Tetrahedron 68 (2012) 7848–7854

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel chiral bridged azepanes: stereoselective ring expansion of 2-azanorbornan-3-yl methanols

Elżbieta Wojaczyńska [a,*], Ilona Turowska-Tyrk [b], Jacek Skarżewski [a]

[a] Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland
[b] Institute of Physical and Theoretical Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

ARTICLE INFO

Article history:
Received 15 April 2012
Received in revised form 17 June 2012
Accepted 10 July 2012
Available online 20 July 2012

Keywords:
2-Azanorbornane
Ring expansion
2-Azabicyclo[3.2.1]octane
Azepane
Stereoselectivity

ABSTRACT

The reaction of 2-azanorbornan-3-yl methanols under Mitsunobu or mesylation conditions with various nucleophiles led to a series of chiral-bridged azepanes with configuration at C-4 dependent on the configuration of the starting alcohol. High yielding, stereoselective ring expansion to novel 2-azabicyclo[3.2.1]octane system occurred via aziridinium intermediates, which were specifically opened by nucleophilic attack at the more substituted carbon.

1. Introduction

Configurationally stable, rigid bicyclic systems with properly placed donor centers are molecular motifs in many effective chiral ligands.[1] Among them, natural products can be found, e.g., sparteine and *Cinchona* alkaloids, as well as synthetic compounds, such as 2-azanorbornyl (2-azabicyclo[2.2.1]heptane) derivatives.[2] The respective *exo*-(1*S*,3*R*,4*R*)-**1** and minor *endo*-(1*S*,3*S*,4*R*)-**1** esters are easily obtained in the cycloaddition of cyclopentadiene to an iminium ion formed in situ from ethyl glyoxylate and (*S*)-1-phenylethylamine (Scheme 1). Compound **1** and the product of its reduction, 2-azanorbornan-3-yl methanol (**2**), turned out to be attractive precursors of different chiral ligands, which were used in various stereoselective processes.[3]

Recently, we have reported the preparation of this type of ligand bearing additional chalcogen (S, Se) and nitrogen donors.[4,5] These derivatives were obtained from *N*-(1-phenylethyl)-2-azanorbornane-3-carboxaldehyde (Scheme 2) and these compounds were highly effective in the Trost–Tsuji reaction giving up to 95% ee.[4] However, we have also described less effective ligands **3** prepared by the direct nucleophilic substitution of the activated hydroxy group in *exo*-**2** (Scheme 3).[4,5] It is noteworthy that a similar synthetic approach to 2-azanorbornylmethanethiol (**3c**) has been described earlier by Hongo et al.[3b] Here we report the results of our current experiments that proved that the structures of **3** must be revised.

The key evidence that led to verification of the previously assigned structures of the ligands **3** was an unexpected single crystal X-ray structure of the *N*-proline amide of supposed *N*-[(*S*)-1-phenylethyl]-2-azanorbornyl-3-methylamine obtained from **3d**.[5]

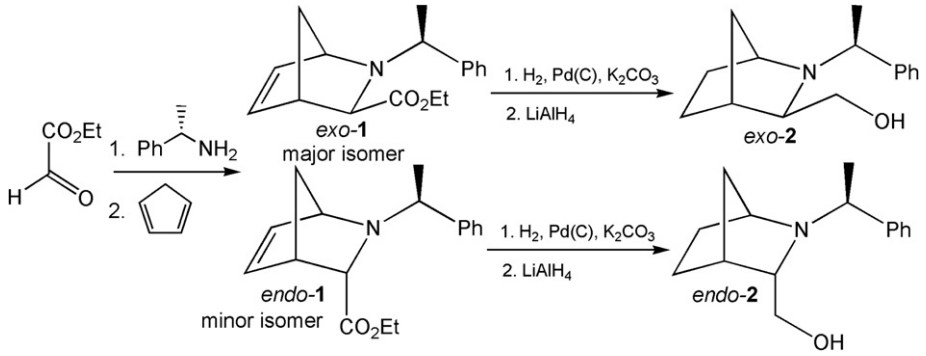
2. Results and discussion

In our preparation of (*N*,*N*)-donating ligands based on 2-azanorbornyl framework, *exo*-**2** was treated with Ph_3P, DEAD, and HN_3.[5] Physicochemical characteristics (HRMS, 1D NMR, IR) of the only reaction product formed were in general agreement with the structure of **3**. Its structure seemed analogous to *exo*-**2** and the product apparently resulted from a simple nucleophilic substitution. However, in the course of the present investigation we came to a conclusion that the Mitsunobu reaction of alcohol *exo*-**2** with an azide ion must proceed in a different manner. Thus, a bicyclic structure **4d** containing a seven-membered ring has been selectively formed. Reduction of the azide **4d** with triphenylphosphine yielded amine **5**, which was converted by the DCC method[6] into the (*S*)-proline derivative **6** in 54% yield (Scheme 4).

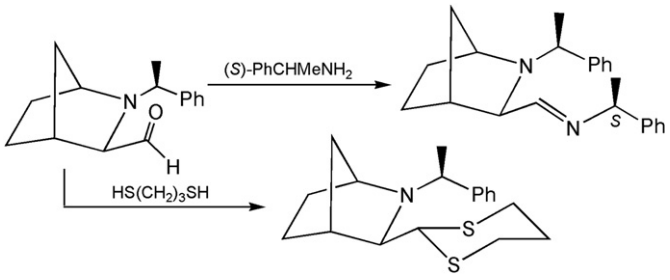
The X-ray structure of **6** shown in Fig. 1 unambiguously proves the presence of an extended bicyclic system. Five stereogenic carbon atoms are present in the molecule, three of them in the 2-azabicyclo[3.2.1]octane fragment have (1*S*,4*S*,5*R*) configuration.

* Corresponding author. Tel.: +48 713202410; fax: +48 713202427; e-mail address: elzbieta.wojaczynska@pwr.wroc.pl (E. Wojaczyńska).

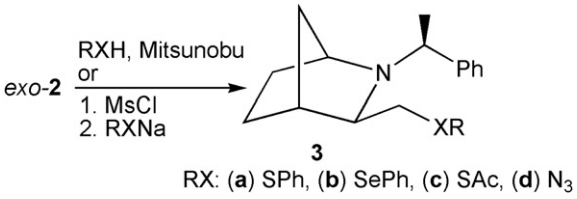
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.07.028



Scheme 1.



Scheme 2.



