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Hydroxylated Pyrrolizidines and Indolizidines; Syntheses using Cycloaddition Reactions of Functionalized Cyclic Nitrones

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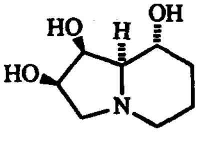
Abstract : Cycloaddition reactions of functionalised Δ^1-pyrroline-*N*-oxides have been used to prepare the hydroxylated pyrrolizidines **11** and **22**, the indolizidine **16**, and the iminoheptitol **12**.

There has been much interest in recent years in the chemistry and biological properties of polyhydroxylated pyrrolidines, piperidines, pyrrolizidines, and indolizidines. This is in large part due to the recognition that compounds of this type can act as potent and specific inhibitors of glycosidases,[1] and that this inhibition has potential application in a number of areas of medicinal importance, as is perhaps most notably illustrated by the anti-HIV activity shown by some compounds of these classes.[2] In the indolizidine subgroup, there has been much synthetic activity directed towards the mannosidase inhibitor swainsonine **1**,[3] the glucosidase inhibitor castanospermine **2**, and their analogues,[4] whilst interest in hydroxylated pyrrolizidines has been maintained by the isolation of australine **3**, alexine **4**, and a number of their stereoisomers.[5]



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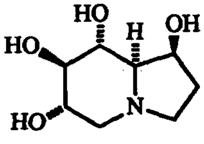

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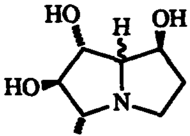
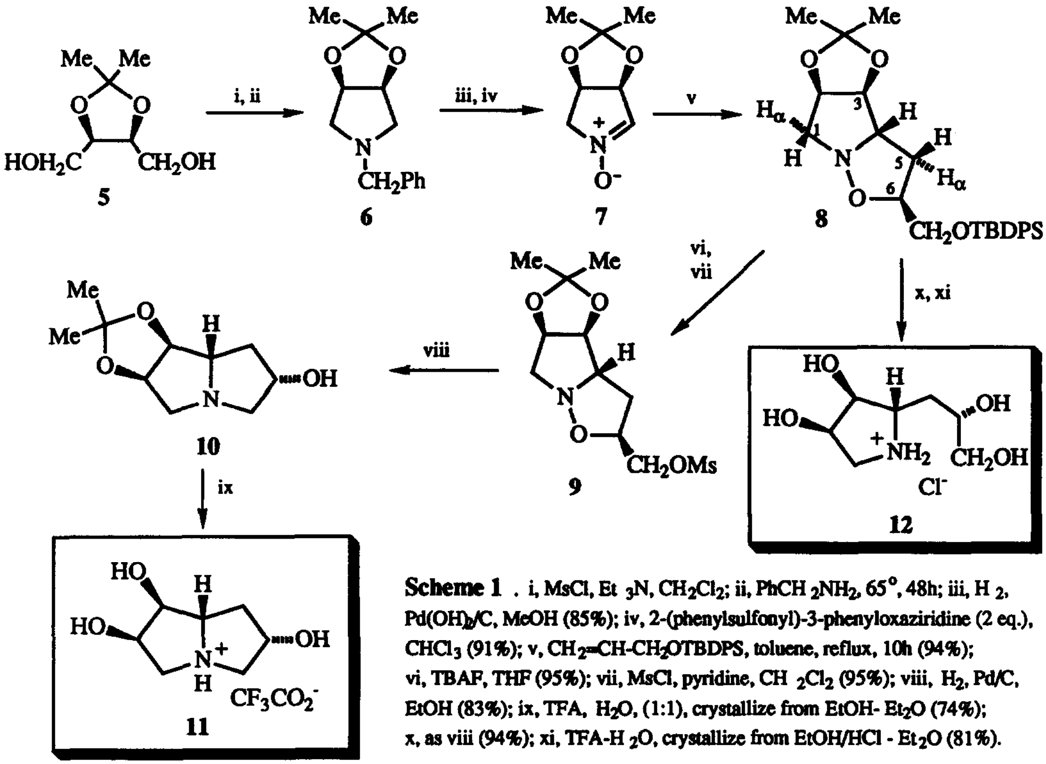


