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On the electronic effects of OH groups. Synthesis and investigation of tetrahydroxylated azabicycloheptanes†

Anette Gregersen, Christian Marcus Pedersen, Henrik Helligsø Jensen and Mikael Bols*
Department of Chemistry, University of Aarhus, DK-8000, Aarhus C, Denmark.
E-mail: mb@chem.au.dk

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Two stereoisomeric 2,3,5,6-tetrahydroxyazabicyclo[2.2.1]heptanes were synthesised and their base strengths determined. The 2,3,5,6-*exo*-isomer **1** and the 2,3-*exo*-5,6-*endo*-isomer **2** were prepared from the Diels–Alder adduct of Boc-pyrrole and tosylacetylene by a route involving osmium catalyzed dihydroxylation and protection, tosyl group reduction and repeated dihydroxylation. Deprotection gave **1**, while **2** was obtained by conversion of the diol into the ditriflate, followed by nucleophilic inversion with KNO_2 and deprotection. Synthesis of the 2,3,5,6-*endo*-isomer by a similar strategy was attempted but failed. The pK_a of **1** and **2** was determined to be 7.0 and 6.4 respectively. This means that the change in base strength as a result of stereoisomerism of an OH is smaller in the [2.2.1]-azabicyclic system than in the piperidines. This is explained by a difference in charge–dipole interactions in the two systems.

Introduction

Being able to predict the effect of substitution on the acid–base strength of organic molecules is well recognised as being crucial for predetermining their suitability as drugs or their reactivity. From the work of Hammett and others much is known about substituent effects on acidity in both aromatic and aliphatic systems.[1–4] Generally, substitution effects are divided into the three components: 1) field effects that act through space and are the sum of coulombic interactions between substituent and acid; 2) inductive effects that act through bonds by polaration of the σ-bond framework; and 3) conjugative effects that act through resonance. Naturally, only the former two are relevant to aliphatic systems. Recent computational work indicates that the field effects are the dominant factor in the substituents effect on the acidity of many aliphatic and aromatic acids.[5–7]

In general, the influence of a substituent's stereochemistry on its effects has received relatively little attention. However, field effects from a substituent will depend on the stereochemistry and conformation of the molecule. Likewise, inductive effects may also be stereoelectronic due to different possibilities of hyperconjugation depending on the molecule's overall geometry.[8] In a recent series of papers we have investigated the stereochemical effect of polar substituents and, in particular, systematic variations in the effect of the hydroxyl group in six-membered rings when placed axially or equatorially.[9–17] We found that the equatorial hydroxyl group in the β- or γ-position was three-times more electronwithdrawing than their axial counterparts in reducing the acidity of a piperidine[10] or in reducing the rate of glycoside hydrolysis.[12,13,16] The cause of this difference may be associated with field effects or possibly hyperconjugation, but appear to be very consistent within six-membered rings in a chair conformation. Our favored explanation is that the substituent effect difference is caused by different charge–dipole interactions in the axial and equatorial case (Fig. 1): When the positive end of the C–O bond dipole is much closer to the positive charge than the negative end we have an unfavorable interaction. The system can stabilize itself by losing the charge, hence a stronger acid/weaker base. In contrast, the more perpendicular the C–O dipole, the weaker the interaction. The present work constitutes an effort to learn more about these effects by studying them in a different system. It was anticipated that similar differences

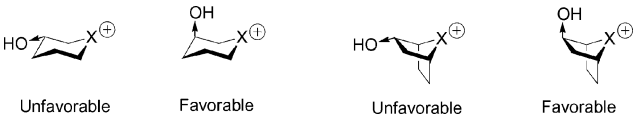
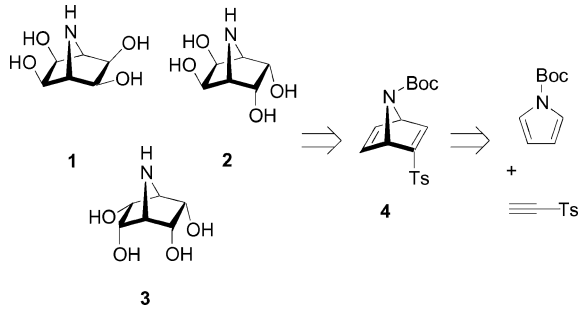


Fig. 1 Charge–dipole interactions in hydroxylated cyclic amines.

in the charge–dipole interactions might be obtained in the azabicyclo[2.2.1]heptane system (Fig. 1). In this system the five-membered rings are in rigid envelope conformations and hydroxyl substituents, being *endo*- or *exo*-configured, will be positioned similar to an equatorial or axial OH-group in the β-position of a piperidine. Thus, the distance between oxygen–nitrogen has been measured to be 3.8 Å and 2.9 Å in the β-hydroxypiperinium ion in the equatorial and axial case,[18] respectively, while in the bicyclic[2.2.1] system O–N distance for *endo*- and *exo*-alcohols was found to be 3.6 and 3.0. Thus, the tetrahydroxyamines **1**, **2** and **3** were envisaged as amines that might display a large variation in base strength simply as a result of stereochemical inversions (Scheme 1). In **1**, four perpendicular charge–dipole interactions, a pseudo-axial polar effect, should render this compound the most basic isomer. In contrast, the all *endo*-isomer **3** would, with four pseudo-equatorial interactions, have the lowest basicity in the series. The *exo–endo*-isomer **2** would be predicted to possess an intermediate basicity. As none of these compounds were known and no pK_a data for any hydroxylated azabicycloheptane were available, we decided to try to synthesise these three compounds and determine their base strength.



Scheme 1 Target molecules **1**–**3** and their precursors.

