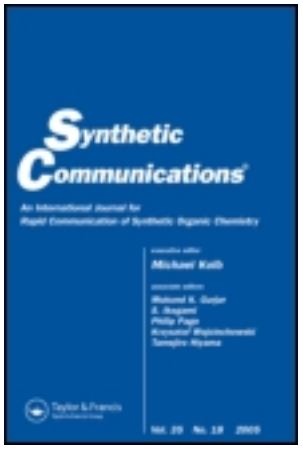

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IMPROVED SYNTHESIS OF MONOPROTECTED 5- AND 6-AMINO-2-AZANORBORNANES

Oleksandr P. Dacenko,[1] Olga V. Manoylenko,[1] Oleksandr O. Grygorenko,[1,2] Pavel K. Mykhailiuk,[1,2] Dmitriy M. Volochnyuk,[1] Oleg V. Shishkin,[3] and Andrey A. Tolmachev[1,2]

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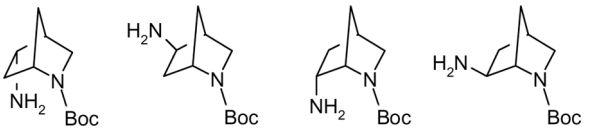
GRAPHICAL ABSTRACT



Abstract *An improved synthesis of Boc-monoprotected 5- and 6-amino-2-azanorbornanes is reported. The synthetic scheme consists of five steps and allows multigram quantities of the title compounds to be obtained. The regio- and stereochemistries of the products are established by two-dimensional NMR experiments.*

Keywords Bicyclic compounds; cycloadditions; diamines; molecular rigidity; peptidomimetics

INTRODUCTION

Aliphatic diamines provide privileged structural functionalities, exemplifying both molecular diversity and a wide scope of biologic properties for peptidomimetics, natural products, and many small molecules of importance to drug discovery.[1] Mounting the diamine moiety on a conformationally rigid scaffold us allows to obtain building blocks possessing well-defined spatial arrangements of amino groups, which could be beneficial for achieving optimal gain in substrate–receptor binding free energy. Examples of successful use of conformationally rigid

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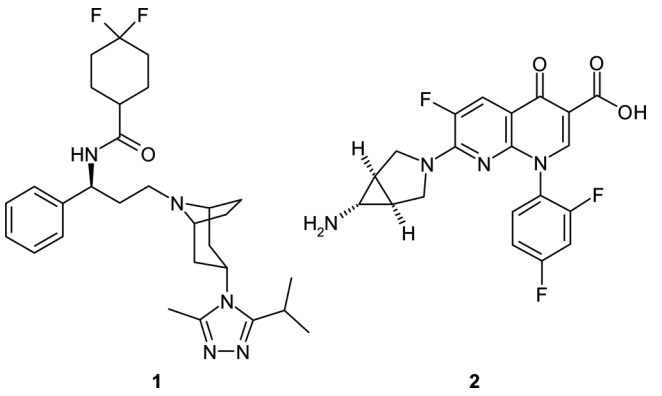


Figure 1. Marketed drugs—derivatives of bicyclic diamines.

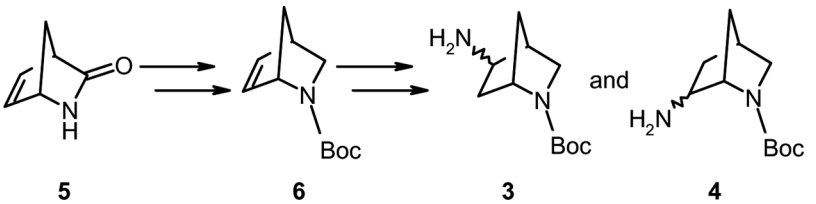
diamines in drug design include the CCR-5 antagonist for the treatment of HIV, maraviroc **1**,[2] and the antibiotic trovafloxacin **2**[3] (Fig. 1).

Recently, derivatives of 2-azanorbornane **3** and **4** were reported as conformationally rigid diamine scaffolds in the design of neurokinin receptor antagonists.[4] Ligands of this biological target are considered to be useful for the treatment or prevention of various disease states, including emesis, asthma, cardiac disorders, and neuronal injury.[5]

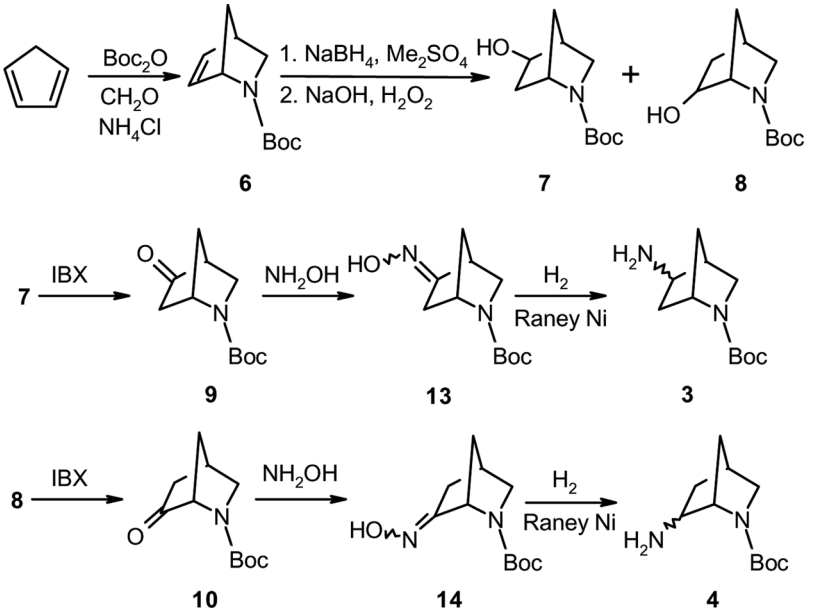
The scheme for the synthesis of compounds **3** and **4** described in the patent[4] commenced from hardly achievable precursor **5** (Scheme 1); moreover, toxic and environmentally unfriendly mercury salts were used at the corresponding steps of the procedure. Stereochemical outcome of the synthesis was not reported; moreover, the complete description of spectral and physical data of the novel compounds was not given.

