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Regioselective rearrangement of 7-azabicyclo[2.2.1]hept-2-aminyl radicals: first synthesis of 2,8-diazabicyclo[3.2.1]oct-2-enes and their conversion into 5-(2-aminoethyl)-2,3,4-trihydroxypyrrolidines, new inhibitors of α-mannosidases

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Abstract—Enantiomerically pure 2,8-diazabicyclo[3.2.1]oct-2-ene derivatives (+)-**5** and (−)-**5** have been obtained from 2-azido-3-tosyl-7-azabicyclo[2.2.1]heptanes (+)-**1** and (−)-**2** and their enantiomers, by ring expansion under radical conditions. Compounds (+)-**5** and (−)-**5** were transformed into hemiaminals **9** ((3*S*,4*R*,5*R*)- and **10** ((3*R*,4*S*,5*S*)-5-(2-aminoethyl)-2,3,4-trihydroxypyrrolidine) that are good inhibitors of α-mannosidases. © 2003 Published by Elsevier Science Ltd.

The 7-azabicyclo[2.2.1]heptane ring system is an attractive target for synthetic chemists since the discovery in 1992 of (−)-epibatidine,[1] a new alkaloid with interesting biological properties (Fig. 1). The [4+2] cycloaddition reaction between *N*-acyl pyrroles and dienophiles has been shown to be a general method for the synthesis of the 7-azabicyclo[2.2.1]hepta-2,5-diene and 7-azabicyclo[2.2.1]hept-2-ene derivatives.[2] In recent years, a number of successful [4+2] cycloadditions have employed acetylene equivalents as dienophiles. Ethynyl *p*-tolyl sulfone derivatives have been found to be one of the most synthetically useful acetylene equivalents[2–4] because of its high reactivity toward dienes and ease of removal of the *p*-toluenesulfonyl moiety under reductive conditions. Desulfonylation reactions[5] have been widely studied, specially in the case of alkyl sulfones,[6] β-keto sulfones[7] and vinyl sulfones[8] derivatives of 7-azabicyclo[2.2.1]heptane.

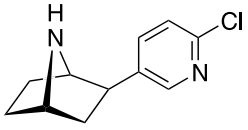

Figure 1. (−)-Epibatidine.

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As part of our search for new 1,2-diamines as leads for glycosidase inhibitors[9] we have reported[10] the synthesis of enantiomerically pure 7-azabicyclo[2.2.1]heptanes-2-yl amines (−)-**3** and (−)-**4** (and their enantiomers) that were derived from β-azidosulfones (+)-**1** and (−)-**2**, respectively, via catalytic hydrogenation of the azido group, followed by desulfonylation of the corresponding β-amino sulfone with sodium amalgam (Scheme 1).

With the hope to find a better route to these amines avoiding the use of large amounts of sodium amalgam (10 equiv.) we explored the possibility to apply a radical induced desulfonylation. We report here our results with the reactions of β-azido sulfones (+)-**1** and (−)-**2** upon treatment with tributyltin hydride (Bu_3SnH)[5,11] in the presence of catalytic amounts of azoisobutyrocarbonitrile (AIBN) and shall show that a highly regioselective radical rearrangement generating a bicyclic imine of a new type (2,8-diazabicyclo[3.2.1]oct-2-ene) has been uncovered. The latter compound has allowed one to prepare the hemiaminal salt (3*S*,4*S*,5*R*)-5-(2-ammonioethyl)-2,3,4-trihydroxy-pyrrolidinium dichloride and its enantiomer that are found to be potent and selective α-mannosidase inhibitors.

