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A Facile Synthesis of a Polyhydroxylated 2-Azabicyclo[3.2.1]octane

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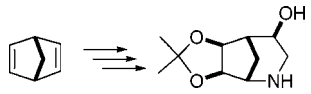
Received September 18, 2006



Synthetic or natural aza-sugars have shown promise as a therapeutic approach to a variety of disease states by acting as transition state mimics to sugar processing enzymes. Although the synthesis of functionalized bicyclo[3.2.1]-octanes has been reported, the procedures are relatively long and low yielding. Herein, we report the facile synthesis of polyhydroxylated 2-azabicyclo[3.2.1]octane that can be selectively functionalized.

The first naturally occurring sugar-mimic, i.e., aza-sugar or polyhydroxylated alkaloid, was isolated in 1966.[1] Since then, numerous aza-sugars have been isolated and can be divided into five general classes: piperidines, pyrrolidines, indolizidines, pyrrolizidines, and nortropanes.[2] Numerous polyhydroxylated alkaloids from these structural classes, synthetic and natural, have shown promise as anti-viral or anti-infective agents as well as in the treatment of diabetes.[2] Aza-sugars inhibit enzymes involved in sugar processing by acting as transition state mimics.[3] 1-Deoxymannojirimycin (DNJ) is an example of a polyhydroxylated monocyclic alkaloid, aza-sugar, that acts as a glycosidase inhibitor.[4] Currently, a derivative of DNJ, *N*-hydroxyethyl-DNJ, is marketed by Glaxo as Miglitol for the treatment of type II diabetes.[5] As part of our program aimed at preparing analogues of the norditerpenoid alkaloid methyllycaconitine, we required an efficient synthesis of the amino-sugar **3**.

Remarkably few examples of this ring system have been reported.[6,7] While the synthesis of the *trans*-6,7-diol [3.2.1] azabicycle has been reported,[8] the route is low yielding and does not allow for the introduction of the 4-hydroxyl group. An alternative synthesis prepared a lactone derivative of **3**, which incorporated the 4-hydroxyl group, but the synthesis is quite long and low yielding.[9] Therefore, we decided to investigate the selective functionalization of *N*-tosyl-2-azabicyclo-[3.2.1]octa-3,6-diene (**2**) as a starting point for our synthesis of **3**. Compound **2** is readily available,[10,11] and the two double bonds can be chemoselectively differentiated to provide the target compound **3** (Scheme 1).

The reaction of tosyl azide[12] with norbornadiene, **1**, yielded the desired *N*-tosyl-2-azabicyclo[3.2.1]octa-3,6-diene **2** in good yield.[10,11] With compound **2** in hand, regioselective dihydroxylation of the unfunctionalized olefin was attempted with OsO_4/NMO under a variety of solvent and temperature conditions. Although the desired product **4** was isolated from OsO_4/NMO-mediated dihydroxylation, low yields, and difficulties with purification prompted the investigation of other dihydroxylation methodologies. Surprisingly, AD-mix α or β chemoselectively dihydroxylates the desired double bond to form the racemic *exo*-diol **4** in excellent yield. The kinetic resolution of [2.2.1] bicyclic systems via AD-mix-mediated dihydroxylation provides little to no enantioselectivity;[13] therefore, it is not surprising that there was no enantioselectivity in the dihydroxylation of **2** to form **4**. Although previous research into the functionalization of [2.2.1] bicyclic systems has elucidated that the chemoselectivity between two olefins is typically the result of sterics and not electronics,[14] further research needs to be done on this [3.2.1] azabicyclic system to determine which dictates the chemoselectivity observed in the dihydroxylation of **2** (Scheme 2).

Yields associated with the protection of the *exo*-diol, as the acetonide **5**, were dependent on the amount of time between purification of **4** and formation of the acetonide, **5**. When diol **4** is stored as a neat liquid at room temperature under an argon atmosphere, two distinct compounds (mass 408 and 779) were observed. Both of these compounds subsequently decomposed to a number of unidentified products. The conversion of **4** to **5** immediately after isolation provided consistently high yields of **5**.

