Conversion of the Iridoid Glucoside Antirrhinoside into 3-Azabicyclo[3.3.0]octane Building Blocks

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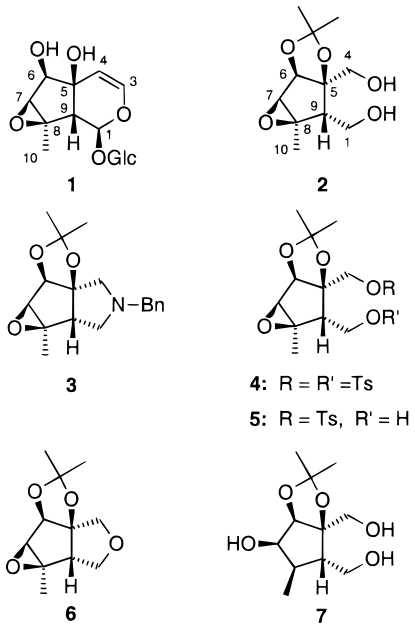
The iridoid glucoside antirrhinoside (**1**) was transformed into polysubstituted 3-azabicyclo[3.3.0]octanes **3**, **12**, and **13** in 4 to 5 steps. Ozonolysis of the diacetonide of **1** and of its 7-deoxy-derivative **8** afforded cyclopentanoids **2** and **10**, respectively. Conditions for the selective conversion of **2** and **10** into the corresponding ditosylates **4** and **11** were investigated. Cyclization of **4** and **11** was achieved with benzylamine and 2-methoxybenzylamine to yield bicyclic pyrrolidines **3**, **12**, and **13**. Additional building blocks **14** and **15** were obtained by selective deprotection of the *N*-benzyl and isopropylidene moieties in **12** and **13**, respectively.

The 3-azabicyclo[3.3.0]octane framework is only known from a few synthetic analogues of biologically active compounds. For example, it is found in analogues of prostacyclin (PGI_2),[1,2] a potential non-peptide substance P antagonist,[3] and in the antidiabetic gliclazide.[4] Usually, 3-azabicyclo[3.3.0]octanes are obtained by desymmetrization of a meso-intermediate, and three different approaches have been developed by Flynn *et al.*[5−7]

Previously, the iridoid glucoside antirrhinoside (**1**) has been converted into a monoterpene pyridine alkaloid,[8] bicyclic piperidine building blocks,[9] chiral cyclopentane building blocks[10] for the preparation of carbocyclic nucleoside analogues,[11] and a natural bicyclic lactone.[12] In the present work, we wish to report on the synthesis of 3-azabicyclo[3.3.0]octane building blocks from **1**.



1 **2** **3** **6** **7**

Results and Discussion

In previous papers[9,10] it was shown that antirrhinoside (**1**) readily could be converted into the corresponding 5,6:4′,6′-diacetonide, which, upon ozonolysis with a reductive workup procedure, was transformed into the partially protected cyclopentane **2**. Here, we intended first to employ **2** for the preparation of the derived pyrrolidine **3** via its ditosylate, but unexpectedly, the tosylation of diol **2** proved sluggish even with a large excess of tosyl chloride at room temperature. The desired ditosylate **4** was obtained only in low yield, together with monotosylate **5** and tetrahydrofuran **6**. To diminish the apparent competing cyclization of **5** to **6**, tosylation at low temperature (−10 °C) with a prolonged reaction time was attempted; however, after 3 days only monotosylate **5** had formed. Therefore, the excess of tosyl chloride was increased, and the reaction temperature was kept at 4 °C for an additional 3 days. The mixture was then allowed to reach room temperature, and ditosylate **4** prevailed in the reaction mixture, although with smaller amounts of **5** and **6**.

Benzylamines were chosen for the cyclization of ditosylates into 3-azabicyclo[3.3.0]octanes to facilitate purification and to allow subsequent modification into pyrrolidines with an unprotected nitrogen. Conversion of ditosylate **4** into *N*-benzylpyrrolidine **3** went smoothly with an excess of benzylamine in hot tetrahydrofuran. Because it was anticipated that the low reactivity of **2** might be due to the presence of the 7,8-epoxy functionality, its removal prior to ditosylation was considered a feasible alternative approach. Nevertheless, reduction of **2** with $LiAlH_4$ afforded only an undesired product (triol **7**) corresponding to a hydride attack at the most hindered position. This unusual regioselectivity may be caused by coordination of the aluminum reagent with the hydroxyl group at C-1 in **2**. Consequently, a strategy with epoxide reduction before the ozonolysis step seemed more promising. Hence, the 5,6:4′,6′-diacetonide of **1** was subjected to $LiAlH_4$ reduction, and this led to an approximately 10:1 mixture of ring-opened products **8** and **9**. This mixture was inseparable on normal-phase chromatography, but analytical samples of each product were obtained by reversed phase chromatography. In large-scale work it proved most facile to carry out the ozonolysis on the mixture of **8** and **9**, and this afforded the separable triols **10** and **7** in an approximately ∼10:1 ratio. In the case of **10**, tosylation at low temperature (−10 °C) gave exclusively ditosylate **11** in almost quantitative yield. Cyclization of **11** was performed with both benzylamine and 2-methoxybenzylamine, and this provided pyrrolidines **12** and **13**, respectively, in good to moderate yield. The reactivity of ditosylate **11** was markedly lower

