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Synthesis of Enantiomerically Pure 1,2-Diamine Derivatives of 7-Azabicyclo[2.2.1]heptane. New Leads as Glycosidase Inhibitors and Rigid Scaffolds for the Preparation of Peptide Analogues

Antonio J. Moreno-Vargas, Catherine Schütz, Rosario Scopelliti, and Pierre Vogel*

Institut de Chimie Moléculaire et Biologique de l'Ecole Polytechnique Fédérale de Lausanne, EPFL-BCH, CH-1015 Lausanne-Dorigny, Switzerland

pierre.vogel@epfl.ch

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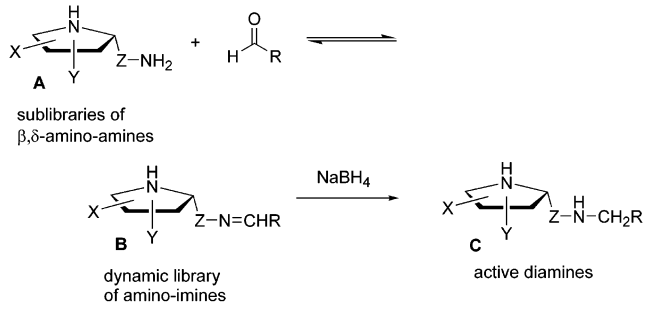
Enantiomerically pure alcohols (−)- and (+)-7-*tert*-butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-en-5-*endo*-ol ((−)-**11** and (+)-**11**) have been obtained from the Diels−Alder adduct of *N*-(*tert*-butoxycarbonyl)pyrroel and 2-bromo-1-*p*-toluenesulfonylacetylene, including a resolution method. These two alcohols were converted into (+)- and (−)-5-*exo*-amino-7-(*tert*-butoxycarbonyl)-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]heptane ((+)-**18** and (−)-**18**) and (+)- and (−)-5-*endo*-amino-7-(*tert*-butoxycarbonyl)-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]heptane ((+)-**19** and (−)-**19**) after adequate functionalization and desulfonylation steps. The corresponding conformationally constrained bicyclic 1,2-diamines (+)-**4**, (−)-**4**, (±)-**5**, (±)-**6**, (+)-**7**, and (−)-**7** were obtained from the protected precursors **18** and **19** and evaluated as glycosidase inhibitors. Diamines (+)-**4**, (−)-**4**, (+)-**6**, and (−)-**6** can be seen as new nonpeptide molecular scaffolds for the design of peptide analogues.

Introduction

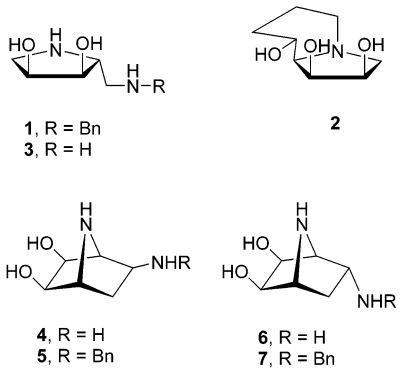
The search for better inhibitors implies the multistep synthesis of a large number of analogues and derivatives and their individual testing. In a recent report, we have shown that (5*R*,3*R*,4*S*)-3,4-dihydroxypyrrolidin-2-yl derivatives such as **1**, simpler synthetic analogues of swainsonine (**2**), are selective and promising α-mannosidase inhibitors.[1]

Previously, our group had found that diamine **3** and other 1,2- and 1,3-diamines of type **A** (Scheme 1) equilibrate rapidly with aldehydes to generate dynamic libraries[2] of imines of type **B** at low concentrations (<1 mM) and in the presence of glycosidases. There is a parallel between the inhibitory activities of the amino-imines **B** and those of the corresponding amino-amines **C** obtained by reduction. This led to the invention of an efficient combinatorial method for the discovery of glycosidase inhibitors.[3]



We now present the synthesis of bicyclic diamines **4**−**7** imitating diamines of type **A** (mannosidase inhibitors).

CHART 1



They are new members of the sublibrary of diamines that can be combined with aldehydes to generate dynamic libraries of glycosidase inhibitors. These bicyclic diamines are structurally related to calystegines, bicyclic alkaloids that possess a *nor*-tropane structure bearing hydroxyl groups varying in position and configuration. Like other

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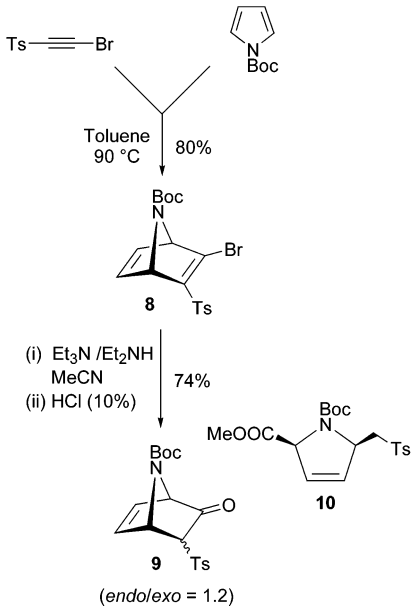
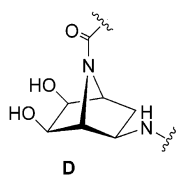
SCHEME 1



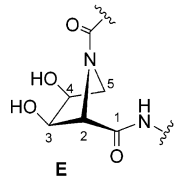
polyhydroxyalkaloids with structural resemblance to sugars, the calystegines exhibit strong and competitive glycosidase inhibitory activity.[4] Other bicyclic alkaloids with their nitrogen centers being bridgehead centers have been shown to have interesting properties as glycosidase inhibitors.[5] The effect of their rigidity on their glycosidase inhibitory activity will be evaluated here.

The incorporation into peptides of conformationally constrained amino acids has become extremely important, since it allows the creation of peptide analogues with valuable physical properties and biological activity.[6] Molecules containing the 7-azabicyclo[2.2.1]heptane ring systems have become popular synthetic targets, and several methods have been reported for their synthesis.[7] These molecules are particulary attractive, as they are rigid proline analogues and scaffolds allowing the construction of peptide chains into defined regions of space.[8] Insertion of these moieties in appropriates sites of small peptides produces specific three-dimensional structures required for binding to their receptors.[9] Templates of this kind may contain diamine[10] or diacid moieties[11] and have been used extensively to nucleate parallel β-sheet structures in peptides.

We consider the 5-amino-7-azabicycloheptane derivatives **4** and **6** to be promising nonpeptidic molecular scaffolds for the preparation of peptidomimetics. The *exo*-diamines (−)-**4** and (+)-**4** would make possible the design of reverse-turn peptide analogues as depicted with **D**. The latter have the structural elements of dihydroxyproline[12] (**E**) locked at 1,5-positions with a methylene bridge. The conformationally rigid and nonlinear architecture of the dihydroxyazanorbornane skeleton, apart from providing attractive models for protein folding studies,[13] may also prevent hydrophobic collapse[11c,14] of the peptide units in the bioactive conformation. Additionally, the presence of the hydroxyl groups can lead to enhanced stability of the secondary structure by hydrogen bonds between the hydroxyl groups and the peptide backbone, as it occurs with the collagen triple helix that is stabilized by the presence of hydroxyprolines.[15]



D



E

Results and Discussion

Synthesis of Racemic 5-Amino-7-azanorbornane Derivatives. The starting material for our study was the known *N*-protected 7-azabicyclo[2.2.1]hept-2,5-diene[16] **8**, which was obtained by Diels−Alder reaction between

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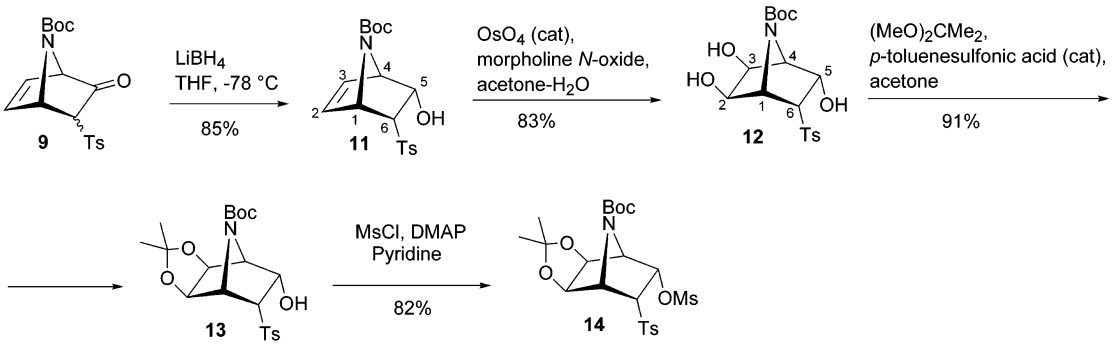
SCHEME 2



