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A Meisenheimer Rearrangement Approach To Bridgehead Hydroxylated Tropane Alkaloid Derivatives.

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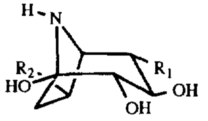
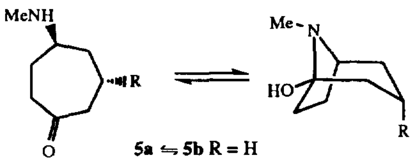
Abstract: Thermolysis of 3-*t*-butyldimethylsiloxy-8-methyl-8-azabicyclo[3.2.1]oct-6-ene *N*-oxide (**11**) and (**12**) in butyronitrile gave 3-*t*-butyldimethylsiloxy-9-methyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (**13**) which upon reductive N-O ring cleavage, hydrogenation, oxidation and deprotection yielded the 3-hydroxy analogue 8-methyl-8-azabicyclo[3.2.1]octane-1,3-diol (**6a** $\leftrightharpoons$ **6b**) of the tropane alkaloid physoperuvine.

Recently there has been considerable interest shown in the newly discovered polyhydroxylated nortropane alkaloids known as the calystegins B_1 (**1**), B_2 (**2**), A_3 (**3**) and C_1 (**4**)[1,2], which have been shown to be strong glycosidase inhibitors[3,4]. Along with physoperuvine (**5a** $\leftrightharpoons$ **5b**)[5] they are the only known nortropane and tropane alkaloids to possess an aminal functionality. The synthesis of physoperuvine has so far been achieved by two routes. The first synthesis was via a ring enlargement of 4-aminocyclohexanone derivatives[6]. The second synthesis is based on the Diels-Alder addition of a nitroso compound to cyclohepta-1,3-diene[7]. This latter method has similarities to our work in this area.



1 R_1 = H, R_2 = OH **2** R_1 = OH, R_2 = H
3 R_1 = H, R_2 = H **4** R_1 = OH, R_2 = OH



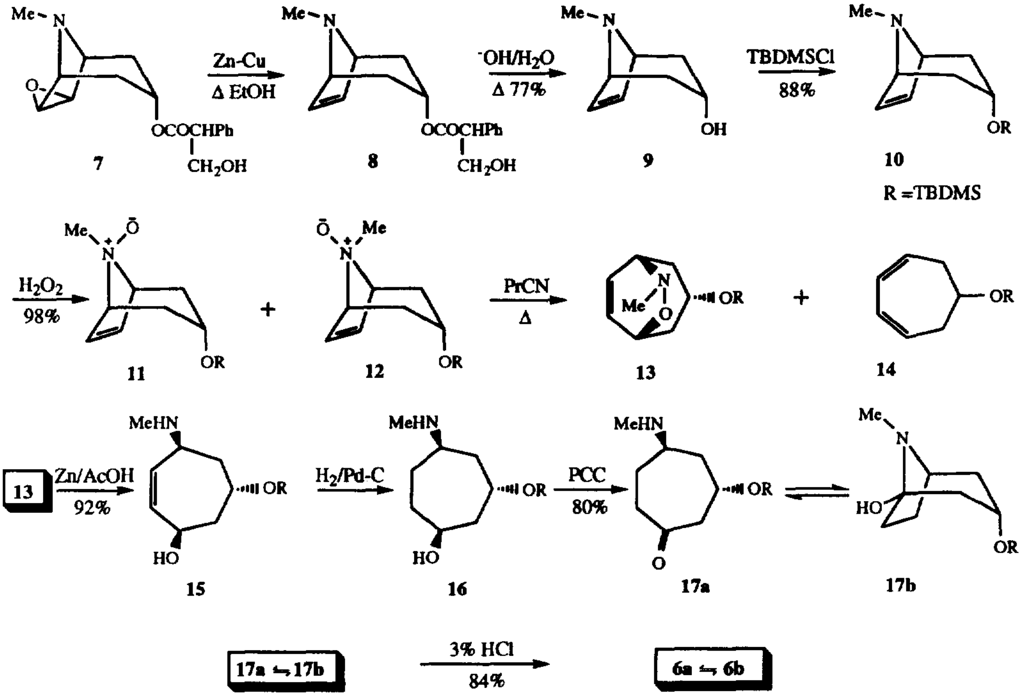
5a $\leftrightharpoons$ **5b** R = H
6a $\leftrightharpoons$ **6b** R =OH

Our initial work has focussed on approaches to the basic bridgehead hydroxylated skeleton present in these alkaloids based on an advanced alkaloid starting material. Herein we report the synthesis of a racemic 3-hydroxy analogue (**6a** $\leftrightharpoons$ **6b**) of physoperuvine, in which the tropane ring was derived from scopolamine **7**.

Scopolamine was used as the starting material because of the epoxide functionality, which upon conversion to the olefin could then facilitate a Meisenheimer rearrangement of a tropane *N*-oxide. This is the key step which allows later development of the bridgehead hydroxyl functionality.