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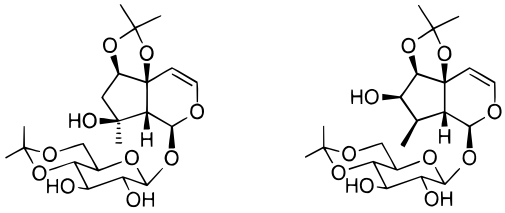
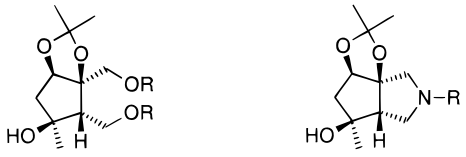
than that of ditosylate **4**; that is, the former required both a higher reaction temperature and an extended reaction time to ensure complete cyclization. The rate-limiting factor in the cyclization of **4** as well as of **11** appears to be the initial monosubstitution inasmuch as no intermediary *N*-benzylamino-substituted tosylates could be detected by analytical TLC during the progress of the reaction.

To enable its possible further elaboration into *N*-acylated derivatives, pyrrolidine **12** was subjected to hydrogenation in the presence of palladium on carbon catalyst, which gave the pure crystalline unprotected pyrrolidine **14** in high yield. Also, the isopropylidene-protecting group in *N*-(2-methoxybenzyl)pyrrolidine **13** was removed by treatment with *p*-toluenesulfonic acid in $CHCl_3$−MeOH to yield trihydroxy-pyrrolidine **15** in good yield.

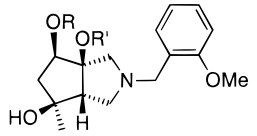


8 **9**



10: R = H
11: R = Ts

12: R = Bn
14: R = H



13: R,R' = >CH(CH$_3$)$_2$
15: R,R' = H, H

In conclusion, the inherent chirality of antirrhinoside (**1**) was utilized (4−5 steps) to prepare enantiopure 3-azabicyclo[3.3.0]octane building blocks **3** and **12**−**15**. The present protocol is devoid of expensive chiral catalysts or reagents, and no resolution of racemates is required.

Experimental Section

General Experimental Procedures. THF was freshly distilled from sodium. All concentrations were performed in vacuo. Elemental analyses were performed by the Microanalytical Department at the H. C. Ørsted Institute (University of Copenhagen) or by Microanalytical Laboratory, Institute of Physical Chemistry, Vienna. Optical rotations (10^{-1} deg cm^2 g^{-1}) were measured on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. TLC was performed on Merck Si gel 60 F_{254} aluminum sheets with detection by charring with H_2SO_4, or by UV light when applicable. MPLC was performed on a Merck Lobar Lichroprep RP_{18} C-column. VLC was performed on predried (120 °C; >24 h) Merck Si gel 60H; the column size is given as height × diameter. NMR spectra were recorded on Bruker HX-250 and Varian Inova 500 or Mercury 300 spectrometers. Chemical shifts are given in parts per million, using the solvent peaks as internal standards ($CDCl_3$: $\delta_H = 7.27$, $\delta_C = 77.0$, CD_3OD: $\delta_H = 3.31$, $\delta_C = 49.0$). Coupling constants (*J* values) are given in hertz. The subscripts a and b indicate the low field and high field protons, respectively, in methylene groups. ^{1}H NMR signals were assigned by COSY experiments, while ^{13}C NMR signals were assigned from HSQC spectra. Primes denote signals arising from the sugar moiety.

Tosylation of Diol 2 at Room Temperature. Diol **2** (100 mg, 0.435 mmol) was dissolved in CH_2Cl_2 (2 mL), and pyridine (0.28 mL, 8 × 0.435 mmol) and TsCl (332 mg, 4 × 0.435 mmol) were added. The mixture was stirred at room temperature for 24 h, and then excess reagent was quenched with ice. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed successively with 0.5 M H_2SO_4, H_2O, aqueous saturated $NaHCO_3$, and H_2O (each 15 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified on a VLC column (3 × 3 cm). Elution with hexane and then hexane−EtOAc (10:1 to 3:1) yielded successively **6** (20 mg, 22%), **4** (44 mg, 19%), and **5** (45 mg, 27%).