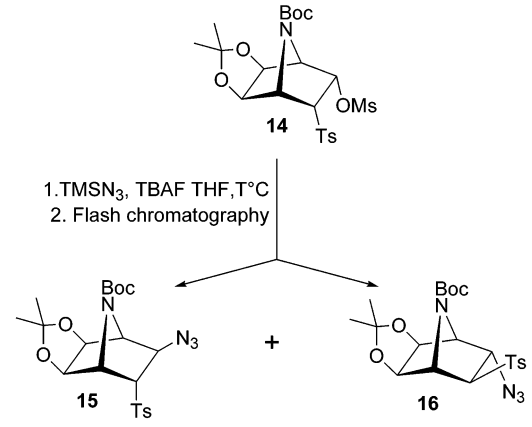
2-bromoethynyl *p*-tolyl sulfone and *N*-Boc-pyrrole in 80% yield, as described by Trudell and co-workers.[17] Treatment of adduct **8** with 1.1 equiv of diethylamine in the presence of 5 equiv of triethylamine in acetonitrile, followed by hydrolysis with 10% HCl, afforded the known[17] ketone **9** in 74% yield as a mixture of isomers (*endo*/*exo* = 1.2) (Scheme 1).

For the purification of compound **9** by chromatographic methods, no methanolic solvents should be used. When the mixture dichloromethane/methanol (60:1) was used as an eluent, 2,5-disubstituted 3-pyrroline **10** was obtained, almost quantitatively, as a result of the retro-Claisen cleavage (or retro-Dieckman reaction) that occurs under mild conditions (25 °C, MeOH, SiO_2). This is the consequence of the strain in bicyclic alkene **9**.[18]

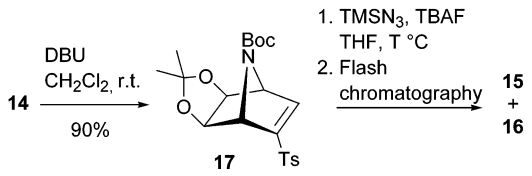
Desulfonylation of **9** employing aluminum−mercury amalgam gave the corresponding desulfonylated ketone in a very low yield (<10%). We thus reduced ketone **9** with $LiBH_4$ (−78 °C, THF). This gave exclusively the *endo*-alcohol **11**, the relative configuration of which was deduced unambiguously from its ^{1}H NMR spectrum (^3J (H-5endo, H-4) = 3.4 Hz, ^3J (H-6endo, H-1) = 3.6 Hz).[19] The stereospecifity of this reduction can be explained by involving first *endo*-epimerization of the tosyl group under basic conditions that then facilitates the *exo*-attack of hydride onto the ketone moiety. Stereoselective dihydroxylation of **11** followed by protection of the *exo*-diol group afforded **13** in 75% overall yield. Mesylation of the *endo*-alcohol of **13** yielded mesylate **14** (82%) (Scheme 2).

Reaction of **14** with Me_3SiN_3 in the presence of Bu_4NF in THF induced the expected S_N2 displacement of the mesylate by the azide anion, giving the *exo*-5-azido product **15**. The reaction is accompanied by the formation of minor amounts of the 5-*endo*-azido-6-*exo*-tosylsulfonyl isomer **16**. The product ratio **15**/**16** diminishes on increasing the temperature. These results can be interpreted in terms of two competitive processes: the desired S_N2 displacement of *endo*-mesylate **14** by the azide anion and the β-elimination of methanesulfonic acid from **14** induced by the basic medium (fluoride anion-induced E_{1cb} elimination) and producing intermediate alkene **17**. This

SCHEME 3



T (°C)	**15/16**	yield
25	5	63%
60	2.5	61%
75	2.1	48%



T (°C)	**15/16**	yield
25	4	68%
60	3.6	56%

product is obtained in 90% yield on treating **14** with DBU in CH_2Cl_2 at 25 °C. This product has been obtained already by Muchowski and co-workers following another route.[20] These authors had shown that **17** adds to oxygen nucleophiles giving mixtures of 5-*exo*-oxy-6-*endo*-tosyl and 5-*endo*-oxy-6-*exo*-tosyl-7-azabicyclo[2.2.1]heptane derivatives. When we treated **17** with Me_3SiN_3/Bu_4NF/THF at various temperatures, mixtures of **15** and **16** were obtained. The **15**:**16** ratios, however, differed from those obtained from **14** under identical conditions. This is consistent with the intervention of an S_N2 displacement process that is retarded less at lower temperatures than

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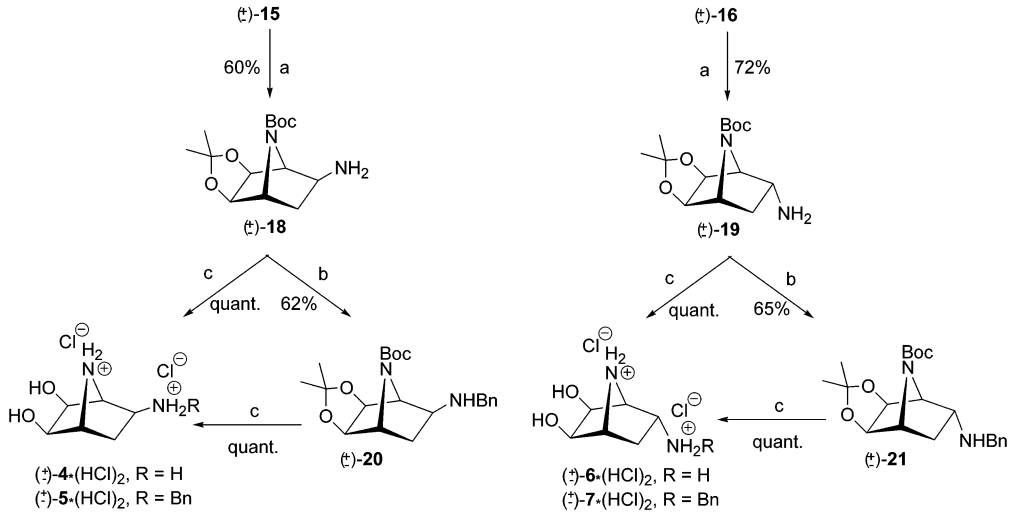
SCHEME 4[a]



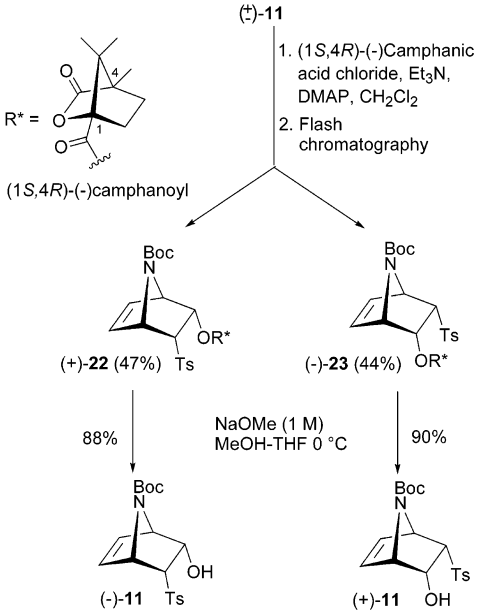
[a] Reagents and conditions: (a) (i) H_2, Pd/C (10%), MeOH; (ii) Na−Hg (5%), THF−MeOH, −15 °C. (b) PhCHO, $NaBH(OAc)_3$, 1,2-dichloroethane. (c) HCl (1 M)/THF (1:1), 80 °C, 6 h.

the elimination process (Scheme 3). The structures of **15** and **16** were deduced from their ^{1}H NMR data (Experimental Section).[19]

Catalytic hydrogenation of azides **15** and **16**, followed by desulfonylation[21] employing sodium−mercury amalgam (5%), led to the corresponding desulfonylated amines **18** and **19** in good-to-moderate yields. Benzylic derivatives **20** and **21** were obtained in good yields from amines **18** and **19**, respectively, by reductive amination with benzaldehyde using sodium triacetoxyborohydride.[22] Deprotection of compounds **18**, **19**, **20**, and **21** under acidic conditions afforded the corresponding unprotected dihydrochloride diamines **4**, **5**, **6**, and **7** quantitatively.

