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Asymmetric Synthesis of 3,4-Diaminocyclohexanol and *endo*-7-Azabicyclo[2.2.1]heptan-2-amine

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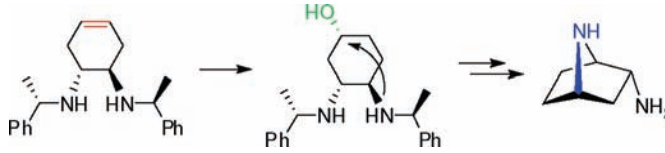
ABSTRACT



Hydroboration of (1*R*,2*R*)-bis[(*S*)-1-phenylethylamino]cyclohex-4-ene and its derivatives with several borane reagents gave diastereomeric mixtures of the 3,4-diaminocyclohexanol derivatives. Cyclization of the prevalent diastereomer with the *R* configuration of the newly formed stereocenter under Mitsunobu conditions, followed by reductive removal of the N-substituents, gave the optically pure *endo*-7-azabicyclo[2.2.1]heptane-2-amine.

The 7-azabicyclo[2.2.1]heptane skeleton is present in a variety of biologically and pharmacologically active compounds.[1] Chiral 7-azabicyclo[2.2.1]heptan-2-amines, *endo*-**1** and *exo*-**1** (Figure 1), are relatively unexplored compounds despite their usefulness as structural fragments of more complex, biologically and pharmacologically active molecules. Racemic *endo*-**1** was prepared in five steps starting from *N*-Boc-pyrrole exploiting a cycloaddition reaction with a 3-bromopropargylic ester to construct the bicyclic skeleton and Curtius rearrangement to form the 2-amino substituent. Then, introduction of the *endo*-7-azabicyclo[2.2.1]heptan-2-yl substituent at N^6 of adenosine under S_NAr conditions afforded a reasonably potent A_1 agonist **2a**, while the corresponding N^7-Boc-derivative **2b** was a highly potent A_1AR agonist.[2] The racemic compound **3**, prepared through the cycloaddition of *N*-Boc-pyrrole with an acetylenic sulfone followed by Michael addition of a benzylic amine, displayed potent activity against PM I, II, and IV. Further, the two enantiomers were resolved by preparative chiral HPLC, and the IC_{50} values of the (−)-enantiomer were 2-fold better than

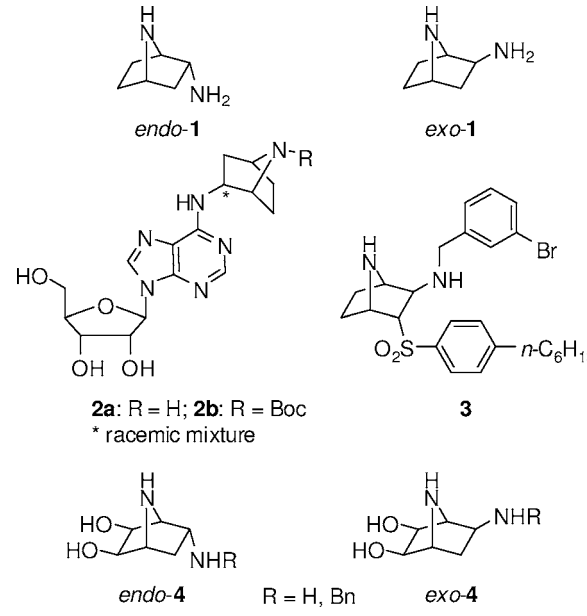


Figure 1. *Endo*- and *exo*-7-azabicyclo[2.2.1]heptan-2-amines and compounds containing these motifs.

(1) Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179–1193.
(2) Ashton, T. D.; Aumann, K. M.; Baker, S. P.; Schiesser, C. H.; Scammels, P. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6779–6784.