Tetrahydrofuran 6: mp 39−40 °C (hexane−EtOAc); $[\alpha]^{22}_D$ +21.7° (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.60 (1H, d, $J_{6,7} = 1.5$ Hz, H-6), 3.90 (2H, m, H-1a and H-4a), 3.78 (1H, dd, $J_{a,b} = 10$ Hz, $J_{1b,9} = 4.5$ Hz, H-1b), 3.63 (1H, d, $J_{a,b} = 9.5$ Hz, H-4b), 3.42 (1H, d, $J_{6,7} = 1.5$ Hz, H-7), 2.79 (1H, dd, $J_{1a,9} = 8.5$ Hz, $J_{1b,9} = 4.5$ Hz, H-9), 1.52, 1.27 (each 3H, s, isopropylidene), 1.40 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.9 (isopropylidene), 97.5 (C-5), 86.7 (C-6), 76.9 (C-4), 69.0 (C-1), 67.5 (C-8), 65.0 (C-7), 53.5 (C-9), 28.1, 26.7 (isopropylidene), 16.5 (C-10); *anal.* C 62.01%, H 7.90%, calcd for $C_{11}H_{16}O_4$, C 62.25%, H 7.60%.

Ditosylate 4: mp 154−156 °C (hexane−EtOAc); $[\alpha]^{22}_D$ −12.5° (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.84−7.30 (8H, 2 × Ts), 4.38 (1H, d, $J_{6,7} = 1.5$ Hz, H-6), 4.26 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{1a,9} = 3$ Hz, H-1a), 4.16 (1H, dd, $J_{a,b} = 10.5$ Hz, $J_{1b,9} = 3$ Hz, H-1b), 4.09 (1H, d, $J_{a,b} = 10.5$ Hz, H-4a), 3.98 (1H, d, $J_{a,b} = 10.5$ Hz, H-4b), 3.34 (1H, d, $J_{6,7} = 1.5$ Hz, H-7), 2.61 (1H, t, $J_{1a,9} = J_{1b,9} = 3$ Hz, H-9), 2.48, 2.45 (each 3H, s, 2 × Ts), 1.50, 1.02 (each 3H, s, isopropylidene), 1.36 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.7, 145.1, 132.3, 131.6, 130.3, 129.9, 128.1, 127.9 (2 × CH_3−*Ph*−SO_3), 114.7 (isopropylidene), 90.2 (C-5), 82.7 (C-6), 70.2 (C-4), 67.1 (C-1), 66.0 (C-8), 63.4 (C-7), 49.0 (C-9), 29.3, 27.8 (isopropylidene), 21.7, 21.6 (2 × *C*H_3−Ph−SO_3), 16.0 (C-10); *anal.* C 55.46%, H 5.84%, calcd for $C_{25}H_{30}O_9S_2$, C 55.75%, H 5.61%.

Monotosylate 5: mp 105−106 °C (hexane−EtOAc); $[\alpha]^{22}_D$ −4.0° (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94−7.34 (4H, m, Ts), 4.58 (1H, d, $J_{a,b} = 10$ Hz, H-4a), 4.44 (1H, d, $J_{6,7} = 1.5$ Hz, H-6), 4.06 (2H, m, H-1a and H-4b), 3.87 (1H, dd, $J_{a,b} = 11$ Hz, $J_{1b,9} = 3.5$ Hz, H-1b), 3.37 (1H, d, $J_{6,7} = 1.5$ Hz, H-7), 2.50 (4H, m, H-9 and Ts), 1.59, 1.12 (each 3H, s, isopropylidene), 1.52 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.1, 132.4, 129.8, 128.1 (CH_3−*Ph*−SO_3), 114.1 (isopropylidene), 90.6 (C-5), 83.2 (C-6), 70.9 (C-4), 66.9 (C-8), 63.6 (C-7), 59.2 (C-1), 50.8 (C-9), 29.6, 28.0 (isopropylidene), 21.6 (*C*H_3−Ph−SO_3), 16.5 (C-10); *anal.* C 56.11%, H 6.26%, calcd for $C_{18}H_{24}O_7S$, C 56.24%, H 6.29%.

Tosylation of Diol 2 at Low Temperature. To diol **2** (343 mg, 1.49 mmol) in CH_2Cl_2−pyridine (2:1, 6 mL) was added TsCl (1.28 g, 4.5 × 1.49 mmol). The mixture was kept at −10 °C for 3 days, at which point only 4-monotosylate **5** had formed. More TsCl (427 mg, 1.5 × 1.49 mmol) was added, and the mixture was kept at 4 °C for an additional 3 days, followed by 3 h at room temperature. Workup and purification, as described above, afforded **6** (15 mg, 4%), **4** (400 mg, 50%), and **5** (88 mg, 15%).