Obtaining Enantiomerically Pure 7-Azabicyclo-[2.2.1]heptane Derivatives. The ease by which we obtained alcohol **11** led us to examine the use of a resolution technique based on enzyme-catalyzed esterification.[23] Employing lipase from *Candida cylindracea* and from *Rhizopus oryzae* as catalysts afforded low enantioselectivity for the acetylations. We turned then to the formation of diastereomeric esters employing (−)-(1*S*,4*R*)-camphanic acid chloride as a resolving agent.[24] The reaction of (±)-**11** with 2 equiv of resolving agent gave a 1:1 mixture of diasteroisomeric esters **22** and **23** that was readly separated by flash column chromatography on silica gel. Removal of the chiral auxiliary from **22** and **23** was realized by treating **22** and **23** with a catalytic amount of NaOMe in MeOH−THF at 0 °C. This afforded the enantiomerically pure *β*-hydroxysulfones (−)-**11** ($[\alpha]_D$ −11.5 (*c* 1.0, CH_2Cl_2)) and (+)-**11** ($[\alpha]_D$ +11.8 (*c* 1.0, CH_2Cl_2)), respectively. Methanolysis under these conditions allowed complete recovery of the chiral auxiliary as methyl camphanate.

SCHEME 5



The syntheses of enantiomerically pure 5-amino-7-azabicyclo[2.2.1]heptanes (+)-**18**, (−)-**18**, (+)-**19**, and (−)-**19** were carried out starting from enantiomerically pure alcohols (−)-**11** and (+)-**11** following the procedure described for racemic mixtures (Scheme 6). We chose compound (−)-**14** for chemical correlation with the known[20] vinyl sulfone (+)-**17**. This allowed us to assign the absolute configuration of the series. The NMR data and [α] value of (+)-**17** were in agreement with those reported for this compound ($[\alpha]_D$ +13 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D$ +15 (*c* 1.0, $CHCl_3$)). Moreover, the absolute configuration of compound **23** was confirmed by X-ray diffraction.[25] Enantiomerically pure diamines (+)-**4**, (−)-**4**, (+)-**7**, and (−)-**7** were synthesized from enantiomerically pure precursors **18** and **19**, in good yields.

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(25) For the details of the X-ray structure of **23**, see Supporting Information.

SCHEME 6

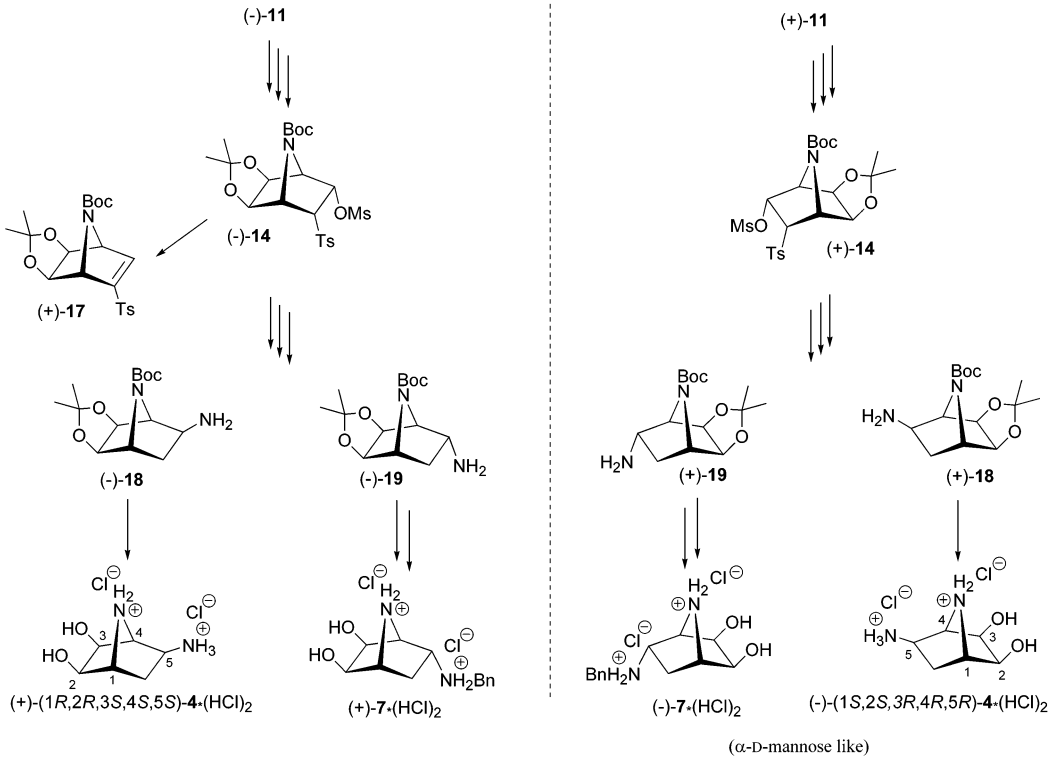

TABLE 1. Inhibitory Activities of 1,2-Diamines 1, 3, (−)-4, (−)-7 (with Configurations Related to That of α-D-Mannosides), 1,2-Diamines (+)-4, (+)-7 (with Configurations Related to that of α-L-Mannosides), and Racemic Analogs (±)-5 and (±)-6 at 1 mM Concentrations[a,b]

enzyme/inhibitor	**1**[c]	**3**[c]	(−)-**4**	(−)-**7**	(+)-**4**	(+)-**7**	(±)-**5**	(±)-**6**
			α-galactosidase					
from coffe beans	ni	ni	38%	ni	ni	ni	ni	ni
E. coli	ni	ni	ni	ni	ni	ni	28%	ni
			β-galactosidase					
from *E. coli*	24%	92%	51%	ni	ni	ni	ni	74%
Bovine liver	26%	ni	ni	65%	ni	90%	39%	ni
Jack beans	ni	76%	ni	54%	ni	ni	ni	50%
			α-glucosidase maltase					
from yeast	ni	84%	80% (168 *μ*M)[d]	ni	ni	33%	ni	54%
			α-glucosidase isomaltase					
from baker's yeast	ni	98%	71%	82%	ni	74%	ni	70%
			amyloglucosidase					
from *Rhizopus mold*	ni	ni	ni	ni	ni	ni	41%	ni
			β-glucosidase					
from almonds	68%	97%	ni	90% (87*μ*M) **K_i = 55 *μ*M** (C)	ni	89% (85*μ*M) **K_i = 117 *μ*M** (C)	74%	ni
Caldocellum saccharolyticum	ni	93%	37%	37%	30%	36%	ni	ni
			α-mannosidase					
from Jack beans	92% **K_i = 7.4 *μ*M** (C)	81% **K_i = 53 *μ*M** (C)	27%	ni	ni	25%	21%	ni

[a] IC_{50} (in parentheses) and K_i in *μ*M, when measured. Measured at optimal pH at 35 °C. For details of the measurements, see ref 26. [b] (C) = competitive inhibition (Lineweaver−Burk plots); ni = no inhibition. [c] See ref 1. [d] IC_{50} evaluated for racemic (±)-**4**.

Glycosidase Inhibition Assays. We tested compounds (+)-**4**, (−)-**4**, (±)-**5**, (±)-**6**, (+)-**7**, and (−)-**7** for their inhibitory activities toward 24 commercially available glycosidases. The data are summarized in Table 1 for two α-galactosidases, three *β*-galactosidases, two α-glucosidsases, one amyloglucosidase, two *β*-glucosidases, and one α-mannosidase. Unless indicated otherwise, these compounds did not show any inhibitory activity at 1 mM concentration toward the following enzymes: α-L-fucosidase from bovine epididymis, α-galactosidase from *Aspergillus niger*, *β*-galactosidases from *A. niger* and *Aspergillus orizae*, α-glucosidase from rice, amyloglucosidase from *A. niger*, α-mannosidase from almonds, *β*-mannosidase from *Helix pomatia*, *β*-xylosidase from *A. niger*, *β*-*N*-

acetylglucosaminidases from jack beans and from bovine epididymis A and B, and α-*N*-acetylgalactosaminidase from bovine liver.