3, α-H
4, β-H

Most synthetic work in this area has used hexose and pentose sugars as chiral precursors. In this letter, we describe the use of 1,3-dipolar cycloaddition reactions of functionalized cyclic nitrones[6] to gain access to pyrrolizidines and indolizidines related to **1**, **3**, and **4**.[7]

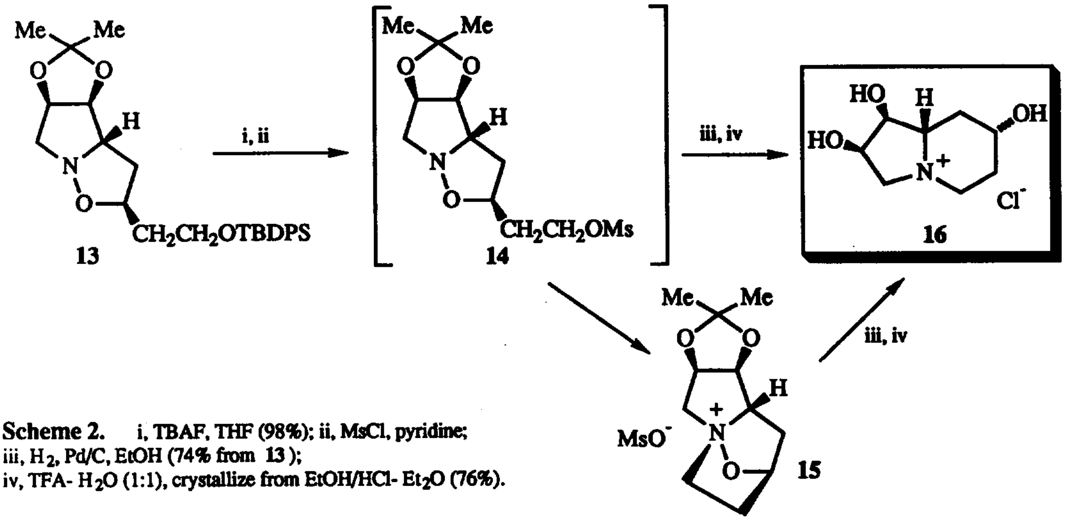
The diol **5** (Scheme 1) is easily accessible from 3,4-*O*-isopropylidene-D- or L-arabinopyranose[8] by periodate cleavage[9] and borohydride reduction. Treatment of **5** with excess methanesulfonyl chloride gave a crystalline dimesylate (84%) which could be converted to amine **6** (84%) with benzylamine. Hydrogenolysis of **6** using Pearlman's catalyst[10] gave a somewhat unstable secondary amine, which on oxidation with 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis' reagent)[11] gave the racemic nitrone **7** as a solid.[12-14] Cycloaddition of 7 and allyl *t*-butyldiphenylsilyl ether in refluxing toluene gave in high yield a single cycloadduct. The structure 8, corresponding to cycloaddition to the more accessible face of 7, and via an *exo*-transition state,[6] was established by detailed n.m.r. studies, including n.O.e. measurements in which significant enhancements between H-1$_\alpha$ and H-6, and between H-3 and H-5$_\alpha$ were particularly noteworthy.[14] Desilylation of 8 gave a crystalline alcohol, which was converted to the mesylate 9. This on hydrogenolysis cleanly gave the pyrrolizidine 10,[14] which could be hydrolysed to (1S^*, 2R^*, 6S^*, 7aS^*)-1,2,6-trihydroxypyrrolizidine, isolable as its crystalline trifluoroacetate 11.[14] Alternatively, direct hydrogenolysis of 8, followed by acid hydrolysis, gave 1,4,5-trideoxy-1,4-imino-D,L-*talo*-heptitol as its crystalline hydrochloride 12,[14] the D-enantiomer of which can be regarded as an extended version of the α-mannosidase inhibitor 1,4-dideoxy-1,4-imino-D-talitol.[15]



Scheme 1 . i, MsCl, Et$_3$N, CH$_2$Cl$_2$; ii, PhCH$_2$NH$_2$, 65°, 48h; iii, H$_2$, Pd(OH)$_2$/C, MeOH (85%); iv, 2-(phenylsulfonyl)-3-phenyloxaziridine (2 eq.), CHCl$_3$ (91%); v, CH$_2$=CH-CH$_2$OTBDPS, toluene, reflux, 10h (94%); vi, TBAF, THF (95%); vii, MsCl, pyridine, CH$_2$Cl$_2$ (95%); viii, H$_2$, Pd/C, EtOH (83%); ix, TFA, H$_2$O, (1:1), crystallize from EtOH- Et$_2$O (74%); x, as viii (94%); xi, TFA-H$_2$O, crystallize from EtOH/HCl - Et$_2$O (81%).