***N*-Benzylpyrrolidine 3.** Ditosylate **4** (363 mg, 0.674 mmol) was dissolved in dry THF (5 mL), and $BnNH_2$ (0.44 mL, 6 × 0.674 mmol) was added. The mixture was heated to 55−60 °C for 24 h. After the reaction mixture had cooled to room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added. Then the mixture was extracted with EtOAc (3 × 50 mL). The organic layers were dried (Na_2SO_4) and concentrated to yield a residue that was purified on a VLC column (4 × 2 cm). Elution with hexane and then hexane−EtOAc (10:1 to 5:1) yielded pure **3** as an oil: (183 mg, 90%), $[\alpha]^{22}_D$ −4.5° (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.22 (5H, m, *Ph*−CH_2), 4.57 (1H, d, $J_{6,7} = 1.5$ Hz, H-6), 3.59, 3.54 (each 1H, d,

J = 13 Hz, Ph−CH_2), 3.41 (1H, d, $J_{6,7}$ = 1.5 Hz, H-7), 2.92 (1H, d, $J_{a,b}$ = 9.5 Hz, H-4a), 2.69 (1H, dd, $J_{a,b}$ = 9 Hz, $J_{1a,9}$ = 3 Hz, H-1a), 2.65 (1H, dd, $J_{1b,9}$ = 9 Hz, $J_{1a,9}$ = 3 Hz, H-9), 2.40 (1H, d, $J_{a,b}$ = 9.5 Hz, H-4b), 2.47 (1H, t, $J_{a,b}$ = $J_{1b,9}$ = 9 Hz, H-1b), 1.54, 1.29 (each 3H, s, isopropylidene), 1.38 (s, 3H, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 128.4, 128.2, 127.1 (*Ph*−CH_2), 113.6 (isopropylidene), 96.6 (C-5), 87.5 (C-6), 68.2 (C-8), 65.3 (C-7), 65.2 (C-4), 59.7 (Ph−*C*H_2), 54.4 (C-1), 52.8 (C-9), 28.2, 27.0 (isopropylidene), 16.5 (C-10); *anal.* C 71.96%, H 7.97%, N 4.61%, calcd for $C_{18}H_{23}NO_3$, C 71.73%, H 7.69%, N 4.65%.

LiAlH$_4$-Reduction of Diol 2. To diol **2** (212 mg, 0.923 mmol) in THF (4 mL) was added $LiAlH_4$ (97 mg, 2.8 × 0.923 mmol), and the mixture was heated to reflux for 9 h. Excess reagent was quenched with EtOAc (2 mL), H_2O (5 mL) was added, and then the mixture was neutralized using CO_2. Again, H_2O (10 mL) was added, and the mixture was filtered. The filtrate was extracted with EtOAc (3 × 20 mL). The organic layers were dried (Na_2SO_4) and concentrated. The crude product was crystallized (Me_2CO−hexane) to give triol **7** (102 mg, 48%); mp 118−120 °C; $[\alpha]^{23}_D$ +31° (*c* 0.57, MeOH); ^{1}H NMR (CD_3OD, 250 MHz) δ 4.42 (1H, d, $J_{6,7}$ = 5 Hz, H-6), 3.94 (1H, t, $J_{6,7}$ = $J_{7,8}$ = 5 Hz, H-7), 3.76 (1H, dd, $J_{a,b}$ = 11.5 Hz, $J_{1a,9}$ = 4 Hz, H-1a), 3.76 (1H, d, $J_{a,b}$ = 12 Hz, H-4a), 3.69 (1H, d, $J_{a,b}$ = 12 Hz, H-4b), 3.68 (1H, dd, $J_{a,b}$ = 11.5 Hz, $J_{1b,9}$ = 6.5 Hz, H-1b), 2.11 (1H, ddd, $J_{8,9}$ = 12 Hz, $J_{1b,9}$ = 6.5 Hz, $J_{1a,9}$ = 4 Hz, H-9), 1.94 (1H, ddq, $J_{8,9}$ = 12 Hz, $J_{8,10}$ = 6.5 Hz, $J_{7,8}$ = 5 Hz, H-8), 1.51, 1.40 (each 3H, s, isopropylidene), 1.06 (3H, d, $J_{8,10}$ = 6.5 Hz, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 115.9 (isopropylidene), 93.3 (C-5), 85.7 (C-6), 72.8 (C-7), 64.8 (C-1), 60.1 (C-4), 55.7 (C-9), 41.0 (C-8), 28.8, 28.6 (isopropylidene), 13.1 (C-10); *anal.* C 56.62%, H 8.51%, calcd for $C_{11}H_{20}O_5$, C 56.88%, H 8.68%.

LiAlH$_4$-Reduction of 5,6:4′,6′-Di-*O*-isopropylidene-antirrhinoside. To a stirred suspension of $LiAlH_4$ (2.62 g, 69.0 mmol) in THF (50 mL) under Ar, was added a solution of antirrhinoside diacetonide[9] (9.38 g, 21.2 mmol) in THF (50 mL). The mixture was heated to reflux for 4 h. After the reaction mixture had cooled to room temperature, excess reagent was slowly quenched with EtOAc (50 mL). The mixture was neutralized with CO_2 (pH 7−8). Then pH was adjusted to 9 by adding saturated aqueous $NaHCO_3$ (50 mL). Then, H_2O (50 mL) was added, and the resulting solution was extracted with EtOAc (6 × 250 mL). The EtOAc layers were washed with brine (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to yield a foam that was purified on a VLC column (5.5 × 5 cm). Gradient elution with hexane to hexane−Me_2CO (2:1) yielded a 10:1 mixture of **8** and **9** (8.12 g, 87%). Analytical samples of each compound were obtained after rechromatography by MPLC.