RESULTS AND DISCUSSION

Unlike the method reported previously,[4] our approach to the synthesis of monoprotected diamines **3** and **4** includes the construction of azabicycloheptene precursor **6** by [4 + 2] cycloaddition (Scheme 2).[6] Transformation of alkene **6** into a mixture of alcohols **7** and **8** was achieved by a hydroboration–oxidation sequence.[7] Chromatographic separation of **7** and **8** appeared to be a rather efficient way to obtain multigram quantities of both isomers, even though the samples of **7** obtained were of only 81% purity.



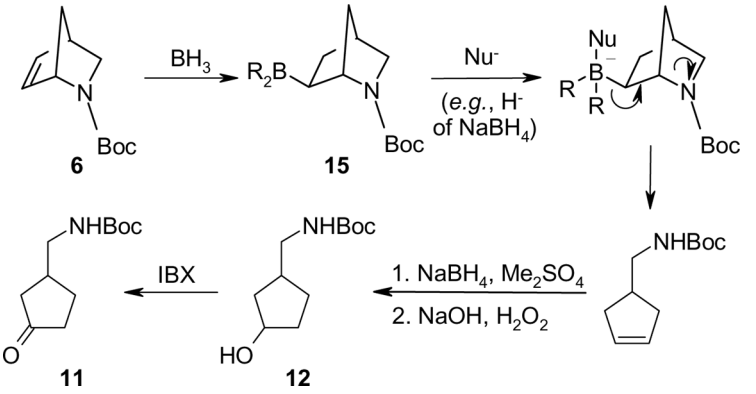
Scheme 1. Literature synthesis of **3** and **4**.



Scheme 2. Synthesis of diamines **3** and **4**.

Compounds **7** and **8** were oxidized to corresponding ketones **9** and **10** by 2-iodoxybenzoic acid (IBX), which appeared to give the greatest yields among other oxidizing reagents including dimethylsulfoxide–oxalyl chloride used by previous authors.[4] Regioisomers **9** and **10** were distinguished by two-dimensional (2D) NMR experiments. An unexpected by-product **11** was isolated in 12% yield from the reaction mixture obtained by oxidation of **7**. We assume that the fragmentation occurs at the hydroboration step, as the sample of **7** obtained after the chromatographic separation contains nearly 15% of a compound suspected to be an alcohol **12** based on gas chromatography–mass spectrometry (GS-MS) data. The detailed mechanism of the formation of the compound **12** is unclear; we propose the fragmentation of an intermediate borane **15** as a key step of the reaction (Scheme 3).[8–10]

The structure of **11** has been established by x-ray diffraction study (Fig. 2, Tables 1–3). The cyclopentane ring in the molecule of **11** adopts a twist conformation. The deviations of the C(3) and C(4) atoms from the mean plane of the remaining atoms of the ring are −0.20 Å and 0.39 Å, respectively. The substituent at the C(4) atom has an equatorial orientation [the C(2)–C(3)–C(4)–C(6) torsion angle is −163.6(3)°]. The carbamide group and the C(8) atom of *tert*-butyl substituent lie in the plane within 0.02 Å. The planar fragment of the substituent adopts in +*sc*-conformation relative to the C(3)–C(4) bond, and it is orthogonal to the C(4)–C(6) bond [the C(3)–C(4)–C(6)–N(1) and C(7)–N(1)–C(6)–C(4) torsion angles are 61.8(4)° and 96.4(3)°, respectively]. The molecule **11** exhibits *s-trans*-conformation with respect to the amide bond [C(6)–N(1)–C(7)–O(3) dihedral angle is −173.6(2)°] in the solid state. In contrast, both *s-trans*- and *s-cis*-conformations are observed in the solution [1:1 ratio of the conformers in dimethylsulfoxide (DMSO-*d*6) at 295 K]. The *tert*-butyl group is turned in such way that the C(8)–C(9) bond has *ap*-orientation



Scheme 3. Formation of compound **11**.

relative to the C(7)–O(3) bond. It can be assumed that such position of the *tert*-butyl group is caused by the weak C-H..O hydrogen bonds between two methyl substituents and carbonyl group: C(10)–H(10a)...O(2) H...O 2.35 Å C-H...O 117° and C(11)–H(11b)...O(2) H...O 2.43 Å C-H...O 118° (van der Waals radii sum[11] 2.87 Å).