Desulfonylation of (+)-**1** upon heating with Bu_3SnH and AIBN in toluene at 110°C (3 h) gave the 2,8-diazabicyclo[3.2.1]oct-2-ene derivative (+)-**5**[12] as major com-

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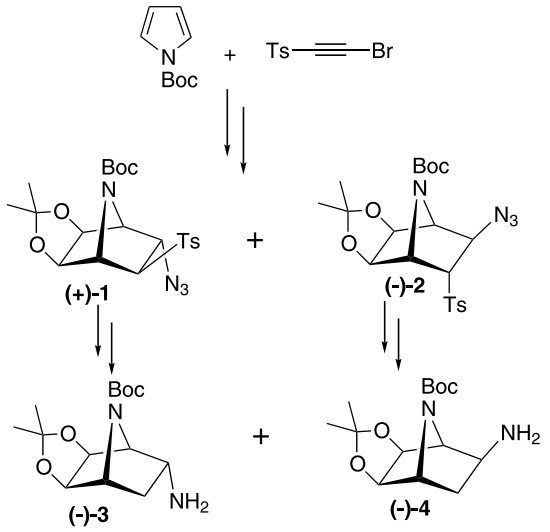
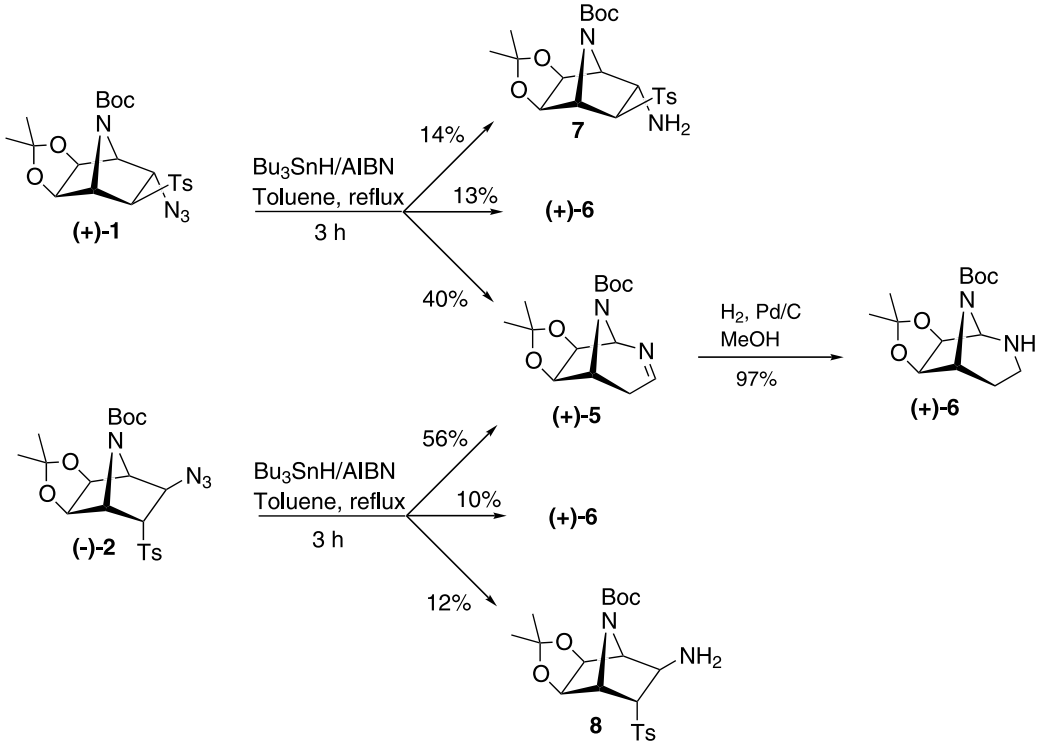


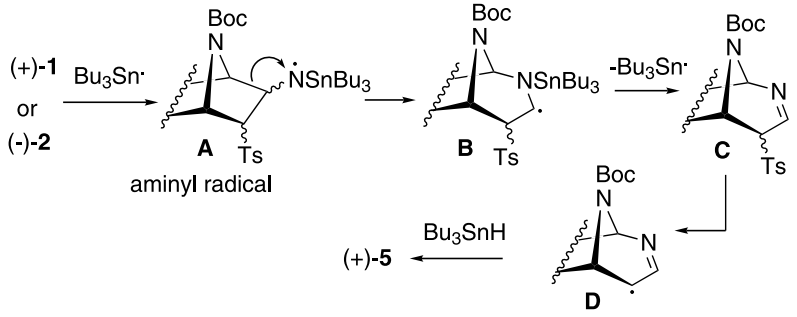
Scheme 1. See Ref. 10.

