the use of thionyl chloride in refluxing dichloromethane gave a significantly higher ratio of secondary chloride **6**, and the mixture of these chlorides was found to slowly evolve almost uniquely into the secondary chloride, which is the more thermodynamically stable isomer, as previously observed



Scheme 2. Synthesis of enantiomerically pure azabicyclo[3.2.0]heptane derivative **13**.

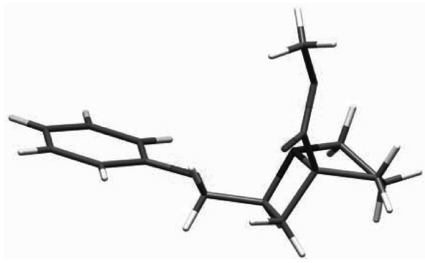
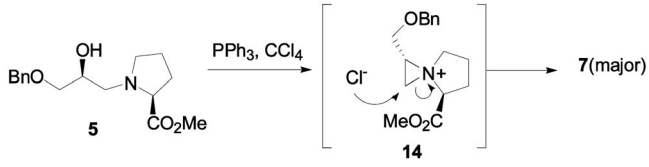


Figure 1. X-ray structure of compound **13**.

for similar substrates.[14] It is therefore important to conduct the alkylation step on a freshly prepared mixture of chlorides. As proven by the determination of the enantiomeric purity of **8**, it is considered that the formation of **7** or **11** involves a stereospecific S_N2 reaction with no racemization during this chlorination.



Scheme 3. Chlorination of the β-amino alcohols proceeds via an aziridinium ion.

The second point of discussion concerns the cyclization step. The addition of HMPA as a cosolvent was found to be mandatory for the success of the ring-closing reaction, which proceeds only at ca. –30 °C as judged by TLC control. The high *cis* diastereoselectivity is in accordance with our previous work on the synthesis of monocyclic azetidines through a similar strategy, and is quite easy to rationalize here.[14] In fact, examination of the two possible transition states **A** or **B** (Figure 2) leading to the formation of *trans*-**15** or *cis*-**13** reveals the clear-cut steric interactions that disfavor the formation of **15**. In transition state **A**, the CH_2OPh pendant group is directed into the *endo* face of the bicyclic nitrogen heterocycle, which generates severe steric interactions that could explain why this pathway is disfavored. It should be noted that the relative configuration in

the starting amino alcohol (compare **5** and **10**) has no influence on (1) the ratio of the produced chloride (1:4 for each diastereoisomer) and (2) on the efficiency and diastereoselectivity of the alkylation step, which most probably involves a planar enolate as the reactive species. In conclusion, the three-step synthesis of functionalized enantiopure azabicyclo[3.2.0]heptane derivatives from cheap and readily available chiral synthons is very efficient and should give access to a large array of these heterocycles by varying the nature of the proline and epoxide derivative.

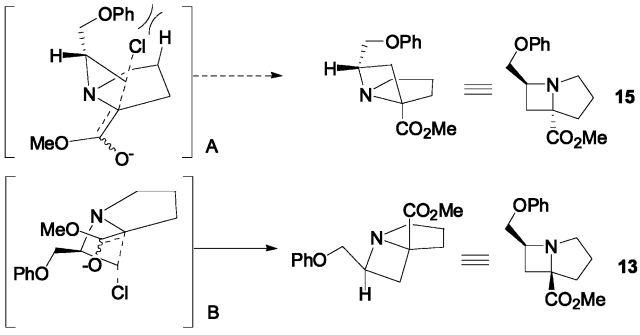
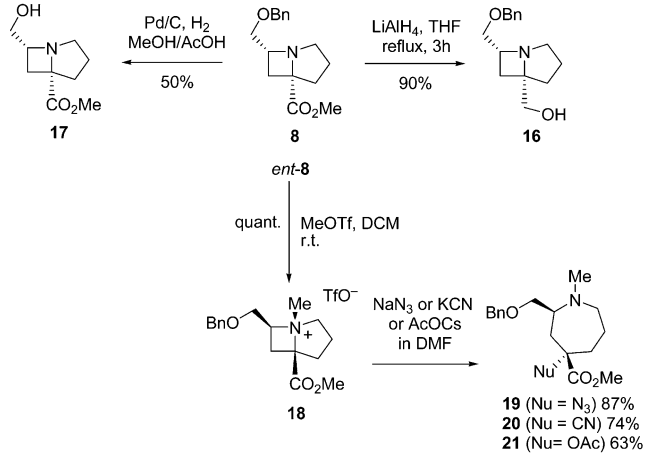


Figure 2. Examination of the possible transition states that may explain the diastereoselectivity of the cyclization step.