The most related compound reported in the literature was a protected derivative of **1** that was prepared by the Prinzbach group starting from cyclitol precursors.[19] While this compound

† Electronic supplementary information (ESI) available: A table of calculated angles, distances and charge dipole energies in compounds **1, 2** and **27**. See http://www.rsc.org/suppdata/ob/b4/b419154d/

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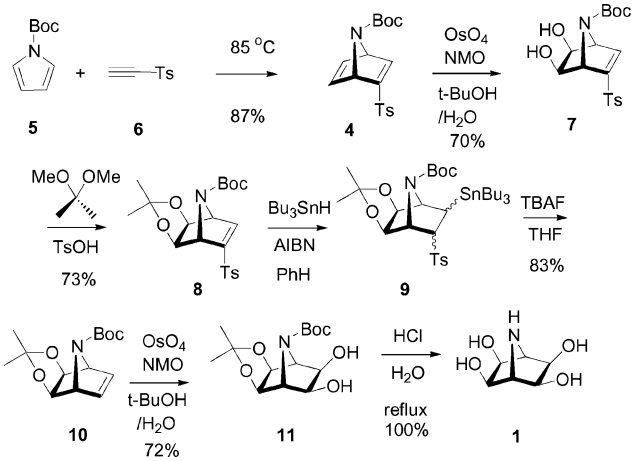
could be prepared and deprotected, we selected a route that would allow us to obtain the molecules also possessing 2,3-*endo*-diols from the same precursor. We chose the Diels–Alder adduct **4** (Scheme 1), which was obtained from the reaction of Boc-pyrrole (**5**) with tosylacetylene (**6**).[20,21] Several recent syntheses[22,23] have employed this strategy effectively to obtain substituted azabicycloheptanes, even with hydroxyl groups.[23] Upon removal of the sulfone the *exo*-selectivity in the rigid bicyclic system ensures control of an osmium catalyzed dihydroxylation reaction of the double bond. Nucleophilic inversion reactions might be employed to obtain the pseudoequatorial compounds.

Results and discussion

Synthesis

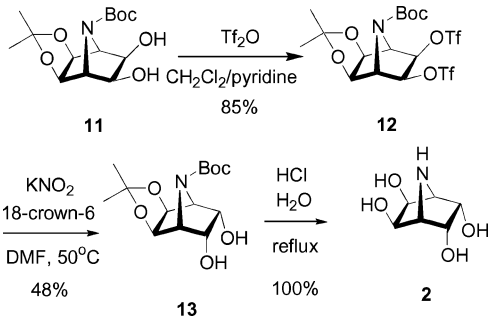
Synthesis of known **8** was carried out essentially as has been previously described:[21] In our hands, the solventless reaction of **6** in two eq. of **5** for 48 h at 85 °C gave adduct **4** in 87% yield (Scheme 2) and OsO_4 catalyzed dihydroxylation of **4** gave the diol **7** in 70% yield. Subsequent isopropylidene protection resulted in **8** in 73% yield. Compound **8** could be reduced using sodium amalgam giving the alkene **10** sometimes in yields as high as 84% yield. However, the reaction depended strongly on the quality of the reagent, saturation of the double bond was often observed as a byproduct and yields were frequently lower. Therefore, a two-step protocol[22,24] involving radical addition of tributyltin hydride to give **9** was preferred, followed by elimination using tetrabutylammonium fluoride (TBAF). This gave the alkene **10** in 83% yield over two-steps. Dihydroxylation of the alkene **10** with OsO_4–NMO gave the *exo*-diol **11**, exclusively, in 72% yield. Finally, treatment with hydrochloric acid led to quantitative deprotection to the tetrol **1**. Tetrol **1** has two signals in a NMR spectrum, which is consistent with the assigned stereochemistry only.



Scheme 2 Synthesis of **1**.

From the intermediate **11** the *endo*–*exo*-tetrol **2** was prepared (Scheme 3). The diol was converted to the ditriflate **12** with Tf_2O in CH_2Cl_2–pyridine, giving 85% yield. Treatment of this triflate with KNO_2 in DMF in the presence of crown ether[25] led to clean di-inversion of configuration, giving 48% yield of the diol **13**. Acidic hydrolysis of **13** with hydrochloric acid gave a quantitative yield of tetrol **2**. Tetrol **2** has three signals in a NMR spectrum, which is consistent with the assigned stereochemistry only.

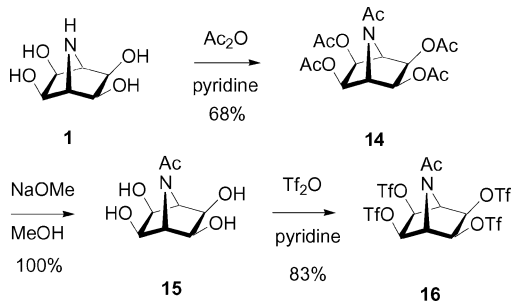
Several attempts to synthesise the all *endo*-tetrol **3** were also made. Conversion of **1** to the pentaacetate **14** with acetic anhydride in pyridine gave 68% yield (Scheme 4). Quantitative *O*-selective deacetylation gave tetrol **15**, which was then converted to the tetratriflate **16** in 83% yield. Reaction of **16** with KNO_2–crown ether however failed to give the desired product, but



Scheme 3 Synthesis of **2**.

led mainly to decomposition or multiple product formation. This failure may be caused by the many possibilities of side-reactions of the intermediate alcohols with triflates such as epoxide formation *etc.*