3

RX: (**a**) SPh, (**b**) SePh, (**c**) SAc, (**d**) N_3

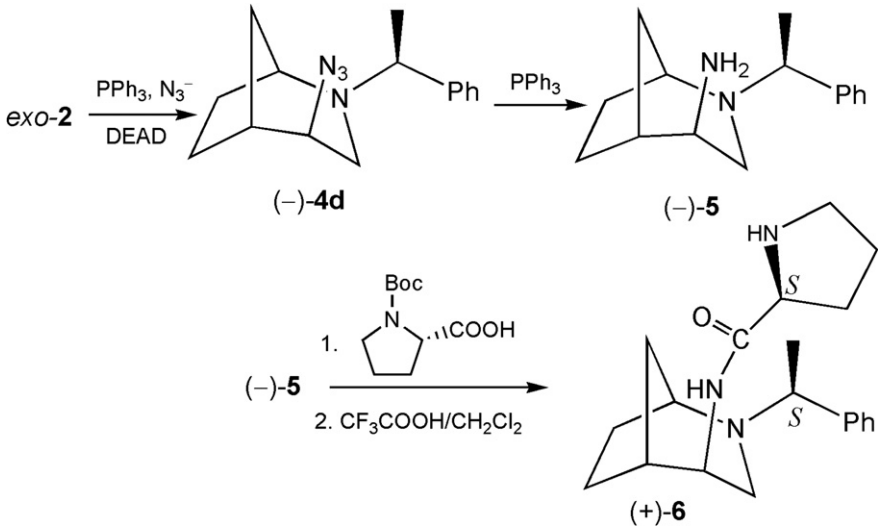
Scheme 3.

Careful examination of the 2D NMR spectra of **5** and **6** led to a conclusion on the structure consistent with the crystallographic data. In particular, the analysis of NOESY and $^{1}H,^{13}C$ HMBC maps revealed couplings possible only if an additional CH_2 group (3-CH_2) is present in the ring (Fig. 2).

The structural evidence showed that under the Mitsunobu reaction[7] conditions (Ph_3P, DEAD, and HN_3)[8] *exo*-**2** underwent transformation to the seven-membered ring system. The reaction is highly regio- and stereoselective since no other isomer of the product could be detected. An identical product **4d** was also obtained when, instead of a Mitsunobu protocol, a DPPA/DBU combination[9] was applied.

In order to additionally confirm the rearrangement of *exo*-**2** under the Mitsunobu reaction conditions, we separately reacted it with *p*-nitrobenzoic acid (PNBA)/Ph_3P/DEAD and with PNBA-chloride. As expected, two different isomeric PNBA-esters were obtained. The Mitsunobu reaction gave the rearranged product **4e**, while the acid chloride clearly gave PNBA-ester of *exo*-**2**.

The observed rearrangement with ring expansion clearly results from the formation of the three-membered aziridinium ring followed by its stereoselective opening by a nucleophile (Scheme 5). Generally, this type of reactivity of β-aminoalcohols requires an activation of the hydroxy group followed by the addition of a nucleophile.[10] It is also documented that the Mitsunobu reaction of chiral aminoalcohols can give optically pure aziridines,[11] which can be in turn easily opened by nucleophiles. Recently, ring expansion of aza-heterocycles through aziridines and aziridinium intermediates has been developed into an attractive synthetic



Scheme 4.

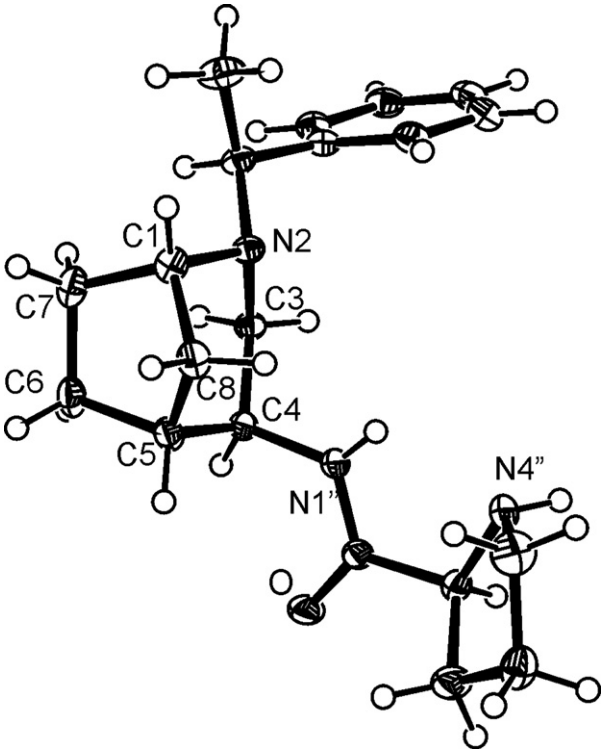


Fig. 1. Molecular structure of **6**. Displacement ellipsoids are drawn at the 30% probability level.

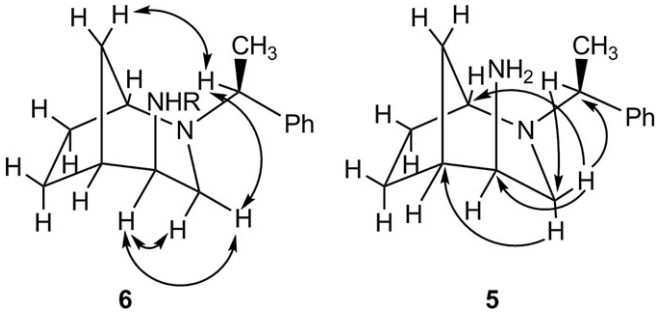


Fig. 2. Selected NOESY (left) and HMBC connectivities (right), crucial for the determination of the molecular structure for **6** (R=(*S*)-prolyl) and **5**, respectively.

method.[12–16] Also compounds bearing an azepane backbone have been prepared through the ring expansion of piperidines.[17,18] In spite of the abundance of chiral azepane rings in various natural products,[19] their stereoselective synthesis still remains a challenge.[17] Rearrangements involving bicyclic and tricyclic amines have been explored,[20] although the ring expansion of 2-azanorbornyl derivatives has not been observed before.[21]

All these led us to reexamine our earlier reported structures of sulfur and selenium analogues (**3a** and **3b**), which were also prepared from *exo*-**2** via the nucleophilic substitutions using the Hata[22] ($(PhS)_2/Bu_3P$) and Grieco[23] ($PhSeCN/Bu_3P$) protocols. Furthermore, the respective thioacetate **3c** has been reported[3b] as a product of the nucleophilic substitution on the mesylate of *exo*-**2** with sodium thioacetate and we repeated its synthesis. The recorded correlation NMR experiments (COSY, NOESY, HSQC/HMQC, HMBC) for the obtained products allowed complete resonance assignments (see Supplementary data), which are in full agreement with the presence of a rearranged skeleton. The DFT calculations for the respective three-membered ring intermediates further support the proposed reaction pathway.[24] The structures of the aziridinium ions determine the observed direction of nucleophilic attack (Schemes 5 and 6). In the three-membered ring of the intermediate, the N–C bond, which is eventually broken is slightly longer than the preserved one, and the attack of nucleophile on more substituted carbon atom is expected with an inversion of configuration. The determined mechanism is in an agreement with the general pathway of aziridinium ring opening by nucleophiles studied previously.[25]