Further transformations of the synthetic scheme included formation of oximes **13** and **14** and their subsequent catalytic hydrogenation, which led to the desired monoprotected amines **3** and **4**. Both compounds appeared to be mixtures of diastereomers **3a, 3b** (1.6:1) and **4a, 4b** (1.6:1), respectively. Samples of **3** and **4** were separated by chromatography to afford pure *exo*- and *endo*-isomers. Relative stereochemistry of the compounds **3** and **4** was assigned using 2D NMR experiments. First of all, assignments of the signals in ^{1}H NMR spectra of the compounds **3a,b** and **4a,b** were made using routine ^{1}H-^{1}H correlation spectroscopy (COSY) experiments. Then, nuclear overhauser effect spectroscopy (NOESY) spectra were recorded for all for isomers. The main criteria used to assign the stereochemistry of the diamine derivatives **3** and **4** were the correlations between the proton at 5(6)-CH and one of the protons at 7-CH_2, observed only in the case of *endo*-isomers **3a** and **4a**. Additional evidence of the regiochemistry of the compounds was also obtained; namely, correlations

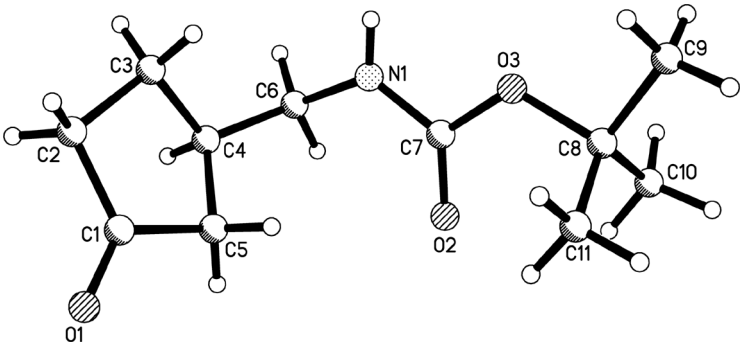


Figure 2. Molecular structure of compound **11**.

Table 1. Bond lengths (Å) in the molecule of **11**

Bond	Length
N(1)–C(7)	1.322(3)
O(1)–C(1)	1.226(4)
O(3)–C(7)	1.336(3)
C(1)–C(2)	1.465(5)
C(2)–C(3)	1.534(4)
C(4)–C(6)	1.510(3)
C(8)–C(10)	1.508(4)
C(8)–C(11)	1.517(4)
N(1)–C(6)	1.444(3)
O(2)–C(7)	1.214(3)
O(3)–C(8)	1.460(3)
C(1)–C(5)	1.492(5)
C(3)–C(4)	1.512(4)
C(4)–C(5)	1.520(3)
C(8)–C(9)	1.513(3)

between *endo*-protons at 3-CH_2 and 5-CH_2 were observed in the case of isomers **4a** and **4b** (Fig. 3)

In conclusion, the synthetic scheme described consists of four steps and results in 37% (**3**) and 25% (**4**) total yields of corresponding monoprotected diamines starting from compound **6**. The approach allows multigram quantities of the target compounds to be obtained.

Table 2. Bond angles (deg) in the molecule of **11**

Bond angle	Value
C(7)–N(1)–C(6)	122.4(2)
O(1)–C(1)–C(2)	126.1(4)
C(2)–C(1)–C(5)	110.2(3)
C(4)–C(3)–C(2)	103.9(3)
C(6)–C(4)–C(5)	115.2(3)
C(1)–C(5)–C(4)	104.0(3)
O(2)–C(7)–N(1)	125.1(3)
N(1)–C(7)–O(3)	111.2(2)
O(3)–C(8)–C(9)	102.0(2)
O(3)–C(8)–C(11)	110.0(2)
C(9)–C(8)–C(11)	110.6(4)
C(7)–O(3)–C(8)	121.1(2)
O(1)–C(1)–C(5)	123.7(4)
C(1)–C(2)–C(3)	104.6(3)
C(6)–C(4)–C(3)	114.4(3)
C(3)–C(4)–C(5)	103.3(3)
N(1)–C(6)–C(4)	117.1(2)
O(2)–C(7)–O(3)	123.6(3)
O(3)–C(8)–C(10)	110.6(2)
C(10)–C(8)–C(9)	111.4(3)
C(10)–C(8)–C(11)	111.9(3)

Table 3. Torsion angles (deg) in the molecule of **11**

Torsion angle	Value
O(1)-C(1)-C(2)-C(3)	172.3(4)
C(1)–C(2)–C(3)–C(4)	28.2(4)
C(2)–C(3)–C(4)–C(5)	−37.6(4)
C(2)–C(1)–C(5)–C(4)	−15.3(4)
C(3)–C(4)–C(5)–C(1)	32.5(3)
C(3)–C(4)–C(6)–N(1)	61.8(4)
C(6)–N(1)–C(7)–O(2)	−5.6(4)
C(8)–O(3)–C(7)–O(2)	−6.2(4)
C(7)–O(3)–C(8)–C(10)	62.3(4)
C(7)–O(3)–C(8)–C(11)	−61.8(4)
C(5)–C(1)–C(2)–C(3)	−7.9(5)
C(2)–C(3)–C(4)–C(6)	−163.6(3)
O(1)–C(1)–C(5)–C(4)	164.4(4)
C(6)–C(4)–C(5)–C(1)	158.0(3)
C(7)–N(1)–C(6)–C(4)	96.4(3)
C(5)–C(4)–C(6)–N(1)	−57.7(4)
C(6)–N(1)–C(7)–O(3)	173.6(2)
C(8)–O(3)–C(70–N(1)	174.6(2)
C(7)–O(3)–C(8)–C(9)	−179.2(3)

EXPERIMENTAL

Solvents were purified according to the standard procedures. All starting materials were purchased from Acros, Merck, and Fluka. Analytical thin-layer chromatography (TLC) was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H NMR, ^{13}C NMR, and all 2D NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) (^{1}H, ^{13}C) as an internal standard. Mass spectra (MS) were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization, CI) and Agilent 5890 series II 5972 GC-MS instrument (electron impact ionization, EI). Elemental analyses were performed on Elementar Vario Micro Cube CHNS/O analyzer.

