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

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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 KNO₂ 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 threetimes more electronwithdrawing than their axial counterparts in reducing the acidity of a piperidine¹⁰ 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

†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/



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 oxygennitrogen 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

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could be prepared and deprotected, we selected a route that would allow us to obtain the molecules also possessing 2,3endo-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 OsO₄ 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 OsO₄-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.





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 KNO₂-crown ether however failed to give the desired product, but



led mainly to decomposition or multiple product formation. This failure may be caused by the many possibilities of sidereactions 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 Bu₃SnH to the conjugated system, giving stannane 18 in 79% yield. Treatment of 18 with TBAF gave the alkene 19 in 82% yield. OsO4 catalyzed dihydroxylation gave the diol 20 in a quantitative yield, which was then converted to the ditriflate 21 with Tf₂O-pyridine in 82% yield. Substitution with KNO₂crown 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 KNO2-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 $(0.30 \text{ kcal mol}^{-1})$, while an equatorial group had a base lowering effect of $1.3 (0.77 \text{ kcal mol}^{-1})$. 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 $\Delta \Delta \approx \frac{69.13 \mu \cos \alpha}{\pi^2}$ where μ is the dipole moment, r is the distance between the centre of the dipole and the charge, a is the angle between dipole and the line to the charge from the middle of the dipole and $D_{\rm E}$ 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 $D_{\rm E}$ is not known, but must be between the $D_{\rm E}$ of the part of molecule the interaction is through, which is usually set to 2 (the dielectric constant of cyclohexane), and the $D_{\rm E}$ of water, which is 78. Reasonably, the $D_{\rm E}$ must be low since most of the interaction takes place through an alkane-like part of the molecule. When $D_{\rm E}$ 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



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

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

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

¹³C-, ¹H- 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 H₂SO₄ added), potassium permanganate (aqueous), Ce-mol (10 g Ce(IV)SO₄ and 15 g (NH₄)₂MoO₄ in 1 L 10% H₂SO₄) 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. ¹H-NMR (CDCl₃): $\delta = 7.76$ (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). ¹³C-NMR (CDCl₃): $\delta = 152.8$ (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(CH₃)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 OsO₄ (0.63 mL of a 2.5 wt% in *tert*-butylalcohol) were added to a stirred solution of NaHCO₃ (0.5 g) in *t*-BuOH–H₂O (4 : 1, 50 mL). The reaction mixture was stirred at room temperature overnight and quenched with excess 10% NaHSO₃. The compound was extracted into ethyl acetate, dried (MgSO₄) and concentrated to give 7 (1.28 g, 70%), which was used without further purification. R_f 0.15 (EtOAc–pentane, 1 : 3). ¹H-NMR (CDCl₃): δ = 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 (MgSO₄) and concentrated to give crude 8. The compound was purified by column chromatography (EtOAc-pentane, 1 : 3, $R_{\rm f}$ 0.49). Yield: 1.04 g (73%). ¹H-NMR (CDCl₃): $\delta = 7.78$ (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, $2 \times 3H$, $2 \times Me$, 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 (CH₂Cl₂ to CH₂Cl₂-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), Na₂HPO₄ (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 (MgSO₄), concentrated *in vacuo* and finally purified by column chromatography (EtOAc–pentane, 1 : 3, $R_{\rm f}$ 0.42). Yield of **10**: 0.57 g (84%). Yields were however frequently lower depending on the quality of the sodium amalgam. ¹H-

NMR (CDCl₃): $\delta = 6.30$ (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). ¹³C-NMR (CDCl₃): $\delta = 155.1$ (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), OsO₄ (0.3 mL of a 2.5 wt% in *t*-BuOH) were added to a stirred solution of NaHCO₃ (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% NaHSO₃. The aqueous phase was extracted with ethyl acetate, dried (MgSO₄) and concentrated to give crude 11. Purification was carried out using column chromatography (EtOAc, $R_{\rm f}$ 0.35). Yield of 11: 0.42 g (72%). ¹H-NMR (CDCl₃): δ = 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% NH₄OH afforded 1 in a quantitative yield (160 mg). ¹H-NMR (D₂O): δ = 4.20 (s, 4H, H2, H3, H5, H6), 4.00 (s, 2H, H1, H4). ¹³C-NMR (D₂O): δ = 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 Tf₂O (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 NaHCO₃. Concentration gave 12 as a syrup. Yield: 64 mg (85%). ¹H-NMR (CDCl₃): $\delta =$ 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-endotetrahydroxy-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 (MgSO₄) and concentrated to give 13. Yield: 49 mg (48%). ¹³C-NMR (CDCl₃): δ = 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). ¹H-NMR (D₂O): δ = 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%). ¹H-NMR (CDCl₃): δ = 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). ¹H-NMR (D₂O): δ = 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 Tf₂O (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 NaHCO₃. The organic layer was dried (MgSO₄) and concentrated to give 16 (85 mg, 83%). ¹H-NMR (CDCl₃): δ = 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.