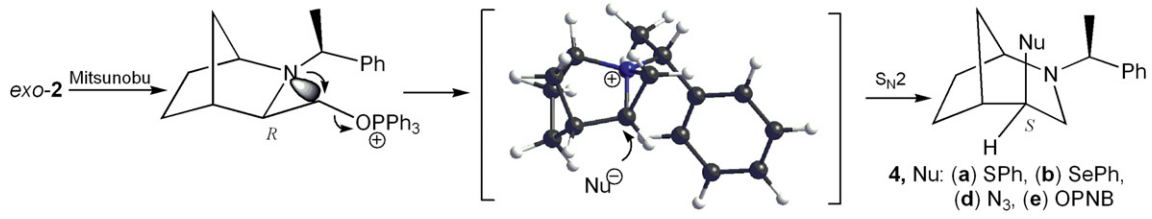
An additional proof for the regio- and stereochemical outcome of the observed rearrangement is an X-ray structure of the sulfoxide obtained from the previously supposed **3a**, which was in fact **4a** (Fig. 3). Thus, the 2-azabicyclo[3.2.1]octane fragment has (1*S*,4*S*,5*R*) configuration.

Moreover, when *endo*-**2** was subjected to the Mitsunobu reaction with hydrazoic acid, we also observed the rearranged azide product, but this time of the (1*S*,4*R*,5*R*) configuration. As previously, the Staudinger reduction furnished the respective amino-derivative. Also here, the direction of nucleophilic attack is in agreement with the calculated structure of the intermediate[24] (Scheme 6), which accounts for the observed regio- and stereoselectivity.

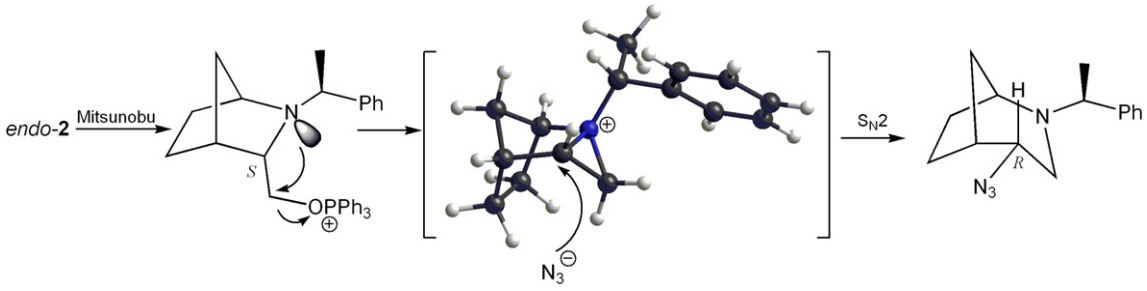
Interestingly, we observed that the reaction of *exo*-**2** with mesyl chloride in the presence of Et_3N at 0 °C did not produce the expected mesylate of *exo*-**2** but gave directly the bridged azepane chloride **4f** in 83% yield. A similar chloride formation in the reaction of piperidine-derived diol with tosyl chloride has already been described in the literature.[17] The stereochemistry at the newly created center (as suggested by the observed NOE correlations) is the same as that of the previous compounds ((1*S*,4*S*,5*R*)-**4a**–**e**, **5**, **6**). The chloride derivative **4f** underwent nucleophilic substitution with sodium thiophenolate giving the corresponding sulfide **7** ($[\alpha]_D^{20}$ −83.0 (dichloromethane)), which clearly differs from (1*S*,4*S*,5*R*)-**4a** ($[\alpha]_D^{20}$ −5.1 (CH_2Cl_2)). This result corroborates with the configuration ascribed to the C-4 center of **4f**.

However, when the mesylate of *exo*-**2** was reacted in situ with the nucleophiles stronger than the chloride anion, the respective nucleophilic substitution products **4** of (1*S*,4*S*,5*R*) configuration were smoothly obtained (Scheme 7).

In summary, we have presented the diastereospecific ring expansion of bicyclic 2-azanorbornyl skeleton upon the reactions of *exo*- and *endo*-2-azanorbornan-3-yl methanols leading exclusively to 2-azabicyclo[3.2.1]octane (instead of the previously described 2-azabicyclo[2.2.1]heptane)[3b,4,5] derivatives. The stereochemical outcome of the reaction was unambiguously proved by the X-ray structures and the observed NOE correlations. A stereoselective



Scheme 5.



Scheme 6.

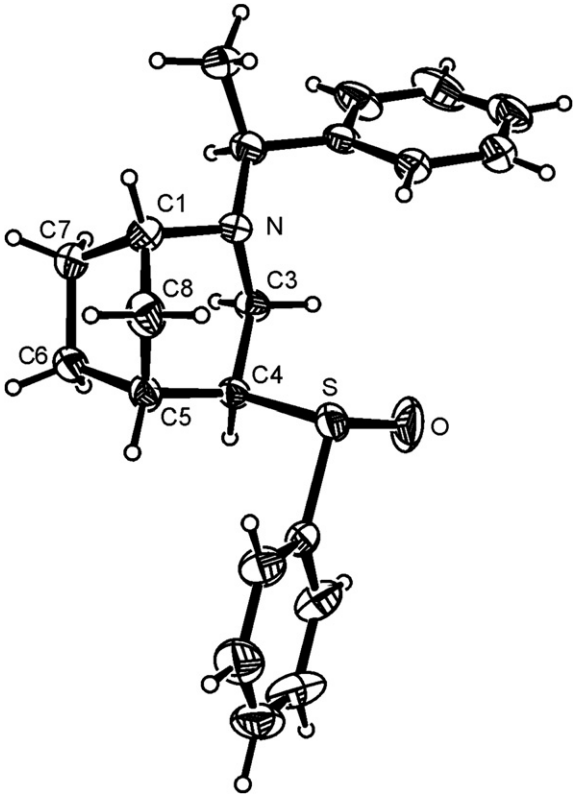


Fig. 3. Molecular structure of (1*S*,4*S*,5*R*)-2-[(*S*)-1-phenylethyl]-4-[(*S*)-phenylsulfinyl]-2-azabicyclo[3.2.1]octane. Displacement ellipsoids are drawn at the 25% probability level.

incorporation of an additional carbon atom into bicyclic skeleton opens up a new route to the synthesis of bridged azepane derivatives of potential biological activity.