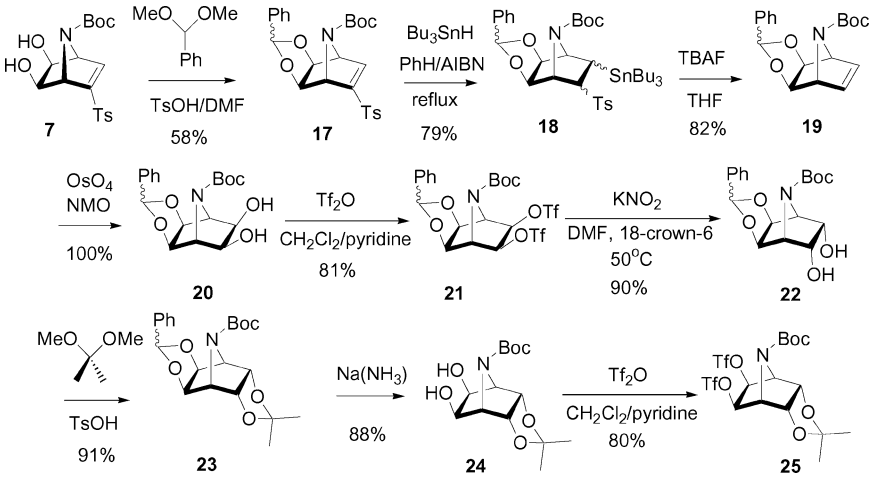
An attempt to carry out the nucleophilic substitutions in two-steps was also made. This required, however, some more protection group chemistry to be able to deprotect one diol in the presence of the other. Therefore, **7** was converted into the benzylidene derivative **17** by reaction with dimethoxytoluene and toluene sulfonic acid (TsOH) in 58% yield (Scheme 5). Two-step reduction of the sulfone was carried out by radical addition of Bu_3SnH to the conjugated system, giving stannane **18** in 79% yield. Treatment of **18** with TBAF gave the alkene **19** in 82% yield. OsO_4 catalyzed dihydroxylation gave the diol **20** in a quantitative yield, which was then converted to the ditriflate **21** with Tf_2O–pyridine in 82% yield. Substitution with KNO_2–crown ether gave an excellent 90% yield of the *endo*-diol **22**. Protection of this diol with dimethoxypropane–TsOH, giving **23** in 91% yield, was followed by dissolving metal reduction of the benzylidene group to the *exo*-diol **24**, being obtained in 88% yield. The *exo*-diol **24** was converted to the ditriflate **25** in 80% yield and several attempts to transform this ditriflate to the all *endo*-hydroxylated tetrol was made. However, disappointingly neither KNO_2–crown ether nor KOAc in DMF was able to provide the desired all *endo*-configured compound. It is likely these difficulties are due to crowding on the *endo*-face of the molecule.



Scheme 4 Attempted synthesis of **3** through tetratriflate **16**.

Base strength

The base strength of the amines **1** and **2** was determined by titration of their hydrochlorides with NaOH. From the tritration curves the pK_a values were determined to be 7.0 for **1** and 6.4 for **2** (Fig. 2). For comparison the unhydroxylated azabicycloheptane **26** has a pK_a of 10.8.[26] This gives an average base lowering effect of the *exo*-hydroxyl group of $(10.8 - 7.0)/4 = 0.95 \approx 1.0$, corresponding to 0.59 kcal mol^{-1}. The base lowering effect of the *endo*-OH will be $(10.8 - 6.4 - (2 \times 0.95))/2 = 1.25 \approx 1.3$, corresponding to 0.77 kcal mol^{-1}. In hydroxypiperidines an axial β-hydroxyl group was found to have a base lowering effect of 0.5 pH units (0.30 kcal mol^{-1}), while an equatorial group had a base lowering effect of 1.3 (0.77 kcal mol^{-1}). Thus, it is clear from the above data that the *endo*-hydroxyl group has a base lowering



Scheme 5 Attempted synthesis of **3** through a protected derivative of **2**.

effect that is very similar to the equatorial OH in piperidines. In contrast, the *exo*-OH has a much greater base lowering effect than a piperidine axial hydroxyl group.

Why are these *exo*-groups so electron withdrawing when compared to axial groups? To answer this question we carried out a detailed analysis of the angles and bond lengths using computer models of the conjugate acid forms of **1**, **2** and *trans*-3,5-dihydroxypiperidine **27**.† The computer models were made in Chem3D Pro and energy minimized using MOPAC PM3. In the model of **27** the angle between the C–O bond and the line between the C–O bond middle and nitrogen atom was 145.8° in the equatorial case and 104.7° in the axial case. In **1** the average angle between C–O dipoles to the charge was 114° for the *exo*-bonds, while the average angle was 151° for the *endo*-dipoles in **2**. The distances between the middle of the dipole and the nitrogen atom is however virtually identical when comparing the equatorial OH in **27** and the *endo*-OH's in **2**, and when comparing the axial OH in **27** with the *exo*-OH's in **1**. Charge–dipole interactions can be calculated using the Kirkwood–Westheimer equation.[5,27] This equation estimates the change in free energy as $\Delta\Delta \approx \frac{69.13\mu\cos\alpha}{D_E r^2}$ where μ is the dipole moment, r is the distance between the centre of the dipole and the charge, α is the angle between dipole and the line to the charge from the middle of the dipole and D_E is the effective dielectric constant. The dielectric constant depends on how much of the interaction is going through the molecule or the solvent. In the present case D_E is not known, but must be between the D_E of the part of molecule the interaction is through, which is usually set to 2 (the dielectric constant of cyclohexane), and the D_E of water, which is 78. Reasonably, the D_E must be low since most of the interaction takes place through an alkane-like part of the molecule. When D_E is set arbitrarily to 13 and a bond dipole moment of 1.7 for the C–O bond is used in the Kirkwood–Westheimer equation, a base lowering effect of the equatorial OH of 0.78 kcal mol^{-1} is obtained, while the axial OH gives 0.31 kcal mol^{-1}. These values are close to those observed experimentally in water. The ratio between the equatorial and axial charge dipole interaction is calculated to 2.5, while the measured substituent effect ratio is 2.6. For the *exo*/*endo*-OH groups the base lowering effect is calculated to 0.87 kcal mol^{-1} and 0.50 kcal mol^{-1}, which are also in relatively close agreement with the values measured in this work. The calculated ratio between *exo* : *endo* becomes 1.7, while the observed ratio was 1.3. Though not a perfect fit, charge–dipole theory nevertheless explains to a large extent the smaller difference in substituent effect between *exo*–*endo* isomers than between equatorial–axial isomers. In the piperidine system, when the C–O dipole is axial it is able to adopt a more perpendicular position than can be accommodated in the azabicyclic system. The remaining discrepancy between observed and calculated values must be caused by other factors. One reasonable explanation to **1** being less basic than predicted could be steric hindrance against protonation. Hydrogen bonding may or may not occur but this probably has little impact on base strength, as was demonstrated from our earlier work with piperidines.[9,10,12]

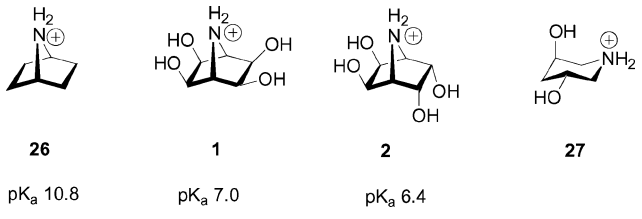


Fig. 2 pK_a values of the conjugated acids **1** and **2**.