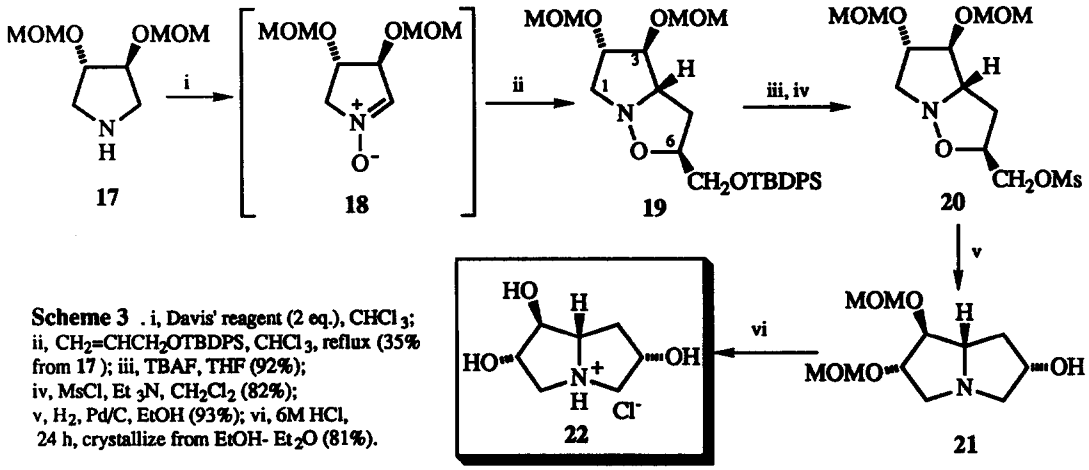
An indolizidine could be prepared in the same way (Scheme 2). Reaction of 7 with the TBDPS ether of homoallyl alcohol in refluxing toluene gave 13 (92%). This was converted to a mesylate 14 which could not be isolated due to its tendency to undergo intramolecular cyclization to 15.[16] Hydrogenation *in situ* of 14, or of 15, and acidic hydrolysis then gave 16, related to 8a-*epi*-swainsonine, which is a mannosidase inhibitor.[15,17]

The alternative 1,2-*trans*- disubstitution pattern could also be obtained by similar methods (Scheme 3). The amine 17 could be obtained from diethyl-L-tartrate in five steps (46% overall).[18] Oxidation to nitrone 18[18] and *in situ* cycloaddition gave 19 as the only isolable cycloadduct.[19] The stereochemistry of 19 was again



Scheme 2. i, TBAF, THF (98%); ii, MsCl, pyridine; iii, H_2, Pd/C, EtOH (74% from **13**); iv, TFA- H_2O (1:1), crystallize from EtOH/HCl- Et_2O (76%).

evident from nuclear Overhauser effects, with significant interaction between, in particular, H-3, H-6, and H-1$_\alpha$. Desilylation and mesylation gave **20**, which on hydrogenolytic cleavage of the N-O bond formed the pyrrolizidine **21**.[19] This could be deprotected in acid to give (1*S*, 2*S*, 6*S*, 7a*S*)-1,2,6-trihydroxypyrrolidine as its hydrochloride **22**.[19]



Scheme 3 . i, Davis' reagent (2 eq.), $CHCl_3$; ii, CH_2=$CHCH_2OTBDPS$, $CHCl_3$, reflux (35% from **17**); iii, TBAF, THF (92%); iv, MsCl, Et_3N, CH_2Cl_2 (82%); v, H_2, Pd/C, EtOH (93%); vi, 6M HCl, 24 h, crystallize from EtOH- Et_2O (81%).

None of products **11**, **12**, **16**, and **22** showed significant levels of inhibition of the replication of HIV-1. Evaluation against glycosidases will be reported elsewhere.