3. Experimental section

3.1. General

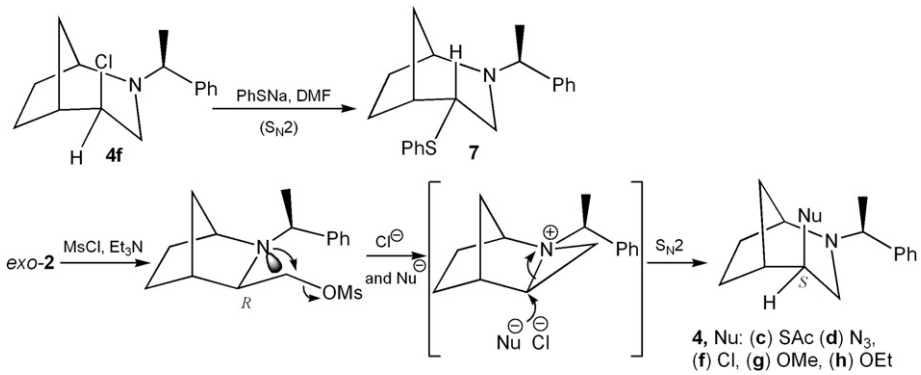
IR spectra were recorded on a Perkin Elmer System 2000 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance DRX 300 (^{1}H, 300 MHz) or a Bruker Avance 600 (^{1}H, 600 MHz) spectrometer using TMS as an internal standard or solvent residual peak as a reference. The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High-resolution mass spectra were recorded using a microTOF-Q and WATERS LCT Premier XE instruments utilizing electrospray ionization mode. Separations of products by chromatography were performed on silica gel 60 (70–230 mesh) purchased from Merck. Thin layer chromatography was carried out using silica gel 60 precoated plates (Merck).

X-ray data were collected at 100 K (compound **6**) and 299 K (**4a**) using a KM4CCD diffractometer. Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC 830423 and CCDC 874403, respectively.

For DFT calculations, a hybrid functional M062X in 6-311+(2d,2p) basis set was used.[24]

3.2. Preparations

Syntheses of Diels–Alder cycloadducts *exo*-(1*S*,3*R*,4*R*)-**1**, *endo*-(1*S*,3*S*,4*R*)-**1**, and respective alcohols *exo*-(1*S*,3*R*,4*R*)-**2**, *endo*-(1*S*,3*S*,4*R*)-**2** were performed as described in the literature.[2c,4] Though the procedure for preparation of sulfide **4a**, selenide **4b**, azide **4d**, amine **5**, and their diastereomers was given in our



Scheme 7.

previous work,[4,5] the structures proposed for these compounds were incorrect. For this reason, the relevant experimental data for these compounds are also reported below.

3.2.1. Preparation of azides.[5] Alcohol *exo*-(1*S*,3*R*,4*R*)-**2** (0.46 g, 2 mmol) and triphenylphosphine (0.68 g, 2.6 mmol, 1.3 equiv) were dissolved in 15 mL of dry toluene and cooled in an ice bath. A 1 M solution of HN_3 in benzene (2.6 mL, 2.6 mmol, 1.3 equiv) was then added in one portion under inert atmosphere, followed by a 40% solution of DEAD in toluene (1.37 mL, 3 mmol, 1.5 equiv), which was added dropwise. The reaction mixture was stirred overnight under argon. After evaporation of solvent, the residue was chromatographed on a silica column using *n*-hexane/ethyl acetate (6:1 v/v), yielding a fraction containing azide (1*S*,4*S*,5*R*)-**4d** (0.45 g, 88%).

(1*S*,4*R*,5*R*)-Isomer was prepared in a similar manner starting from *endo*-(1*S*,3*S*,4*R*)-**2**.

Alternatively, azide **4d** was prepared by the use of diphenylphosphorylazide/DBU.

DBU (0.92 g, 0.92 mL, 6 mmol) and $(PhO)_2P(O)N_3$ (1.66 g, 1.30 mL, 6 mmol) were added to a stirred solution of alcohol *exo*-(1*S*,3*R*,4*R*)-**2** (0.92 g, 4 mmol) in 20 mL of dry toluene at 0 °C under inert atmosphere. After stirring for 2 h at 0 °C and 24 h at room temperature, water (10 mL) and 5% HCl (10 mL) were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate, 9:1 v/v) giving **4d** as yellow oil (0.78 g, 76%).

*3.2.1.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-azide-2-azabicyclo [3.2.1]octane (**4d**).* $[\alpha]_D^{20}$ −71.3 (*c* 0.60, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.28–1.48 (m, 3H), 1.33 (d, 3H, *J*=6.6 Hz), 1.68–1.82 (m, 2H), 2.12 (d, 1H, *J*=11.7 Hz), 2.24 (AB_qX, 1H, J_1=13.2 Hz, J_2=3.6 Hz), 2.30–2.38 (m, 1H), 2.56 (AB_q, 1H, *J*=13.2 Hz), 3.23–3.29 (m, 1H), 3.36 (q, 1H, *J*=6.6 Hz), 3.58–3.63 (m, 1H), 7.20–7.38 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.5, 21.9, 27.2, 34.2, 38.9, 47.8, 56.0, 60.7, 62.5, 127.0, 127.5, 128.4, 145.2 ppm. HRMS (ESI) 257.1678 ($[M+H]^+$); for $(C_{15}H_{21}N_4)^+$ *M*=257.1766. IR (film): 701, 770, 1264, 1453, 1749, 2097 (N_3), 2953, 3026 cm^{-1}.

3.2.1.2. (1S,4R,5R)-2-[(S)-1-Phenylethyl]-4-azide-2-azabicyclo [3.2.1]octane. Yield 85%. $[\alpha]_D^{20}$ +34.5 (*c* 0.58, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.15–1.50 (m, 3H), 1.23 (d, 3H, *J*=6.6 Hz), 1.52–2.10 (m, 4H), 2.36 (s, 1H), 2.40–2.52 (m, 1H), 2.98–3.12 (m, 2H), 3.40 (br s, 1H), 7.17–7.45 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.9, 22.0, 27.0, 33.6, 38.8, 47.1, 570, 60.6, 62.0, 126.9, 127.6, 128.3, 145.2 ppm. HRMS (ESI): 257.1757 ($[M+H]^+$); for $(C_{15}H_{21}N_4)^+$ *m*/*z*=257.1766. IR (film): 548, 702, 767, 955, 1029, 1046, 1160, 1263, 1453, 1492, 1748, 2096 (N_3), 2810, 2871, 2972, 3026 cm^{-1}.

*3.2.2. Synthesis of chloride **4f**, thioacetate **4c**, and ethers **4g** and **4h*** Mesylation of alcohol *exo*-(1*S*,3*R*,4*R*)-**2** followed by the reaction with nucleophiles gave ring-expanded derivatives **4c**, **4f**–**4h**. To a solution of **2** (0.25 g, 1.08 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (0.15 mL, 1.17 mmol) and mesyl chloride (0.15 g, 1.30 mmol) at 0 °C, and the reaction mixture was stirred for 5 h at 0 °C.

After evaporation of solvent, ethanol (15 mL) and potassium thioacetate (0.37 g, 3.25 mmol) were added and the solution was stirred for 24 h under inert atmosphere. Solvent was removed in vacuo, and the residue was dissolved in ethyl ether (10 mL). After washing with water (3×5 mL), the organic layer was dried with $MgSO_4$ and evaporated. The solid residue was chromatographed on a silicagel column with ethyl ether, yielding compound **4c** (0.28 g, 90%).