5-Hydroxy-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (7)

A solution of **6** (180 g) in tetrahydrofuran (THF, 750 mL) and finely powdered sodium borohydride (28.5 g) were placed into a three-necked flask equipped with a dropping funnel, a thermometer, and inert gas inlet under a nitrogen atmosphere. After stirring for 10 min, the mixture was warmed to 30 °C, and a solution of dimethylsulfate (95 g) in THF (200 ml) was added dropwise at 30–40 °C. The resulting mixture was stirred for 3 h, then cooled to 5 °C and quenched by dropwise addition of water (30 ml). A solution of potassium hydroxide (31 g) in water (180 ml) was added at ambient temperature followed by 30% hydrogen peroxide (45 ml) (the temperature was kept lower than 30 °C). The mixture was stirred for additional 40 min and then

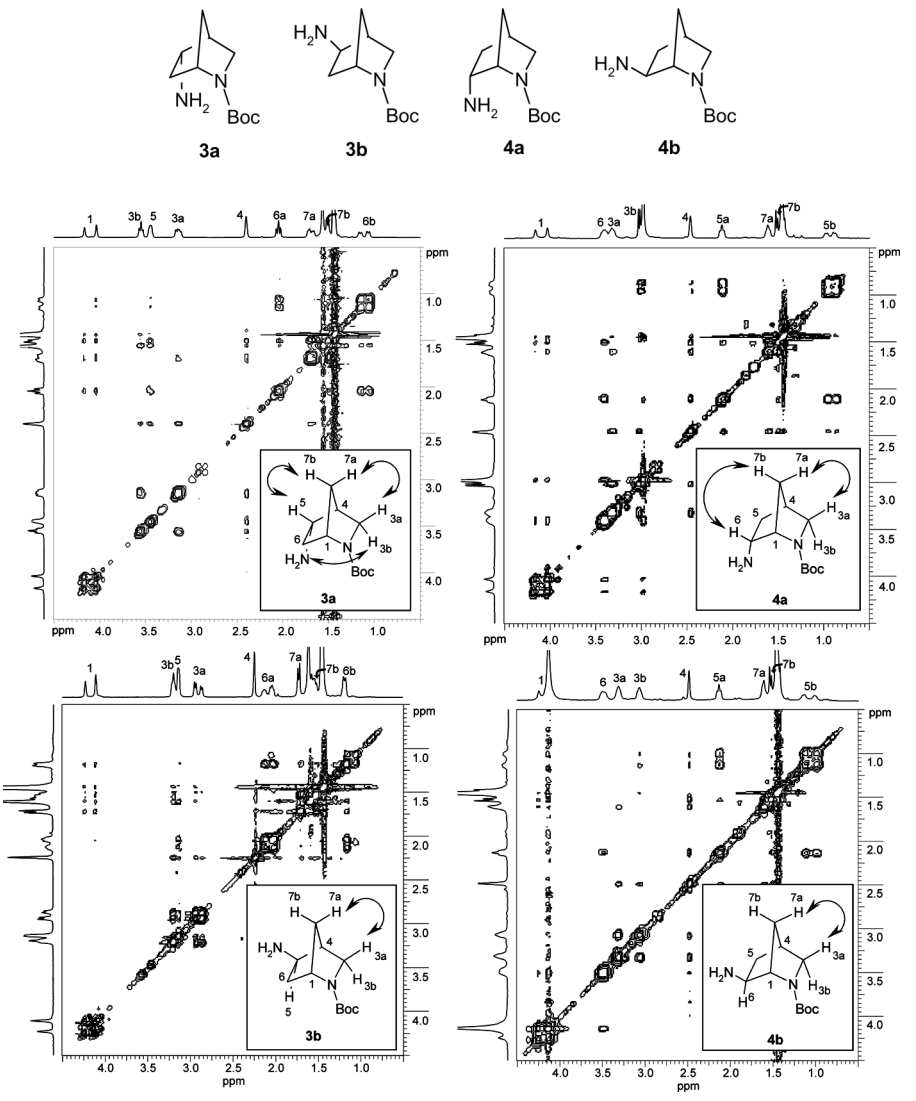


Figure 3. NOESY spectra of the compounds **3a**, **3b**, **4a**, and **4b**.

diluted with diethyl ether (1 L). The organic phase was separated, washed thoroughly with brine, dried over sodium sulfate, and evaporated in vacuo to give 175 g of a mixture of alcohols **7** and **8.** The latter was subjected to column chromatography on silica gel [benzene–hexane–acetonitrile (3:1:1) as an eluent; $R_f(\mathbf{7}) = 0.15$, $R_f(\mathbf{8}) = 0.18$)] to give **7** (11 g, 56%) and **8** (5.8 g, 30%) as colorless oils. A sample of **7** obtained by chromatography contained 81% of the title compound and 4% of its epimer [m/z 213 (M^+)], and 15% of alcohol **12** [m/z 159 ($M^+ - (CH_3)_2C{=}CH_2$) and 142 ($M^+ - (CH_3)_3CO$)]. The assumptions on the structure of the contaminants were made from GC-MS data and are not definitive. The compound was used in the next step without further purification. MS (m/z): 213 (M^+), 157, 112, 68, 57,

41. ^{1}H NMR (DMSO-*d*6, δ): 4.83 (s, 1H), 4.02 and 3.99 (2 s, 1H), 3.80 (s, 1H), 3.06 (m, 1H), 2.72 (d, J = 10.7 Hz, 1H), 2.30 (s, 1H), 1.83 (m, 1H), 1.68 (d, *J* = 10.1 Hz, 1H), 1.38 [s, 9H, (C*H*$_3$)$_3$CO], 1.26–1.45 (m, 2H). ^{13}C NMR (DMSO-*d*6, δ): 154.0 (*C*=O), 78.5 [*C*(CH$_3$)$_3$], 71.6 (5-*C*H), 56.2 and 55.2, 48.5 and 48.2, 45.1 and 44.5, 43.3 and 42.9, 34.1 and 33.6, 28.7 [C(*C*H$_3$)$_3$].