Diamine (−)-**4** with the (1*S*,2*S*,3*R*,4*R*,5*R*)-configuration and its 5-*endo* isomer (**6**, not made enantiomerically pure) were designed to imitate (2*R*,3*R*,4*S*)-2-aminomethylpyrrolidine-3,4-diol (**3**), a moderate and competitive inhibitor of α-mannosidases[1] (Table 1). Diamine **3** is not a selective inhibitor, as it inhibits several other glycosidases more or less efficiently.[1] We now observe that this is also the case for (−)-**4**, which in fact is a weaker α-mannosidase inhibitor than **3**. We had shown[1] that upon benzylation of the primary amine moiety of **3**, which gives **1**, a more selective and more potent inhibitor of α-mannosidases is obtained. The benzylamino analogue of (−)-**4** is not a better inhibitor than (−)-**4**, as shown with the data obtained with (±)-**5** (Table 1). These results demonstrate that the change in conformation and increase of rigidity of the 7-azanorbornane (−)-**4** compared with **3** are detrimental to the α-mannosidase inhibitory activity. This is confirmed by the observation that the *endo*-benzylamino analogue (−)-**7** and the nonbenzylated diamine (±)-**6** do not inhibit α-mannosidase from jack beans and from almonds. It is now clear that systems **1** and **3** that possess a conformational greater freedom are much better leads for the search of α-mannosidase inhibitors than bicyclic analogues such as **4** and **6**.

Unexpectedly, both enantiomers of 5-*endo*-benzylamino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol (−)-**7** and (+)-**7** are good competitive inhibitors of *β*-glucosidase from almonds, with K_i = 55 and 117 μM, respectively. These diamines inhibit also, to a smaller extent, *β*-galactosidase from bovine liver (65 and 90%, respectively, at 1 mM concentration) and isomaltase from baker yeast (82 and 74%, respectively).

Conclusion

Making use of the pioneer works of Muchowski[20] and Trudell,[16,17] we have developed an efficient approach to the synthesis of enantiomerically pure 5-*exo* (**4**) and 5-*endo*-amino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol (**6**). Exploratory inhibition studies with 24 commercially available glycosidases have shown that both enantiomers of 5-*endo*-benzylamino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol ((−)-**7**, (+)-**7**) are competitive inhibitors of *β*-glucosidases from almonds, whereas their nonbenzylated analogues **6** are not. Diamines **4** and **6** are rigid analogues of 2-aminomethylpyrrolidine-3,4-diol (**3**). Contrary to (2*R*,3*R*,4*S*)-2-benzylaminomethylpyrrolidine-3,4-diol (**1**),[1] which is a good inhibitor of α-mannosidases, neither (−)-**7** nor (+)-**7** inhibit these enzymes, showing that the monocyclic mimics of D-mannosyl cation are recognized much better by α-mannosidase than puckered and more rigid systems. Both enantiomers of 5-*exo*- (**4**) and 5-*endo*-amino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol can be viewed as scaffolds for the construction of peptidomimetics and analogues with conformational constraints.

Experimental Section[27]

General Methods. Chemical shifts in ^{1}H and ^{13}C NMR spectra are reported in parts per million (*δ*) relative to the peaks for $CDCl_3$ (7.27 and 77.0, respectively), DMSO (2.50 and 39.5, respectively), and CD_3OD (3.34 and 49.9, respectively) as the internal standard. Coupling constants (*J*) in ^{1}H NMR spectra are reported in hertz.

(±)-(2*RS*,5*SR*)-Methyl-1-*tert*-butoxycarbonyl-5-(*p*-toluenesulfonyl)methyl-2,5-dihydropyrrol-2-carboxylate ((±)-10) (IUPAC: 1-*tert*-butyl 2-methyl (2*RS*,5*SR*)-5-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate). The crude of (±)-**9**,[17] coming from the precedent reaction where 26 mmol of (±)-**8** was used, was added to silica gel in a chromatographic column and eluted with 60:1 CH_2Cl_2/MeOH to give (±)-**10** (5.2 g, 52% overall yield) as an amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6, 353 K) *δ* 7.83 (d, 2 H, ^3J = 8.3), 7.50 (d, 2 H, ^3J = 8.3), 6.14 (dt, 1 H, ^3J = 6.3, 2.1, ^4J = 2.1), 5.92 (dt, 1 H, ^3J = 6.3, 2.1, ^4J = 2.1), 4.96 (q, 1 H, J = 2.1), 4.78 (m, 1 H), 4.58 (br s, 1 H), 3.94 (br d, 1 H, ^2J = 13.8), 3.68 (s, 3 H), 3.20 (dd, 1 H, ^2J = 13.8, ^3J = 10.4), 2.45 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K, mixture of rotamers) *δ* 171.0, 170.8, 153.0, 152.8,145.5, 145.2, 137.2,132.6, 132.5, 130.5, 130.4, 128.3, 125.9, 125.5, 81.8, 81.4, 66.7, 66.3, 61.1, 59.5, 59.7, 53.0, 52.8, 28.7, 28.6, 22.0; CIMS *m*/*z* 396 [3%, $(M + H)^+$]. Anal. Calcd for $C_{19}H_{25}NSO_6$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.44; H, 6.31; N, 3.54.

(±)-(1*SR*,4*RS*,5*SR*,6*RS*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-en-5-*endo*-ol ((±)-11) (IUPAC: *tert*-butyl (1*SR*,4*RS*,5*SR*,6*RS*)-5-hydroxy-6-[(4-methylphenyl)sulfonyl]-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate). To a solution of (±)-**9**[17] (890 mg, 2.45 mmol) in anhydrous THF (15 mL) at −78 °C was added a solution of $LiBH_4$ in THF (2 M, 2.45 mmol, 1.22 mL). The mixture was stirred for 15 min at −78 °C, and then a saturated aqueous solution of NH_4Cl was added and the mixture allowed to warm to 20 °C under stirring. The solution was diluted with AcOEt, washed with water and brine, and concentrated. The resulting residue was purified by column chromatography (Et_2O/light petroleum ether, 1:1) to give (±)-**11** (760 mg, 85%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6, 323 K) *δ* 7.80 (d, 2 H, ^3J = 8.3), 7.45 (d, 2 H, J = 8.3), 6.58 (dd, 1 H, ^3J = 5.7, 2.0), 6.47 (dd, 1 H, ^3J = 5.7, 2.2), 4.96 (br s, 1 H), 4.65 (m, 1 H, ^3J = 3.4, 7.4), 4.58 (m, 1 H), 4.42 (m, 1 H), 3.89 (dd, 1 H, ^3J = 7.4, 3.6), 2.43 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR (100.5 MHz, DMSO-d_6, 323 K) *δ* 152.6, 143.2, 137.3, 133.9, 133.5, 128.8, 127.3, 79.4, 70.1, 65.7, 63.6, 60.9, 27.0, 20.2; Anal. Calcd for $C_{18}H_{23}NSO_5$: C, 59.16; H, 6.34; N, 3.83; S, 8.77. Found: C, 59.17; H, 6.46; N, 3.88; S, 8.75.

(±)-(1*RS*,2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-2,3-*exo*-triol ((±)-12) (IUPAC: *tert*-butyl (1*RS*,2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)-2,3,5-trihydroxy-6-[(4-methylphenyl)sulfonyl]-7-azabicyclo[2.2.1]heptane-7-carboxylate). To a solution of (±)-**11** (646 mg, 1.77 mmol) in acetone/H_2O (9:1, 50 mL) were added NMO (363 mg, 2.66 mmol) and a solution of OsO_4 in CCl_4 (0.1 M, 0.8 mL). After stirring for 2 h, a saturated aqueous solution of $NaHSO_3$ was added. Then, the crude was extracted with AcOEt, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 40:1→20:1) to give (±)-**12** (640 mg, 83%) as a white solid: ^{1}H NMR (400 MHz, 323 K $CDCl_3$) *δ* 7.82 (d, 2 H, ^3J = 8.3), 7.38 (d, 2 H, ^3J = 8.3), 5.01 (d, 1 H, ^3J = 6.1), 4.68 (d, 1 H, ^3J = 6.1), 4.50 (m, 1 H,), 4.31 (m, 1 H), 4.27 (dd, 1 H, ^3J = 4.9, ^5J = 1.5), 3.74 (m, 1 H), 3.65 (br s, 1 H) 3.58 (dd, 1 H, ^3J = 9.4, 4.9), 2.49 (s, 3 H), 2.44 (br s, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 323 K) *δ* 155.6, 145.4, 137.2, 130.2, 127.9, 81.4, 69.4, 68.8, 68.3, 67.2, 64.7, 63.8, 28.1, 21.5; CIMS *m*/*z* 417 [50%, $(M + NH_4)^+$], *m*/*z* 400 [55%, $(M + H)^+$]. Anal. Calcd for $C_{18}H_{25}NSO_7$: C, 54.12; H, 6.31; N, 3.51; S, 8.77. Found: C, 54.15; H, 6.28; N, 3.59; S, 8.03.