A similar mesylation procedure followed by the addition of sodium methanolate (prepared by dissolving of sodium in methanol) or a solution of KOH in ethanol led to derivatives **4g** and **4h**, respectively. These compounds were purified by column chromatography with diethyl ether as eluent.

Attempted isolation of mesylate from the reaction mixture obtained by treatment of **2** with $MsCl/Et_3N$ led to chloride derivative **4f**. The crude product was chromatographed on silica gel column with *n*-hexane/ethyl acetate (5:1 v/v).

*3.2.2.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-acetylthiomethyl-2-azabicyclo[3.2.1]octane (**4c**).* Yellow oil., $[\alpha]_D^{20}$ −78.7 (*c* 0.89, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.31 (d, 3H, *J*=6.3 Hz), 1.36–1.45 (m, 2H), 1.50–1.53 (m, 1H), 1.75–1.82 (m, 2H), 1.96 (br d, 1H, *J*=11.6 Hz), 2.29 (s, 3H), 2.32–2.35 (m, 1H), 2.51 (d, 1H, *J*=13.6 Hz), 2.60–2.64 (m, 1H), 3.38–3.42 (m, 1H), 3.50 (br s, 1H), 3.59 (br s, 1H), 7.23 (t, 1H, *J*=6.6 Hz), 7.28–7.33 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.4, 22.7, 29.3, 30.7, 36.6, 39.8, 45.2, 49.9, 56.3, 62.3, 126.7, 127.3, 128.3, 145.5, 196.1 ppm. MS (ESI): *m*/*z*=290.1580 (calculated for $C_{17}H_{24}NOS^+$ ($[M+H]^+$) *m*/*z*=290.1573). IR (film): 638, 701, 769, 955, 1112, 1135, 1351, 1453, 1491, 1686, 2793, 2864, 2951, 3024, 3060 cm^{-1}.

*3.2.2.2. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-chloro-2-azabicyclo [3.2.1]octane (**4f**).* Yellow oil, yield 83%. $[\alpha]_D^{20}$ −37.8 (*c* 1.64, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.28–1.48 (m, 3H), 1.33 (d, 3H, *J*=6.6 Hz), 1.68–1.82 (m, 2H), 2.39–2.55 (m, 3H), 2.75 (AB_q, 1H, *J*=13.8 Hz), 3.43 (q, 1H, *J*=6.6 Hz), 3.59 (t, 1H, *J*=5.0 Hz), 3.87–3.92 (m, 1H), 7.20–7.36 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.6, 22.2, 28.4, 33.7, 42.4, 51.4, 56.0, 61.2, 62.0, 126.8, 127.3, 128.3, 145.4 ppm. MS (ESI): *m*/*z*=250.1379 (calculated for $C_{15}H_{21}NCl^+$ ($[M+H]^+$) *m*/*z*=250.1357). IR (film): 546, 681, 702, 769, 957, 1137, 1261, 1452, 1491, 1686, 2098, 2795, 2806, 2952, 3025, 3061, 3082 cm^{-1}.

*3.2.2.3. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-methoxy-2-azabicyclo [3.2.1]octane (**4g**).* Yellow oil, yield 39%. $[\alpha]_D^{20}$ −33.0 (*c* 0.18, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.23–1.29 (m, 2H), 1.28 (d, 3H, *J*=6.4 Hz), 1.33–1.37 (m, 1H), 1.66–1.72 (m, 1H), 1.72–1.79 (m, 1H), 2.02 (AB_q, 1H, *J*=12.6 Hz), 2.14 (d, 1H, *J*=11.4 Hz), 2.39–2.42 (m, 1H), 2.62 (AB_q, 1H, *J*=12.6 Hz), 2.97 (br s, 1H), 3.21 (s, 3H), 3.34–3.37 (m, 1H), 3.57 (t, 1H, *J*=4.9 Hz), 7.20 (t, 1H, *J*=7.3 Hz), 7.27 (t, 2H, *J*=7.5 Hz), 7.31 (d, 2H, *J*=7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ=21.5, 21.7, 26.5, 33.1, 37.6, 47.5, 56.0, 56.1, 62.6, 79.3, 126.7, 127.5, 128.3, 145.7 ppm. MS (ESI): *m*/*z*=246.1852 (calculated for $C_{16}H_{24}NO^+$ ($[M+H]^+$) *m*/*z*=246.1852). IR (film): 701, 770, 1103, 1118, 1452, 1677, 1735, 2817, 2865, 2970, 3025, 3060 cm^{-1}.

*3.2.2.4. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-ethoxy-2-azabicyclo [3.2.1]octane (**4h**).* Yellow oil, yield 88%. $[\alpha]_D^{20}$ −29.7 (*c* 0.74, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.17 (t, 3H, *J*=7.0 Hz), 1.25–1.39 (m, 3H), 1.35 (d, 3H, *J*=6.6 Hz), 1.66–1.78 (m, 2H), 2.04 (dd, 1H, J_1=13.3 Hz, J_2=3.4 Hz), 2.22 (AB_q, 1H, *J*=11.4 Hz), 2.37–2.41 (m, 1H), 2.64 (AB_q, 1H, *J*=13.3 Hz), 3.08–3.10 (m, 1H), 3.33–3.39 (m, 2H), 3.40 (q, 1H, *J*=6.6 Hz), 3.55–3.61 (m, 1H), 7.23 (t, 1H, *J*=7.3 Hz), 7.31 (t, 2H, *J*=7.4 Hz), 7.36 (d, 2H, *J*=7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ=15.6, 21.7, 21.9, 26.6, 33.2, 38.4, 47.8, 56.2, 62.4, 63.6, 77.5, 126.6, 127.5, 128.2, 146.0 ppm. MS (ESI): *m*/*z*=260.1705 (calculated for $C_{17}H_{26}NO^+$ ($[M+H]^+$) *m*/*z*=260.2009). IR (film): 701, 769, 956, 1106, 1371, 1452, 1491, 1599, 2792, 2948, 2971, 3024, 3061 cm^{-1}.

3.2.3. Preparation of PNBA derivatives Alcohol *exo*-(1*S*,3*R*,4*R*)-**2** (0.23 g, 1 mmol), triphenylphosphine (0.34 g, 1.46 mmol), and 4-nitrobenzoic acid (0.18 g, 1.08 mmol) were dissolved in dry THF (10 mL) at 0 °C under inert atmosphere and DEAD (0.17 mL, 1.08 mmol) was added dropwise to the reaction mixture, which was then stirred for 24 h at room temperature. After removal of

solvent, the crude product was chromatographed on silica column using ethyl acetate as eluent, yielding ring-expanded compound **4e** as yellow oil (0.19 g, 50%).