6-Hydroxy-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (8)

Compound **8** was obtained together with compound **7**. MS (*m*/*z*): 213 (M$^+$), 157, 112, 68, 57, 41. Anal. calcd. for $C_{11}H_{19}NO_3$: C, 62.01; H, 8.76; N, 6.49. Found: C, 61.87; H, 8.48; N, 6.29. ^{1}H NMR (DMSO-*d*6, δ): 4.94 (dd, *J* = 11.0 Hz and 3.1 Hz, 1H), 3.82 (s, 0.5H), 3.76 (s, 0.5H), 3.69 (s, 1H), 3.04 (d, *J* = 8.6 Hz, 0.5H, 3-C*H*H), 2.99 (d, *J* = 8.8 Hz, 0.5H, 3-C*H*H), 2.69 (d, *J* = 9.0 Hz, 1H, 3-CH*H*), 2.43 (s, 1H, 4-C*H*), 1.69 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 1.40 [s, 4.5H, (C*H*$_3$)$_3$CO], 1.38 [s, 4.5H, (C*H*$_3$)$_3$CO], 1.28 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (DMSO-*d*6, δ): 154.0 and 153.8 (*C*=O), 78.6 and 78.5 [(CH$_3$)$_3$*C*O], 71.7 and 71.4 (6-*C*H), 61.4 and 60.4 (1-*C*), 52.0 and 51.6 (3-*C*H$_2$), 39.8 and 39.7 (*C*H$_2$), 36.0 and 35.4 (4-*C*H), 33.7 and 33.1 (*C*H$_2$), 28.7 and 28.6 [*C*H$_3$)$_3$CO].

5-Oxo-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (9)

Toluene (300 ml) and 2-iodoxybenzoic acid (43 g) were added to a solution of crude alcohol **7** (24 g, 113 mmol) in dimethylsufoxide (130 ml). The resulting mixture was warmed to 60 °C over 3 h (TLC control), cooled, poured into saturated aqueous sodium carbonate (200 ml), and filtered. The filtrate was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed [benzene–hexane–acetonitrile (3:1:1) as an eluent] to give ketone **9** (17.1 g, 81 mmol, 72%) and compound **11** (3.0 g, 14 mmol, 12%). White solid, mp 96 °C. MS *(m/z)*: 211 (M$^+$), 155, 138, 68, 57. Anal. calcd. for $C_{11}H_{17}NO_3$: C, 62.54%; H, 8.11%; N, 6.63%. Found: C, 62.28%; H, 7.93%; N, 6.68%. ^{1}H NMR (DMSO-*d*6, δ): 4.01 (s, 0.4H, 1H, 1-*C*H), 3.95 (s, 0.6H, 1H, 1-C*H*), 3.32 (m, 1H), 3.07 (m, 1H), 2.78 (s, 1H, 4-C*H*), 2.23 (m, 1H), 1.97 (m, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.38 [s, 9H, (C*H*$_3$)$_3$CO]. ^{13}C NMR (DMSO-*d*6, δ): 206.4 and 205.9 (5-*C*=O), 154.0 and 153.5 (N*C*=O), 79.6 [(CH$_3$)$_3$*C*O], 62.6 and 61.6, 51.0 and 50.6, 41.6, 36.2 and 35.8, 34.9 and 34.2, 28.5.

6-Oxo-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (10)

Compound **10** was prepared in 97% yield (25 g) from compound **8** analogously to **9**. White solid, mp 84 °C. MS (*m*/*z*): 211 (M$^+$), 183, 127, 68, 57. Anal. calcd. for $C_{11}H_{17}NO_3$: C, 62.54%; H, 8.11%; N, 6.63%. Found: C, 62.50%; H, 8.02%; N, 6.89%. ^{1}H NMR (DMSO-*d*6, δ): 4.44 (s, 0.5H, 1-C*H*), 4.40 (s, 0.5H, 1-C*H*), 3.37 (m, 1H, *exo*-3-C*H*H), 3.13 (m, 1H, *endo*-3-CH*H*), 2.82 (4-C*H*), 2.27 (m, 1H, *exo*-5-C*H*H), 2.06 (m, 1H, *endo*-5-CH*H*), 1.99 (m, 2H, 7-C*H*$_2$), 1.41 [s, 9H,

(CH_3)$_3$CO]. ^{13}C NMR (DMSO-*d*6, δ): 213.9 and 213.7 (6-*C*=O), 154.0 and 153.8 (N*C*=O), 79.3 [(CH_3)$_3$*C*O], 56.6 and 55.7, 50.8 and 50.2, 47.9 and 47.6, 45.9 and 45.6, 37.4 and 36.9, 28.6 [(*C*H$_3$)$_3$CO], 28.8 and 27.8.

tert-Butyl [(3-Oxocyclopentyl)methyl]carbamate (11)