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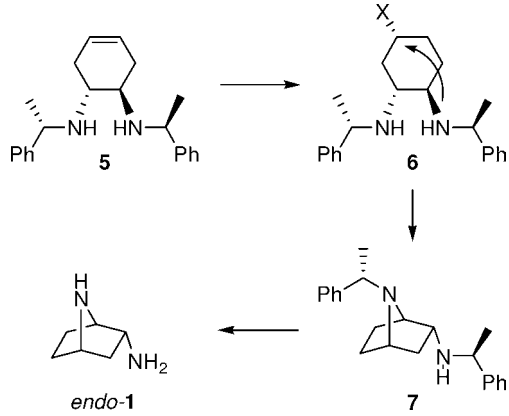
those of the racemate.[3] The analogous preparation of N^7- and C-substituted derivatives of *exo*-**1**, which were particularly active as α7 nicotinic acetylcholine receptors, was reported in a patent.[4] A longer sequence of steps, also including a cycloaddition step of *N*-Boc pyrrole and a resolution step, was necessary to prepare the dihydroxy derivatives *exo*- and *endo*-**4**, which were active as glycosidase inhibitors.[5]

These previously described routes led to racemic compounds which were resolved to the enantiomers, considerably reducing the yield of the desired optically pure compounds. Hence, we envisioned an alternative asymmetric synthesis of (+)- and (−)-*endo*-**1** starting from enantiomerically pure *trans*-1,2-diaminocyclohex-4-ene derivatives which are easily prepared in two steps from the glyoxal diimines derived from (*R*)- or (*S*)-1-phenylethanamine, e.g., **5** (Scheme 1).[6,7] Our

Scheme 1. Planned Route to *endo*-**1**



idea was to exploit the reactivity of the cyclohexene function to introduce a substituent with leaving group ability and the proper stereochemistry, as in structure **6**. This compound would undergo easy ring closure by nucleophilic displacement by the *trans*-disposed amino group to give the bicyclic compound **7**. Then, routine hydrogenolysis would afford the desired compound *endo*-**1**.

(3) (a) Hof, F.; Schütz, A.; Fäh, C.; Meyer, S.; Bur, D.; Liu, J.; Goldberg, D. E.; Diederich, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2138–2141. (b) Zürcher, M.; Gottschalk, T.; Meyer, S.; Bur, D.; Diederich, F. *ChemMedChem.* **2008**, *3*, 237–240.

(4) Wishka, D. G.; Walker, D. P.; Corbett, J. W.; Reitz, S. C.; Rauckhorst, M. R.; Groppi, V. E., Jr. Substituted 7-aza[2.2.1]bicycloheptanes for the treatment of deseases, EP 1 425 286 B1, 2004.

(5) Moreno-Vargas, A. J.; Schütz, C.; Scopelliti, R.; Vogel, P. *J. Org. Chem.* **2003**, *68*, 5632–5640.

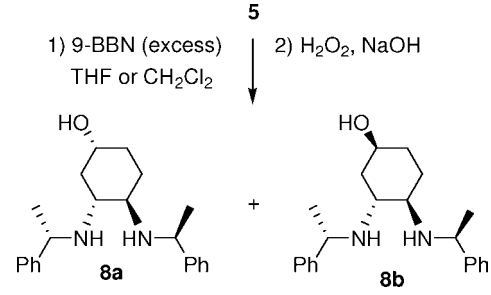
(6) Alvaro, G.; Grilli, S.; Martelli, G.; Savoia, D. *Eur. J. Org. Chem.* **1999**, 1523–1526.

(7) Racemic *trans*- and *cis*-1,2-diaminocyclohex-4-ene were used to prepare all the diastereomers of 4,5-diaminocyclohexan-1,2-diols: Witiak, D. T.; Rotella, D. P.; Filippi, J. A.; Gallucci, J. *J. Med. Chem.* **1987**, *30*, 1327–1336. Witiak, D. T.; Wei, Y. *J. Org. Chem.* **1991**, *56*, 5408–5417 *N*,*N*′-$(Boc)_2$-(*S*,*S*)-1,2-diaminocyclohex-4-ene was prepared by a long sequence of steps including the catalytic asymmetric ring opening of the *N*-(3,5-dinitro)benzoyl derivative of cyclohexa-1,4-diene monoaziridine: Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312–6313.