Diacetonide 8: mp 114−116 °C (MeOH); $[\alpha]^{23}_D$ −160° (*c* 0.44, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.39 (1H, d, $J_{3,4}$ = 6.5 Hz, H-3), 5.55 (1H, br s, H-1), 5.08 (1H, dd, $J_{3,4}$ = 6.5 Hz, $J_{4,9}$ = 1.5 Hz, H-4), 4.67 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.31 (1H, dd, $J_{6,7a}$ = 7 Hz, $J_{6,7b}$ = 5 Hz, H-6), 3.89 (1H, dd, $J_{a',b'}$ = 10.5 Hz, $J_{5',6a'}$ = 5.3 Hz, H-6a′), 3.77 (1H, t, $J_{a',b'}$ = $J_{5',6b'}$ = 10.5 Hz, H-6b′), 3.52, 3.49 (each 1H, br t, J = 9 Hz, H-3′ and H-4′), 3.29 (2H, m, H-2′ and H-5′), 2.63 (1H, br s, H-9), 2.19 (1H, dd, $J_{a,b}$ = 14 Hz, $J_{6,7a}$ = 7 Hz, H-7a), 2.05 (1H, dd, $J_{a,b}$ = 14 Hz, $J_{6,7b}$ = 5 Hz, H-7b), 1.54, 1.51, 1.42, 1.39 (each 3H, s, 2 × isopropylidene), 1.22 (3H, s, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 144.0 (C-3), 113.7 (isopropylidene), 106.2 (C-4), 100.8 (isopropylidene), 100.3 (C-1′), 92.9 (C-1), 84.7 (C-6), 81.4 (C-5), 79.5 (C-8), 75.3 (C-2′), 74.9 (C-4′), 74.4 (C-3′), 68.8 (C-5′), 63.1 (C-6′), 59.1 (C-9), 48.3 (C-7), 29.4, 28.8, 27.6, 19.3 (2 × isopropylidene), 25.2 (C-10); *anal.* C 56.48%, H 7.06%, calcd for $C_{21}H_{32}O_{10}$, C 56.75%, H 7.26%.

Diacetonide 9: $[\alpha]^{25}_D$ −136° (*c* 0.58, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.33 (1H, d, $J_{3,4}$ = 6.5 Hz, H-3), 5.36 (1H, br s, H-1), 5.08 (1H, dd, $J_{3,4}$ = 6.5 Hz, $J_{4,9}$ = 1.5 Hz, H-4), 4.64 (1H, d, $J_{1',2'}$ = 8 Hz, H-1′), 4.31 (1H, d, $J_{6,7}$ = 5 Hz, H-6), 3.98 (1H, br t, $J_{6,7}$ = $J_{7,8}$ = 5 Hz, H-7), 3.90 (1H, dd, $J_{a',b'}$ = 10.5 Hz, $J_{5',6a'}$ = 5.5 Hz, H-6a′), 3.79 (1H, t, $J_{a',b'}$ = $J_{5',6b'}$ = 10.5 Hz, H-6b′), 3.53, 3.48 (each 1H, br t, J = 9 Hz, H-3′ and H-4′), 3.30−3.25 (2H, m, H-2′ and H-5′), 2.30 (1H, br d, $J_{8,9}$ = 12.5 Hz, H-9), 1.87 (1H, ddq, $J_{8,9}$ = 12.5 Hz, $J_{8,10}$ = 7 Hz, $J_{7,8}$ = 5 Hz, H-8), 1.56, 1.51, 1.48, 1.39 (each 3H, s, 2 × isopropylidene), 1.10 (3H, d, $J_{8,10}$ = 7 Hz, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 142.7 (C-3), 115.9 (isopropylidene), 107.2 (C-4), 100.7 (isopropylidene), 100.4 (C-1′), 93.8 (C-1), 87.9 (C-6), 83.0 (C-5), 75.2 (C-2′), 74.9 (C-4′), 74.4 (C-3′), 72.1 (C-7), 68.8 (C-5′), 63.1 (C-6′), 52.8 (C-9), 41.6 (C-8), 29.4, 28.3, 28.0, 19.3 (2 × isopropylidene), 12.4 (C-10); *anal.* C 55.29%, H 7.21%, calcd for $C_{21}H_{32}O_{10}\bullet{}^1/_2H_2O$, C 55.61%, H 7.13%.