Compound **11** was obtained together with compound **9**. White solid, mp 80 °C. MS (*m*/*z*): 157 [M^+ – (CH_3)$_2$C=CH_2], 140 [M^+ – (CH_3)$_3$CO], 96, 83, 57 [(CH_3)$_3$C$^+$]. Anal. calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.68; H, 9.13; N, 6.31. ^{1}H NMR (DMSO-*d*6, δ): 6.94 (br. s, 1H, N*H*), 2.96 (m, 2H, C*H*$_2$NHBoc), 2.05–2.30 (m, 4H), 1.95 (m, 1H), 1.85 (d, $J = 8.7$ Hz, 0.5H), 1.81 (d, $J = 8.3$ Hz, 0.5H), 1.52 (m, 1H), 1.37 [s, 9H, C(C*H*$_3$)$_3$]. ^{13}C NMR (DMSO-*d*6, δ): 218.7 (*C*=O), 156.2 (N*C*=O), 78.0 [*C*(CH_3)$_3$], 44.4, 46.2, 37.9, 37.2, 28.7 [C(C*H*$_3$)$_3$], 26.7.

5-Oximino-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (13)

Triethylamine (16 ml, 0.115 mol) and hydroxylamine hydrochloride (6.9 g, 99 mmol) were added to a solution of ketone **9** (15 g, 71 mmol) in ethanol. The resulting mixture was refluxed for 2 h, then cooled and evaporated in vacuo. The residue was triturated with water, filtered, and dried to give oxime **13** in almost quantitative yield as a white solid, which was used in the next step without further purification. MS (*m*/*z*, CI): 227 (MH^+). ^{1}H NMR (DMSO-*d*6, δ): 10.40 (s, 0.2H, NO*H*), 10.32 (s, 0.8H, NO*H*), 4.28 and 4.25 (2 s, 1H, 1-C*H*), 3.31 (br. m, 1H), 3.05 (m, 2H), 2.25 (m, 2H), 1.79 (m, 1H), 1.66 and 1.64 (2 s, 1H), 1.40 [s, 9H, C(C*H*$_3$)$_3$]. ^{13}C NMR (DMSO-*d*6, δ): 161.0, 154.0 and 153.8, 79.0, 56.5 and 55.5, 51.3 and 51.0, 43.0 and 42.4, 38.6 and 38.2, 36.5 and 35.8, 28.6.

6-Oximino-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (14)

Compound **14** was obtained in almost quantitative yield from compound **10** analogously to **13** as a white solid, which was used in the next step without further purification. MS (*m*/*z*, CI): 227 (MH^+). ^{1}H NMR (DMSO-*d*6, δ): 10.40 (s, 0.6H, NO*H*), 10.36 (s, 0.4H, NO*H*), 4.38 and 4.33 (2 s, 1H, 1-C*H*), 3.27 and 3.22 (2d, $J = 7.9$ Hz, 1H, 3-C*H*H), 2.94 and 2.91 (2d, $J = 7.9$ Hz, 1H, 3-CH*H*), 2.68 (s, 1H, 4-C*H*), 2.34 (s, 0.4H), 2.31 (s, 0.6H), 2.08 (s, 0.6H), 2.04 (s, 0.4H), 1.72 (d, $J = 8.5$ Hz, Hz, 0.6H), 1.67 (d, $J = 8.5$ Hz, 0.4H), 1.51 and 1.49 (2d, $J = 8.5$ Hz, 1H), 1.38 [s, 9H, C(C*H*$_3$)$_3$]. ^{13}C NMR (DMSO-*d*6, δ): 159.4 and 159.2, 154.0 and 153.3, 79.0, 59.2 and 58.0, 51.4 and 51.0, 38.4 and 38.0, 35.9 and 35.3, 32.4, 28.6.

5-Amino-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (3)

Oxime **13** was dissolved in 10% methanolic ammonia (300 ml) and hydrogenated over Raney nickel (3 g) at 40 bars at ambient temperature for 8 h. The reaction mixture was filtered over celite and evaporated in vacuo. The residue was dissolved in