pound isolated by column chromatography on silica gel (40% yield) (Scheme 2). Primary amine **7** resulting from the reduction of azide (+)-**1** without skeletal rearrangement was isolated as minor compound (14%), together with secondary amine (+)-**6**[13] (13%) resulting from the reduction of imine (+)-**5**. Hydrogenation of imine (+)-**5** in MeOH in the presence of a catalytical amount of 10% Pd on charcoal provided pure (+)-**6** in 97% yield. Treatment of the diastereoisomeric β-azido sulfone (−)-**2** with Bu_3SnH/AIBN as above gave the same intracyclic imine (+)-**5** in 56% yield, together with primary amine **8** (12%) and (+)-**6** (10%, after column chromatography on silica gel). When pure amines **7** and **8** were treated with Bu_3SnH/AIBN as above, no trace of product of rearrangement could be detected. After 3 h at 110°C, and in the presence of an excess of Bu_3SnH/AIBN, **7** and **8** were recovered unchanged almost quantitatively. This indicates that reductions of azides into the primary amines compete with the radical rearrangement transforming (+)-**1** and (−)-**2** into imine (+)-**5**. After heating (+)-**1** and (−)-**2** (toluene and xylene at reflux) in the absence of Bu_3SnH/AIBN, all the starting materials were recovered, while heating of (+)-**1** in the presence of Bu_3SnH (without AIBN) only produced amine **7**.

The presence of Bu_3SnH/AIBN was absolutely necessary to induce the rearrangement, suggesting that aminyl radicals of type **A** (Scheme 3) are probably involved in the mechanism. It is known that alkyl azides generate aminyl radicals[14] by loss of N_2 in the presence of Bu_3SnH/AIBN. Radicals **A** undergo regiospecific 1,2-shift of the σ (C(1)–C(2)) bond forming intermediate radicals **B** that finally afford rearranged imines after $Bu_3Sn^{\bullet}$ elimination. The radical desulfonylation takes place after the rearrangement because the C-4 centered radical contiguous to a C=N bond (radical **D**, Scheme 3) is more stable than other secondary alkyl radicals, explaining that only desulfonylated products were isolated for rearranged species. Interestingly, the same high regioselectivity is observed for both the *endo*-aminyl radical (arising from (+)-**1**) and the *exo*-aminyl radical (arising from (−)-**2**) in their rearrangement into (+)-**5**. The greater migratory aptitude of the σ (C(1)–C(2)) in radicals of type **A** compared with that of the σ (C(2)-H) or σ (C(3)–C(2))



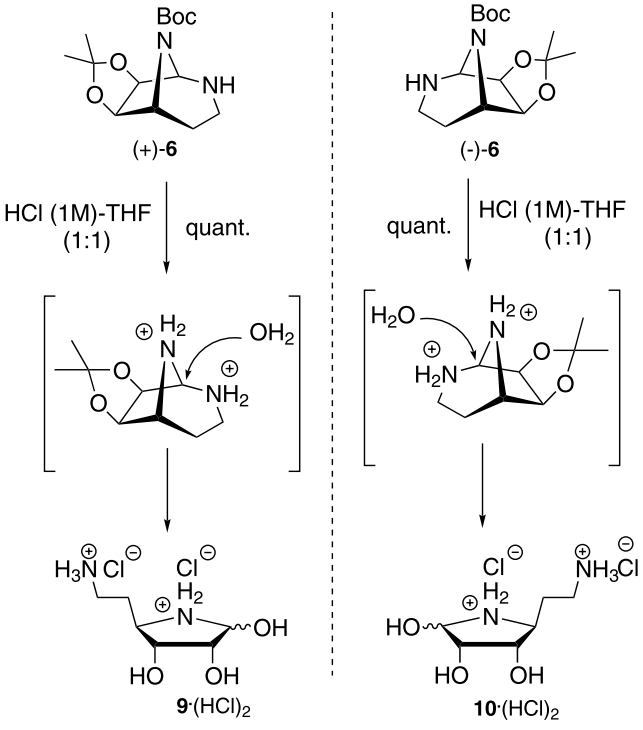
Scheme 2. Ring expansion in the reductive desulfonylation of β-azido sulfones (+)-**1** and (−)-**2**.