Ozonolysis of Diacetonides 8 and 9. A 10:1 mixture of **8** and **9** (2.89 g, 6.51 mmol) was dissolved in CH_2Cl_2−MeOH (3:1, 80 mL). Upon cooling to −78 °C, the mixture was treated with ozone for 30 min. Then Ar was passed through the solution for 30 min, at which point EtOH (40 mL) and $NaBH_4$ (0.74 g, 3 × 6.51 mmol) were added. The mixture was stirred below −65 °C for an additional 2 h, when another portion of $NaBH_4$ (0.74 g) was added. The reaction mixture was stirred at room temperature for the next 12 h and was then neutralized with HOAc (2 mL) and concentrated. The residue was partitioned between EtOAc (250 mL) and brine-saturated $NaHCO_3$ (2:1, 150 mL). The aqueous layer was extracted with more EtOAc (5 × 250 mL). The EtOAc phases were dried (Na_2SO_4 and $NaHCO_3$) and concentrated. The crude product (1.40 g) was purified on a VLC column (4 × 4.5 cm). Elution with hexane and then hexane−Me_2CO (5:1 to 2:1) afforded successively **7** (89 mg, 6%) and **10** (1.02 g, 67.5%).

Triol 10: mp 116−118 °C (hexane-Me_2CO); $[\alpha]^{23}_D$ +7.9° (*c* 0.63, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.39 (1H, dd, $J_{6,7a}$ = 6.5 Hz, $J_{6,7b}$ = 5.5 Hz, H-6), 3.79 (2H, d, $J_{1,9}$ = 7 Hz, H-1), 3.75 (1H, d, $J_{a,b}$ = 11.5 Hz, H-4a), 3.67 (1H, d, $J_{a,b}$ = 11.5 Hz, H-4b), 2.48 (1H, t, $J_{1,9}$ = 7 Hz, H-9), 2.11 (1H, dd, $J_{a,b}$ = 13.5 Hz, $J_{6,7a}$ = 6.5 Hz, H-7a), 2.04 (1H, dd, $J_{a,b}$ = 13.5 Hz, $J_{6,7b}$ = 5.5 Hz, H-7b), 1.53, 1.38, (each 3H, s, isopropylidene), 1.16 (3H, s, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 113.6 (isopropylidene), 93.3 (C-5), 82.5 (C-6), 80.1 (C-8), 64.5 (C-4), 62.2 (C-9), 59.3 (C-1), 48.0 (C-7), 29.6, 28.4 (isopropylidene), 24.7 (C-10); *anal.* C 56.70%, H 8.50%, calcd for $C_{11}H_{20}O_5$, C 56.88%, H 8.68%.

Ditosylation of Triol 10. Triol **10** (0.36 g, 1.55 mmol) was dissolved in CH_2Cl_2-pyridine (3:1, 8 mL), then the mixture was cooled to −78 °C, and TsCl (1.03 g, 3.5 × 1.55 mmol) was added. The mixture was allowed slowly to warm to −10 °C, and was then kept at −10 °C for 5 days. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and was then washed successively with 0.5 M H_2SO_4, H_2O, aqueous saturated $NaHCO_3$, and H_2O (each 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a VLC column (4 × 3 cm). Elution with hexane and then hexane−EtOAc (5:1 to 2:1) gave ditosylate **11** (0.83 g, 99%): mp 95−97 °C (hexane−EtOAc); $[\alpha]^{22}_D$ + 2.3° (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80−7.74 (4H, m, Ts), 7.39−7.35 (4H, m, Ts), 4.45 (1H, dd, $J_{6,7b}$ = 5.5 Hz, $J_{6,7a}$ = 2 Hz, H-6), 4.14 (1H, dd, $J_{a,b}$ = 10.5 Hz, $J_{1a,9}$ = 5.5 Hz, H-1a), 4.13 (1H, d, $J_{a,b}$ = 11 Hz, H-4a), 4.10 (1H, dd, $J_{a,b}$ = 10.5 Hz, $J_{1b,9}$ = 5.5 Hz, H-1b), 4.08 (1H, d, $J_{a,b}$ = 11 Hz, H-4b), 2.54 (1H, dt, $J_{1a,9}$ = $J_{1b,9}$ = 5.5 Hz, $J_{7a,9}$ = 1.5 Hz, H-9), 2.46 (6H, s, 2 × Ts), 2.10 (1H, ddd, $J_{a,b}$ = 15 Hz, $J_{6,7a}$ = 2 Hz, $J_{7a,9}$ = 1.5 Hz, H-7a), 1.97 (1H, dd, $J_{a,b}$ = 15 Hz, $J_{6,7b}$ = 5.5 Hz, H-7b), 1.45, 1.21 (each 3H, s, isopropylidene), 1.15 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3, 145.2, 132.3, 132.1, 130.1, 130.0, 128.0, 127.9 (CH_3−*Ph*−SO_3), 112.3 (isopropylidene), 90.4 (C-5), 82.5 (C-6), 80.4 (C-8), 69.1 (C-4), 66.5 (C-1), 58.9 (C-9), 45.5 (C-7), 28.2, 26.4 (isopropylidene), 23.9 (C-10), 21.7 (*C*H_3−Ph−SO_3); *anal.* C 55.55%, H 6.05%, calcd for $C_{25}H_{32}O_9S_2$, C 55.54%, H 5.97%.