*3.2.3.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-(4-nitrobenzoyloxy)-2-azabicyclo[3.2.1]octane (**4e**).* $[\alpha]_D^{20}$ +43.8 (*c* 3.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.36 (d, 3H, *J*=6.6 Hz), 1.38–1.44 (m, 1H), 1.47–1.53 (m, 2H), 1.78–1.85 (m, 2H), 2.27 (d, 1H, *J*=11.5 Hz), 2.41 (AB_qX, 1H, J_1=13.9 Hz, J_2=3.2 Hz), 2.56–2.60 (m, 1H), 2.72 (AB_q, 1H, *J*=13.8 Hz), 3.45 (q, 1H, *J*=6.6 Hz), 3.71 (t, 1H, *J*=4.7 Hz), 4.86 (br s, 1H), 7.21 (t, 1H, *J*=7.3 Hz), 7.27 (t, 2H, *J*=7.3 Hz), 7.36 (d, 2H, *J*=7.1 Hz), 8.27 (d, 2H, *J*=8.9 Hz), 8.35 (d, 2H, *J*=8.9 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ=21.7, 21.8, 26.4, 33.9, 38.1, 48.6, 55.7, 62.3, 74.3, 123.6, 126.8, 127.2, 128.3, 130.7, 136.4, 145.6, 150.5, 164.2 ppm. MS (ESI): *m*/*z*=381.1792 (calculated for $C_{22}H_{25}N_2O_4^+$ ($[M+H]^+$) *m*/*z*=381.1809). IR (film): 702, 720, 1015, 1061, 1104, 1119, 1277, 1302, 1346, 1529, 1607, 1722, 2870, 2973, 3056 cm^{-1}.

Direct esterification of alcohol *exo*-(1*S*,3*R*,4*R*)-**2** with 4-nitrobenzoic chloride in the presence of Et_3N gave *(1S,3R,4R)-2-[(S)-1-Phenylethyl]-3-(4-nitrobenzoyloxy)methyl-2-azabicyclo[2.2.1]heptane*. Yellow oil, yield 63%. $[\alpha]_D^{20}$ −49.6 (*c* 0.49, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.32–1.39 (m, 2H), 1.37 (d, 3H, *J*=6.4 Hz), 1.43–1.49 (m, 1H), 1.66–1.74 (m, 1H), 1.84 (br d, 1H, *J*=9.7 Hz) 2.03–2.09 (m, 1H), 2.27–2.28 (m, 1H), 2.41 (dd, 1H, J_1=9.6 Hz, J_2=3.4 Hz), 3.18 (dd, 1H, J_1=10.8 Hz, J_2=3.6 Hz), 3.56 (q, 1H, *J*=6.4 Hz), 3.65 (t, 1H, *J*=10.3 Hz), 3.70 (br s, 1H), 7.27 (t, 1H, *J*=7.4 Hz), 7.33 (t, 2H, *J*=7.5 Hz), 7.40 (d, 2H, *J*=7.4 Hz), 8.08 (d, 2H, *J*=9.3 Hz), 8.25 (d, 2H, *J*=9.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ=22.7, 22.8, 28.7, 35.1, 39.8, 58.7, 61.1, 66.9, 67.4, 123.4, 127.5, 128.1, 128.4, 130.6, 135.8, 146.0, 150.4, 164.1 ppm. MS (ESI): *m*/*z*=381.1803 (calculated for $C_{22}H_{25}N_2O_4^+$ ($[M+H]^+$) *m*/*z*=381.1809). IR (film): 702, 720, 1104, 1116, 1275, 1295, 1347, 1455, 1527, 1606, 1641, 1727, 2872, 2972, 3029 cm^{-1}.

3.2.4. Reduction of azides.[5] Azide **4d** (0.42 g, 1.6 mmol) was dissolved in 20 mL of methanol. Triphenylphosphine (0.63 g, 2.4 mmol, 1.5 equiv) was added and the reaction mixture was heated overnight under reflux. The solvent was evaporated, and the residue was chromatographed on silica column. Elution with chloroform yielded the unreacted phosphine and phosphine oxide, while a chloroform/methanol mixture (90:10 v/v) eluted the desired product **5** as yellow oil (0.34 g, 92%).

*3.2.4.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-amine-2-azabicyclo[3.2.1]octane (**5**).* $[\alpha]_D^{20}$ −17.5 (*c* 0.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.25–1.37 (m, 3H), 1.31 (d, 3H, *J*=6.6 Hz), 1.60–1.70 (m, 2H), 1.87 (br s, 2H), 2.03 (d, 1H, *J*=10.2 Hz), 2.10–2.20 (m, 1H), 2.24 (d, 2H, *J*=2.7 Hz), 2.54–2.62 (m, 1H), 3.34 (q, 1H, *J*=6.6 Hz), 3.56 (t, 1H, *J*=2.4 Hz), 7.20–7.30 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.3, 21.4, 28.0, 33.4, 41.5, 50.9, 52.2, 56.4, 62.6, 126.8, 127.4, 128.3, 145.6 ppm. HRMS (ESI): 231.1846 ($[M+H]^+$); for $(C_{15}H_{23}N_2)^+$ *m*/*z*=231.1861. IR (film): 549, 701, 771, 952, 1134, 1453, 1491, 1599, 2812, 2864, 2947, 3025, 3365 cm^{-1}.

(1*S*,4*R*,5*R*)-Isomer was prepared analogously using (1*S*,4*R*,5*R*)-azide in place of its diastereomer **4d**.

3.2.4.2. (1S,4R,5R)-2-[(S)-1-Phenylethyl]-4-amine-2-azabicyclo[3.2.1]octane. Yellow oil, yield 56%. $[\alpha]_D^{20}$ −19.8 (*c* 0.61, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.10–1.40 (m, 4H), 1.23 (d, 3H, *J*=6.6 Hz), 1.70–1.80 (m, 1H), 1.85–1.95 (m, 1H), 2.10–2.20 (m, 1H), 2.29 (br s, 2H), 2.38–2.49 (m, 2H), 2.71–2.80 (m, 1H), 2.92–3.10 (m, 1H), 3.35 (q, 1H, *J*=6.6 Hz), 7.21–7.35 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.0, 22.1, 27.9, 33.0, 41.6, 50.6, 51.1, 57.6, 61.9, 126.7, 127.5, 128.3, 146.0 ppm. HRMS (ESI): 231.1882 ($[M+H]^+$); for $(C_{15}H_{23}N_2)^+$ *m*/*z*=231.1861. IR (film): 543, 703, 772, 967, 1050, 1180, 1305, 1370, 1453, 1492, 1602, 1741, 2790, 2820, 2873, 2971, 3468 cm^{-1}.