(8) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093–4095.

Our first attempt was to perform a hydroboration reaction on the diaminocyclohexene derivative **5** because the hydroboration of *N*,*N*′-bis[1(*S*)-phenylethyl]-4(*R*),5(*R*)-diaminoocta-1,7-diene, the precursor of **5**,[6] was previously described using 9-BBN.[8] In our hands, using freshly prepared 9-BBN (2.5 equiv), a partial conversion of the alkene function to give the alcohol **8** (ca. 20%, dr 3:1) was observed by ^{1}H NMR analysis of the crude product obtained after the usual treatment with H_2O_2−NaOH (Scheme 2). In further

Scheme 2. Preparation of N,N′-Disubstituted-3,4-diaminocyclohexanols **8a**,**b**

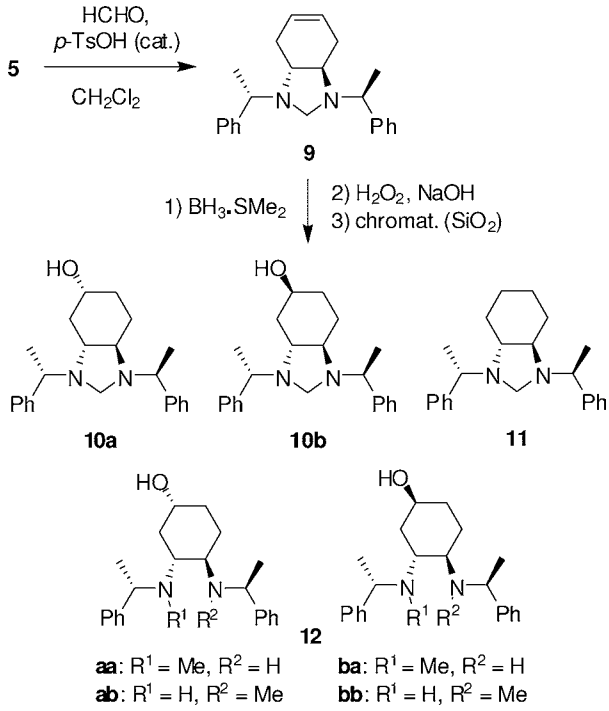


experiments carried out increasing progressively the amounts of 9-BBN up to 10 equiv, the conversion of **5** to the alcohol **8** (dr 75:25) progressively raised to 98%. The diastereoisomers **8a** and **8b** were obtained pure by column chromatography (SiO_2) in 62% and 18% yield, respectively. Fractions containing both diastereoisomers were also eluted (7%). The equatorial and axial dispositions of the OH substituent in the cyclohexane ring in **8a** and **8b**, respectively, were assessed by NMR studies and later confirmed by the outcomes of the subsequent ring closure step.

Other commercially available reagents, including BH_3•Et_3N, BH_3•PPh_3, catecholborane, and $BHBr_2$•SMe_2, proved ineffective. However, the use of BH_3•SMe_2 (3 equiv) allowed us to obtain a moderate conversion to the diaminocyclohexanols **8a** and **8b**. Increased amounts of the borane reagent, more forcing conditions for the oxidative step, and increased reaction times did not raise the yield of **8** over 50% (dr 65:35, determined by ^{1}H NMR analysis). The starting material was totally consumed, but other compounds were present in the crude mixture and were collected together in the first fractions eluted by column chromatography. They are presumably organoboron species, but their structure could not be determined.