dichloromethane, filtered, and evaporated again. The crude product was distilled (71 °C/0.1 mmHg) to afford amine **3** (13.8 g, 92%) as a colorless oil. The compound is a 1.6:1 mixture of diastereomers **3a** and **3b**, respectively. MS (*m/z*): 212 (M^+), 169, 156, 139, 113, 95, 82, 57, 41. A sample of **3** was subjected to flash chromatography (Combiflash Companion chromatograph, 12 g RediSep column, 2-propanol as an eluent, 30 ml/min flow, detection at 215 nm) to afford pure diastereomers **3a** and **3b**. *Endo*-isomer **3a** (eluted first): ^{1}H NMR ($CDCl_3$, δ): 4.14 (s, 0.5H, 1-C*H*), 4.01 (s, 0.5H, 1-C*H*), 3.52 (t, $J = 10.6$ Hz, 1H, *exo*-3-C*H*H), 3.41 (m, 1H, 5-C*H*), 3.13 (d, $J = 10.5$ Hz, 0.5H, *endo*-3-CH*H*), 3.09 (d, $J = 10.5$ Hz, 0.5H, 3-CH*H*), 2.37 (s, 1H, 4-C*H*), 2.02 (m, 1H, 6-C*H*H), 1.69 (d, $J = 10.0$ Hz, 0.5H, 7-C*H*H), 1.64 (d, $J = 9.6$ Hz, Hz, 0.5H, 7-C*H*H), 1.54 (s, 2H, NH_2), 1.48 (d, $J = 9.8$ Hz, 1H, 7-CH*H*), 1.41 (s, 9H, C(CH_3)$_3$), 1.12 (d, $J = 13.2$ Hz, 0.5H, 6-CH*H*), 1.04 (d, $J = 13.0$ Hz, 0.5H, 6-CH*H*). ^{13}C NMR ($CDCl_3$, δ): 154.4 and 154.2 (*C*=O), 79.1 and 79.0 [*C*(CH$_3$)$_3$], 57.9 and 56.9 (1-*C*H), 51.0 and 50.9 (5-*C*H), 45.0 and 44.5 (3-*C*H$_2$), 44.1 and 43.8 (4-*C*H), 41.3 and 41.4 (*C*H$_2$), 38.2 and 37.8 (CH$_2$), 28.7 [C(*C*H$_3$)$_3$]. *exo*-Isomer **3b** (eluted second): ^{1}H NMR ($CDCl_3$, δ): 4.20 (s, 0.5H, 1-C*H*), 4.08 (s, 0.5H, 1-C*H*), 3.17 (m, 1H, 3-C*H*H), 3.11 (m, 1H, 5-C*H*), 2.91 (d, $J = 10.0$ Hz, 0.5H, 3-CH*H*), 2.84 (d, $J = 9.8$ Hz, 0.5H, 3-CH*H*), 2.22 (s, 1H, 4-C*H*), 2.10 (m, 0.5H, 6-C*H*H), 2.01 (m, 0.5H, 6-C*H*H), 1.70 (d, $J = 10.3$ Hz, 1H, 7-C*H*H), 1.58 (s, 2H, NH_2), 1.53 (d, $J = 10.2$ Hz, 0.5H, 7-CH*H*), 1.50 (d, $J = 10.3$ Hz, 0.5H, 7-CH*H*), 1.42 [s, 9H, C(CH$_3$)$_3$], 1.16 (d, $J = 11.8$ Hz, 1H, 6-CH*H*). ^{13}C NMR ($CDCl_3$, δ): 154.6 and 154.3 (*C*=O), 79.1 and 79.0 [*C*(CH$_3$)$_3$], 56.7 and 55.7 (1-*C*H), 53.4 and 53.3 (6-*C*H), 50.4 and 49.9 (3-*C*H$_2$), 45.9 and 45.4 (4-*C*H), 42.9 and 42.7 (CH$_2$), 33.9 and 33.5 (CH$_2$), 28.6 [C(*C*H$_3$)$_3$].

6-Amino-2-aza-bicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (4)

Compound **4** was prepared in 87% yield (20 g) as a colorless oil from oxime **14** analogously to **3**. The compound is a 1.6:1 mixture of diastereomers **4a** and **4b**, respectively. Bp 73 °C/0.1 mmHg. MS (*m/z*): 212 (M^+), 169, 139, 68, 57, 41. A sample of **4** was subjected to flash chromatography (Combiflash Companion chromatograph, 12 g RediSep column, 2-propanol as an eluent, 30 ml/min flow, detection at 215 nm) to afford pure diastereomers **4a** and **4b**. *Endo*-isomer **4a** (eluted first): ^{1}H NMR ($CDCl_3$, δ): 4.14 (s, 0.5H, 1-C*H*), 4.01 (s, 0.5H, 1-C*H*), 3.39 (m, 1H, 6-C*H*), 3.30 (m, 1H, 3-C*H*H), 3.00 (d, $J = 9.5$ Hz, 1H, 3-CH*H*), 2.97 (s, 2H, NH_2), 2.44 (s, 1H, 4-C*H*), 2.10 (m, 1H, 5-C*H*H), 1.60 (m, 1H, 7-C*H*H), 1.50 (d, $J = 9.8$ Hz, Hz, 1H, 7-CH*H*), 1.44 [s, 9H, C(CH_3)$_3$], 0.95 (d, $J = 11.0$ Hz, 0.5H, 5-C*H*H), 0.86 (d, $J = 11.2$ Hz, 0.5H, 5-CH*H*). ^{13}C NMR ($CDCl_3$, δ): 155.7 (*C*=O), 79.6 [*C*(CH$_3$)$_3$], 61.8, 60.6, 55.2, 54.8, 53.8, 53.0, 37.8, 37.4, 37.3, 37.2, 37.1, 36.8, 36.7, 28.6 [C(*C*H$_3$)$_3$]. *Exo*-isomer **4b** (eluted second): ^{1}H NMR ($CDCl_3$, δ): 4.23 (s, 0.5H, 1-C*H*), 4.13 (br. s, 2H, NH_2), 4.10 (s, 0.5H, 1-C*H*), 3.50 (br. s, 0.5H, 6-C*H*), 3.46 (br. s, 0.5H, 6-C*H*), 3.30 (br. s, 1H, 3-C*H*H), 3.06 (br. s., 1H, 3-CH*H*), 2.47 (s, 1H, 4-C*H*), 2.12 (m, 1H, 5-C*H*H), 1.60 (m, 1H, 7-C*H*H), 1.52 (d, $J = 10.1$ Hz, 1H, 7-CH*H*), 1.44 [s, 9H, C(CH_3)$_3$], 1.12 (br. d, $J = 10.5$ Hz, 0.5H, 5-C*H*H), 0.99 (br. d, $J = 10.0$ Hz, 0.5H, 5-CH*H*). ^{13}C NMR ($CDCl_3$, δ): 155.7 (*C*=O), 79.9 [*C*(CH$_3$)$_3$], 61.2, 59.9, 54.8, 54.4, 53.7, 52.9, 37.7, 37.3, 37.1, 36.3, 35.4, 28.6 [C(*C*H$_3$)$_3$].