Scopolamine was deoxygenated to give a near quantitative yield of 6,7-dehydrohyoscyamine **8**[8] (Scheme 1). The tropic acid group of **8** had to be replaced by a better protecting group so as to obviate thermally induced *N*-oxide displacement of the tropic acid residue[9]. Basic hydrolysis of **8** gave the alcohol **9**[8] which was then protected as the *t*-butyldimethylsilyl ether **10**[10].

The base **10** was then *N*-oxidised by stirring for two days with 35% H_2O_2 and ethanol. The diastereomeric *N*-oxides **11** and **12** were produced in a 1.5:1 ratio with a total yield of 98% based on ^{1}H NMR analysis of the reaction product. The diastereomer **12** could be separated by fractional crystallisation from diethyl ether. The structural assignment of **11** and **12** was based on ^{13}C NMR and NOESY experiments[11]. For the *N*-oxide **11**, nOe's were observed for the *N*-methyl group and both vinylic protons 6 and 7, but not with the *N*-oxide **12**; with this latter *N*-oxide nOe's were noted for the *N*-methyl group and the axial hydrogens at positions 2 and 4. In the ^{13}C NMR spectrum of **11** the *N*-methyl group (equatorial) gave a signal at 55.8ppm while the corresponding signal for **12** (axial *N*-methyl group) was further upfield at 48.7ppm. These results are consistent with those observed for protonated tropane alkaloids[12].



Scheme 1

Thermolysis of **11** in refluxing butyronitrile for two hours gave the desired rearranged compound **13**[13] in 53% yield after column chromatography. Kibayashi *et al.*[14] and Malpass *et al.*[15] have described the preparation of this type of bicyclic oxaza ring system by Diels-Alder addition reactions. The diastereomer **12**, after refluxing for three hours in butyronitrile, gave compound **13** in only a 15% isolated yield. The thermolysis of **11** and **12** was monitored by ^{1}N NMR analysis of samples taken at approximatly thirty minute time intervals. No Cope elimination product was detected in the thermolysis of the *N*-oxide **11**, due to the steric constraints on obtaining the preferred[16] planar transition state for this elimination.

In the rearrangement of both **11** and **12**, the TBDMS protected cyclohepta-3,5-dien-1-ol **14** was also isolated. A separate experiment demonstrated that **14** is produced from **13**, presumably as a result of a retro Diels-Alder reaction. This result accounts for the poor yield of **13** from **12**, although the reason for the slower rearrangement of **12** to **13** is not clear.

Only one diastereomer of **13**, with the 3α-siloxy group, was obtained from the *N*-oxide thermolysis experiments, suggesting that it derives directly from a Meisenheimer rearrangement. The relative stereochemistry of the siloxy group was confirmed by coupling constants and nOe's which were supported by computer modelling. The Meisenheimer rearrangement of tropane *N*-oxides does not appear to have been reported previously.

Reductive N-O ring cleavage of **13** was achieved with Zn/AcOH to give **15**[17]. Hydrogenation of **15** then gave compound **16**[18] in quantitative yield. The oxidation of **16** with PCC gave the desired TBDMS protected analogue (**17a** $\rightleftharpoons$ **17b**)[19].

The TBDMS group was then removed by stirring (**17a** $\rightleftharpoons$ **17b**) in a 3% aqueous HCl solution overnight. Basification with ammonia solution followed by the removal of the solvent under reduced pressure and separation of the remaining salts by washing with acetone gave racemic (**6a** $\rightleftharpoons$ **6b**)[20]. The structure of (**6a** $\rightleftharpoons$ **6b**) was confirmed by the NMR, IR and mass spectral data. Positive ion ES/MS gave a peak at m/z 158 assigned to MH^+ for (**6a** $\rightleftharpoons$ **6b**), while high resolution mass spectrometric analysis (EI) verified the molecular formula of $C_8H_{15}NO_2$. The ^{13}C NMR spectrum of (**6a** $\rightleftharpoons$ **6b**) in CD_3OD showed that the major compound in solution was **6b**, with signals for a quaternary carbon (δ98.1), 2 methine carbons (δ65.2 and 64.1), 1 methyl carbon (δ33.1) and 4 methylene carbons (δ45.9, 38.1, 30.3 and 24.2).

Meisenheimer rearrangement technology should be extendable to other appropriately substituted nitrogen bridged systems to allow access to new bridgehead hydroxylated derivatives.