The next step was introduction of the hydroxyl at C-4. It has been noted that exocyclic hydroboration of related [2.2.1]heptene systems is controlled by the steric bulk of the bridgehead substituents.[15] Our expectation was that **5** would follow this general trend. Treatment of **5** with 9-BBN followed by an oxidative workup yielded the desired compound, **6a**, albeit in moderate yields. Clearly **5** appears to follow this general rule of [2.2.1] systems of preferential hydroboration in the *exo* position. In an effort to improve the yield, hydroboration with

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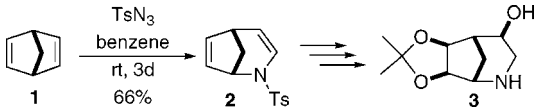
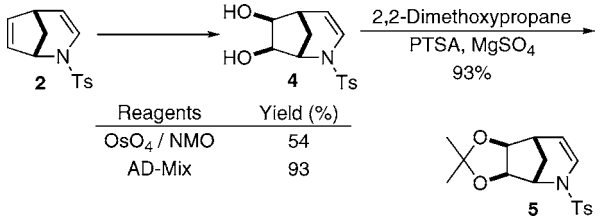
10.1021/jo0619231 CCC: $37.00
Published on Web 01/05/2007

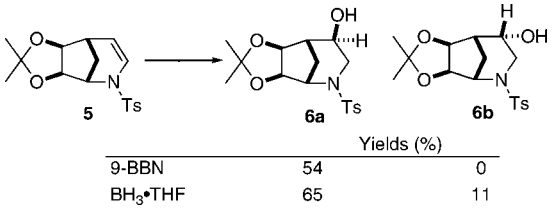
SCHEME 1. General Plan for Synthesis of 3



SCHEME 2. Osmylation of Diene 2



SCHEME 3. Hydroboration/oxidation of Enamine



BH_3•THF was tested and subsequently provided a higher yield of **6a** with a small amount of the *endo* isomer, **6b**, which was easily separated via recrystallization (Scheme 3).

The relative stereochemistry of bicyclo[2.2.1]heptane systems is often determined by the coupling constant between adjacent hydrogens as a result of the dihedral angle between the two hydrogens.[14,16] This method appears to be applicable to the azabicyclo[3.2.1]octane system as well.

As shown in Figure 1, the dihedral angle between $3H_{exo}$ and $4H_{endo}$ protons of **6a** is calculated to be 77°.[17] The observed coupling constant as expected is <1.0 Hz. The dihedral angle between $3H_{endo}$ and $4H_{endo}$ of **6a** is calculated to be 41.8° and a 3.0 Hz coupling constant is observed. The calculated dihedral angle in the minor isomer, **6b**, between $3H_{exo}$ and $4H_{exo}$ protons is 33.9° and shows a coupling constant of 6.6 Hz. The coupling constant between $3H_{endo}$ and $4H_{exo}$ is not observable. NOESY experiments provided additional confirmation (Figure 2). $4H_{endo}$ of **6a** showed strong cross-peaks with both H_6 and H_7 but not to H_8. $4H_{exo}$ of **6b** showed a strong cross-peak to H_8 but not to H_6 or H_7.

The final step in this synthesis is the removal of the *N*-tosyl protecting group. The removal of a tosyl group from a nitrogen is often a non-straightforward transformation. The rather drastic reaction conditions used for these deprotections are not always amenable to the presence other functionality. We initially examined sodium napthalenide mediated N-detosylation of **6a** which yielded a complex mixture of products.[18] We next examined the relatively mild photolytic N-detosylation.[19] After optimizing irradiation time, compound **3** was isolated in consistently good yields (Scheme 4).

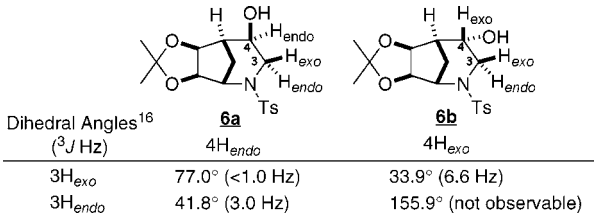


FIGURE 1. Dihedral angles and observed coupling constants for diastereomeric alcohols.

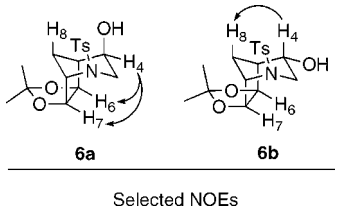
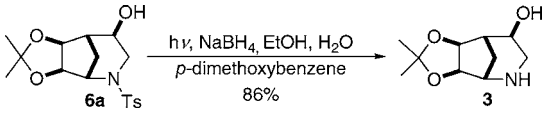


FIGURE 2. Observed NOESY cross-peaks.

SCHEME 4. Detosylation of Azabicycle



In summary, we have elucidated a facile synthesis of a polyhydroxylated [3.2.1] azabicycle that can be further functionalized. Selective functionalization of the secondary amine and the differentiable hydroxyl groups will provide access to a host of derivatives.