Conclusions

We have investigated the effect of configuration on the base lowering effect of hydroxyl groups in the azabicycloheptane system. We find that the difference in base strength of the *endo*- and *exo*-hydroxyl groups is relatively small, with the *endo*-OH group lowering pK_a of the conjugate acid by 0.3 pH units more than the *exo*-OH. The higher substituent effect of the *endo*-OH is consistant with a less favourable charge–dipole interaction when in the conjugate acid form.

Experimental

General

^{13}C-, ^{1}H- and H,H-COSY NMR were recorded on a Varian Gemini 200 (200 MHz) NMR Instrument and, when specifically noted, on a Mercury 400 (400 MHz) NMR Instrument. The spectra were referenced to solvent residues. MS was recorded on a Micromass LC-TOF instrument. Chromatography was performed in Merck 60 silica. TLC was performed on Merck silica 60 E_{254} coated glass plates and developed using either vanillin (3 g in 100 mL EtOH with 1 mL H_2SO_4 added), potassium permanganate (aqueous), Ce–mol (10 g Ce(IV)SO_4 and 15 g $(NH_4)_2MoO_4$ in 1 L 10% H_2SO_4) or ninhydrin (2% in *n*-BuOH) and subsequent heating.

(±)-7-*tert*-Butoxycarbonyl-2-(4-toluenesulfonyl)-7-azabicyclo [2.2.1]hepta-2,5-diene (4)[21]. A mixture of ethynyl *p*-tolyl sulfone (**6**, 1.00 g, 5.55 mmol) and 1-*tert*-butoxycarbonylpyrrole (**5**, 2.0 mL, 12.0 mmol) was heated under an inert atmosphere at 85 °C for 48 h. The compound was purified by column chromatography (EtOAc–pentane, 1 : 4, R_f 0.3) and afforded

1.68 g of **4** (87%) as a light yellow powder. ^{1}H-NMR ($CDCl_3$): $\delta = 7.76$ (d, 2H, Ts, $J = 4.0$ Hz), 7.58 (br s, 1H, H3), 7.35 (d, 2H, Ts, $J = 4.0$ Hz), 6.90 (d, 1H, H5, $J_{5,6} = 2.6$ Hz), 6.87 (d, 1H, H6, $J_{6,5} = 2.6$ Hz), 5.38 (br s, 1H, H4), 5.19 (br s, 1H, H1), 2.42 (s, 3H, Me), 1.24 (s, 9H, Boc). ^{13}C-NMR ($CDCl_3$): $\delta = 152.8$ (C=O), 145.2, 143.9, 142.0, 140.5 (C3, C4, C6, C7), 139.1, 134.6 (substituted Ar), 129.4, 129.0, 127.4, 127.0 (unsubstituted Ar), 80.4 ($C(CH_3)_3$), 66.7, 65.8 (C1,C4) 26.8 (3 × Me), 20.63 (Me). MS (ES): $m/z = 370.2$ $(M + Na)^+$, calculated 371.1.

(±)-7-*tert*-Butoxycarbonyl-5,6-*exo*-dihydroxy-2-(4-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (7)[21]. A solution of **4** (1.68 g, 4.83 mmol) in THF (6.3 mL), NMO (1.5 eq., 0.98 g) and OsO_4 (0.63 mL of a 2.5 wt% in *tert*-butylalcohol) were added to a stirred solution of $NaHCO_3$ (0.5 g) in *t*-BuOH–H_2O (4 : 1, 50 mL). The reaction mixture was stirred at room temperature overnight and quenched with excess 10% $NaHSO_3$. The compound was extracted into ethyl acetate, dried ($MgSO_4$) and concentrated to give **7** (1.28 g, 70%), which was used without further purification. R_f 0.15 (EtOAc–pentane, 1 : 3). ^{1}H-NMR ($CDCl_3$): $\delta = 7.79$ (d, 2H, Ar, $J = 8.4$ Hz), 7.38 (d, 2H, Ar, $J = 8.4$ Hz), 7.06 (d, 1H, H3, $J_{3,4} = 1.1$ Hz), 4.72 (br s, 1H, H1), 4.59 (br s, 1H, H4), 3.97 (d, 1H, H6, $J_{6,5} = 5.8$ Hz), 3.89 (d, 1H, H5, $J_{5,6} = 5.8$ Hz), 2.39 (s, 3H, Me), 1.13 (s, 9H, 3 × Me) MS (ES): $m/z = 404.1$ $(M + Na)^+$, calculated 404.1.

7-*tert*-Butoxycarbonyl-5,6-*exo*-dihydroxy-5,6-*O*-isopropylidene-2-(4-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (8)[21]. A solution of **7** (1.28 g, 3.4 mmol) in dimethoxypropane–acetone (1 : 1, 10.8 mL) containing *p*-toluenesulfonic acid monohydrate (35 mg, 0.19 mmol) was stirred at room temperature overnight. The solution was made neutral with a few drops of triethylamine, concentrated, dissolved in EtOAc and washed with 1.0 M HCl. The organic layer was dried ($MgSO_4$) and concentrated to give crude **8**. The compound was purified by column chromatography (EtOAc–pentane, 1 : 3, R_f 0.49). Yield: 1.04 g (73%). ^{1}H-NMR ($CDCl_3$): $\delta = 7.78$ (d, 2H, Ar, $J = 8.0$ Hz), 7.37 (d, 2H, Ar, $J = 8.0$ Hz), 7.06 (d, 1H, H3, $J_{3,4} = 2.6$ Hz), 4.81 (br s, 1H, H4), 4.65 (br s, 1H, H1), 4.50 (d, 1H, H5, $J_{5,6} = 5.4$ Hz), 4.34 (d, 1H, H6, $J_{6,5} = 5.6$ Hz), 2.45 (s, 3H, Me), 1.44, 1.30 (2s, 2 × 3H, 2 × Me, acetonide), 1.25 (s, 9H, Boc). MS (ES): $m/z = 443.9$ $(M + Na)^+$, calculated 444.1.