 (\pm) -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%) ¹H-NMR (CDCl₃): $\delta = 7.80$ (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, $-C(CH_3)_3$). ¹³C-NMR (CDCl₃): $\delta =$ 145.6 (C=O), 144.6 (C2), 136.2 (Ts), 135.8 (Ts), 130.4 (Ts), 130.2 (Ar), 130.0 (C₃), 128.4 (Ts), 128.3 (Ar), 127.2 (Ar), 109.8 (PhCH-), 81.2 (-CMe₃), 80.3 (C5), 79.6 (C6), 65.2 (C1), 64.2 (C4), 27.9 (C(CH₃)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%). ¹H-NMR (CDCl₃): δ = 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, H₃), 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 (CH₂Cl₂ to CH₂Cl₂–EtOAc, 10 : 1) to give the alkene **19**. Yield: 75 mg (82%). 'H-NMR (CDCl₃):

δ = 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). ¹³C-NMR (CDCl₃): δ = 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 (CMe₃, Boc), 63.1, 62.4 (C1, C4), 28.5 (–C(CH₃)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). OsO₄ (0.1 mL of a 2.5 wt% in *tert*-butylalcohol) was added to a stirred solution of NaHCO₃ (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% NaHSO₃. The aqueous phase was extracted with ethyl acetate, dried (MgSO₄) and concentrated to give the desired product in a quantitative yield (152 mg). ¹H-NMR (CDCl₃): δ = 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 Tf₂O (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 KHSO₄ (10%), NaHCO₃ (sat.) then brine and dried over MgSO₄. Concentration gave 21 as a syrup. Yield: 0.245 g (81%). ¹H-NMR (CDCl₃): $\delta = 7.30-7.46$ (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). ¹³C-NMR (CDCl₃): $\delta = 152.1$ (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 (CMe₃, Boc), 79.3 (C2, C3), 76.6, 76.9 (C5, C6), 63.0, 61.6 (C1, C4), 26.9 (-C(CH₃)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 (MgSO₄) and concentrated to give 22. Yield: 119 mg (90%). ¹H-NMR (CDCl₃) (rotamers present): δ = 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). ¹³C-NMR (CDCl₃): δ = 154.5 (C=O), 135.8 (Ar), 129.7 (Ar), 128.3 (Ar), 127.2 (Ar), 103.8 (PhCH-), 80.5 (–CMe₃), 77.9 (C2, C3), 65.6, 65.2 (C5, C6), 62.9, 61.8 (C1, C4), 28.4 (–CCH₃). 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 dimethoxy-propane: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 KHSO₄ (10%). The organic layer was dried (MgSO₄) and concentrated to give **23**. Yield: 120 mg (91%). ¹H-NMR (CDCl₃): δ = 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 (-CH₃, 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 NH₃ (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 NH₄Cl and the ammonia was allowed to evaporate. The crude mixture was diluted with water, extracted with EtOAc, washed (KHSO₄), dried and concentrated to give crude **24**. Yield: 82 mg (88%). 'H-NMR (CDCl₃): $\delta = 4.54$ (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, -CH₃(acetonide)). ¹³C-NMR (CDCl₃): $\delta = 157.2$ (C=O), 117.1 (CMe₂), 81.3 (-CMe₃), 77.1 (C1, C4), 69.3 (C2, C3, C5, C6), 28.9 (-CCH₃), 25.8 (-CH₃), 24.7 (-CH₃). 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 Tf₂O (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 KHSO₄ (10%), NaHCO₃ (sat.), brine and dried over MgSO₄. Concentration gave **25** as a syrup. Yield: 0.123 g (80%). ¹H-NMR (CDCl₃): 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)). ¹³C-NMR (CDCl₃): δ = 153.5 (C=O), 118.1 (CMe₂), 82.7 (-CMe₃), 81.7 (C2, C3), 64.3 (C5, C6), 63.3 (C1, C4), 27.9 (-CCH₃), 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 p K_a was determined from the resulting titration curve and was the average of three determinations (error ± 0.1).

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