***N*-Benzylpyrrolidine 12.** Ditosylate **11** (797 mg, 1.47 mmol) was dissolved in THF (20 mL), and $BnNH_2$ (1.28 mL, 8 × 1.47 mmol) was added. The mixture was heated to 60 °C for 24 h and then to reflux for 3 days. Workup, as described above for **3**, gave a residue, which was purified on a VLC column (3 × 3 cm). Elution with hexane, and then hexane−EtOAc (20:1 to 10:1) afforded **12** as a colorless syrup (371 mg, 83%): $[\alpha]^{22}_D$ + 9.2° (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35−7.20 (5H, m, *Ph*−CH_2), 4.40 (1H, d, $J_{6,7b}$ = 4 Hz, H-6), 3.56, 3.47 (each 1H, d, J = 13 Hz, Ph−CH_2), 2.88 (1H, d,

$J_{a,b}$ = 10 Hz, H-4a), 2.71 (1H, dd, $J_{a,b}$ = 10 Hz, $J_{1a,9}$ = 8 Hz, H-1a), 2.64 (1H, d, $J_{a,b}$ = 10 Hz, H-4b), 2.54 (1H, ddd, $J_{1a,9}$ = 8 Hz, $J_{1b,9}$ = 6 Hz, $J_{7a,9}$ = 2 Hz, H-9), 2.25 (1H, dd, $J_{a,b}$ = 10 Hz, $J_{1b,9}$ = 6 Hz, H-1b), 2.18 (1H, dd, $J_{a,b}$ = 15 Hz, $J_{7a,9}$ = 2 Hz, H-7a), 2.02 (1H, dd, $J_{a,b}$ = 15 Hz, $J_{6,7b}$ = 4 Hz, H-7b), 1.52, 1.30 (each 3H, s, isopropylidene), 1.20 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 128.4, 128.2, 127.0 (*Ph*−CH_2), 110.3 (isopropylidene), 97.3 (C-5), 86.8 (C-6), 81.5 (C-8), 63.3 (C-4), 61.5 (C-9), 60.0 (Ph−*C*H_2), 56.5 (C-1), 43.8 (C-7), 27.2, 24.7 (isopropylidene), 23.3 (C-10); *anal.* C 70.97%, H 8.06%, N 4.55%, calcd for $C_{18}H_{25}NO_3$, C 71.26%, H 8.31%, N 4.62%.

Hydrogenation of *N*-Benzylpyrrolidine 12. Compound **12** (371 mg) was hydrogenated for 4 days in MeOH (5 mL) in the presence of 5% Pd/C (40 mg). The catalyst was filtered off on activated C over Celite, which then was washed with more MeOH. Concentration of the filtrate yielded **14** (237 mg, 91%): mp 64−65 °C (MeOH); $[\alpha]^{25}_D$ +27° (*c* 0.55, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 4.45 (1H, d, $J_{6,7b}$ = 4.5 Hz, H-6), 3.20 (1H, br d, $J_{a,b}$ = 12.5 Hz, H-4a), 3.13 (1H, br dd, $J_{a,b}$ = 10.5 Hz, $J_{1a,9}$ = 8.5 Hz, H-1a), 2.96 (1H, d, $J_{a,b}$ = 12.5 Hz, H-4b), 2.45 (1H, dt, $J_{1a,9}$ = $J_{1b,9}$ = 8.5 Hz, $J_{7a,9}$ = 1.5 Hz, H-9), 2.37 (1H, dd, $J_{a,b}$ = 10.5 Hz, $J_{1b,9}$ = 8.5, H-1b), 2.10 (1H, br d, $J_{a,b}$ = 15 Hz, H-7a), 2.01 (1H, br dd, $J_{a,b}$ = 15 Hz, $J_{6,7b}$ = 4.5 Hz, H-7b), 1.46, 1.30 (each 3H, s, isopropylidene), 1.19 (3H, s, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 111.8 (isopropylidene), 101.4 (C-5), 87.4 (C-6), 81.7 (C-8), 64.7 (C-9), 58.4 (C-4), 50.3 (C-1), 44.3 (C-7), 27.2, 25.1 (isopropylidene), 24.1 (C-10); *anal.* C 61.73%, H 9.17%, N 6.44%, calcd for $C_{11}H_{19}NO_3$, C 61.95%, H 8.98%, N 6.57%.