7-*tert*-Butoxycarbonyl-2,3-*exo*-dihydroxy-2,3-*O*-isopropylidene-7-aza-bicyclo[2.2.1]hept-5-ene (10).

A. Addition–elimination of tributylstannane. To a stirred solution of **8** (234 mg, 0.47 mmol) and AIBN (5 mg) in benzene was added tributyltin hydride (0.28 g, 0.95 mmol, 0.26 mL) *via* a syringe under an inert atmosphere. The reaction mixture was refluxed for three hours and cooled to room temperature. The crude mixture was concentrated *in vacuo*, dissolved in MeCN and washed with hexanes to remove waste tin compounds. The MeCN phase was concentrated *in vacuo* and the product was purified by column chromatography (gradient: pentane to EtOAc–pentane, 1 : 9) to give the intermediate **9** (303 mg (90%)). Stannane **9** (303 mg, 0.43 mmol) was solved in dry THF and TBAF (1.0 mL of a 1 M solution in THF) was added. The reaction mixture was refluxed overnight, cooled to room temperature and concentrated *in vacuo*. The crude product was purified using column chromatography (CH_2Cl_2 to CH_2Cl_2–EtOAc, 10 : 1) to give alkene **10**. Yield: 105 mg (83%).

B. Reduction with sodium amalgam. A solution of **8** (1.07 g, 2.54 mmol), Na_2HPO_4 (1.44 g, 10.1 mmol) and 5% Na(Hg) (32.3 g, 76.2 mmol) in dry THF–dry MeOH (1 : 1, 30 mL) was heated under an inert atmosphere to 50 °C and stirred for 48 h. The reaction mixture was quenched with water and the amalgam was removed by filtration. The aqueous phase was extracted with ethyl acetate, dried ($MgSO_4$), concentrated *in vacuo* and finally purified by column chromatography (EtOAc–pentane, 1 : 3, R_f 0.42). Yield of **10**: 0.57 g (84%). Yields were however frequently lower depending on the quality of the sodium amalgam. ^{1}H-NMR ($CDCl_3$): $\delta = 6.30$ (d, 2H, H2, H3, $J = 6.2$ Hz), 4.66 (d, 2H, H5, H6, $J = 15.4$ Hz), 4.26 (s, 2H, H1, H4), 1.46, 1.40 (s, 2 × 3H, 2 × Me acetonide), 1.30 (s, 9H, Boc). ^{13}C-NMR ($CDCl_3$): $\delta = 155.1$ (C=O, Boc), 136.8, 135.7 (C2,C3), 116.0 ($C(Me)_2$ acetonide), 80.1 ($C(Me)_3$ Boc), 62.9, 62.1, 61.1 (C1, C4, C5, C6), 28.6, 26.5 (2 × Me acetonide), 25.4 (3 × Me Boc). HRMS (ES): $m/z = 290.1368$ $(M + Na)^+$, calculated 290.1369.

7-*tert*-Butoxycarbonyl-2,3-*O*-isopropylidene-2,3,5,6-*exo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (11). A solution of **10** (0.37 g, 1.38 mmol) in THF (3.3 mL), NMO (1.5 eq., 0.29 g), OsO_4 (0.3 mL of a 2.5 wt% in *t*-BuOH) were added to a stirred solution of $NaHCO_3$ (0.134 g, 1.38 mmol) in *t*-BuOH (10.7 mL) and water (2.7 mL). The reaction mixture was stirred at room temperature overnight and quenched with excess 10% $NaHSO_3$. The aqueous phase was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to give crude **11**. Purification was carried out using column chromatography (EtOAc, R_f 0.35). Yield of **11**: 0.42 g (72%). ^{1}H-NMR ($CDCl_3$): $\delta = 4.18$ (br s, 2H, H2, H3), 4.10 (s, 2H, H5, H6), 3.67 (dd, 2H, H1, H4, $J = 5.9$ Hz, 16.8 Hz), 1.40 (s, 9H, Boc), 1.32, 1.19 (s, 6H, 2 × Me acetonide). HRMS (ES): $m/z = 324.1430$ $(M + Na)^+$, calculated 324.1423.

2,3,5,6-*exo*-Tetrahydroxy-7-azabicyclo[2.2.1]heptane (1). **11** (300 mg, 1.0 mmol) was refluxed in 1.0 M HCl for 2 h and the compound was purified by ion-exchange chromatography on Amberlite IR-120 (H^+). Elution with 5% NH_4OH afforded **1** in a quantitative yield (160 mg). ^{1}H-NMR (D_2O): $\delta = 4.20$ (s, 4H, H2, H3, H5, H6), 4.00 (s, 2H, H1, H4). ^{13}C-NMR (D_2O): $\delta = 70.4$ (C1, C4), 66.9 (C2, C3, C5, C6), HRMS (ES): $m/z = 162.0769$ $(M + H)^+$, calculated 162.0766.

7-*tert*-Butoxycarbonyl-2,3-di-*O*-trifluoromethanesulfonyl-5,6-*O*-isopropylidene-2,3,5,6-*exo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (12). To a solution of **11** (40 mg, 0.13 mmol) in dichloromethane (1 mL) and pyridine (0.11 mL) was added dropwise Tf_2O (6 eq., 0.064 mL) at 0 °C. The mixture was stirred for 1 h and quenched with water. After extraction with EtOAc the collected organic phases were washed with 1.0 M hydrochloric acid and sat. aqueous $NaHCO_3$. Concentration gave **12** as a syrup. Yield: 64 mg (85%). ^{1}H-NMR ($CDCl_3$): $\delta = 4.76$ (s, 2H, H5, H6), 4.59 (d, 1H, H3, $J_{3,2} = 2.0$ Hz), 4.48 (d, 1H, H2, $J_{2,3} = 2.0$ Hz), 4.20 (s, 2H, H1, H4), 1.50 (s, 9H, Boc), 1.45, 1.25 (s, 2 × 3H, 2 × Me acetonide). HRMS (ES): $m/z = 588.0418$ $(M + Na)^+$, calculated 588.0409.