Reactivity of the Synthesized Azabicyclo[3.2.0]heptane Derivatives

Next, some synthetic transformations of compound **8** depicted in Scheme 4 were studied. Functional group transformations could be conducted successfully, and the heterocycle survived $LiAlH_4$ reduction of the ester moiety to give primary alcohol **16**. The ring system was also found to be resistant to hydrogenolytic cleavage of the OBn group to give alcohol **17**. These experiments demonstrate that "tailoring" of the functional groups is possible, which is essential for optimization of these amines as organocatalysts.



Scheme 4. Synthetic transformations of azabicyclo[3.2.0]heptane derivative **8**.

Most interestingly, these compounds were found to be suitable precursors for the production of azepanes, a skeleton of continuous interest for the preparation of bioactive compounds.[15] Thus, treatment of *ent*-**8** with methyl trifluoromethanesulfonate gave almost quantitative yield of ammonium ion **18**, which was obtained as a single diastereoisomer and whose presumed structure is depicted in Scheme 4 (alkylation is expected to occur on the *exo* face, see X-ray structure of **13** in Figure 1). Reaction of this ammonium salt with NaN_3, KCN, or AcOCs in DMF gave corresponding azepanes **19**–**21**, which result from clean regioselective nucleophilic opening by an S_N2 reaction, as judged by the stereochemical integrity of the produced compounds.

Conclusion

We showed in this work that the azabicyclo[3.2.0]heptane skeleton can be efficiently synthesized in a three-step sequence from commercially available chiral synthons. Examination of the catalytic activity of these nitrogen heterocycles in organocatalyzed reactions is currently under study in our group.

Experimental Section

General Comments: ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively; chemical shifts are reported in ppm relative to TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All the reactions were carried out under an atmosphere of argon. Column chromatography was performed on silica gel 230–400 mesh by using various mixtures of diethyl ether (Et_2O), ethyl acetate (AcOEt) petroleum ether (PE), and cyclohexane (CyH). TLC was run on Merck Kieselgel $60F_{254}$ plates. THF and ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. The mention of a "usual workup" means: (1) decantation of the organic layer, (2) extraction of the aqueous layer with ether, (3) drying the combined organic layers over $MgSO_4$, and (4) solvent evaporation under reduced pressure. Stereoisomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures before purification. Mass spectra were recorded with a Hewlett–Packard MS Engin HP5989B equipped with an ESI source Analytica Branford. HRMS spectra were recorded by the "Service Central d'Analyses du CNRS".

(*S*)-Methyl 1-[(*S*)-3-(Benzyloxy)-2-hydroxypropyl]pyrrolidine-2-carboxylate (5): To a suspension of (*S*)-OBn glycidol (**4**; 2.95 g, 18 mmol) in ethanol (180 mL) was added L-proline (4.14 g, 36 mmol) and triethylamine (36 mL). The resultant mixture was stirred under an atmosphere of nitrogen at reflux overnight and then evaporated. The crude residue was dissolved in methanol (40 mL) and thionyl chloride (1.57 mL, 21.6 mmol) was added dropwise at –15 °C. The resulting mixture was allowed to reach r.t. and then heated at reflux for 1 h. After cooling to r.t., concentration under vacuo gave a crude residue that was dissolved in ethyl acetate, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with sodium sulphate and concentrated, and the crude residue was further purified by flash chromatography (SiO_2, PE/AcOEt, 2:3) to give compound **5** as a thick oil. Yield: 3.68 g (70%). R_f = 0.50 (PE/AcOEt,