***N*-(2′-Methoxybenzyl)pyrrolidine 13.** Ditosylate **11** (2.07 g, 3.83 mmol) was dissolved in THF (15 mL), and 2-methoxybenzylamine (1.50 mL, 3.1 × 3.83 mmol) was added. The mixture was heated to reflux for 2 days. The solvent was removed in vacuo, and the residue was purified on a VLC column (4.5 × 4 cm). Elution with hexane, and then hexane−EtOAc (6:1) yielded successive fractions of almost pure **13** (453 mg, 36%) and pure *N*-(2′-methoxybenzyl)pyrrolidine **13** (229 mg, 18%) as syrups: $[\alpha]^{24}_D$ +9.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (1H, dd, J_o = 8, J_m = 2 Hz, *Ar*−CH_2), 7.23 (1H, dt, J_o = 8, J_m = 2 Hz, *Ar*−CH_2), 6.94 (1H, br t, J_o = 8 Hz, *Ar*−CH_2), 6.87 (1H, br d, J_o = 8 Hz, *Ar*−CH_2), 4.45 (1H, d, $J_{6,7b}$ = 4.5 Hz, H-6), 3.82 (3H, s, 2′-OMe), 3.64 (1H, s, 8-OH), 3.60, 3.56 (each 1H, d, *J* = 14 Hz, Ar−C*H*$_2$), 2.94 (1H, d, $J_{a,b}$ = 10 Hz, H-4a), 2.77 (1H, dd, $J_{a,b}$ =10 Hz $J_{1a,9}$ = 8 Hz, H-1a), 2.68 (1H, d, $J_{a,b}$ = 10 Hz, H-4b), 2.54 (1H, ddd, $J_{1a,9}$ = 8 Hz, $J_{1b,9}$ = 6 Hz, $J_{7a,9}$ = 2 Hz, H-9), 2.30 (1H, dd, $J_{a,b}$ = 10 Hz, $J_{1b,9}$ = 6 Hz, H-1b), 2.17 (1H, dd, $J_{a,b}$ = 15 Hz, $J_{7a,9}$ = 2 Hz, H-7a), 2.03 (1H, dd, $J_{a,b}$ = 15 Hz, $J_{6,7b}$ = 4.5 Hz, H-7b), 1.53, 1.32, (each 3H, s, isopropylidene), 1.22 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 129.6, 127.8, 126.6, 120.4, 110.3 (2-MeO−*Ph*−CH_2), 110.2 (isopropylidene), 97.5 (C-5), 86.9 (C-6), 81.5 (C-8), 63.3 (C-4), 61.6 (C-9), 56.5 (C-1), 55.3 (Ar−OCH_3), 52.9 (2-MeO−Ph−*C*H_2), 43.8 (C-7), 27.2, 24.8 (isopropylidene), 23.3 (C-10); *anal.* C 68.34%, H 8.05%, N 4.28%, calcd for $C_{19}H_{27}NO_4$, C 68.43%, H 8.17%, N 4.20%.

Deprotection of *N*-(2′-Methoxybenzyl)pyrrolidine 13. Acetonide **13** (54 mg, 0.16 mmol) was dissolved in $CHCl_3$−MeOH (3:1, 6.5 mL), and then *p*-TsOH·H_2O (30 mg, 0.16 mmol) was added. The mixture was heated to reflux for 12 h. The solvent was removed in vacuo, and Et_3N (10 μL) was added to the residue, which was purified on a VLC column (4 × 2 cm). Elution with hexane, $CHCl_3$, and then $CHCl_3$−EtOH (25:1) yielded deprotected pyrrolidine **15** (40 mg, 85%): $[\alpha]^{25}_D$ +18° (*c* 0.48, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.28−7.18, 6.95−6.85 (each 2H, m, *Ar*−CH_2), 3.79 (3H, s, 2′-OMe), 3.77 (1H, dd, $J_{6,7a}$ = 4.5 Hz, $J_{6,7b}$ = 3 Hz, H-6), 3.59, 3.54 (each 1H, *J* = 13 Hz, Ph−C*H*$_2$), 2.71 (1H, dd, $J_{a,b}$ = 10 Hz, $J_{1a,9}$ = 7.5 Hz, H-1a), 2.55 (1H, d, $J_{a,b}$ = 10 Hz, H-4a), 2.49 (1H, d, $J_{a,b}$ = 10 Hz, H-4b), 2.44 (1H, dd, $J_{a,b}$ = 10 Hz, $J_{1b,9}$ = 5 Hz, H-1b), 2.23 (1H, ddd, $J_{1a,9}$ = 7.5 Hz, $J_{1b,9}$ = 5 Hz, $J_{7b,9}$ = 2 Hz, H-9), 1.95 (1H, dd, $J_{a,b}$ = 13.5 Hz, $J_{6,7a}$ = 4.5 Hz, H-7a), 1.87 (1H, ddd, $J_{a,b}$ = 13.5 Hz, $J_{6,7b}$ = 3 Hz, $J_{7b,9}$ = 2 Hz, H-7b), 1.20 (3H, s, H-10); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.1, 131.5, 129.4, 127.4, 121.2, 111.6 (2-MeO−*Ph*−CH_2), 89.9 (C-5), 80.9 (C-8), 78.1 (C-6), 66.8 (C-4), 62.7 (C-9), 57.4 (C-1), 55.8 (Ar−OCH_3), 54.1 (2-MeO−Ph−*C*H_2), 46.6 (C-7), 23.7 (C-10); *anal.* C 65.49%, H 7.88%, N 4.70%, calcd for $C_{16}H_{23}NO_4$, C 65.51%, H, 7.90%, N 4.77%.

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