An Easy Access to 2,6-Dihydroxy-9-azabicyclo[3.3.1]nonane, a Versatile Synthon

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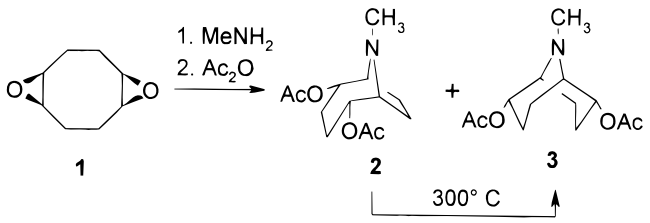
In the course of our studies on magnetic properties of nitroxide biradicals,[1] we needed to prepare biradicals deriving from 2,7-diazatwistane. To apply a strategy used by Ganter and Szczepanski for the synthesis of 2-aza,7-oxa-twistane[2] and of 2-aza,7-thia-twistane,[3] it was necessary to obtain access to large quantities of 2,6-dihydroxy-9-azabicyclo[3.3.1]nonane **4**.

The preparation of the *N*-methyl diacetate **3** by Kluge et al.[4] on the basis of Ganter and Portmann's work[5] (Scheme 1), seemed to be an efficient synthesis of a derivative of **4**. However, although **3** was indeed obtained in excellent yield, this method suffered from the use of sealed tubes, which had to be used twice to convert **1** into **3**, and furthermore, **2** and **3** were difficult to isolate from water.

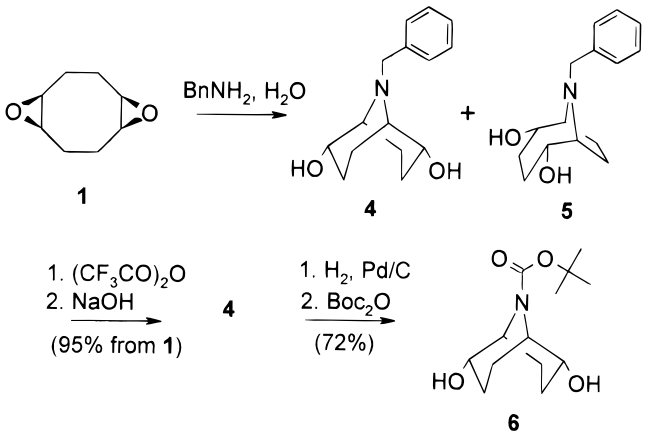
Benzyl is a more convenient protecting group, and because *N*-benzyl derivatives were also expected to be less soluble in water, methylamine was replaced by benzylamine. The addition reaction of **1** with benzylamine easily took place at lower temperatures (refluxing water), resulting in a 50/50 mixture of the isomeric diols **4** and **5**, formed in quantitative yield (Scheme 2). These diols were easily extracted from water and then quantitatively transformed[6] into the bistrifluoroacetate of **4** by trifluoroacetic anhydride in refluxing dichloromethane, thus avoiding the use of sealed tubes. After hydrolysis with aqueous sodium hydroxide, **4** was directly obtained by simple filtration, in 95% yield from **1**. After deprotection by hydrogenolysis, a carbamate **6** was prepared using standard conditions.

This synthesis thus provides an access to **4** in high yield. Because the successive reactions are quantitative, it is not necessary to isolate the intermediates and the only purification required is the final filtration. This molecule has been used in the first synthesis of quinolizidine **207I**[7] and in the preparation of 12-benzyl-5-methyl-5,6,7,8,10,11-hexahydro-6,10-imino-9*H*-cycloocta[*b*]indol-9-one,[8] a key intermediate in the synthesis of indole alkaloids.[9]

Scheme 1



Scheme 2



Experimental Section

General Methods. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. CH_2Cl_2 and NEt_3 were distilled from CaH_2. THF was distilled from KOH. NMR spectra were recorded in $CDCl_3$ or MeOD at 400 MHz for ^1H and 50 MHz for ^{13}C using chloroform (7.30 ppm for ^1H, 77.00 ppm for ^{13}C) or methanol (3.33 ppm for ^1H, 49.00 ppm for ^{13}C) as internal reference unless otherwise stated. Analytical thin-layer chromatography was performed on Merck silica gel plates (60 F_{254}). Flash chromatography was performed using Merck silica gel (Geduran SI 60, 0.040−0.063 mm). Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie.