Experimental Section

***N*-Tosyl-2-azabicyclo[3.2.1]octa-3,6-diene (2).**[10,11] Tosyl azide[12] (13.4 g, 146.0 mmol) was dissolved in anhydrous benzene (100 mL) under an argon atmosphere at rt. Freshly distilled norbornadiene (10.56 mL, 49.0 mmol) was added in one aliquot, while the tosyl azide solution was being stirred vigorously. After 5 min, the rate of stirring was decreased and the reaction was stirred for 3 days at rt. The reaction was then concentrated and chromatographed (gradient elution; 0−50% EtOAc in hexane) to yield 9.59 g (66%) of **2** as white crystals: $R_f = 0.70$ (1:1, EtOAc/hexane); mp = 81−84 °C (lit. uncorrected mp 76−79 °C); ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 9.0 Hz), 7.32 (d, 2H, J = 9.0 Hz), 6.30 (dd, 1H, J = 9.0, 3.0 Hz), 6.15 (dd, 1H, J = 2.73 Hz), 5.26 (m, 2H), 4.75 (s, 1H), 2.66 (m, 1H), 2.44 (s, 3H), 1.74 (m, 1H), 1.31 (d, 1H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 143.6, 139.2, 137.1, 129.7, 126.7, 121.9, 121.2, 110.6, 59.6, 36.0, 34.6, 21.6.

***N*-Tosyl-2-azabicyclo[3.2.1]oct-3-ene-6,7-diol (4).** Methanesulfonamide (1.76 g, 18.5 mmol), AD-mix α (25.9 g, 2.8 g/mmol), acetone (92.5 mL), and H_2O (92.5 mL, HPLC grade) were added to a 2 L double-neck round-bottom flask. The reaction was flushed with argon for 10 min while being stirred vigorously with a mechanical stirrer at rt. Compound **2** (2.42 g, 9.25 mmol) was dissolved in acetone (15.2 mL) and transferred to the reaction flask in one aliquot, with an additional acetone (15.2 mL) wash of the addition vessel. The reaction was stirred vigorously for 3 h at rt then quenched with Na_2SO_3 (30.5 g) followed by the addition of EtOAc (305 mL). After 5 min of vigorous stirring, the reaction was partitioned between EtOAc and H_2O (120 mL). The aqueous layer was then extracted again with EtOAc. The organic layers were combined and washed with NaOH (2 × 120 mL, 2 M), dried over $MgSO_4$, filtered, concentrated, and chromatographed (gradient elution; 0−100% EtOAc in hexane) to yield 2.54 g (93%) of **4** as

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a white foam: $R_f = 0.17$ (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 2H, $J = 8.25$ Hz), 7.24 (d, 2H, $J = 8.19$ Hz), 6.36 (d, 1H, $J = 7.74$ Hz), 5.02 (t, 1H, $J = 7.68$ Hz), 4.00 (m, 3H), 3.85 (bs, 2H), 2.34 (s, 3H), 2.25 (m, 1H), 1.72 (m, 1H), 0.76 (d, 1H, $J = 11.97$ Hz); ^{13}C NMR ($CDCl_3$) δ 144.0, 135.7, 130.0, 126.9, 124.5, 110.2, 78.6, 76.5, 62.0, 40.0, 24.1, 21.6.

6,7-*exo*-Isopropylidenedioxy-*N*-tosyl-2-azabicyclo[3.2.1]oct-3-ene (5). Compound **4** (4.92 g, 16.6 mmol) was immediately transferred to a round-bottom flask and dissolved in acetone (120 mL, ACS grade). Anhydrous magnesium sulfate (21.4 g), *p*TSA (50 mg, 0.26 mmol), and 2,2-dimethoxypropane (31 mL, 250 mmol) were added, and the reaction was stirred overnight at rt. The reaction was filtered, concentrated and chromatographed (gradient elution; 0−100% EtOAc in hexane) to yield 5.17 g (93%) of **5** as a clear viscous liquid: $R_f = 0.63$ (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 2H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz), 6.51 (dd, 1H, $J = 7.5$, 0.5 Hz), 5.09 (t, 1H, $J = 7.0$ Hz), 4.45 (d, 1H, $J = 5.0$ Hz), 4.38 (d, 1H, $J = 5.5$ Hz), 4.21 (d, 1H, $J = 3.5$ Hz), 2.44 (s, 3H), 2.38 (m, 1H), 1.89 (m, 1H), 1.40 (s, 3H), 1.23 (s, 3H), 0.89 (d, 1H, $J = 12.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 143.9, 135.9, 129.9, 126.8, 124.8, 109.4, 109.0, 85.1, 84.4, 59.0, 36.9, 25.7, 23.86, 23.57, 21.46. Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 61.04; H, 6.51; N, 4.10.