7-*tert*-Butoxycarbonyl-2,3-*O*-isopropylidene-2,3-exo-5,6-*endo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (13). A solution of **12** (193 mg, 0.34 mmol), potassium nitrite (10 eq., 0.29 g) and 18-crown-6 (1 eq., 0.09 g) in dry DMF (0.5 mL) was heated at 50 °C for 3 days. The reaction mixture was quenched with water and extracted with ethyl acetate, washed with KCl (sat.), dried ($MgSO_4$) and concentrated to give **13**. Yield: 49 mg (48%). ^{13}C-NMR ($CDCl_3$): $\delta = 155.0$ (C=O, Boc), 110.0 ($C(Me)_2$, acetonide), 80.5 ($C(Me)_3$, Boc), 65.5, 65.0, 63.5, 62.0, 60.6, 60.5 (C1, C2, C3, C4, C5, C6), 28.6 (Me, Boc), 25.8, 24.3 (Me acetonide). MS (ES): $m/z = 324.0$ $(M + Na)^+$, calculated 324.1.

2,3-*endo*-5,6-*exo*-Tetrahydroxy-7-azabicyclo[2.2.1]heptane (2). Compound **13** (49 mg) was refluxed in 1.0 M hydrochloric acid for 2 h and the product was purified on ion-exchange resin (IR-120, H^+) eluting with ammonia 5%, giving **2** in a quantitative yield (26 mg). ^{1}H-NMR (D_2O): $\delta = 4.59$ (br s, 2H, H2, H3), 4.32 (dd, 2H, $J = 2.6$ Hz), 4.10 (dd, 2H, $J = 2.6$ Hz) (H1, H4 and H5, H6). MS (ES): $m/z = 162.0$ $(M + H)^+$, calculated 162.0. HRMS (ES): $m/z = 184.0586$ $(M + Na)^+$, calculated 184.0583.

2,3,5,6,7-Penta-*N*,*O*-acetyl-2,3,5,6-*exo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (14). A solution of **1** (150 mg, 1.0 mmol) in pyridine–acetic acid anhydride (1 : 1, 2 mL) was stirred overnight at room temperature. The mixture was quenched with water and concentrated to give crude **14** (254 mg, 68%).

^{1}H-NMR ($CDCl_3$): $\delta = 4.96$ (d, 2H, $J = 6.0$ Hz), 4.92 (d, 2H, $J = 6.0$ Hz), 4.68 (d, 1H, $J = 2.8$ Hz), 4.16 (d, 1H, $J = 2.8$ Hz) (H1, H2, H3, H4, H5, H6), 2.06 (s, 3H, NAc), 2.02 (s, 6H, 2 × Ac), 1.98 (s, 6H, 2 × Ac).

7-Acetyl-7-aza-bicyclo[2.2.1]heptane-2,3,5,6-*exo*-tetraol (15). Compound **14** (254 mg) was dissolved in methanol and a catalytic amount of sodium in methanol was added. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with dry-ice and the mixture was concentrated to give **15** in a quantitative yield (139 mg). ^{1}H-NMR (D_2O): $\delta =$ 4.21 (s, 1H, H1), 3.98 (s, 1H, H4), 3.91 (s, 4H, H2, H3, H5, H6), 2.08 (s, 3H, NAc).

7-Acetyl-2,3,5,6-tetra-*O*-trifluoromethanesulfonyl-7-azabicyclo [2.2.1]heptane-2,3,5,6-*exo*-tetraol (16). To a solution of **15** (30 mg, 0.137 mmol) in dry dichloromethane (1.5 mL) and dry pyridine (0.17 mL) at 0 °C was added dropwise Tf_2O (12 eq., 0.132 mL). The mixture was stirred for 1 h and quenched with water. After extraction, the organic layer was washed with 1.0 M hydrochloric acid and sat. aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated to give **16** (85 mg, 83%). ^{1}H-NMR ($CDCl_3$): $\delta = 5.42$ (d, 2H, H3, H5, $J =$ 4.0 Hz), 5.28 (d, 2H, H2, H6, $J = 4.0$ Hz), 5.22 (d, 1H, H1, $J =$ 4.0 Hz), 4.63 (d, 1H, H4, $J = 4.0$ Hz), 2.18 (s, 3H, NAc). MS (ES): $m/z = 754.3$ $(M + Na)^+$, calculated 753.9.

(±)-5,6-*O*-Benzylidene-7-*tert*-butoxycarbonyl-5,6-*exo*-dihydroxy-2-(4-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (17). A solution of the diol **7** (310 mg, 0.81 mmol) in dimethoxytoluene (3 mL) containing a catalytic amount of *p*-toluenesulfonic acid monohydrate was stirred at room temperature overnight. The product **17** was purified by column chromatography (EtOAc–pentane, 3 : 1, $R_f = 0.25$). Yield: 172 mg (58%) ^{1}H-NMR ($CDCl_3$): $\delta = 7.80$ (d, $J = 8.2$, 2H, Ts), 7.47 (m, 2H, Ar), 7.38 (d, $J = 8.1$, 2H, Ts), 7.31–7.36 (m, 3H, Ar), 7.15 (m, 1H, H3), 5.98 (s, 1H, PhCH-), 4.98 (bs, 1H, H1), 4.81 (bs, 1H, H4), 4.56 (d, 1H, $J = 5.7$, H6), 4.43 (d, 1H, $J = 5.6$, H5), 2.46 (s, 3H, Ts), 1.19 (s, 9H, $-C(CH_3)_3$). ^{13}C-NMR ($CDCl_3$): $\delta =$ 145.6 (C=O), 144.6 (C2), 136.2 (Ts), 135.8 (Ts), 130.4 (Ts), 130.2 (Ar), 130.0 (C_3), 128.4 (Ts), 128.3 (Ar), 127.2 (Ar), 109.8 (PhCH-), 81.2 ($-CMe_3$), 80.3 (C5), 79.6 (C6), 65.2 (C1), 64.2 (C4), 27.9 ($C(CH_3)_3$), 21.8 (Ts). HRMS (ES): calculated for (M + Na) = 492.1457, found: 492.1470.

