Tetrahedron Letters, Vol.31, No.4, pp 469-472, 1990
Printed in Great Britain

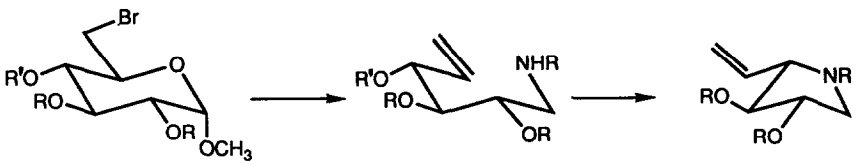
0040-4039/90 $3.00 + .00
Pergamon Press plc

A SHORT, VERSATILE APPROACH TO POLYHYDROXYLATED PYRROLIDINES UTILIZING A REDUCTIVE ELIMINATION-REDUCTIVE AMINATION AS A KEY STEP

Ronald C. Bernotas
Merrell Dow Research Institute, 2110 E. Galbraith Rd.
Cincinnati, Ohio 45215

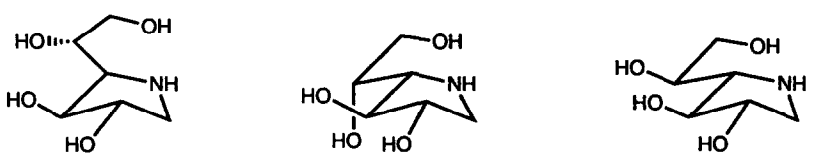
Summary: An efficient synthesis of epimeric alpha-vinyl pyrrolidines starting from methyl 4,6-O-benzylidene gluco- and galactopyranosides gave ready access to hydroxylated pyrrolidines.

Many polyhydroxylated piperidines, indolizidines, and pyrrolidines are potent glycosidase inhibitors both *in vitro* and *in vivo*.[1] Recent studies have shown some of these inhibitors possess promising antimetastatic[2] and antiviral activities[3] which may result from their ability to block glycosidase-dependent glycoprotein processing in cells. The therapeutic potential of such hydroxylated azacycles combined with the challenge of efficiently constructing these highly functionalized molecules makes them attractive targets for synthesis.[4] We have developed an approach to these compounds which takes advantage of a one pot reductive elimination-reductive amination used to convert bromopyranoside **1a** into amino alkene **2a**.[5] We reasoned that a similar reaction applied to partially deprotected **1b**



1a R = R' = CH_2Ph **2a** R = R' = CH_2Ph **3**
1b R = CH_2Ph, R' = H **2b** R = CH_2Ph, R' = H

could produce amino alcohol **2b** which, upon cyclization, could furnish vinyl pyrrolidine **3**. Furthermore, by varying the carbohydrate starting material, a series of epimeric pyrrolidines might be made by essentially the same route. The viability of this approach for rapid and efficient production of polyhydroxylated pyrrolidines was demonstrated by the syntheses of tetrols **4**, **5**, and **6**.



4 **5** **6**

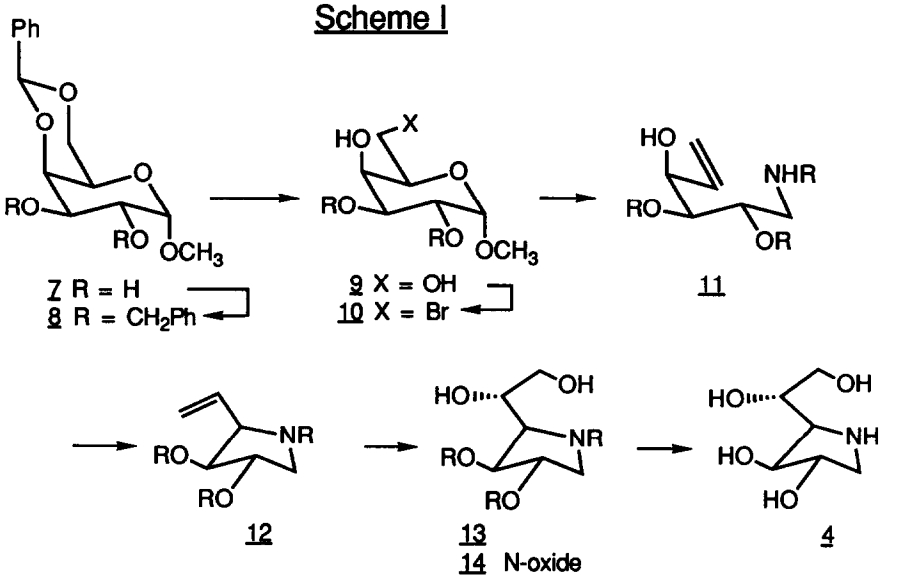
Preparation of pyrrolidine 4 by this route started with readily available methyl 4,6-O-benzylidene-alpha-D-galactopyranoside 7[6] which was benzylated ($NaH/PhCH_2Br/DMF$, rt, 100%) to afford 8 (Scheme I). Removal of the benzylidene group under mild acidic conditions (H_2SO_4/MeOH, rt, 98%) produced diol 9 which was selectively transformed into primary bromide 10[7] (Ph_3P/CBr_4/pyridine, 70%).[8] Reductive elimination-reductive amination ($Zn/NaBH_3CN/PhCH_2NH_2$/1-PrOH/H_2O, reflux, 2h, 82%) proceeded smoothly to produce amino alcohol 11 in a single step. It was found that the intramolecular cyclization of 11 was best effected under Mitsunobo conditions;[9] thus, hydroxyl activation and displacement (Ph_3P/DEAD/THF, rt, 95%) cleanly provided 12. No products from potential side reactions (S_N1, S_N2') were observed. The overall yield of vinyl pyrrolidine 12 from 7 was 53%.