2:3). $[\alpha]_D^{20}$ = –31.5 (*c* = 0.23, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.70–1.91 (m, 3 H, 4-H, 4′-H, 3-H), 2.00–2.17 (m, 1 H, 3′-H), 2.29–2.40 (m, 1 H, 5-H), 2.55–2.70 (m, 2 H, NCH_2CHOH), 3.14–3.24 (m, 1 H, 5′-H), 3.28 (dd, *J* = 9.1, 5.3 Hz, 1 H, 2-H), 3.38 (dd, *J* = 10.1, 4.9 Hz, 1 H, OC*H*HCHOH), 3.44 (dd, *J* = 10.1, 4.9 Hz, 1 H, OCH*H*CHOH), 3.64 (s, 3 H, OCH_3), 3.82 (quint, *J* = 4.7 Hz, 1 H, C*H*OH), 4.50 (s, 2 H, OCH_2Ph), 7.15–7.31 (m, 5 H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.9 (C-4), 29.6 (C-3), 52.0 (OCH_3), 53.6 (C-5), 58.2 (NCH_2CHOH), 65.9 (C-2), 68.2 (*C*HOH), 72.6 (OCH_2CHOH), 73.5 (PhCH_2O), 127.7, 127.8, 128.4 (*C*Ph), 138.3 (*ipso*-*C*Ph), 175.0 (CO) ppm. MS (CI): *m*/*z* (%) = 294 (100) $[M + H]^+$, 235 (5), 234 (30), 142 (10). HRMS (ESI): calcd. for $C_{16}H_{24}NO_4$ $[M + H]^+$ 294.1705; found 294.1714.

(*S*)-Methyl 1-[(*R*)-3-(Phenoxy)-2-hydroxypropyl]pyrrolidine-2-carboxylate (10): Epoxide-β-CD complex (1 mmol) was placed in a mortar and L-proline methyl ester (1.1 mmol) dissolved in acetone (1 mL) was added. The solid was ground vigorously for 6 h. The completion of the reaction was confirmed by TLC. The complex was transferred to a conical flask, ethyl acetate (20 mL) was added, and the suspension was stirred for 20 min. This suspension was filtered, and the filtrate was concentrated to afford the crude compound, which was purified by column chromatography by using silica gel treated with triethylamine (AcOEt/PE, 1:4) to give compound **10** as a light yellow oil. Yield: 254 mg (91%). $[\alpha]_D^{20}$ = –62.4 (*c* = 0.01, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.79–2.02 (m, 3 H, 4-H, 4′-H, 3-H), 2.07–2.23 (m, 1 H, 3′-H), 2.42–2.56 (m, 1 H, 5-H), 2.68–2.87 (m, 2 H, NCH_2CHOH), 3.26–3.41 (m, 2 H, 5-H, 2-H), 3.73 (s, 3 H, OMe), 3.80–3.91 (m, 1 H, C*H*OH), 3.94–4.09 (m, 2 H, CH_2OPh), 6.83–6.94 (m, 3 H, Ar*H*), 7.18–7.27 (m, 2 H, Ar*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.7 (C-4), 29.8 (C-3), 52.0 (OCH_3), 53.6 (C-5), 58.3 (NCH_2CHOH), 66.0 (C-2), 67.6 (*C*HOH), 70.2 (OCH_2CHOH), 114.6, 120.7, 129.3 (*C*Ph), 158.8 (*ipso*-*C*Ph), 174.9 (CO) ppm. IR (KBr): ν̃ = 3444, 2924, 1734, 1637, 1596, 1244, 1040, 755, 692 cm^{-1}. HRMS: calcd. for $C_{15}H_{22}NO_4$ $[M + H]^+$ 280.1548; found 280.1545.

General Procedure for the Preparation of Chlorides 6, 7, 11, 12: A solution of amino alcohol (1 mmol) in DCM (5 mL) was cooled to 0 °C under an atmosphere of argon. Carbon tetrachloride (2.00 mmol) was added dropwise followed by triphenylphosphane (2 mmol), and the resulting mixture was allowed to reach r.t. and stirred for 5 h. After completion of the reaction, the mixture was concentrated in vacuo at room temperature to minimize the formation of the aziridinium ion. The crude reaction mixture was purified by flash chromatography.