*3.2.5. Preparation of amide **6*** Amine **5** (0.23 g, 1 mmol), *N*-Boc-L-proline (0.22 g, 1.11 mmol), potassium carbonate (0.28 g, 2.02 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.21 g, 1.0 mmol) were dissolved in 15 mL of acetonitrile and stirred for 24 h at room temperature. The precipitated (dicyclohexylurea) was filtered off, and the filtrate was evaporated to dryness. The solid residue was chromatographed on a silica column with $CHCl_3$/methanol (9:1 v/v) as eluent. The resulting amide was deprotected by dissolving in 3 mL of TFA/CH_2Cl_2 (1:4), and stirring for 2 h at room temperature. The reaction mixture was neutralized with concentrated aqueous ammonia and extracted with dichloromethane. Evaporation of solvent yielded compound **6** as a colorless solid (0.20 g, 60%). A single crystal of **6** suitable for X-ray measurement was obtained by a slow crystallization from dichloromethane.

*3.2.5.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-[(S)-prolylamine]-2-azabicyclo[3.2.1]octane (**6**).* Mp=148–149 °C. $[\alpha]_D^{20}$ +10.0 (*c* 0.39, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26–1.42 (m, 6H), 1.67–1.80 (m, 4H), 1.82–1.91 (m, 2H), 2.11–2.17 (m, 1H), 2.28–2.38 (m, 3H), 2.50 (s, 1H, NH), 3.02–3.08 (m, 2H), 3.36–3.38 (m, 1H), 3.57–3.68 (m, 3H), 7.20–7.38 (m, 5H, ArH), 8.20 (d, 1H, *J*=7.2 Hz, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.3, 22.0, 26.2, 27.4, 30.9, 34.6, 38.4, 47.4, 47.9, 49.4, 56.2, 60.7, 62.5, 126.9, 127.3, 128.4, 151.0, 174.9 ppm. HRMS (ESI): *m*/*z*=328.2386; calculated for $(C_{20}H_{30}N_3O)^+$ ($[M+H]^+$) *m*/*z*=328.2383. IR (KBr): 747, 1294, 1370, 1670, 2858, 2935, 2978, 3195 cm^{-1}.

*3.2.6. Preparation of sulfide **4a**.*[4] Tributylphosphine (1.62 g, 1.97 mL, 8 mmol) was added by a syringe to the solution of alcohol *exo*-(1*S*,3*R*,4*R*)-**2** (0.46 g, 2 mmol) and diphenyldisulfide (1.31 g, 6 mmol) in dry toluene (6 mL). The mixture was transferred to the ampoule, filled with argon, and sealed. This reaction mixture was kept at the oil bath at 80 °C for 3 days. Diethyl ether (20 mL) was added to the cooled solution, the organic layer was washed with 10% aqueous NaOH, water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and product **4a** was purified by column chromatography using hexane/ethyl acetate (9:1 v/v) as eluent (0.26 g, 40%).

*3.2.6.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-phenylsulfanyl-2-azabicyclo[3.2.1]octane (**4a**).* Yellow oil. $[\alpha]_D^{20}$ −5.1 (*c* 1.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.23–1.32 (m, 6H), 1.60–1.66 (m, 1H), 1.75–1.77 (m, 1H), 1.93–1.98 (m, 1H), 2.11–2.14 (m, 1H), 2.20–2.28 (m, 2H), 2.43–2.48 (m, 1H), 3.45 (q, 1H, *J*=6.42 Hz), 3.64 (br s, 1H), 6.62–6.63 (m, 2H, ArH), 7.04–7.06 (m, 3H, ArH), 7.28–7.36 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=22.9, 23.8, 29.1, 35.3, 37.7, 40.7, 59.9, 61.6, 68.9, 125.4, 127.8, 128.4, 128.7, 128.7, 129.0, 132.4, 136.9 ppm. HRMS (ESI): 324.1653 ($[M+H]^+$); for $(C_{21}H_{26}NS)^+$ *M*=324.1786. IR (film) 737, 761, 1163, 1304, 1452, 1480, 1583, 2870, 2969, 3059 cm^{-1}.

*3.2.7. Preparation of sulfide **7*** Chloride derivative **4f** (0.10 g, 0.4 mmol) was added to a solution of sodium thiophenolate (0.4 mmol) in 4 mL of ethanol. The solution was stirred for 24 h at room temperature. After evaporation of solvent, diethyl ether (5 mL) was added, and the organic layer was washed with 10% aqueous NaOH, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and product **7** was purified by column chromatography using hexane/ethyl acetate (9:1 v/v) as eluent (0.032 g, 25%).

*3.2.7.1. (1S,4R,5R)-2-[(S)-1-Phenylethyl]-4-phenylsulfanyl-2-azabicyclo[3.2.1]octane (**7**).* Yellow oil. $[\alpha]_D^{20}$ −83.3 (*c* 0.42, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.27–1.44 (m, 3H), 1.33 (d, 3H, *J*=6.5 Hz), 1.73–1.79 (m, 2H), 2.35 (br d, 1H, *J*=11.7 Hz), 2.40–2.46 (m, 2H),

2.64 (AB_q, 1H, J=12.3 Hz), 3.04 (br s, 1H), 3.40 (q, 1H, J=6.6 Hz), 3.62 (t, 1H, J=4.8 Hz), 7.15–7.38 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.6, 22.7, 29.7, 34.9, 39.3, 48.9, 51.5, 56.5, 62.4, 126.6, 126.7, 127.4, 128.2, 128.8, 132.0, 136.5, 145.7 ppm. MS (ESI): m/z=324.1791 (calculated for $C_{21}H_{26}NS^+$ ($[M+H]^+$) m/z=324.1780). IR (film): 701, 756, 1025, 1135, 1285, 1453, 1479, 1584, 1686, 2791, 2862, 2948, 3024 cm^{-1}.

*3.2.8. Oxidation of (1S,4S,5R)-2-[(S)-1-phenylethyl]-4-phenylsulfanyl-2-azabicyclo[3.2.1]octane (sulfide **4a**)* Vanadyl acetylacetonate (5.2 mg, 0.02 mmol) and (*S*)-(−)-*N*-(3-phenyl-5-nitrosalicylidene) valinol (0.03 mmol) were dissolved in a test tube in dichloromethane (4 mL), and the solution was stirred for 5 min at 25 °C. After the addition of sulfide **4a** (0.65 g, 2 mmol) the solution was cooled to 0 °C and 30% H_2O_2 (0.26 mL, 2.3 mmol) was added dropwise within 10 min. The mixture was stirred for 20 h at 0 °C and extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was submitted to chromatography on silica (*t*-BuOMe/$CHCl_3$/*n*-hexane 3:2:4) and the major diastereomer was recrystallized from methylene chloride/*n*-hexane, yielding sulfoxide **6** as a white powder (0.41 g, 60%). A single crystal of **6** suitable for X-ray measurement was obtained by a slow crystallization from *n*-hexane/dichloromethane mixture.