Completion of the synthesis of 4 required conversion of the alkene of 12 into a diol. This was achieved by a catalytic osmylation procedure[10] (4-methylmorpholine-N-oxide/OsO_4 (0.01 mole eq)/dioxane/water, rt, 24h) which afforded an easily separable mixture of desired diol 13 (61%), its N-oxide 14 (10%) and recovered starting material (6%). This surprisingly high diastereoselectivity may result from the same factors which control the selectivity in the osmylation of allylic ether and alcohol systems;[11] here, as in the related systems, OsO_4 preferentially approaches the olefin from the face opposite the allylic heteroatom. In the case of 12, the steric bulk of the N-benzyl group could also play a major role in controlling the diastereoselectivity of the reaction. Finally, removal of the protecting groups by catalytic hydrogenation of the hydrochloride salt of 13 (10% Pd·C/EtOH) gave, after ion exchange and recrystallization, pyrrolidine 4[12] in 86% yield (m.p. 200-202°C (dec.), lit.[13] m.p. 200-202°C). Hydrogenation of 14 (10% Pd·C/HCl/H_2O/EtOH) also produced 4 (92%, isolated as the hydrochloride salt).

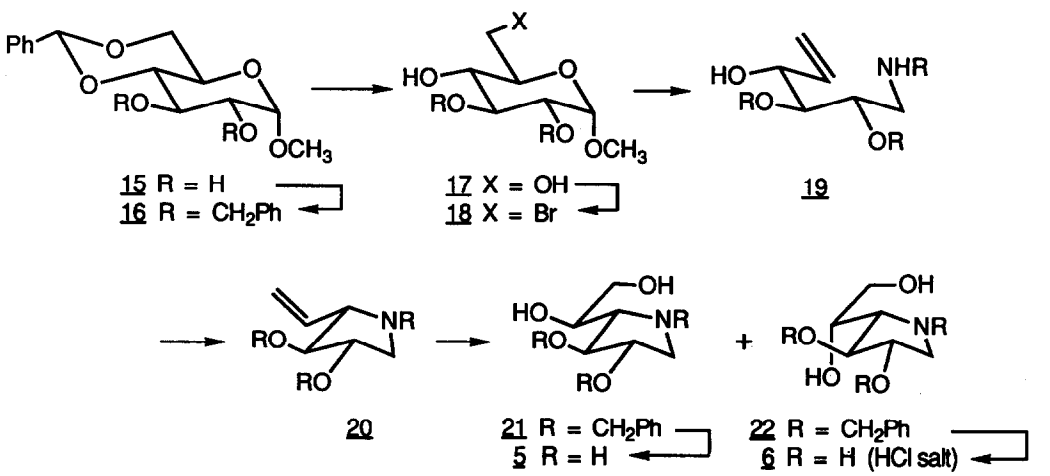
The versatility of this approach was demonstrated by its application to the syntheses of 5 and 6 (Scheme II). Beginning with commercially available methyl 4,6-O-benzylidene-alpha-D-glucopyranoside 15 (the C-4 epimer of 7), a similar five step sequence produced pyrrolidine 20 in 58% overall yield. In comparison to the reaction of its vinyl epimer 12, the osmium tetroxide catalyzed oxidation of 20 was less selective, resulting in a separable mixture of diastereomeric diols 21 and 22 (75:25 respectively, 68% combined yield) along with recovered 20 (16%). The hydrochloride salts of diols 21 and 22 were individually debenzylated to give 5 (as the free amine after ion exchange) and 6 (as the hydrochloride salt) in 80% and 89% recrystallized yields, respectively.[14]

In conclusion, readily available carbohydrate starting materials were efficiently converted into alpha-vinyl pyrrolidines by a short yet versatile route. The syntheses of tetrols 4, 5, and 6 demonstrated that these alpha-vinyl pyrrolidines can be readily transformed into more highly functionalized molecules. We are currently extending this approach to the synthesis of novel glycosidase inhibitors.