Scheme 3. Rearrangement through aminyl radical intermediates.

bond is noteworthy. It demonstrates the favorable effect of the BocN substituent on the 1,2-shift activation barrier. The 6-*exo*-oxy substitution may also play a favorable role.

To our knowledge there is no previous report on the synthesis of 2,8-diazabicyclo[3.2.1]oct-2-enes, although the synthesis of 2,8-diazabicyclo[3.2.1]octanes[15] and related structures[16] have been reported. Starting from the enantiomer β-azido sulfones (−)-**1** and (+)-**2**, the corresponding enantiomerically pure derivatives (−)-**5** and (−)-**6** were synthesized following the procedure described above. Compound (+)-**6** and (−)-**6** were deprotected under aqueous acidic conditions (HCl 1 M-THF, 1:1) (Scheme 4). Under these conditions the Boc groups are rapidly cleaved to give the corresponding unstable isopropylidene aminals, which are immediately hydrolyzed[17] to give hemiaminals **9**[18,19] and **10**, as a mixture of anomers, in quantitative yields.



Scheme 4. Acidic deprotection of 2,8-diazabicyclo[3.2.1]octanes.

We have assayed[20] hemiaminals **9** and **10** for their inhibitory activities toward 25 commercially available glycosidases. The data are summarized in Table 1 for two α-galactosidases, three β-galactosidases, two β-glucosidases, two α-mannosidases, one β-xylosidase and one α-*N*-acetylgalactosaminidase. These compounds did not show any inhibitory activity at 1 mM concentration toward the following enzymes: α-galactosidase from *Escherichia coli*, β-galactosidases from *Aspergillus niger* and from *Aspergillus orizae*, α-L-fucosidase from bovine epididymis, α-glucosidases from yeast, from rice and from baker yeasts, amyloglucosidases from almonds and from *Caldocellum saccharolyticum*, β-mannosidases from *Helix pomatia* and β-*N*-acetylglucosaminidase from jack beans, from bovine epididymis A and B.

Hemiaminals (3*S*,4*S*,5*R*)-5-(2-ammonioethyl)-2,3,4-trihydroxypyrrolidinium dichloride **9** $(HCl)_2$ and its enantiomer **10** $(HCl)_2$ resulted to be good inhibitors of α-mannosidases from jack beans, with $K_i = 2.5$ and 0.94 μM, respectively, and from almonds, with $K_i = 1.9$ and 1.2 μM, respectively. Both enantiomers present similar inhibitory properties (Table 1). However, the mode of inhibition depends on the enzyme and on the absolute configuration of the 2,3,4-trihydroxypyrrolidine. Under the pH conditions[20] used for the inhibition tests, these hemiaminals can equilibrate with the corresponding imines through water elimination. Related imines of this kind have been reported[21] to be inhibitors of α-mannosidases.

In summary, we have described the first case of radical ring expansion in 2-azido-3-tosyl-7-azabicyclo[2.2.1]-heptane systems that gives access to a new kind of bicyclic structures related with the epibatidine, the enantiomerically pure 2,8-diazabicyclo[3.2.1]oct-2-enes (+)- and (−)-**5**. These compounds were transformed in two steps into hydroxylated hemiaminals **9** and **10**, that are good and relatively selective α-mannosidase inhibitors.

Table 1. Inhibitory activities of (3*S*,4*S*,5*R*)-5-(2-ammonioethyl)-2,3,4-trihydroxypyrrolidinium dichloride **9** $(HCl)_2$ and its enantiomer **10** $(HCl)_2$. Percentage of inhibition at 1 mM concentration (%), IC_{50} and K_i in μM, when measured. Optimal pH, 35°C[a,b]

Enzyme/inhibitor	**9**	**10**
α-Galactosidase		
Coffee beans	ni	55%
Aspergillus niger	30%	84%
β-Galactosidase		
Escherichia coli	23%	ni
Bovine liver	34%	44%
Jack beans	ni	59%
β-Glucosidase		
Almonds	59%	82%
Caldocellum saccharolyticum	38%	71%
α-Mannosidase		
Jack beans	97% $IC_{50}=4.8$ $K_i=2.5$ (N)	97% $IC_{50}=4.5$ $K_i=0.94$ (M)
Almonds	98% $IC_{50}=4.9$ $K_i=1.9$ (C)	98% $IC_{50}=4.4$ $K_i=1.2$ (M)
β-Xylosidase		
Aspergillus niger	33%	37%
α-*N*-Acetylgalacto-saminidase		
Chicken liver	ni	54%

[a] For the conditions of measurements, see Ref. 20.