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14. Selected data: **7**:- m.p. 111-112°C; $\delta_H(CD_3OD)$ 3.94 (1H, dq, *J* 15.1, 1.2, H- 5β), 4.26 (1H, dddd, *J* 15.1, 5.2, 2.1, 0.6, H-5_{α}), 4.97 (1H, br. t, *J* 5.3, H-4), 5.34 (1H, br.d, *J* 5.7, H-3), 7.12 (1H, q, *J* ca. 1.5, H-2); δ_C 137.7 (C-2). **8**: - δ_H ($CDCl_3$) 2.09 (1H, ddd, *J* 12.8, 8.6, 6.7, H- 5α), 2.35 (1H, ddd, *J* 12.8, 8.3, 4.9, H-5β), 3.19 (1H, dd, J_{gem} 13.0, $J_{1\alpha,2}$ 5.7, H-1α), 3.37 (1H, dd, $J_{1\beta,2}$ 2.6, H-1β), 3.58 and 3.68 (each 1H, dd, H-7), 3.75 (1H, br.t, H-4), 4.30 (1H, m, H-6), 4.60 (1H, dd, $J_{3,2}$ 6.5, $J_{3,4}$ 1.7, H-3), 4.89 (1H, dt, *J* 6.1, 2.6, H-2). **10**:- m.p. 128-129°C; $\delta_H(CD_3OD)$ 1.63 and 2.26 (each 1H, ddd, H-7), 2.77 (1H, dd, *J* 12.8, 2.4, H-5_a), 3.05 (1H, dd, *J* 12.8, 5.6, H-5_b), 3.22 (2H, m, H-3), 3.44 (1H, br.t, *J*~8.5, H-7a), 4.38 (1H, m, H-6), 4.65 (1H, dd, $J_{1,2}$ 6.0, $J_{1,7a}$ 1.1, H-1), 4.88 (1H, ddd, H-2). **11**:- m.p. 153-154°C; δ_H (D_2O) 2.17 (1H, br.d, H-7), 2.34 (1H, ddd, H-7), 3.34 (1H, d, *J* 13.4), 3.44 (1H, dd, *J* 13.4, 3.5), 3.54 (1H, dd, *J* 12.7, 2.9), 3.75 (1H, d, *J* 12.6), 4.07 (1H, m, H-7a), 4.4 (1H, m), 4.46 (1H, dd, *J* 7.8, 3.7, H-2), 4.68 (1H, m). **12**:- m.p. 142-143°C; δ_H (D_2O) 1.9 (2H, m, H-5), 3.29 (1H, dd, *J* 13.2, 1.8, H-1_{β}), 3.45-3.6 (3H, m), 3.66 (1H, dt, H-4), 3.85 (1H, m, H-6), 4.07 (1H, dd, *J* 9.2, 4.1, H-3), 4.33 (1H, dt, H-2).
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19. Selected data: **19**:- syrup, $[\alpha]_D$ +46.5 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$) 2.33 (2H, m, 5-H), 3.11 (1H, dd, *J* 12.5, 6.0, H-1_{α}), 3.59 (1H, m, H-4), 3.60 (1H, dd, *J* 12.5, 6.2, H-1_{β}), 3.68 and 3.76 (each 1H, dd, H-7), 3.99 (1H, t, *J* 4.4, H-3), 4.13 (1H, dt, *J* 6.1, 4.3, H-2),4.35 (1H, m, H-6). **21**:- syrup, $[\alpha]_D$ -49.4 (*c* 0.87, MeOH); δ_H (CD_3OD) 1.95 and 2.2 (each 1H, m, H-7), 2.80 (1H, dd, *J* 10.7, 5.0), 2.95-3.1 (2H, m), 3.25-3.4 (8H, m), 4.1 (2H, m), 4.33 (1H, q, *J* 5.4, 6-H) 4.6 -4.75 (4H, 2ABdd, MOM). **22**:- m.p. 116-117°C; $[\alpha]_D$ -9.2 (*c* 0.75, H_2O); δ_H (D_2O) 2.2-2.5 (2H, m, 7-H_2),3.25-3.45 (2H, m), 3.67 (1H, dd, *J* 12.2, 4.9), 3.86 (1H, dd, *J* 12.3, 5.1), 4.05 (1H, m, H-7a), 4.2 -4.4 (2H, m, H-1, H-2), 4.57 (1H, q, *J* 5.1, H-6).

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