Scheme I



Scheme II



Acknowledgements: We thank Dr. John M. Kane for helpful discussions.

FOOTNOTES AND REFERENCES

[1] See Setoi, H., Kayakiri, H., Takeno, H., Hashimoto, M., Chem. Pharm. Bull., **35**, 3995 (1987) and 3b for leading references.

[2] Humphries, M. J., Matsumoto, K., White, S. L., Olden, K., Cancer Research, **46**, 5215 (1986).

[3] (a) Sunkara, P.S., Inamura, N., Bowlin, T. L., Liu, P. S., Sjoerdsma, A., Biochem. Biophys. Res. Comm., **148**, 206 (1987). (b) Fleet, G. W. J., Tyms, A. S., et al., FEBS Letters, **237**, 128 (1988).

[4] For leading references see Pederson, R. L., Kim, M.-J. K., Wong, C.-H., Tetrahedron Letters, **29**, 4645 (1988), and references 2b and 6.

[5] Bernotas, R. C., Ganem, B., Tetrahedron Letters, **26**, 1123 (1985); see also Bernotas, R. C., Pezzone, M. A., Ganem, B., Carbohydrate Research, **167**, 305 (1987).

[6] Sorkin, E., Reichstein, T., Helv. Chim. Acta, **28**, 1 (1945).

[7] All new compounds gave satisfactory elemental analysis (C, H and N $\pm$ 0.4%) and spectral analysis (IR, CIMS, ^{1}H NMR, ^{13}C NMR) except **14** (IR, CIMS, ^{1}H NMR only).

[8] Anisuzzaman, M., Whistler, R. L., Carbohydrate Research, **61**, 511 (1978).

[9] Mitsunobu, O., Synthesis, **1981**, 1.

[10] Van Rheenen, V., Kelley, R. C., Cha, D. Y., Tetrahedron Letters, **23**, 1973 (1976).

[11] Cha, J. K., Christ, W. J., Kishi, Y., Tetrahedron, **40**, 2247 (1984); see Brimacombe, J. S., Kabir, A. K. M. S., Carbohydrate Research, **168**, C5-C7 (1987) for pyranose examples.

[12] Fleet, G. W. J., Son, J. C., Tetrahedron, **44**, 2637 (1988).

[13] Kuszmann, J., Kiss, L., Carbohydrate Research, **153**, 45 (1986).

[14] Assignment of the epimers was based on a comparison of the physical states and optical rotations of the free amines of **5** (crystalline, $[\alpha]_D^{20}$ = +2.8° (c = 2.0, H_2O)) and **6** (syrup, $[\alpha]_D^{20}$ = -1.4° (c = 2.4, water)). Compound **6** has been reported as a syrup with $[\alpha]_D^{20}$ = -0.8° (c = 2, water); see Paulsen, H., Steinert, K, Heyns, K., Chem. Ber., **103**, 1599 (1970). Spectral data **5**: IR (KBr) 3400-3200 (broad), 2970, 2940, 2905, 2800-2300 (broad), 1510, 1300, 1130, 1105, 1070, 1025, 920 cm^{-1}; CIMS (isobutane) 164 (100%, M+H$^+$), 102 (4%); ^{1}H NMR (D_2O) 4.11 (1H, m), 4.04 (1H, m), 3.77-3.70 (2H, m), 3.57 (1H, dd, J = 7.9, 12.4 Hz), 3.04 (1H, dd, J = 5.1, 12.3 Hz), 2.87-2.81 (2H, m); ^{13}C NMR (D_2O) 81.65, 80.47, 75.07, 68.37, 66.34, 53.57; m.p. 134-135°C.
6·HCl: IR (KBr): 3550-2900 (broad), 1565, 1110, 1020, 970 cm^{-1}; CIMS (isobutane) 164 (100%, M+H$^+$), 146 (5%), 102 (8%); ^{1}H NMR (D_2O) 4.35 (1H, m), 4.18 (1H, broad t, J = 3.8 Hz), 4.01 (1H, m), 3.80 (1H, dd, J = 3.6, 12.2 Hz), 3.68 (1H, dd, J = 5.0, 12.0 Hz), 3.60-3.53 (2H, m), 3.35 (1H, dd, J = 3.0, 12.7 Hz); ^{13}C NMR (D_2O) 78.94, 76.97, 71.48, 69.12, 65.69, 52.29; m.p. 103-104°C; $[\alpha]_D^{20}$ = -20.4° (c = 1.0, water).

(Received in USA 10 November 1989)