[b] (C), competitive; (M), mixed type; (N), non-competitive inhibition; ni, no inhibition at 1 mM concentration.

Acknowledgements

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12. Data for (+)-**5**: $[\alpha]_D$ +7 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 323 K, δ ppm, *J* Hz) δ 7.58 (br. s, 1H, H-3), 5.61 (br. s, 1H, H-1), 4.59 (d, 1H, $J_{6,7}=5.5$, H-6), 4.43 (d, 1H, H-7), 4.30 (br. s, 1H, H-5), 2.86 (dd, 1H, $J_{4a,4b}=18.9$, $J_{4a,5}=4.4$, H-4a), 2.04 (dd, 1H, $J_{3,4b}=2.2$, H-4b), 1.48 (s, 9H, $(CH_3)_3C$), 1.43, 1.28 (s each, 3H each, $(CH_3)_2C$); ^{13}C NMR (100.4 MHz, $CDCl_3$, δ ppm) δ 161.7 (C-3), 153.6 (CO), 112.2 ($(CH_3)_2C$), 84.2, 83.2 (C-6, C-7), 80.3 ($(CH_3)_3C$), 73.9 (C-1), 56.1 (C-5), 34.3 (C-4), 28.3 ($(CH_3)_3C$), 26.2, 24.7 ($(CH_3)_2C$); CIMS 283 (75% $[M+H]^+$).
13. Data for (+)-**6**: $[\alpha]_D$ +50 (*c* 0.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K, δ ppm, *J* Hz, mixture of two rotamers) δ 5.00, 4.91 (s each, 1H, H-1), 4.73 (d, 1H, $J_{6,7}=5.6$, H-6), 4.63 (br. d, 1H, H-7), 4.38, 4.22 (br. s each, 1H, H-5), 2.93 (dd, 1H, $J_{3a,4a}=6.23$, $J_{3a,3b}=14.7$, H-3a), 2.79 (m, 1H, H-3b), 1.94 (m, 1H, H-4a), 1.50 (s, 9H, $(CH_3)_3C$), 1.48 (m, 1H, H-4b), 1.44, 1.35 (s each, 3H each, $(CH_3)_2C$); ^{13}C NMR (100.4 MHz, $CDCl_3$, δ ppm, mixture of two rotamers) δ 154.1, 153.6 (CO), 111.3 ($(CH_3)_2C$), 83.1, 82.5, 82.2, 81.8 (C-6, C-7), 79.9, 79.8 ($(CH_3)_3C$), 73.4, 72.5 (C-1), 59.5, 58.3 (C-5), 39.1, 39.0 (C-3), 29.3, 29.0 (C-4), 28.4 ($(CH_3)_3C$), 26.0 ($(CH_3)_2C$), 24.4, 24.3 ($(CH_3)_2C$); CIMS 285 (38% $[M+H]^+$).
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18. Data for **9** (major anomer): ^{1}H NMR (400 MHz, CD_3OD, 298 K, δ ppm, J Hz) δ 4.89 (d, 1H, $J_{2,3}=2.1$, H-2), 4.16 (dd, 1H, $J_{4,5}=7.6$, $J_{3,4}=4.5$, H-4), 4.12 (dd, 1H, H-3), 3.55 (q, 1H, $J_{5,1'a}=J_{5,1'b}=7.7$, H-5), 3.20 (t, 2H, $J_{2',1'}=7.9$, H-2′a and H-2′b), 2.28 (m, 2H, H-1′a and H-1′b); ^{13}C NMR (100.4 MHz, CD_3OD, 298 K, δ ppm) δ 97.9 (C-2), 75.3 (C-4), 74.1 (C-3), 60.0 (C-5), 37.7 (C-2′), 30.2 (C-1′).
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