(*S*)-Methyl 1-[(*S*)-3-(Benzyloxy)-1-chloropropan-2-yl]pyrrolidine-2-carboxylate (7) and (*S*)-Methyl 1-[(*S*)-3-(Benzyloxy)-2-chloropropyl]pyrrolidine-2-carboxylate (6): Following the above procedure, a mixture of chlorides **6** and **7** was obtained after flash chromatography (SiO_2, PE/AcOEt, 4:1) as a thick oil. Yield: 617 mg (60%). R_f = 0.50 (PE/AcOEt, 4:1). $[\alpha]_D^{20}$ = –42.6 (*c* = 1.10, $CHCl_3$). ^1H NMR [300 MHz, $CDCl_3$, 25 °C, mixture of regioisomers (primary chloride/secondary chloride, 4:1)]: δ = 1.65–1.91 (m, 3 H, 4-H, 4′-H, 3-H, mixture of isomers), 1.93–2.10 (m, 1 H, 3′-H, mixture of isomers), 2.51 (appt q, *J* = 8.1 Hz, 1 H, 5-H, minor isomer), 2.80 (appt q, *J* = 7.5 Hz, 1 H, 5-H, major isomer), 2.92 (appt d, *J* = 6.4 Hz, 2 H, NCH_2CHCl, minor isomer), 2.98–3.10 (m, 2 H, 5′-H, mixture of isomers), 3.11–3.20 (m, 1 H, NC*H*CH_2Cl, major isomer), 3.29 (dd, *J* = 8.7, 4.6 Hz, 1 H, 2-H, minor isomer), 3.57 (s, 3 H, OCH_3, major isomer), 3.60 (s, 3 H, OCH_3, minor isomer), 3.50–3.70 [m, 6 H, OCH_2CHN, CH_2Cl (major isomer), OCH_2CHCl (minor isomer)], 3.76 (dd, *J* = 8.7, 4.6 Hz, 1 H, 2-H, major isomer), 4.04 [q, *J* = 5.7 Hz, 1 H, NCH_2CHCl (minor isomer)], 4.43 (s, 2 H, PhCH_2O, major isomer), 4.50 (s, 2 H, PhCH_2O, minor isomer), 7.13–7.31 (m, 5 H, Ph*H*, mixture of isomers) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, major isomer): δ = 23.6 (C-4), 29.7 (C-3), 43.3 (CH_2Cl), 49.6 (C-5), 51.7 (OCH_3), 60.8 (C-2), 62.4 (N$CHCH_2Cl$) 69.4 (OCH_2CHN), 73.3 (PhCH_2O), 127.6, 128.4 (*C*Ph), 138.1 (*ipso*-*C*Ph), 175.4 (CO) ppm. MS (ESI): *m*/*z* (%) = 334 (100) $[M + Na]^+$, 312 (30) $[M + H]^+$, 276 (90), 142 (30). HRMS (ESI): calcd. for $C_{16}H_{23}ClNO_3$ $[M + H]^+$ 312.1366; found 312.1367.

(*S*)-Methyl 1-[(*R*)-2-Chloro-3-phenoxypropyl]pyrrolidine-2-carboxylate (11) and (*S*)-Methyl 1-[(*R*)-1-Chloro-3-phenoxypropan-2-yl]pyrrolidine-2-carboxylate (12): Following the above procedure, a mixture of chlorides **11** and **12** was obtained after flash chromatography (SiO_2, PE/AcOEt, 4:1) as a thick oil. Yield: 640 mg (85%). R_f = 0.50 (PE/AcOEt, 4:1). $[\alpha]_D^{20}$ = – 23.1 (*c* = 0.61, $CHCl_3$). ^1H NMR [300 MHz, $CDCl_3$, 25 °C, mixture of regioisomers (primary chloride/secondary chloride, 4:1)]: δ = 1.61–1.87 (m, 3 H, 4-H, 4′-H, 3-H, mixture of isomers), 1.90–2.06 (m, 1 H, 3′-H, mixture of isomers), 2.53 (appt q, *J* = 8.0 Hz, 1 H, 5-H, minor isomer), 2.79 (appt q, *J* = 8.0 Hz, 1 H, 5-H, major isomer), 2.97 (appt d, *J* = 6 Hz, 2 H, NCH_2CHCl, minor isomer), 3.01–3.10 (m, 2 H, 5′-H, mixture of isomers), 3.23–3.32 [m, 2 H, 2-H (minor isomer), 6-H (major isomer)], 3.49 (s, 3 H, OCH_3, major isomer), 3.51 (s, 3 H, OCH_3, minor isomer), 3.63–3.70 (appt d, *J* = 5.8 Hz, CH_2Cl, 2 H, major isomer), 3.72 (dd, *J* = 8.7, 3.1 Hz, 1 H, 2-H, major isomer), 3.98 (dd, *J* = 9.6, 5.6 Hz, 1 H, OC*H*HCH mixture of isomers), 4.04–4.18 (m, 2 H, OCH*H*CH of two isomers, NC*H*Cl of minor isomer), 6.70–6.90 (m, 3 H, Ph*H*, mixture of isomers), 7.10–7.20 (m, 2 H, Ph*H*, mixture of isomers) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, major isomer): δ = 23.8 (C-4), 29.8 (C-3), 43.0 (CH_2Cl), 49.5 (C-5), 51.8 (OCH_3), 60.4 (C-2), 62.8 (N$CHCH_2Cl$), 67.2 (PhOCH_2), 114.6, 121.1, 129.5 (*C*Ph), 158.4 (*ipso*-*C*Ph), 175.3 (CO) ppm. MS (ESI): *m*/*z* (%) = 320 (50) $[M + Na]^+$, 298 (15) $[M + H]^+$, 262 (100), 142 (30). HRMS (ESI): calcd. for $C_{15}H_{21}ClNO_3$ $[M + H]^+$ 298.1210; found 298.1227.