(26) Appropriate *p*-nitrophenyl glycoside substrates buffered to optimum pH of the enzymes were used; for details, see: (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, B.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem*. **1995**, *60*, 6806. (b) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett*. **1994**, *1*, 1.

(27) For reasons of simplicity, IUPAC names have not been used systematically (see Scheme 2 for atom numbering) but are given in parentheses in this section.

(−)-(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-2,3-*exo*-triol ((−)-12). This compound was prepared in the manner described for (±)-**12** except that pure (−)-**11** was used. Yield: 80%. Mp 64−66 °C; $[\alpha]_D$ −5 (*c* 1.03, CH_2Cl_2).

(+)-(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-2,3-*exo*-triol ((+)-12). This compound was prepared in the manner described for (±)-**12** except that pure (+)-**11** was used. Yield: 82%. Mp 62−64 °C; $[\alpha]_D$ +5.6 (*c* 0.97, CH_2Cl_2).

(±)-(1*RS*,2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-ol ((±)-13) (IUPAC: *tert*-butyl (3a*RS*,4*SR*,5*RS*,6*SR*,7*RS*,7a*SR*)-5-hydroxy-2,2-dimethyl-6-[(4-methylphenyl)sulfonyl]hexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). A solution of (±)-**12** (743 mg, 1.68 mmol) in anhydrous acetone (15 mL) containing 2,2-dimethoxypropane (1 mL) and PTSA monohydrate (40 mg) was stirred at room temperature for 7−8 min. Then, a saturated aqueous solution of $NaHCO_3$ was added, and the crude was extracted with AcOEt, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 50:1) to give (±)-**13** (672 mg, 91%) as a white solid: mp > 180 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6, 323 K) δ 7.83 (d, 2 H, ^3J = 8.3), 7.47 (d, 2 H, ^3J = 8.3), 5.60 (d, 1 H, ^3J = 5.7), 5.20 (d, 1 H, ^3J = 5.6), 4.87 (d, 1 H, H-6), 4.39 (m, 1 H), 4.11 (dd, 1 H, ^5J = 1.2, ^3J = 5), 4.05 (m, 1 H), 3.95 (m, 1 H), 2.41 (s, 3 H), 1.35 (s, 9 H), 1.32, 1.27 (s each, 3 H each); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ 152.6, 144.3, 137.8, 129.8, 127.9, 109.5, 79.3, 76.5, 67.4, 63.5, 63.1, 60.8, 27.8, 25.4, 24.3, 20.9; CIMS *m*/*z* 457 [41%, $(M + NH_4)^+$], *m*/*z* 440 [55%, $(M + H)^+$]. Anal. Calcd for $C_{21}H_{29}NSO_7$: C, 57.39; H, 6.65; N, 3.19; S, 7.29. Found: C, 57.35; H, 6.70; N, 3.24; S, 7.30.

(−)-(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-ol ((−)-13). This compound was prepared in the manner described for (±)-**13** except that pure (−)-**12** was used. Yield: 84%. Mp > 180 °C dec; $[\alpha]_D$ −19.5 (*c* 0.975, CH_2Cl_2).

(+)-(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane-5-*endo*-ol ((+)-13). This compound was prepared in the manner described for (±)-**13** except that pure (+)-**12** was used. Yield: 82%. Mp > 180 °C dec; $[\alpha]_D$ +18.3 (*c* 1.145, CH_2Cl_2).

(±)-(1*RS*,2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-5-*endo*-methanosulfonyloxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((±)-14) (IUPAC: *tert*-butyl (3a*RS*,4*SR*,5*RS*,6*SR*,7*RS*,7a*SR*)-2,2-dimethyl-5-[(4-methylphenyl)sulfonyl]-6-[(methylsulfonyl)oxy]hexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). To a stirred solution of (±)-**13** (490 mg, 1.02 mmol) in anhydrous pyridine (5 mL) cooled at 0 °C were added MsCl (0.15 mL, 2.04 mmol) and a catalytic amount of DMAP. After the mixture was stirred for 12 h, a few drops of water were added, the mixture was stirred for 15 min and concentrated. The resulting residue was dissolved in CH_2Cl_2, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2/acetone, 50:1→40:1) to give (±)-**14** (431 mg, 82%) as a white solid: mp = 118−121 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 333 K) δ 7.86 (d, 2 H, ^3J = 8.3), 7.52 (d, 2 H, ^3J = 8.3), 5.23 (d, 1 H, ^3J = 5.4), 5.18, (dd, 1 H, ^3J = 5, 9.6), 4.77 (d, 1 H, ^3J = 5.4), 4.46 (dd, 1 H, ^5J = 1.2, ^3J = 5), 4.42 (dd, 1 H, ^3J = 4.6, 9.6), 4.16 (br d, 1 H, ^3J = 4.6), 3.11 (s, 3 H), 2.45 (s, 3 H), 1.39 (s, 9 H), 1.34, 1.26 (s each, 3 H each); ^{13}C NMR (100.5 MHz, DMSO-d_6, 333 K) δ 151.1, 144.4, 135.8, 129.2, 127.1, 109.4, 79.3, 75.9, 75.5, 71.2, 61.4, 59.5, 60.3, 36.5, 27.1, 24.5, 23.5, 20.2; CIMS *m*/*z* 535 [45%, $(M + NH_4)^+$]. Anal. Calcd for $C_{22}H_{31}NS_2O_9$: C, 51.05; H, 6.09; N, 2.71. Found: C, 50.69; H, 6.20; N, 2.90.

(−)-(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-5-*endo*-methano-sulfonyloxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((−)-14). This compound was prepared in the manner described for (±)-**14** except that pure (−)-**13** was used. Yield: 84%. Amorphous solid. $[\alpha]_D$ −1.0 (*c* 1.2, $CHCl_3$).

(+)-(1*R*,2*S*,3*R*,4*S*,5*R*,6*S*)-7-*tert*-Butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-5-*endo*-methano-sulfonyloxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((+)-14). This compound was prepared in the manner described for (±)-**14** except that pure (+)-**13** was used. Yield: 87%. Amorphous solid. $[\alpha]_D$ +1.1 (*c* 0.9, $CHCl_3$).