(±)-5,6-Benzylidene-7-*tert*-butoxycarbonyl-5,6-*exo*-dihydroxy-2-*p*-toluenesulfonyl-3-tributylstannyl-7-azabicyclo[2.2.1]hepthane (18). To a stirred solution of **17** (140 mg, 0.30 mmol) and AIBN (3 mg) in benzene was added tributyltin hydride (0.17 g, 0.6 mmol, 0.16 mL) *via* a syringe under an inert atmosphere. The reaction mixture was refluxed for three hours and cooled to room temperature. The crude mixture was concentrated *in vacuo*, dissolved in MeCN and washed with hexanes. The MeCN phase was concentrated *in vacuo* and the product was purified with column chromatography (gradient: pentane to EtOAc–pentane, 1:9) to give the product **18** as a thick sirup, which upon standing became a waxy solid. Yield: 181 mg (79%). ^{1}H-NMR ($CDCl_3$): $\delta = 7.79$ (d, $J = 8.0$, 2H, Ts), 7.46 (m, 2H, Ar), 7.39 (d, $J = 8.0$, 2H, Ts), 7.26–7.32 (m, 3H, Ar), 5.58 (s, 1H, Ph–CH-), 5.27 (d, $J = 5.6$, 1H), 4.43 (d, $J = 5.6$, 1H), 4.39 (bs, 2H), 3.60 (bs, 1H), 2.46 (s, 3H, Me), 1.58 (s, 1H, H_3), 1.2–1.5 (m, 21 H, Boc, Bu), 0.90 (t, $J = 7.2$, 9H, Bu). MS (ES): calculated for (M + Na) = 784.3, found: 784.2.

2,3-*O*-Benzylidene-7-*tert*-butoxycarbonyl-2,3-*exo*-dihydroxy-7-azabicyclo[2.2.1]hept-5-ene (19). Compound **18** (155 mg, 0.20 mmol) was solved in dry THF and TBAF (0.41 mL of a 1 M solution in THF) was added. The reaction mixture was refluxed overnight, cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2 to CH_2Cl_2–EtOAc, 10 : 1) to give the alkene **19**. Yield: 75 mg (82%). ^{1}H-NMR ($CDCl_3$): $\delta = 7.53$ (m, 2H, Ar), 7.34 (m, 3H, Ar), 6.40 (bd, 2H, H5, H6), 5.95 (s, 1H, Ph–CH-), 4.87 (bs, 1H, H2, H3) 4.77 (s, 2H, H1, H4), 1.42 (s, 9H, Boc). ^{13}C-NMR ($CDCl_3$): $\delta = 154.7$ (C=O, Boc), 137.5, 136.1 (C5, C6), 136.6 (Ar), 130.6 (Ar), 128.5 (Ar), 127.5 (Ar), 109.5 (PhCH-), 80.6, 80.1 (C2, C3), 80.4 (CMe_3, Boc), 63.1, 62.4 (C1, C4), 28.5 ($-C(CH_3)_3$, Boc). HRMS (ES): calculated for (M + Na) = 338.1368, found: 338.1363.

2,3-*O*-Benzylidene-7-*tert*-butoxycarbonyl-2,3,5,6-*exo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (20). To a solution of the alkene **19** (140 mg, 0.44 mmol) in THF (1 mL) was added *N*-methylmorpholine-*N*-oxide (67 mg, 0.66 mmol). OsO_4 (0.1 mL of a 2.5 wt% in *tert*-butylalcohol) was added to a stirred solution of $NaHCO_3$ (50 mg) in *t*-BuOH (4 mL) and water (1 mL). The reaction mixture was stirred at room temperature overnight and quenched with excess 10% $NaHSO_3$. The aqueous phase was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated to give the desired product in a quantitative yield (152 mg). ^{1}H-NMR ($CDCl_3$): $\delta = 7.48$ (m, 2H, Ar), 7.36 (m, 3H, Ar), 5.31 (s, 1H, PhCH-), 4.47/4.33 (2 bs, 2H, H5, H6), 4.22 (s, 2H, H1, H4), 3.82/3.74 (2 bs, 2H, H2, H3), 1.40 (s, 9H, Boc). HRMS (ES): calculated for (M + Na) = 372.1423, found: 372.1426.

5,6-*O*-Benzylidene-7-*tert*-butoxycarbonyl-2,3-di-*O*-trifluoromethanesulfonyl-2,3,5,6-*exo*-tetrahydroxy-7-azabicyclo[2.2.1] heptane (21). To a solution of **20** (170 mg, 0.48 mmol) in dichloromethane (4 mL) and pyridine (0.4 mL) was added dropwise Tf_2O (6 eq., 0.24 mL) at 0 °C. The mixture was stirred for 1 h and quenched with water. After extraction the organic layer was washed with $KHSO_4$ (10%), $NaHCO_3$ (sat.) then brine and dried over $MgSO_4$. Concentration gave **21** as a syrup. Yield: 0.245 g (81%). ^{1}H-NMR ($CDCl_3$): $\delta = 7.30$–7.46 (m, 5H, Ar), 5.65 (s, 1H, Ph–CH-), 4.91 (s, 2H, H2, H3), 4.82 (d, $J =$ 2.0 Hz, 1H, H5), 4.67 (d, $J = 2.03$ Hz, 1H, H6), 4.26 (s, 2H, H1, H4), 1.42 (s, 9H, Boc). ^{13}C-NMR ($CDCl_3$): $\delta = 152.1$ (C=O, Boc), 133.3 (Ar), 129.2 (Ar), 127.4 (Ar), 126.0 (Ar), 117.3 (q, $J = 1280$ Hz, Tf), 105.6 (Ph–CH), 80.53 (CMe_3, Boc), 79.3 (C2, C3), 76.6, 76.9 (C5, C6), 63.0, 61.6 (C1, C4), 26.9 ($-C(CH_3)_3$, Boc). HRMS (ES): calculated for (M + Na) = 636.0408, found 636.0330.