4-*exo*-Hydroxy-6,7-*exo*-isopropylidenedioxy-*N*-tosyl-2-azabicyclo[3.2.1]octane (6). Compound **5** (0.77 g, 2.31 mmol) was dissolved in anhydrous THF (4.36 mL), flushed with argon, and cooled to −78 °C. BH_3·THF (4.36 mL, 4.20 mmol) was added slowly over 5 min, and the reaction was kept at −78 °C for 30 min before being warmed to rt. After hydroboration was complete (3 h, determined by TLC), EtOH (12.9 mL), NaOH (4.3 mL, 6.0 M), and H_2O_2 (10.4 mL, 30%) were slowly added, and the reaction was heated to 60 °C for 1 h. The reaction was cooled to room temperature, and excess K_2CO_3 was added followed by vigorous stirring for 5 min. The reaction was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. Compound **6a** was purified via recrystallization in boiling EtOAc to yield 0.53 g (65%) of **6a** as white crystals. The mother liquor was concentrated and chromatographed (gradient elution; 0−100% EtOAc in hexane) to yield 92 mg (11%) of **6b** as a viscous colorless liquid: **6a**, $R_f = 0.20$; **6b**, $R_f = 0.30$ (1:1, EtOAc/hexane). **6a**: mp = 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2H, $J = 8.2$ Hz), 7.34 (d, 2H, $J = 8.1$ Hz), 4.25 (m, 2H), 4.04 (d, 1H, $J = 5.3$ Hz), 3.85 (s, 1H), 3.65 (d, 1H, $J = 14.0$ Hz), 2.70 (dd, 1H, $J = 14.0$, 3.1 Hz), 2.45 (s, 4H), 2.28 (s, 1H), 1.96 (d, 1H, $J = 12.7$ Hz), 1.83 (m, 1H), 1.42 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.7, 136.0, 129.8, 127.4, 110.6, 80.9, 80.2, 65.4, 59.0, 48.2, 45.6, 25.8, 25.6, 23.6, 21.6. Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96. Found: C, 57.62; H, 6.60; N, 3.80. HPLC (Discovery-C8 column): **6a** had a retention time of 10.4 min and a purity of 95%. **6b**: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, $J = 8.3$ Hz), 7.34 (d, 2H, $J = 8.0$ Hz), 4.55 (d, 1H, $J = 5.37$ Hz), 4.19 (d, 1H, $J = 3.87$ Hz), 3.87 (m, 2H), 3.80 (d, 1H, $J = 5.40$ Hz), 2.52 (s, 1H), 2.45 (s, 3H), 2.35 (bs, 1H), 2.19 (m, 1H), 2.00 (m, 1H), 1.40 (s, 3H), 1.31 (d, 1H, $J = 12.69$ Hz); 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.8, 135.9, 130.0, 127.2, 110.2, 80.7, 78.4, 65.8, 58.0, 47.0, 46.6, 30.7, 25.6, 23.5, 21.6. HPLC (Discovery-C8 column): **6b** had a retention time of 10.7 min and a purity of 98%.

4-*exo*-Hydroxy-6,7-*exo*-isopropylidenedioxy-2-azabicyclo[3.2.1]-octane (3). Compound **6a** (0.531 g, 1.5 mmol) and 1,4-dimethoxybenzene (0.62 g, 4.5 mmol) were placed in a 250 mL Pyrex round-bottom flask and dissolved in absolute EtOH (90 mL). A solution of $NaBH_4$ (0.567 g, 15 mmol) in H_2O (10 mL, HPLC grade) was added to the 250 mL round-bottom flask. The 250 mL round-bottom flask was flushed with argon for 30 min before being placed adjacent to a high-pressure Xe−Hg lamp (455 W). The reaction was then vigorously stirred during 3 h of irradiation. The reaction was then flushed with argon for 30 min before being concentrated to dryness. The residue was triturated with EtOAc, dried over Na_2SO_4, filtered, concentrated, and chromatographed (gradient elution; 0−100% EtOAc in hexane) to yield 0.26 g (86%) of **3** as an off white powder: mp = 110−113 °C; ^{1}H NMR ($CDCl_3$) δ 4.53 (d, 1H, $J = 5.2$ Hz), 4.37 (d, 1H, $J = 5.2$ Hz), 4.18 (s, 2H), 3.69 (bs, 1H), 3.26 (d, 1H, $J = 3.0$ Hz), 2.75 (d, 1H, $J = 14.3$ Hz), 2.62 (dd, 1H, $J = 14.3$, 3.4 Hz), 2.35 (m, 1H), 1.96 (d, 1H, $J = 12.2$ Hz), 1.68 (m, 1H), 1.38 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 110.1, 82.6, 80.6, 66.6, 57.9, 47.4, 46.0, 26.8, 25.8, 23.7. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.09; H, 8.85; N, 6.75.

Acknowledgment. We thank Dr. Kumar Pichumani for NMR assistance. This work was supported by Ohio University through a NanoBioTechnology Initiative fellowship (DDR) and by NIH Grant No. DA013939.

Supporting Information Available: ^{1}H, ^{13}C NMR and 2D spectra for all prepared compounds as well as HPLC traces for compounds **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0619231