3.2.8.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-[(S)-phenylsulfinyl]-2-azabicyclo[3.2.1]octane. De 70%. $[\alpha]_D^{20}$ −168.0 (0.50, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ=1.27–1.45 (m, 3H), 1.40 (d, 3H, J=6.6 Hz), 1.58–1.70 (m, 2H), 1.83 (br s, 1H), 2.16 (d, 1H, J=11.4 Hz), 2.37 (br s, 1H), 2.54 (dd, 1H, J_1=13.8 Hz, J_2=3.9 Hz), 3.45 (d, 1H, J=13.8 Hz), 3.58–3.61 (m, 2H), 7.20–7.40 (m, 5H), 7.47–7.52 (m, 3H), 7.65–7.75 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=20.5, 23.6, 29.5, 34.8, 35.7, 42.4, 56.8, 62.5, 70.2, 125.4, 127.0, 127.5, 128.4, 129.2, 131.3, 144.0, 144.4 ppm. MS (ESI): m/z=340.1725 (calculated for $C_{21}H_{26}NOS^+$ ($[M+H]^+$) m/z=340.1730). IR (KBr): 699, 749, 1021, 1037, 1287, 1442, 1489, 2951, 3440 cm^{-1}.

3.2.9. Preparation of selenide.[4] PhSeCN (0.15 mL, 1.2 mmol) was added by a syringe to the solution of alcohol *exo*-(1*S*,3*R*,4*R*)-**2** (0.23 g, 1 mmol) in dry toluene (15 mL) under argon atmosphere. The mixture was cooled to 0 °C in an ice bath, and tributylphosphine (0.74 mL, 3 mmol) was injected to the stirred solution. The mixture was kept at room temperature for 20 h. After evaporation of solvent, chloroform (10 mL) was added to the reaction mixture, and it was washed with 10% aqueous NaOH, water and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and product (**4b**) was purified by column chromatography with hexane/ethyl acetate (9:1 v/v) as eluent (0.089 g, 24%).

*3.2.9.1. (1S,4S,5R)-2-[(S)-1-Phenylethyl]-4-phenylselenalyl-2-azabicyclo[3.2.1]octane (**4b**).* Yellow oil. $[\alpha]_D^{20}$ −80.3 (*c* 0.66, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.29–1.32 (d, 3H, J=6.64 Hz), 1.34–1.43 (m, 3H), 1.54–1.58 (m, 1H), 1.70–1.78 (m, 2H), 2.19–2.24 (m, 1H), 2.49–2.54 (m, 1H), 2.67–2.72 (m, 1H), 3.08–3.11 (m, 1H), 3.37 (q, 1H, J=6.65 Hz), 3.60 (t, 1H, J=4.78 Hz) 7.15–7.61 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ=21.6, 22.6, 30.1, 36.3, 40.3, 48.4, 50.1, 56.4, 62.4, 126.7, 127.1, 127.4, 128.3, 128.8, 131.6, 132.8, 134.4 ppm. ^{77}Se NMR: δ=382.7 ppm. HRMS (ESI): 372.1195 ($[M+H]^+$); for $(C_{21}H_{26}NSe)^+$ M=372.1232. IR (film) 692, 738, 1437, 1452, 1476, 1578, 2946, 3057 cm^{-1}.

Acknowledgements

The work was financed by a statutory activity subsidy from the Polish Ministry of Science and Higher Education for the Faculty of Chemistry of Wrocław University of Technology.

Supplementary data

Tables showing spectral assignments for 2-azabicyclo[3.2.1]octane derivatives together with an example of analysis of 2D NMR spectra and DFT optimized structures. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.028.

References and notes

1. *Privileged Chiral Ligands and Catalysts*; Zhou, Q., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2011.
2. (a) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781–6784; (b) Nakano, H.; Kumagai, N.; Kabuto, C.; Matsuzaki, H.; Hongo, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1233–1236; (c) Ekegren, J. K.; Modin, S. A.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **2002**, *13*, 447–449.
3. (a) Brandt, P.; Andersson, P. G. *Synlett* **2000**, 1092–1106; (b) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391–1401; (c) Lu, J.; Xu, Y.-H.; Liu, F.; Loh, T.-P. *Tetrahedron Lett.* **2008**, *49*, 6007–6008.
4. Wojaczyńska, E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2252–2257.
5. Wojaczyńska, E. *Tetrahedron: Asymmetry* **2011**, *21*, 161–166.
6. Pedrosa, R.; Andrés, J. M.; Manzano, R.; Rodríguez, P. *Eur. J. Org. Chem.* **2010**, 5310–5319.
7. (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382; (b) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
8. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100–2113.
9. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
10. Métro, T.-X.; Duthion, B.; Gomez Pardo, D.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89–102.
11. (a) Pfister, J. R. *Synthesis* **1984**, 969–970; (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267–6270.
12. Tymoshenko, D. O. *Arkivoc* **2011**, *i*, 329–345.
13. Mena, M.; Bonjoch, J.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930–5935.
14. Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442–4445.
15. Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830–3833.
16. (a) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935–1938; (b) Oxenford, S. J.; Moore, S. P.; Carbone, G.; Barker, G.; O'Brien, P.; Shipton, M. R.; Gilday, J.; Campos, K. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1563–1568.
17. Chong, H.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2080–2086.
18. Cutri, S.; Bonin, M.; Micouin, L.; Husson, H.-P.; Chiaroni, A. *J. Org. Chem.* **2003**, *68*, 2645–2651.
19. O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651.
20. (a) Wilken, J.; Kossenjans, M.; Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Liebigs Ann./Recl.* **1997**, *12*, 573–579; (b) Röper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1661–1664; (c) Ogier, L.; Turpin, F.; Baldwin, R. M.; Riché, F.; Law, H.; Innis, R. B.; Tamagnan, G. *J. Org. Chem.* **2002**, *67*, 3637–3642; (d) Timén, Å. S.; Fischer, A.; Somfai, P. *Chem. Commun.* **2003**, 1150–1151; (e) Timén, Å. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958–9963; (f) Verhelst, S. H. L.; Paez Martinez, B.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598–9603; (g) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901–903; (h) Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Tetrahedron* **2005**, *61*, 2075–2104.
21. Gayet, A.; Andersson, P. G. *Adv. Synth. Catal.* **2005**, *347*, 1242–1246.
22. Hata, T.; Sekine, M. *Chem. Lett.* **1974**, 837–838.
23. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
24. Dr. Robert Wieczorek is gratefully acknowledged for performing DFT calculations. All optimized structures are shown in Supplementary data.
25. (a) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304–307; (b) Silva, M. A.; Goodman, J. M. *Tetrahedron Lett.* **2005**, *46*, 2067–2069; (c) D'hooghe, M.; Catak, S.; Stanković, S.; Waroquier, M.; Kim, Y.; Ha, H.; Van Speybroeck, V.; De Kimpe, N. *Eur. J. Org. Chem.* **2010**, 4920–4931.