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13. Compound **13**. ^{1}H NMR* δ: 6.50-6.40 (m, H7), 6.3-6.2 (m, H6), 4.6-4.47 (m, H3), 4.42 (t, J 7.8 Hz, H1), 3.48-3.40 (m, H5), 2.60 (s, NCH_3), 2.40-2.24 (m, axial H2 and H4), 1.68-1.45 (m, equatorial H2 and H4), 0.86 (s, $C(CH_3)_3$) and 0.06 (d, J 1.5 Hz $Si(CH_3)_2$); ^{13}C NMR δ: 132.5 (C7), 129.6 (C6), 68.8 (C3), 68.8 (C1), 67.6 (C5), 46.4 (NCH_3), 41.0 (C2 or C4), 39.8 (C2 or C4), 25.7 ($C(\underline{C}H_3)_3$), 17.9 ($\underline{C}(CH_3)_3$) and -4.8 ($Si(CH_3)_2$); MS m/z 269 (M^+, 0.8%; Calcd. for $C_{14}H_{27}NO_2Si$: 269.1811, found: 269.1807), 226 (13), 144 (13), 101 (20) and 75 (100); IR (neat) 2952, 2928, 2856, 1647, 1462, 1257, 1085, 883, 836 and 775 cm^{-1}.
   *NMR spectra were run in $CDCl_3$ (unless stated otherwise) at 300MHz (^{1}H) and 75.5MHz (^{13}C).
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17. Compound **15** 4-methylamino-6-*t*-butyldimethylsiloxycyclohept-2-enol. ^{1}H NMR δ: 6.00 (m, H2), 5.75 (m, H3), 4.55 (b, H6), 4.26 (b, H1), 3.61 (b, H4), 2.43 (s, NCH_3) and 1.70-1.95 (m, H5 and H7). ^{13}C NMR δ: 139.6 (C2), 131.0 (C3), 66.6 (C1), 64.6 (C6), 53.2 (C4), 43.1 (C5 or C7), 38.9 (C5 or C7), 32.3 (NCH3), 25.7 (($C(\underline{C}H_3)_3$), 18.0 ($\underline{C}(CH_3)_3$), -4.9 and -4.8 ($Si(\underline{C}H_3)_2$); MS m/z 271 (M^+, 7%; Calcd. for $C_{14}H_{29}NO_2Si$: 271.1967, found: 271.1969), 253 (14), 226 (17), 183 (20), 110 (32), 96 (58) and 74 (100); IR (neat) 3296, 2931, 2857, 1660, 1471, 1255, 1077, 837 and 775 cm^{-1}.
18. Compound **16**. ^{1}H NMR δ: 4.21 (m, 1H), 4.00 (b, 1H), 2.85 (b, 1H), 2.38 (s, NCH_3), 2.20-1.65 (m, 8H), 0.84 (s, $C(CH_3)_3$), and 0.06 (s, $Si(CH_3)_2$); ^{13}C NMR δ: 67.5 (C1), 65.3 (C3), 56.8 (C5), 43.8, 37.2, 32.4, 30.76 (NCH3), 26.0, 25.7 ($C(\underline{C}H_3)_3$), 17.8 ($\underline{C}(CH_3)_3$), -5.0 ($Si(CH_3)_2$); MS m/z 273 (M^+, 0.5%; Calcd. for $C_{14}H_{31}NO_2Si$: 273.2124, found: 273.2122), 242, 200, 185, 75(100), and 57; IR (neat) 3280, 2929, 2857, 1472, 1253, 1070, 886 and 775 cm^{-1}.
19. Compound (**17a** $\rightleftharpoons$ **17b**). ^{1}H NMR ($CDCl_3$) **17a** δ: 4.20 (b, H3), 3.04 (b, H5), 2.40 (s, NCH3) 2.53-1.69 (b, H2, H4, H6 and H7); ^{13}C NMR **17a** δ: 201.8, 65.8, 57.8, 47.6, 41.0, 38.0, 32.6, 27.6, 25.7 ($C(\underline{C}H_3)_3$), 17.9 ($\underline{C}(CH_3)_3$) and -5.1 ($Si(CH_3)_2$); MS m/z 271 (M^+, 3%; Calcd. for $C_{14}H_{29}NO_2Si$: 271.1967, found: 271.1962), 214 (20), 96 (57), 75 (100) and 57 (84); IR (KBr) 3128, 2947, 2882, 2866, 1464, 1342, 1266, 1200, 1075, 1031, 1005, 880, 834 and 770 cm^{-1}; IR ($CHCl_3$) 1703 cm^{-1}.
20. Compound (**6a** $\rightleftharpoons$ **6b**). ^{1}H NMR (CD_3OD) **6b** δ: 4.24 (b, H3), 3.82 (b, H5), 2.72 (s, NCH3), 2.8-1.8 (b, H2, H4, H6 and H7), ^{13}C NMR (CD_3OD) **6b** δ: 98.1 (C1), 65.2, 64.1, 45.9, 38.1, 33.1, 30.3 and 24.2; MS m/z 157 (M^+, 12%; Calcd. for $C_8H_{15}NO_2$: 157.1103, found: 157.1105), 140 (12), 129 (10), 113 (18), 98 (17), 86 (29), 70 (60) and 57 (100); IR (neat) 3422, 1693, 1637, 1472, 1424, 1366, 1271, 1233, 1212, 1157 and 1039 cm^{-1}.

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