General Procedure for the Synthesis of Bicyclic Azetidines 8 and 13: To a solution of the chloride (1 mmol) in a mixture of THF (5 mL) and HMPA (0.5 mL) was added dropwise at –90 °C a solution of LiHMDS (1 M in THF, 1.5 mL, 1.5 mmol). The reaction was monitored by TLC and then quenched by the addition of an aqueous saturated solution of NH_4Cl at 0 °C. Extraction of the reaction mixture by using ether followed by the usual workup gave the crude residue of bicyclic azetidine.

(5*S*,7*R*)-Methyl 7-[(Benzyloxy)methyl]-1-azabicyclo[3.2.0]heptane-5-carboxylate (8): Following the above procedure, pure compound **8** was obtained after flash chromatography (SiO_2, PE/AcOEt, 1:4) as a colorless solid. Yield: 558 mg (58%). R_f = 0.20 (PE/AcOEt, 1:4). M.p. 34–35 °C. $[\alpha]_D^{20}$ = –62.1 (*c* = 1.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.82–2.02 (m, 3 H, 4-H, 4′-H, 3-H), 2.05–2.22 (m, 2 H, 3′-H, 6-H), 2.40 (dd, *J* = 12.2, 6.7 Hz, 1 H, 6′-H), 2.82 (dd, *J* = 9.3, 3.7 Hz, 2 H, 2-H, 2′-H), 3.05 (quint, *J* = 6.2 Hz, 1 H, 7-H), 3.43 (dd, *J* = 9.5, 6.2 Hz, 1 H, OC*H*HCH), 3.51 (dd, *J* = 9.6, 6.3 Hz, 1 H, OCH*H*CH), 3.65 (s, 3 H, OCH_3), 4.47 (d, part of AB syst., *J* = 12.1 Hz, OCH*H*Ph), 4.55 (d, part of AB syst., *J* = 12.1 Hz, OCH*H*Ph) 7.15–7.31 (m, 5 H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.7 (C-4), 30.5 (C-6), 36.1 (C-3), 52.3 (OCH_3), 55.9 (C-2), 58.3 (C-7), 70.8 (C-5), 73.4 (PhCH_2O), 74.7 (OCH_2CH), 127.6, 127.8, 128.3 (CH), 138.3 (*ipso*-*C*Ph), 176.2 (CO) ppm. MS (ESI): *m*/*z* (%) = 298 (100) $[M + Na]^+$, 276 (30) $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600; found 276.1590.

(5*R*,7*S*)-Methyl 7-(Phenoxymethyl)-1-azabicyclo[3.2.0]heptane-5-carboxylate (13): Following the above procedure, pure compound