(±)-(1*SR*,2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-5-*exo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidene-dioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((±)-15) (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*RS*,6*SR*,7*SR*,7a*RS*)-2,2-dimethyl-5-[(4-methylphenyl)sulfonyl]-6-[(methylsulfonyl)oxy]hexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate) **and (±)-(1*SR*,2*RS*,3*SR*,4*SR*,5*SR*,6*RS*)-5-*endo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*exo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((±)-16)** (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*SR*,6*RS*,7*SR*,7a*RS*)-5-azido-2,2-dimethyl-6-[(4-methylphenyl)sulfonyl]hexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). Mesylate (±)-**14** (214 mg, 0.414 mmol) was dissolved at 25 °C in THF (6 mL). Trimethylsilyl azide (72 μL, 0.54 mmol) was added via syringe followed by a solution of TBAF in THF (1 M, 558 μL, 0.54 mmol). The solution was stirred for 30 min at 60 °C. Then, the mixture was concentrated and purified by column chromatography on silica gel (Et_2O/light petroleum ether, 1:2→1:1) to give first (±)-**15** (81 mg, 42%) and then (±)-**16** (34 mg, 17%) as white solids. **Data for (±)-15**: mp = 128−130 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) δ 7.88 (d, 2 H, ^3J = 8.3), 7.51 (d, 2 H, ^3J = 8.3), 4.96 (d, 1 H, ^3J = 5.4), 4.42 (d, 1 H, ^3J = 5.4), 4.36, (dd, 1 H, ^5J = 1.7, ^3J = 4.9), 4.23 (d, 1 H, ^5J = 1.7), 4.12 (d, 1 H, ^3J = 4.2), 3.71 (t, 1 H, ^3J = 4.6), 2.46 (s, 3 H), 1.40 (s, 9 H), 1.34, 1.23 (s each, 3 H each); ^{13}C NMR (100.5 MHz, DMSO-d_6, 363 K) δ 152.0, 144.5, 135.0, 129.1, 126.8, 110.2, 78.9, 77.7, 76.0, 67.8, 64.6, 59.3, 59.0, 26.9, 24.3, 23.5, 19.9; CIMS *m*/*z* 465 [30%, $(M + H)^+$]. Anal. Calcd for $C_{21}H_{28}N_4SO_6$: C, 54.30; H, 6.08; N, 12.06; S, 6.90. Found: C, 54.54; H, 6.00; N, 11.94; S, 6.75. **Data for (±)-16:** ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) δ 7.83 (d, 2 H, ^3J = 8.1), 7.50 (d, 2 H, ^3J = 8.1), 4.51 (d, 1 H, ^3J = 5.4), 4.45 (t, 1 H, ^3J = 5), 4.40 (d, 1 H, ^3J = 5.4), 4.37 (br s, 1 H), 4.28 (br s, 1 H), 3.33 (d, 1 H, ^3J = 4.7), 2.45 (s, 3 H), 1.39 (s, 9 H), 1.29, 1.21 (s each, 3 H each); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 153.4, 152.9, 146.3, 145.0, 134.5, 133.8, 130.8, 130.7, 129.8, 129.3, 112.4, 112.3, 82.2, 81.6, 81.2, 81.0, 78.3, 77.9, 69.4, 69.2, 61.7, 60.7, 61.0, 59.7, 59.6, 28.6, 25.5, 25.8, 24.9, 24.7, 22.1; CIMS *m*/*z* 465 [25%, $(M + H)^+$]. Anal. Calcd for $C_{21}H_{28}N_4SO_6$: C, 54.30; H, 6.08; N, 12.06. Found: C, 54.34; H, 6.24; N, 11.87.

(−)-(1*S*,2*R*,3*S*,4*S*,5*R*,6*S*)-5-*exo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((−)-15). This compound was prepared in the manner described for (±)-**15** except that pure (−)-**14** was used. Yield: 45%. Mp 107−109 °C; $[\alpha]_D$ −48 (*c* 1.1, $CHCl_3$).

(+)-(1*R*,2*S*,3*R*,4*R*,5*S*,6*R*)-5-*exo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((+)-15). This compound was prepared in the manner described for (±)-**15** except that pure (+)-**14** was used. Yield: 46%. Mp 110−112 °C; $[\alpha]_D$ +50 (*c* 1.1, $CHCl_3$).

(+)-(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-5-*endo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*exo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((+)-16). This compound was prepared in the manner described for (±)-**16** except that pure (−)-**14** was used. Amorphous solid. Yield: 15%. $[\alpha]_D$ +11.6 (*c* 1.06, $CHCl_3$).

(−)-(1*R*,2*S*,3*R*,4*R*,5*R*,6*S*)-5-*endo*-Azido-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-6-*exo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptane ((−)-16). This com-

pound was prepared in the manner described for (±)-**16** except that pure (+)-**14** was used. Yield: 13%. $[\alpha]_D$ −12.6 (*c* 0.8, $CHCl_3$).

(+)-(1*S*,2*R*,3*S*,4*R*)-7-*tert*-Butoxycarbonyl-6-*p*-toluenesulfonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-hept-5-ene ((+)-17)[20a] (IUPAC: *tert*-butyl (3a*R*,4*S*,7*R*,7a*S*)-2,2-dimethyl-5-[(4-methylphenyl)sulfonyl]-3a,4,7,7a-tetrahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). To a solution of (−)-**14** (110 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (3 mL) was added DBU (70 mL, 0.46 mmol), and the mixture was stirred for 15 min at room temperature. After this time, the solution was concentrated and the resulting residue purified by column chromatography on silica gel (Et_2O/light petroleoum ether, 1:2→1:1) to give (+)-**17** (83 mg, 90%) as a white foam.

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-*exo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((±)-18) (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*SR*,7*RS*,-7a*RS*)-5-amino-2,2-dimethylhexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). To a solution of azido compound (±)-**15** (98 mg, 0.21 mmol) in MeOH (6 mL) was added 10% Pd/C (15 mg), and the resulting suspension was hydrogenated at atmospheric pressure for 30 min. The solution was filtered (Celite), the filter cake was rinsed with methanol, and the combined filtrate was evaporated to provide 90 mg of crude. The residue was dissolved in THF (4 mL)−MeOH (4 mL) and cooled at −15 °C under N_2 atmosphere. Then, finely crushed 5% sodium amalgam (0.8 g, 2.08 mmol) was added in one portion. After 1 h and 30 min, the reaction mixture was filtered through Celite, concentrated in vacuo, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1→10:1) to give (±)-**18** (36 mg, 60% overall yield) as a colorless oil: ^{1}H NMR (600 MHz, DMSO-d_6, 333 K) δ 4.14 (d, 1 H, ^3J = 5.6), 4.08 (d, 1 H, ^3J = 5.6), 4.03 (dd, 1 H, ^3J = 5.5, ^5J = 1.1), 3.77 (br s, 1 H), 2.83 (dd, 1 H, ^3J = 7.5, 3.0), 1.56 (dd, 1 H, ^2J = 12.9, ^3J = 7.5), 1.41 (s, 9 H), 1.30, 1.19 (s each, 3 H each), 1.07 (m, 1 H); ^{13}C NMR (150 MHz, DMSO-d_6, 333 K) δ 154.1, 109.9, 80.7, 79.0, 77.7, 66.9, 57.3, 49.3, 35.0, 28.0, 25.3, 24.1; HREIMS *m*/*z* 284.1755, calcd for $C_{14}H_{24}N_2O_4$ 284.1736.

(−)-(1*R*,2*R*,3*S*,4*S*,5*S*)-5-*exo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((−)-18). This compound was prepared in the manner described for (±)-**18** except that pure (−)-**15** was used. Yield: 58%. Colorless oil. $[\alpha]_D$ −9.6 (*c* 1.4, $CHCl_3$).

(+)-(1*S*,2*S*,3*R*,4*R*,5*R*)-5-*exo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((+)-18). This compound was prepared in the manner described for (±)-**18** except that pure (+)-**15** was used. Yield: 60% yield. Colorless oil. $[\alpha]_D$ +9.5 (*c* 1.25, $CHCl_3$).

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-5-*endo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo-[2.2.1]heptane ((±)-19) (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*RS*,7*RS*,7a*RS*)-5-amino-2,2-dimethylhexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). This product was prepared in the manner described for (±)-**18** except that (±)-**16** was used as starting material. In this case, a column chromatography on silica gel (CH_2Cl_2/MeOH, 30:1→15:1) was used in the purification. Yield: 72%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 4.84 (m, 1 H), 4.23 (d, 1 H, ^3J = 5.6), 4.25, 4,15 (d each, 1 H, ^3J = 5.7), 4.19, 4.10 (d each, 1 H, ^3J = 4.2), 3.51 (dt, 1 H, ^3J = 10.3, 4.5), 2.18 (ddd, 1 H, ^2J = 12.7, ^3J = 10.3, 4.2), 1.46 (s, 9 H), 1.44, 1.25 (s each, 3 H each), 1.35 (br s, 2 H), 0.73 (dd, 1 H, ^2J = 12.7, ^3J = 4.5); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 155.0, 110.1, 81.9, 81.6, 79.5, 77.6, 77.2, 62.9, 62.0, 60.0, 59.1, 49.6, 49.2, 34.0, 33.9, 28.4, 25.7, 24.3; HREIMS *m*/*z* 284.1749, calcd for $C_{14}H_{24}N_2O_4$ 284.1736.

(−)-(1*R*,2*R*,3*S*,4*S*,5*R*)-5-*endo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((−)-19). This compound was prepared in the manner described for (±)-**19** except that pure (+)-**16** was used. Yield: 64%. Colorless oil. $[\alpha]_D$ −11.2 (*c* 1.3, $CHCl_3$).