X-Ray Diffraction Study of 11

Crystals for x-ray diffraction studies were obtained by slow crystallization from benzene–hexane–acetonitrile (3:1:1) solution. The crystals of **11** ($C_{11}H_{19}NO_3$) are monoclinic. At 293 K, $a = 13.794(3)$ Å, $b = 9.567(2)$ Å, $c = 9.383(1)$ Å, $\beta = 93.06(2)^\circ$, $V = 1236.5(4)$ Å^3, $M_r = 213.27$, $Z = 4$, space group $P2_1/c$, $d_{calc} = 1.146\,g/cm^3$, $\mu(MoK_\alpha) = 0.083\,mm^{-1}$, $F(000) = 464$. Intensity of 6868 reflections (2144 independent, $R_{int} = 0.085$) were measured on an automatic Xcalibur 3 diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω scaning, $2\Theta_{max} = 50^\circ$).

The structure was solved by direct method using the Shelxtl package.[12] Positions of hydrogen atoms were located from electron-density difference maps and refined using a riding model with $U_{iso} = nU_{eq}$ ($n = 1.5$ for methyl groups and 1.2 for other hydrogen atoms), except for the atom involved in the N–H...O hydrogen bond, which was refined using the isotropic model. Full-matrix least-squares refinement against F^2 in anisotropic approximation for nonhydrogen atoms was converged to $wR_2 = 0.171$ for 2098 reflections ($R_1 = 0.064$ for 912 reflections with $F > 4\sigma(F)$, $S = 0.825$). Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request (deposition number CCDC 752271).

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REFERENCES

1. (a) Kotti, S. R. S. S.; Timmons, C.; Li, G. Vicinal diamino functionalities as privileged structural elements in biologically active compounds and exploitation of their synthetic chemistry. *Chem. Biol. Drug. Des.* **2006**, *67*, 101–114; (b) Shivanyuk, A. N.; Volochnyuk, D. M.; Komarov, I. V.; Nazarenko, K. G.; Radchenko, D. S.; Kostyuk, A.; Tolmachev, A. A. Conformationally restricted monoprotected diamines as scaffolds for design of biologically active compounds and peptidomimetics. *Chem. Today* **2007**, *25*, 12–12; (c) Lucet, D.; Le Gall, T.; Mioskowski, C. The chemistry of vicinal diamines. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627.
2. Levy, J. A. HIV pathogenesis: 25 years of progress and persistent challenges. *AIDS* **2009**, *23*, 147–160.
3. Gootz, T. D.; Zaniewski, R.; Haskell, S.; Schmieder, B.; Tankovic, J.; Girard, D.; Courvalin, P.; Polzer, R. J. Activity of the new fluoroquinolone trovafloxacin (CP-99,219) against DNA gyrase and topoisomerase IV mutants of *Streptococcus pneumoniae* selected in vitro. *Antimicrob. Agents Chemother*. **2006**, *40* (12), 2691–2697.
4. Blythin, D. J.; Chen, X.; Friary, R. J.; McCormick, K. D.; Piwinski, J. J.; Shih, N.-Y., Shue, H.-J. Piperazino derivatives as neurokinin antagonists. U.S. Patent 5968929, 1999.
5. Elliott, J.; Seward, E. M. Neurokinin receptor antagonists. *Exp. Opin. Therap. Pat.* **1997**, *7*, 43–54.
6. Bunnelle, W. H.; Daanen, J. F.; Ryther, K. B.; Schrimpf, M. R.; Dart, M. J.; Gelain, A.; Meyer, M. D.; Frost, J. M.; Anderson, D. J.; Buckley, M.; Curzon, P.; Cao, Y.-J.; Puttfarcken, P.; Searle, X.; Ji, J.; Putman, C. B.; Surowy, C.; Toma, L.; Barlocco, D. Structure–activity studies and analgesic efficacy of N-(3-pyridinyl)-bridged bicyclic

diamines, exceptionally potent agonists at nicotinic acetylcholine receptors. *J. Med. Chem.* **2007**, *50*, 3627–3644.
7. Mitch, C. H.; Quimby, S. J.; Reel, J. K.; Whitesitt, C. A. Heterocyclic compounds. PCT Int. Appl. WO 9740016, 1997.
8. Pasto, D. J.; Snyder Sr., R. Transfer reactions involving boron, X: The stereochemistry of eliminations involving 3-substituted organoboranes. *J. Org. Chem.* **1966**, *31*, 2777–2784.
9. Brown, H. C.; Keblys, K. A. Hydroboration, XXI: The reaction of unsaturated alkyl chlorides and *p*-toluenesulfonates with diborane and disiamylborane. *J. Am. Chem. Soc.* **1964**, *86*, 1791–1795.
10. Ley, S. V.; Antonello, A.; Balskus, E. P.; Booth, D. T.; Christensen, S. B.; Cleator, E.; Gold, H.; Högenauer, K.; Hünger, U.; Myers, R. M.; Oliver, S. F.; Simic, O.; Smith, M. D.; Søhoel, H.; Woolford, A. J. A. Synthesis of the thapsigargins. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12073–12078.
11. Zefirov, Y. V. Reduced intermolecular contacts and specific interactions in molecular crystals. *Crystallogr. Rep*. **1997**, *42*, 865–886.
12. Sheldrick, G. M. A short history of Shelx. *Acta Crystallogr., Sect. A* **2008**, *A64*, 112–122.