13 was obtained after flash chromatography (SiO_2, PE/AcOEt, 1:4) as a colorless solid. Yield: 412 mg (60%). R_f = 0.30 (PE/AcOEt, 1:4). M.p. 74–75 °C. $[\alpha]_{578}^{20}$ = +50.9 (c = 0.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.86–2.01 (m, 3 H, 4-H, 4′-H, 3-H), 2.08–2.30 (m, 2 H, 3′-H, 6-H), 2.52 (dd, J = 9.3, 5.0 Hz, 1 H, 6′-H), 2.87 (dd, J = 9.3, 5.0 Hz, 2 H, 2-H, 2′-H), 3.22 (quint, J = 6.4 Hz, 1 H, 7-H), 3.69 (s, 3 H, OCH_3), 3.94 (appt q, J = 9.5 Hz, 2 H, PhOCH_2CH), 6.80–6.98 (m, 3 H, Ph*H*), 7.26 (t, J = 11.0 Hz, 2 H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.7 (C-3), 30.5 (C-6), 36.1 (C-4), 52.3 (O*C*H$_3$), 55.9 (C-2), 57.6 (C-7), 70.8 (C-5), 71.8 (Ph*C*H$_2$O), 114.5, 120.7, 129.4 (CH), 158.8 (*ipso*-*C*Ph), 176.1 (CO) ppm. MS (CI): m/z (%) = 284 (100) $[M + Na]^+$, 300 (17). HRMS (ESI): calcd. for $C_{15}H_{20}NO_3$ $[M + H]^+$ 261.1443; found 262.1450.

(5*S*,7*R*) {7-[(Benzyloxy)methyl]-1-azabicyclo(3.2.0)heptan-5-yl}-methanol (16): To a solution of methyl ester **8** (566 mg, 2.06 mmol) in THF (10 mL) was added lithium aluminium hydride (118 mg, 3.10 mmol) portionwise at 0 °C. After stirring for few minutes at this temperature, the reaction mixture was refluxed for 3 h. After the completion of reaction, the excess LAH was quenched by the addition of 2 N NaOH (5 mL) and the reaction mixture was filtered off. The filtrate was concentrated and dried. The obtained product was pure enough for further reactions. Yield: 458 mg (90%); R_f = 0.30 (AcOEt/MeOH/NH_4OH, 9:1:1). M.p. 71–73 °C. ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 1. 45–2.14 (m, 6 H, 3-H, 3′-H, 4-H, 4′-H, 6-H, 6′-H), 2.50–2.68 (m, 2 H, 2-H, 2′-H), 3.00 (quint, J = 6.6 Hz, 1 H, 7-H), 3.26–3.50 (m, 4 H, OCH_2CHN, NCqCH_2OH), 4.38 (d, part of AB syst, J = 11.8 Hz, 1 H, PhCH*H*O), 4.41 (d, part of AB syst, J = 11.8 Hz, 1 H, PhCH*H*O) 7.10–7.28 (m, 5 H, Ph*H*) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 25.3 (C-3), 28.2 (C-4), 34.4 (C-6), 55.3 (C-2), 58.6 (C-7), 66.5 (NCq*C*H$_2$OH), 71.8 (C-5), 73.3 (Ph*C*H$_2$O), 74.4 (O*C*H$_2$CH), 127.7, 127.8, 127.9 (CH), 138.8 (*ipso*-*C*Ph) ppm. CIMS: m/z (%) = 248 (100) $[MH]^+$, 230 (7), 140 (15), 91 (90). HRMS (ESI): calcd. for $C_{15}H_{21}NO_2$ $[M^+]$: 247.1572; found 247.1570.

(5*S*,7*R*)-Methyl 7-(Hydroxymethyl)-1-azabicyclo[3.2.0]heptane-5-carboxylate (17): To a mixture of azetidine (500 mg, 1.82 mmol) in methanol (9 mL) and acetic acid (1 mL) was added 10% Pd on charcoal (160 mg), and the suspension was hydrogenated at 15 atm for 96 h. After completion of the reaction the mixture was filtered through Celite, and the filtrate was concentrated and dried in vacuo. The crude residue was then dissolved in aqueous $NaHCO_3$ (1 mL), and the mixture was then extracted with DCM (3 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo to give the desired alcohol. The obtained amino alcohol was pure enough for further reactions. Yield: 161 mg (50%). R_f = 0.40 [AcOEt/MeOH/30% NH_4OH, 9:1:1]. M.p. 183–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1. 86–2.03 (m, 3 H, 3-H, 3′-H, 4-H), 2.04–2.25 (m, 2 H, 6-H, 4′-H), 2.47 (dd, J = 12.2, 6.7 Hz 1 H, 6′-H), 2.75–2.85 (m, 2 H, 2-H, 2′-H), 3.02 (quint, J = 4.5 Hz, 1 H, 7-H), 3.42 (dd, J = 11.6, 4.8 Hz, 1 H, CHC*H*HOH), 3.52 (dd, J = 11.6, 4.8 Hz, 1 H, CHCH*H*OH), 3.68 (s, 3 H, OCH_3), 4.20 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 25.6 (C-4), 28.7 (C-6), 35.9 (C-3), 52.3 (O*C*H$_3$), 55.5 (C-2), 60.2 (C-7), 64.6 (*C*H$_2$OH), 70.3 (C-5), 175.7 (CO) ppm. MS (ESI): m/z (%) = 208 (100) $[M + Na]^+$, 186 (100) $[M + H]^+$, 126 (90), 108 (40). HRMS (ESI): calcd. for $C_8H_{14}NO_3$ $[M + H]^+$ (for the hydrolyzed ester) 172.0974; found 172.0981.