2,3-*O*-Benzylidene-7-*tert*-butoxycarbonyl-2,3-*exo*-5,6-*endo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (22). A solution of **21** (230 mg, 0.375 mmol), potassium nitrite (10 eq., 0.32 g) and 18-crown-6 (1 eq., 0.10 g) in dry DMF (0.5 mL) was heated at 50 °C for 5 days. The reaction mixture was quenched with water and extracted with ethyl acetate, washed with KCl (sat.), dried ($MgSO_4$) and concentrated to give **22**. Yield: 119 mg (90%). ^{1}H-NMR ($CDCl_3$) (rotamers present): $\delta = 7.45$ (d, $J = 7.2$ Hz, 2H, Ar), 7.38(m, 3H, Ar), 5.71 (s, 1H, PhCH-), 4.73 (s, 2H, H2, H3), 4.60, 4.40 (2 bs, 2H, H1, H4), 4.00 (bs, 2H, H5, H6), 1.22–1.35 (m, 9H, Boc). ^{13}C-NMR ($CDCl_3$): $\delta = 154.5$ (C=O), 135.8 (Ar), 129.7 (Ar), 128.3 (Ar), 127.2 (Ar), 103.8 (PhCH-), 80.5 ($-CMe_3$), 77.9 (C2, C3), 65.6, 65.2 (C5, C6), 62.9, 61.8 (C1, C4), 28.4 ($-CCH_3$). HRMS (ES): calculated for (M + Na) = 372.1423, found 372.1415.

2,3-*O*-Benzylidene-7-*tert*-butoxycarbonyl-5,6-*O*-isopropylidene-2,3-*exo*-5,6-*endo*-tetrahydroxy-7-azabicyclo[2.2.1]heptane (23). A solution of **22** (0.119 g, 0.339 mmol) in dimethoxypropane:acetone (1:1, 3 mL) containing *p*-TsOH (5 mg) was stirred at room temperature overnight. The solution was made neutral with a few drops of triethylamine, concentrated, dissolved in EtOAc and washed with $KHSO_4$ (10%). The organic layer was dried ($MgSO_4$) and concentrated to give **23**. Yield: 120 mg (91%). ^{1}H-NMR ($CDCl_3$): $\delta = 7.51$ (m, 2H, Ar), 7.34 (m, 3H, Ar), 5.60 (s, 1H, PhCH-), 4.83 (bs, 2H, H2, H3), 4.65 (bs, 2H, H1, H4), 3.75, 3.65 (bs, 2H, H5, H6), 1.49, 1.25 ($-CH_3$, acetonide), 1.33 (s, 9H, Boc). HRMS (ES): calculated for (M + Na) = 412.1735, found 412.1736.

2,3-*O*-Isopropylidene-2,3-*endo*-5,6-*exo*-tetrahydroxy-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptane (24). A solution of **23** (120 mg, 0.308 mmol) in dry THF was added to 80 mL NH_3 (l) at −78 °C. To the solution was added sodium (45 mg) and it was stirred until the blue color was persistent. The reaction mixture was quenced with NH_4Cl and the ammonia was allowed to evaporate. The crude mixture was diluted with water, extracted with EtOAc, washed ($KHSO_4$), dried and concentrated to give crude **24**. Yield: 82 mg (88%). ^{1}H-NMR ($CDCl_3$): δ = 4.54 (s, 2H, H2, H3), 4.43 (s, 2H, H5, H6), 4.27 (b s, 2H, H1, H4), 1.45 (s, 9H, Boc), 1.30, 1.25 (s, 6H, –CH_3(acetonide)). ^{13}C-NMR ($CDCl_3$): δ = 157.2 (C=O), 117.1 (CMe_2), 81.3 (–CMe_3), 77.1 (C1, C4), 69.3 (C2, C3, C5, C6), 28.9 (–CCH_3), 25.8 (–CH_3), 24.7 (-CH_3). HRMS (ES): calculated for (M + Na) = 324.1419, found: 324.1423.

7-*tert*-Butoxycarbonyl-5,6-di-*O*-trifluoromethanesulfonyl-2,3-*O*-isopropylidene-2,3-*endo*-5,6-*exo*-tetrahydroxy-7-azabicyclo [2.2.1]heptane (25). To a solution of **24** (82 mg, 0.272 mmol) in dichloromethane (2 mL) and pyridine (4 mL) was added dropwise Tf_2O (6 eq., 0.28 mL) at 0 °C. The mixture was stirred for 1 h and quenched with water. After extraction, the organic layer was washed with $KHSO_4$ (10%), $NaHCO_3$ (sat.), brine and dried over $MgSO_4$. Concentration gave **25** as a syrup. Yield: 0.123 g (80%). ^{1}H-NMR ($CDCl_3$): δ = 5.51 (s, 2H, H2, H3), 4.73 (bs, 2H, H1, H4), 4.63 (s, 2H, H5, H6), 1.46 (s, 9H, Boc), 1.32 (s, 3H, Me (acetonide)), 1.25 (s, 3H, Me (acetonide)). ^{13}C-NMR ($CDCl_3$): δ = 153.5 (C=O), 118.1 (CMe_2), 82.7 (–CMe_3), 81.7 (C2, C3), 64.3 (C5, C6), 63.3 (C1, C4), 27.9 (–CCH_3), 25.9 (Me (acetonide)), 24.5 (Me acetonide). HRMS (ES): calculated for (M + Na) = 588.0409, found 588.0414.

Determination of pK_a of amines

The amine hydrochloride (30 mg) was dissolved in 15–20 ml distilled water and subjected to titration with 0.1 M NaOH, following the pH using a pH electrode. The pK_a was determined from the resulting titration curve and was the average of three determinations (error ±0.1).

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