9-Benzyl-9-azabicyclo[3.3.1]nonane-2-*endo*,6-*endo*-diol (4). A solution of diepoxyde **1** (10 g, 71.33 mmol) and benzylamine (7.8 mL, 71.33 mmol) in water (100 mL) was refluxed overnight. After the mixture was cooled to room temperature, 200 mL of a 2.5 N NaOH solution was added, and after extraction with CH_2Cl_2 (2 × 250 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (700 mL) and, under argon, cooled to −55 ± 5 °C. While the temperature was kept below −50 °C, TFAA (22 mL, 156 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. Triethylamine (45 mL, 320 mmol) was added, and after refluxing for 8 h, this solution was concentrated under reduced pressure. THF (90 mL) and 2.5 N NaOH (360 mL) were then added, and the resulting solution was stirred overnight. After extraction with CH_2Cl_2 (3 × 400 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. $CHCl_3$ (20 mL) was added, and after the mixture was cooled to −20 °C, a white slurry appeared. It was filtered and rinsed with $CHCl_3$ to yield 17.5 g (95%) of white crystals (melting below 40 °C) of diol **4**: ^1H NMR (400 MHz, MeOD) δ 1.86−2.00 (m, 2H), 2.00−2.14 (m, 4H), 2.14−2.24 (m, 2H), 2.86−2.91 (m,2H), 4.16 (s, 2H), 4.24−4.30 (m, 2H), 7.37−7.44 (m, 1H), 7.45−7.51 (m, 2H), 7.53−7.59 (m, 2H); ^{13}C NMR (50 MHz, MeOD) δ 20.77, 30.41, 55.82, 57.10, 68.30, 127.67, 128.95, 129.20, 140.81; HRMS calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1638.

***tert*-Butyl 2,6-*endo*,*endo*-Dihydroxy-9-azabicyclo[3.3.1]-nonane-9-carboxylate (6).** Argon was bubbled trough a solu-

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tion of amine **4** (7.23 g, 29.27 mmol), acetic acid (5 mL, 87.81 mmol), and 10% palladium on charcoal (500 mg) in methanol (300 mL). The resultant suspension was stirred overnight under an atmosphere of hydrogen maintained by fixing a balloon filled with hydrogen to the flask. After filtration through Celite, the solvent was removed under reduced pressure.To the resulting oil were added triethylamine (20 mL, 274 mmol), methanol (150 mL), and di-*tert*-butyl dicarbonate (12.78 g, 58.54 mmol). The resulting solution was refluxed overnight and then concentrated under reduced pressure. After addition of CH_2Cl_2 (100 mL) and water (50 mL), the organic phase was washed with a NH_4Cl solution (50 mL), dried over Na_2SO_4, and concentrated to a rose-colored solid, which was recrystallized from EtOAc to yield white crystals (4.31 g), mp 153 °C. The filtrate was purified by flash chromatography eluting with 95:5 CH_2Cl_2/MeOH to afford an additional 1.12 g: total yield, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.63−1.87 (m, 4H), 1.90−2.03 (m, 3H), 2.10−2.23 (m, 2H), 2.83 (br, 1H), 3.87−3.98 (m, 2H), 4.04−4.09 (m, 1H), 4.15−4.20 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.11, 21.60, 28.25, 28.58, 29.24, 49.18, 50.47, 68.27, 69.04, 79.89, 154.35; CIMS *m*/*z* (relative intensity) 258 (MH^+, 4), 219 (100). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.72; H, 8.99; N, 5.52.

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