Aiming to avoid formation of such boron−nitrogen species and, if possible, to increase the diastereoselectivity, we thought to protect the secondary amines of **5** by forming the aminal with formaldehyde, as this protection can be readily accomplished as well as removed (Scheme 3). Actually, the aminal **9** was quantitatively formed by reaction of **5** with an excess of paraformaldehyde in dichloromethane. Then, the hydroboration occurred smoothly using 2.5 equiv of BH_3•SMe_2 followed by oxidation. Column chromatography (SiO_2) afforded the inseparable mixture of **10a**,**b** in 70% yield (**10a**/**10b** = 60:40). Also eluted were the cyclohexane

Scheme 3. Hydroboration of the Aminal Derivative **9**



derivative **11** (20% yield) and a mixture of the four possible regio- and diastereoisomers of *N*-methyl derivatives **12** (10% overall). The latter compounds resulted from an unexpected cleavage/rearrangement of the aminal moiety. A similar but somewhat different rearrangement was reported for an aminoborane complex coming from the diborane reduction of benzooxazole and sulfur and selenium analogues.[9] Hydrolysis of the compounds **10a**,**b** dissolved in THF, with 2 N HCl at 80 °C for 5 h, finally gave the diaminoalcohols **8a**,**b** in 75% yield after column chromatography.

We also prepared the diaminocyclohexene ditosylate salt **13**, which was chosen for its solubility in organic solvents. Complete conversion of the starting material was observed yet when 6 equiv of BH_3•SMe_2 was used, whereas no byproduct or borane complexes were observed in the crude product after oxidation. The yield of the isolated mixture of **8a**,**b** was 75%; however, the dr was nearly 1:1 (Scheme 4).

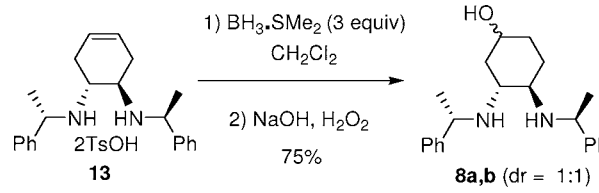
It should be underlined that the optically pure intermediates **8a**,**b** are valuable molecules, as oxygen-substituted diaminocyclohexanes are potent opioid analgesics, and have been heretofore prepared only as racemic compounds.[10]

The diastereoisomer **8a** had the correct configuration of the secondary alcohol allowing ring closure by the nucleophilic attack of the amino group present at the opposite C4 of the cyclohexane ring. In the past, only a few examples

(9) Knapp, K. K.; Keller, P. C.; Rund, J. V. *J. Chem. Soc., Chem. Commun.* **1978**, 971.

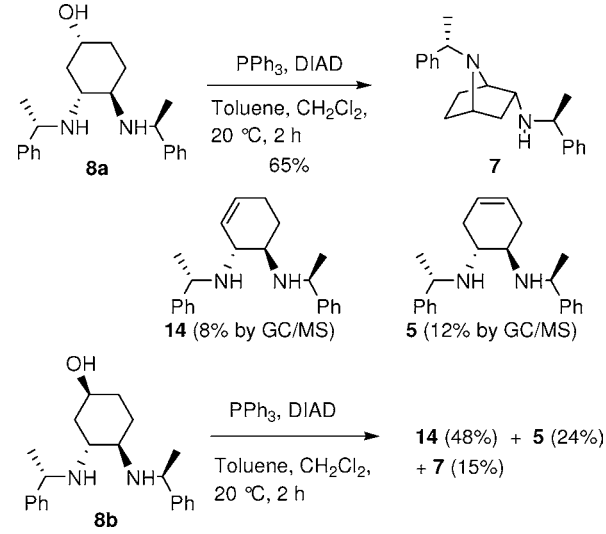
(10) (a) Clark, C. R.; Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Jarvis, T. C.; Rees, D. C.; Schofield, D. *J. Med. Chem.* **1988**, *31*, 831–836. (b) Halfpenny, P. R.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Rees, D. C. *J. Med. Chem.* **1990**, *33*, 286–291. (c) Schlichter, W. H.; Frahm, A. W. *Tetrahedron: Asymmetry* **1992**, *3*, 329–332.