(+)-(1*S*,2*S*,3*R*,4*R*,5*S*)-5-*endo*-Amino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((+)-19). This compound was prepared in the manner described for (±)-**19** except that pure (−)-**16** was used. Yield: 61%. $[\alpha]_D$ +10.7 (*c* 1.0, $CHCl_3$).

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-*exo*-Benzylamino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo-[2.2.1]heptane ((±)-20) (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*SR*,7*RS*,7a*RS*)-5-(benzylamino)-2,2-dimethylhexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). To a solution of (±)-**18** (17 mg, 0.06 mmol) in anhydrous 1,2-dichloroethane (1 mL) were added benzaldehyde (0.06 mmol, 6 μL) and $NaBH(OAc)_3$ (18 mg, 0.08 mmol). The mixture was stirred for 1 h at 25 °C. Then, a saturated aqueous solution of $NaHCO_3$ was added and the resulting solution was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 50:1→20:1) to give (±)-20 (14 mg, 63%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, mixture of rotamers) δ 7.34−7.24 (m, 5 H), 4.43, 4.30 (2s, 1 H, H-1), 4.38, 4.23 (2d, 1 H, ^3J = 5.4), 4.13−4.09 (m, 2 H), 3.91, 3.84 (2d, 1 H, ^2J = 12.8), 3.76 (d, 1 H, ^2J = 12.8), 2.74 (m, 1 H), 1.60 (dd, 1 H, ^2J = 13.2, ^3J = 5.6), 1.55 (br s, 1 H), 1.49 (s, 9 H), 1.45, 1.27 (2s, 2 × 3 H), 1.43−1.37 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, mixture of rotamers) δ 155.5, 139.6, 128.6, 128.5, 128.3, 128.2, 127.2, 127.1, 111.4, 81.9, 81.7, 80.2, 79.7, 62.2, 61.0, 58.1, 57.2, 55.9, 55.5, 51.5, 34.1, 33.6, 28.5, 25.7, 25.6, 24.4, 24.3; HREIMS *m*/*z* 374.2204, calcd for $C_{21}H_{30}N_2O_4$ 374.2206.

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-5-*endo*-Benzylamino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo-[2.2.1]heptane ((±)-21) (IUPAC: *tert*-butyl (3a*SR*,4*SR*,5*RS*,7*RS*,7a*RS*)-5-(benzylamino)-2,2-dimethylhexahydro-4,7-epimino-1,3-benzodioxole-8-carboxylate). This compound was prepared in the manner described for (±)-**20** except that (±)-**19** was used as starting material. Yield: 65%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) δ 7.34−7.21 (m, 5 H), 4.73 (d, 1 H, ^3J = 5.6), 4.19 (d, 1 H, ^3J = 5.6), 4.02 (d, 1 H, ^3J = 4.5), 3.99 (d, 1 H, ^3J = 5.9), 3.69 (s, 2 H), 3.05 (dt, 1 H, ^3J = 10.3, 4.5), 1.95 (ddd, 1 H, ^2J = 12.7, ^3J = 10.3, 5.9), 1.38 (s, 9 H), 1.32, 1.23 (2s, 2 × 3 H), 0.82 (dd, 1 H, ^2J = 12.7, ^3J = 4.5); ^{13}C NMR (100.5 MHz, DMSO-d_6, 363 K) δ 152.5, 139.0, 126.9, 126.8, 125.4, 108.2, 80.2, 77.2, 76.3, 59.9, 58.0, 54.5, 51.0, 30.5, 27.1, 24.6, 23.5; HREIMS *m*/*z* 374.2201, calcd for $C_{21}H_{30}N_2O_4$ 374.2206.

(−)-(1*R*,2*R*,3*S*,4*S*,5*R*)-5-*endo*-Benzylamino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo-[2.2.1]heptane ((−)-21). This compound was prepared in the manner described for (±)-**21** except that pure (−)-**19** was used. Yield: 60%. Colorless oil. $[\alpha]_D$ −9 (*c* 0.8, $CHCl_3$).

(+)-(1*S*,2*S*,3*R*,4*R*,5*S*)-5-*endo*-Benzylamino-7-*tert*-butoxycarbonyl-2,3-*exo*-isopropylidenedioxy-7-azabicyclo[2.2.1]-heptane ((+)-21). This compound was prepared in the manner described for (±)-**21** except that pure (+)-**19** was used. Yield: 56%. Colorless oil. $[\alpha]_D$ +8.2 (*c* 0.56, $CHCl_3$).

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-*exo*-Amino-7-azabicyclo-[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((±)-4·2HCl) (IUPAC: (1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-ammonio-2,3-dihydroxy-7-azoniabicyclo[2.2.1]heptane dichloride). Amine (±)-**18** (14 mg, 0.049 mmol) was dissolved in THF (0.5 mL)−HCl 1 M (0.5 mL), and the mixture was stirred at 80 °C for 6 h. The solvent was evaporated and the excess HCl removed in vacuo to give dihydrochloride of (±)-**4** (11 mg, 100%) as an amorphous white solid: ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 4.24 (br s, 1 H), 4.22 (d, 1 H, ^3J = 6.2), 4.18 (dd, 1 H, ^5J = 1.4, ^3J = 5.2), 4.15 (d, 1 H, ^3J = 6.2), 3.80 (dd, 1 H, ^3J = 8.8, 4.5), 2.38 (dd, 1 H, ^2J = 14.6, ^3J = 8.8), 2.21 (dt, 1 H, ^2J = 14.6, ^3J = 4.8); ^{13}C NMR (100.5 MHz, CD_3OD, 298 K) δ 72.7, 71.4, 69.7, 66.7, 49.5, 31.2; HRCIMS *m*/*z* 145.0974, calcd for $C_6H_{12}N_2O_2$ + H 145.0977.

(+)-(1*R*,2*R*,3*S*,4*S*,5*S*)-5-*exo*-Amino-7-azabicyclo[2.2.1]-heptane-2,3-*exo*-diol Dihydrochloride ((+)-4·2HCl). This compound was prepared in the manner described for (±)-**4**

except that pure (−)-**18** was used. Yield: 100%. Amorphous solid. $[\alpha]_D$ +7.6 (*c* 0.88, CH_3OH).

(−)-(1*S*,2*S*,3*R*,4*R*,5*R*)-5-*exo*-Amino-7-azabicyclo[2.2.1]-heptane-2,3-*exo*-diol Dihydrochloride ((−)-4·2HCl). This compound was prepared in the manner described for (±)-**4** except that pure (+)-**18** was used. Yield: 100%. Amorphous solid. $[\alpha]_D$ −7.3 (*c* 0.695, CH_3OH).

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-*exo*-Benzylamino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((±)-5·2HCl) (IUPAC: (1*RS*,2*RS*,3*SR*,4*SR*,5*SR*)-5-(benzylammonio)-2,3-dihydroxy-7-azoniabicyclo[2.2.1]heptane dichloride). This compound was prepared in the manner described for (±)-**4** except that amine (±)-**20** was used as starting material. Yield: 100%. Colorless oil. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 7.64 (m, 2 H), 7.49 (m, 3 H), 4.47 (s, 1 H), 4.37 (d, 1 H, ^2J = 12.9), 4.34 (d, 1 H, ^2J = 12.9), 4.22 (m, 2 H), 4.17 (d, 1 H, ^3J = 6.1), 3.90 (dd, 1 H, ^3J = 7.9, 5.5), 2.47−2.38 (m, 2 H); ^{13}C NMR (100.5 MHz, CD_3OD, 298 K) δ 131.9, 131.2, 130.9, 130.4, 71.8, 70.7, 67.4, 65.6, 55.5, 51.2, 29.4; HRCIMS *m*/*z* 235.1442, calcd for $C_{13}H_{18}N_2O_2$ + H 235.1446.

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-5-*endo*-Amino-7-azabicyclo-[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((±)-6·2HCl) (IUPAC: (1*R*,2*R*,3*S*,4*S*,5*R*)-5-ammonio-2,3-dihydroxy-7-azoniabicyclo[2.2.1]heptane dichloride). This compound was prepared in the manner described for (±)-**4** except that amine (±)-**19** was used as starting material. Yield: 100%. Amorphous solid. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 4.52 (d, 1 H, ^3J = 6.2), 4.30 (d, 1 H, ^3J = 6.2), 4.24 (dd, 1 H, ^5J = 1.4, ^3J = 4.6), 4.10 (d, 1 H, ^3J = 5.7), 3.92 (dt, 1 H, ^3J = 11.1, 5.0), 2.54 (ddd, 1 H, ^2J = 14.5, ^3J = 11.1, 5.7), 1.73 (dd, 1 H, ^2J = 14.5, ^3J = 5.0); ^{13}C NMR (100.5 MHz, CD_3OD, 298 K) δ 73.4, 68.7, 67.6, 67.5, 47.8, 28.7; HRCIMS *m*/*z*: 145.0976. Calcd. for $C_6H_{12}N_2O_2$ + H: 145.0977.