(1S,5*R*,7*S*)-7-Benzyloxymethyl-5-methoxycarbonyl-1-methyl-1-azoniabicyclo[3.2.0]heptane (18): To a solution of *ent*-**8** (300 mg, 1.09 mmol) in dry dichloromethane (5 mL) was added dropwise at 0 °C methyl trifluoromethanesulfonate (0.250 mL, 2.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and was allowed to reach r.t. (0.5 h). The reaction mixture was then concentrated under reduced pressure, and the residue was triturated with small portions of petroleum ether. Drying under vacuum gave **18** as a thick oil. Yield: 480 mg (quant.). $[\alpha]_D^{20}$ = –51.1 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]acetone): δ = 2.30–2.68 (m, 4 H, 3-H, 4-H or 6-H), 2.80–2.95 (m, 1 H, 3-H, 4-H or 6-H), 3.21 (dd, J = 11.9, 8.7 Hz, 1 H, 4-H or 6-H), 3.32 (s, 3 H, NMe), 3.54 (td, J = 11.5, 5.1 Hz, 1 H, 2-H), 3.78 (s, 1 H, OCH_3), 3.95–4.18 (m, 3 H, 2′-H, CH_2O), 4.62 (s, 2 H, PhCH_2O), 4;65–4.79 (m, 1 H, 7-H), 7.20–7.45 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 24.8 (C-3, C-4, or C-6), 25.9 (C-3, C-4, or C-6), 36.7 (C-3, C-4, or C-6), 42.8 (N*C*H$_3$), 54.1 (O*C*H$_3$), 66.8, 67.8 (*C*H$_2$), 70.8 (C-7), 83.5 (*C*H$_2$O), 83.6 (C-5), 128.7, 128.8, 129.3 (*C*HAr), 138.4 (*ipso*-*C*Ph), 168.1 (C=O) ppm.

Methyl (2*S*,4*S*)-4-Azido-2-benzyloxymethyl-1-methylazepane-4-carboxylate (19): To a solution of **18** (140 mg, 0.32 mmol) in DMF (4 mL) was added sodium azide (0.032 g, 0.48 mmol). The resulting suspension was stirred at r.t. for 2 h. The addition of water and Et_2O was then followed by the usual workup, and the residue was purified by flash chromatography. Title compound **19** was obtained as a clear oil. Yield: 93 mg (87%). R_f = 0.50 (AcOEt/MeOH, 9:1). $[\alpha]_D^{20}$ = –15.2 (c = 2.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.72–1.92 (m, 4 H, 5-H, 6-H), 2.00–2.17 (m, 2 H, 3-H), 2.41 (s, 3 H, NMe), 2.85–3.01 (m, 3 H, 2-H, 6-H), 3.21 (dd, part of ABX syst., J = 7.1, 9.4 Hz, 1 H, NCH*H*CHO), 3.42 (dd, part of ABX syst., J = 4.8, 9.4 Hz, 1 H, NCH*H*CHO), 3.85 (s, 3 H, OMe), 4.51 (s, 2 H, PhCH_2O), 7.32–7.55 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.9 (C-6), 35.1 (C-3), 35.9 (C-5), 40.6 (N*C*H$_3$), 52.9 (O*C*H$_3$), 55.2 (C-7), 57.6 (C-2), 73.1 (C-4), 72.7 (O*C*H$_2$CH), 73.2 (Ph*C*H$_2$O), 127.6, 127.7, 128.4 (*C*Ph), 138.2 (*ipso*-*C*Ph), 173.7 (CO) ppm. IR (neat): $\tilde{\nu}$ = 2108, 1745 cm^{-1}. MS (CI): m/z (%) = 333.3 (100) $[M + H]^+$.