Scheme 4. Hydroboration of the Ditosylate **13**



have been reported for the construction of the 7-azabicyclo-[2.2.1]heptane skeleton by Mitsunobu-type protocols.[1] Particularly, the cyclization of 4-benzylaminocyclohexanol was achieved by reaction with PPh_3/CCl_4,[11] and the PPh_3/DEAD system was employed in the total synthesis of epibatidine.[12] In our hands, the reaction of **8a** with PPh_3/DIAD in toluene occurred smoothly to give the desired bicyclic product **7** together with the cyclohexenes **5** and **14** in the relative ratio 80:12:8, as detected by GC-MS analysis (Scheme 5). The product **7** was isolated in 65% yield, and its structure was confirmed by NMR studies and NOE experiments.

Scheme 5. Synthesis of (−)-7-Azabicyclo[2.2.1]heptan-2-amine Bishydrochloride



Under the same conditions, the diastereoisomer **8b** was not completely consumed and was mainly converted to the cyclohexenes **5** (24%) and **14** (48%) after chromatographic separation, although minor amounts of the bicyclic compound **7** (15%) and unreacted **8b** (15%) were recovered. The different reactivity of **8b** with respect to **8a** is explained by the axial disposition of the OH group, which is prone to undergo dehydration by an *anti*-elimination mechanism.

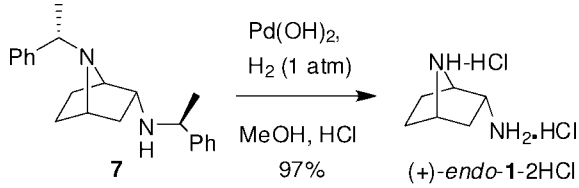
The final step to obtain the N,N′-unsubstituted *endo*-**7**-azabicyclo[2.2.1]heptan-2-amine **1** was the reductive removal

(11) Hassner, A.; Belostotskii, A. M. *Tetrahedron Lett.* **1995**, *36*, 1709–1712.

(12) Sestanj, K.; Melenski, E.; Jirkovsky, I. *Tetrahedron Lett.* **1994**, *35*, 5417–5420.

of the benzylic substituents by hydrogenation in the presence of palladium hydroxide in methanol in the presence of 2.5 equiv of HCl/MeOH. By this way, the dihydrochloride of (−)-*endo*-(1*R*,2*R*,4*S*)-**1** was obtained in 97% yield after simple filtration of the heterogeneous catalyst (Scheme 6).

Scheme 6. Synthesis of (+)-*endo*-7-Azabicyclo[2.2.1]heptane-2-amine Bishydrochloride



In conclusion, the first asymmetric synthesis of *endo*-2-amino-7-azabicyclo[2.2.1]heptane, *endo*-**1**, has been achieved through the hydroboration of the chiral 1,2-diaminocyclohex-4-ene **5** exploiting the asymmetric induction of (*S*)-1-phenylethylamine as the chiral auxiliary. 9-BBN is the reagent of choice to perform the hydroboration reaction directly on **5**, despite a large excess (10 equiv) of this reagent being required to achieve an almost complete conversion to the desired 3,4-diaminocyclohexanol **8**. This was obtained with a moderate diastereoselectivity in favor of equatorial alcohol **8a** which had the required configuration for the efficient cyclization to the bicyclic compound **7**. Although separation of the diastereoisomers **8a** and **8b** was achieved by column chromatography, ring closure by a Mitsunobu protocol would be conveniently achieved on the diastereoisomeric mixture **8a**,**b** because **8b** also partially underwent cyclization to **7**, which was easily separated from unreacted **8b** and byproducts (cyclohexenes).

It is noteworthy that both enantiomers of *endo*-7-azabicyclo[2.2.1]heptane-2-amine **1** are available by the described route since the chiral auxiliary that was removed from **7** by routine hydrogenolysis is commercially available in either *S* or *R* configurations.

Further transformations of the diaminocyclohexene **5**, e.g., by epoxidation and *cis*-dihydroxylation of the C═C bond, are currently investigated in our laboratory.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copy of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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