(±)-(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-5-*endo*-Benzylamino-7-azabicyclo[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((±)-7·2HCl) (IUPAC: (1*RS*,2*RS*,3*SR*,4*SR*,5*RS*)-5-(benzylammonio)-2,3-dihydroxy-7-azoniabicyclo[2.2.1]heptane dichloride). This compound was prepared in the manner described for (±)-**4** except that amine (±)-**21** was used as starting material. Yield: 100%. Colorless oil. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 7.62 (m, 2 H), 7.50 (m, 3 H, H-3 of Ph), 4.58 (d, 1 H, ^3J = 6.2), 4.41 (d, 1 H, ^2J = 13.0), 4.34 (d, 1 H, ^2J = 13.0), 4.32 (m, 2 H), 4.08 (d, 1 H, ^3J = 5.7), 3.92 (dt, 1 H, ^3J = 10.8, 5.1), 2.45 (ddd, 1 H, ^2J = 14.7, ^3J = 10.8, 5.7), 1.79 (dd, 1 H, ^2J = 14.7, ^3J = 5.3); ^{13}C NMR (100.5 MHz, CD_3OD, 298 K) δ 132.4, 132.1, 131.4, 73.4, 68.9, 67.3, 67.1, 54.4, 53.6, 27.8; HRCIMS *m*/*z* 235.1442, calcd for $C_{13}H_{18}N_2O_2$ + H 235.1446.

(+)-(1*R*,2*R*,3*S*,4*S*,5*R*)-5-*endo*-Benzylamino-7-azabicyclo-[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((+)-7·2HCl). This compound was prepared in the manner described for (±)-**7** except that pure (−)-**21** was used. Yield: 100%. Colorless oil. $[\alpha]_D$ −13.5 (*c* 0.665, CH_3OH).

(−)-(1*S*,2*S*,3*R*,4*R*,5*S*)-5-*endo*-Benzylamino-7-azabicyclo-[2.2.1]heptane-2,3-*exo*-diol Dihydrochloride ((−)-7·2HCl). This compound was prepared in the manner described for (±)-**7** except that pure (+)-**21** was used. Yield: 100%. Colorless oil. $[\alpha]_D$ +12.9 (*c* 0.315, CH_3OH).

(+)-(1*S*,4*R*,5*S*,6*R*)-7-*tert*-Butoxycarbonyl-5-*endo*-[(1*S*,4*R*)-camphanoyloxy]-6-endo-*p*-toluenesulfonyl-7-azabicyclo-[2.2.1]hept-2-ene ((+)-22) (IUPAC: *tert*-butyl (1*R*,4*S*,5*R*,6*S*)-5-[(4-methylphenyl)sulfonyl]-6-({[(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-1-yl]carbonyl}oxy)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate) **and (−)-(1*R*,4*S*,5*R*,6*S*)-7-*tert*-Butoxycarbonyl-5-*endo*-[(1*S*,4*R*)-camphanoyloxy]-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-ene ((−)-23)** (IUPAC: *tert*-butyl (1*S*,4*R*,5*S*,6*R*)-5-[(4-methylphenyl)sulfonyl]-6-({[(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]hept-1-yl]carbonyl}oxy)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate). To a cold (0 °C) solution of (±)-**11** (2.66 g, 7.24 mmol) in anhydrous CH_2Cl_2 (100 mL) were added Et_3N (2 mL, 14.46 mmol), (1*S*,4*R*)-(−)-camphanic acid chloride (3.16 g, 14.48 mmol), and a catalytic amount of DMAP. After stirring for 2 h at room temperature, a saturated aqueous solution of citric acid was added. The crude was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (light petroleum ether/AcOEt, 4:1→3:1) eluting first **22** (1.86 g, 47%) and second **23** (1.78 g, 44%), both as white solids. **Data for 22**: mp = 143.5−145 °C; $[\alpha]_D$ +25.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.79 (d, 2 H, ^3J = 7.9), 7.40 (d, 2 H, ^3J = 7.9), 6.77 (br s, 1 H), 6.45 (dd, ^3J = 5.7, 1.9), 5.89 (dd, 1 H, ^3J = 8.0, 4.2), 5.07 (br s, 1 H), 4.41 (br s, 1 H), 3.89 (dd, 1 H, ^3J = 8.0, 3.3), 2.47 (s, 3 H), 2.51−2.44 (m, 1 H), 2.06−2.03 (m, 1 H), 1.91−1.86 (m, 1 H), 1.70−1.63 (m, 1 H), 1.37 (s, 9 H), 1.13, 1.10, 1.03 (3s, 3 × 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) δ 178.5, 166.9, 154.3, 145.8, 137.4, 136.6, 133.5, 130.7, 128.3, 91.3, 82.3, 73.2, 65.9, 63.6, 62.1, 55.2, 54.7, 31.0. 29.3, 28.4, 22.1, 17.1, 17.0, 10.1. Anal. Calcd for $C_{28}H_{35}NSO_8$: C, 61.63; H, 6.46; N, 2.57. Found: C, 61.42; H, 6.45; N, 2.49. **Data for 23**: mp = 135−136 °C; $[\alpha]_D$ −38.7 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.77 (d, 2 H, ^3J = 8.2), 7.40 (d, 2 H, ^3J = 8.2), 6.83 (br s, 1 H), 6.46 (br d, 1 H), 5.91 (dd, 1 H, ^3J = 8.1, 4.0), 5.04 (br s, 1 H), 4.45 (br s, 1 H), 3.88 (dd, 1 H, ^3J = 8.1, 3.4), 2.64−2.57 (m, 1 H), 2.47 (s, 3 H), 2.09−2.03 (m, 1 H), 1.93−1.87 (m, 1 H), 1.70−1.64 (m, 1 H), 1.37 (s, 9 H), 1.10, 1.09, 0.99 (3s, 3 × 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) δ 178.2, 167.1, 154.3, 145.9, 137.5, 137.4, 133.2, 130.8, 128.3, 91.6, 82.4, 73.2, 65.8, 63.5, 62.1, 55.4, 54.6, 31.1, 29.5, 28.4, 22.1, 17.6, 17.5, 10.1. Anal. Calcd for $C_{28}H_{35}NSO_8$: C, 61.63; H, 6.46; N, 2.57. Found: C, 61.27; H, 6.50; N, 2.46.

(−)-(1*S*,4*R*,5*S*,6*R*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-en-5-*endo*-ol ((−)-11). To a solution of **22** (1.49 g, 2.58 mmol) in anhydrous 6:1 MeOH−THF (100 mL) cooled at 0 °C, a catalytic amount of NaOMe/MeOH (1 M) was added (pH = 8). The solution was stirred for 4 h at 0 °C under pH = 8 (adding NaOMe/MeOH (1 M) when it was necessary to maintain a constant pH). Then, Dowex resin was added until neutral pH was reached; the solution was filtered, and the filtrate was concentrated. The resulting residue was purified by chromatography column chromatography (AcOEt/light petroleum ether, 1:3) to give (−)-**7** (829 mg, 88%) as a white foam. $[\alpha]_D$ −11.5 (*c* 1.0, CH_2Cl_2).

(+)-(1*R*,4*S*,5*R*,6*S*)-7-*tert*-Butoxycarbonyl-6-*endo*-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-en-5-*endo*-ol ((+)-11). This compound was prepared in the manner described for (−)-**11** except that pure **23** (640 mg, 1.11 mmol) was used. Yield: 90%. White foam after purification by column chromatography on silica gel (AcOEt/light petroleum ether, 1:3). $[\alpha]_D$ +11.8 (*c* 1.0, CH_2Cl_2).

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Supporting Information Available: Crystal structure data for compound **23**, ^{1}H and ^{13}C NMR spectra, ^{1}H and ^{13}C NMR data with peak assignments, a complete list of α values, and IR data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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