(2*S*,4*S*)-Methyl 2-Benzyloxymethyl-4-cyano-1-methylazepane-4-carboxylate (20): To a solution of **18** (35 mg, 0.08 mmol) in DMF (1 mL) was added sodium cyanide (16 mg, 0.24 mmol). The resulting suspension was stirred at r.t. for 2 h. The addition of water and Et_2O was then followed by the usual workup, and the residue was purified by flash chromatography. Title compound **20** was obtained as a clear oil. Yield: 19 mg (74%). R_f = 0.50 (AcOEt/MeOH, 9:1). $[\alpha]_D^{20}$ = –2.3 (c = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.82–1.95 (m, 2 H, 5-H, 3-H or 6-H), 2.05–2.22 (m, 4 H, 5-H, 3-H or 6-H), 2.47 (s, 3 H, NMe), 2.85–3.05 (m, 2 H, 7-H), 3.02–3.15 (m, 1 H, 2-H), 3.37 (dd, part of ABX syst., J = 4.6, 9.4 Hz, 1 H, NCH*H*CHO), 3.45 (dd, part of ABX syst., J = 4.6, 9.4 Hz, 1 H, NCH*H*CHO), 3.75 (s, 3 H, OMe), 4.48 (s, 2 H, PhCH_2O), 7.20–7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 31.8 (C-6), 30.1 (C-3), 36.7 (C-5), 41.6 (N*C*H$_3$), 47.7 (C-4), 53.0 (O*C*H$_3$), 53.7 (C-7), 59.7 (C-2), 73.1 (C-4), 71.7 (O*C*H$_2$CH), 73.2 (Ph*C*H$_2$O), 118.8 (CN), 128.4, 128.6, 128.8 (*C*Ph), 138.0 (*ipso*-*C*Ph), 171.2 (CO) ppm. IR (neat): $\tilde{\nu}$ = 1730, 1206 cm^{-1}. MS (CI): m/z (%) = 317.3 (100) $[M + H]^+$.

(2*S*,4*S*)-Methyl 4-Acetoxy-2-benzyloxymethyl-1-methylazepane-4-carboxylate (21): To a solution of **18** (70 mg, 0.16 mmol) in DMF (2 mL) was added cesium acetate (92 mg, 0.48 mmol). The resulting suspension was stirred at r.t. for 2 h. The addition of water and Et_2O was then followed by the usual workup, and the residue was purified by flash chromatography. Title compound **21** was obtained as a clear oil. Yield: 33 mg (63%). R_f = 0.50 (AcOEt/MeOH, 9:1). $[\alpha]_D^{20}$ = – 42.5 (c = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.30–1.45 (m, 1 H, 5-H, 3-H or 6-H), 1.52–1.70 (m, 1 H, 5-H, 3-H or 6-H), 2.01–2.22 (m, 3 H, 5-H, 3-H or 6-H), 2.08 (s,

3H CH_3CO), 2.39 (s, 3 H, NMe), 2.80–3.05 (m, 3 H, 2-H, 7-H), 3.27 (dd, part of ABX syst., J = 5.0, 9.2 Hz, 1 H, NCHHCHO), 3.38 (dd, part of ABX syst., J = 6.5, 9.2 Hz, 1 H, NCHHCHO), 3.65 (s, 3 H, OMe), 4.44 (s, 2 H, PhCH_2O), 7.28–7.36 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.0 (C-3, C-5, or C-6), 21.2 (CH_3CO), 34.3 (C-3, C-5, or C-6), 36.9 (C-3, C-5, or C-6), 39.7 (NCH_3), 53.6 (OCH_3), 55.7 (C-7), 57.4 (C-2), 73.1 (C-4), 73.1 (OCH_2CH), 73.2 (PhCH_2O), 82.0 (C-4), 127.6, 128.6, 128.8 (*C*Ph), 138.3 (*ipso*-*C*Ph), 170.3, 172.6 (CO) ppm. IR (neat): $\tilde{\nu}$ = 1730, 1213 cm^{-1}. MS (CI): *m*/*z* (%) = 350.4 (100) $[M + H]^+$.

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