Tetrahedron Letters, Vol. 34, No. 7, pp. 1211-1214, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Cycloaddition Reactions of Carbohydrate Derivatives. Part IV.[1] Synthesis of a Tetrahydroxyindolizidine through a Cyclic Nitrone Prepared from D-xylose.

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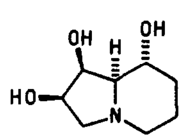
Abstract: Intramolecular conjugate addition of the oxime from aldehyde 5 led to the formation of cyclic nitrone 6. 1,3-Dipolar cycloaddition of the latter with methyl acrylate gave the bicyclic 7 with high diastereoselection. Subsequent four-step transformation of 7 resulted in the tetrahydroxyindolizidine derivative 11.

1,3-Dipolar cycloaddition reactions of nitrones are very useful approaches towards the synthesis of complex natural products.[2,3] Cyclic nitrones seem to be especially attractive for the construction of nitrogen-containing polycycles. Regio- and diastereoselectivity of cycloadditions of those dipoles have been studied thoroughly by Ali et al..[4,5] Recently Grigg et al. reported on a novel method of generation of cyclic nitrones by intramolecular conjugate addition of oximes (1,3-azaprotio cyclotransfer reaction) and studied the cycloaddition reactions of the intermediates.[6] We realized that application of such a reaction to sugar derived systems would not only lead to interesting saccharide nitrones[7] but it can also serve as a strategy for the synthesis of polyhydroxylated indolizidines, analogs of biologically active natural products such as swainsonine[8] 1 and castanospermine[9] 2.



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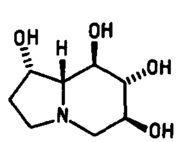

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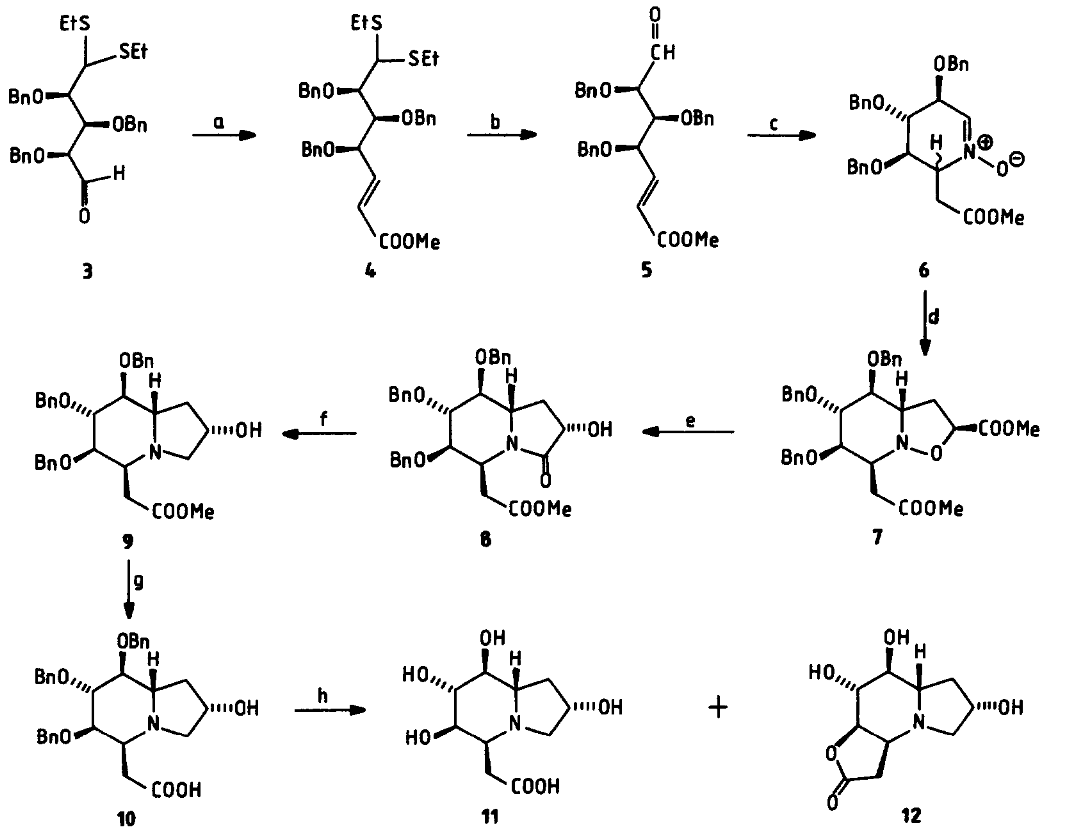
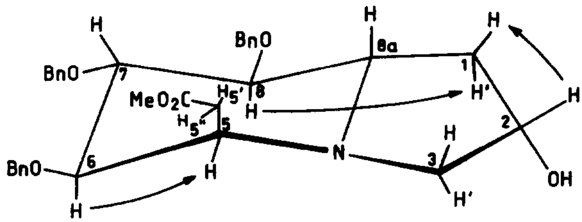
For the preparation of the unsaturated aldehyde 5 the dialdose mercaptal 3, obtained from D-xylose in five steps,[10] was chosen. Wittig reaction of 3 yielded the carboxylate 4[11] with *trans* configuration. Mercury salt promoted demercaptalization of 4 gave 5. The latter was allowed to react with hydroxylamine in ethanol-water mixture at room temperature giving rise to a diastereomeric mixture of the nitrones 6. Addition of methyl acrylate to the reaction mixture resulted in the



(a) Ph_3PCHCO_2Me, boiling benzene, 91%; (b) $HgCl_2$, $CdCO_3$, acetone/H_2O, 60%; (c) H_2NOH, EtOH/H_2O, rt; (d) addition of methyl acrylate, 36% (for c,d); (e) Zn, AcOH, 50°C, 87%; (f) $Me_2S{\cdot}BH_3$, boiling THF, 69%; (g) $Ba(OH)_2$, EtOH/H_2O, reflux, then CO_2, 80%; (h) H_2/Pd(C), AcOH, 45% for 11, 53% for 12.

precipitation of the bicyclic 7 in crystalline form after 16 hours in 36% yield. In the mother liquor another isomer could be detected by NMR. The ratio of the two diastereomers was 3:1 in favour of 7. Three new chiral centers were generated in two subsequent steps 5→6→7, therefore the stereochemical outcome of these reactions is very remarkable.

Reduction of the N-O bond of 7 with zinc in acetic acid gave, after subsequent lactamization, indolizidine 8. The lactam carbonyl of 8 was reduced with borane-dimethyl sulfide to obtain 9. The configurations at the chiral centers C-2, C-5 and C-8a in 9 were established by NMR. NOE enhancements were detected between H-5 and H-6, H-1' and H-8 as well as H-1 and H-2 as depicted below.



The value of $J_{8,8a}$ (9 Hz) reveals a *trans* diaxial relationship between protons. The ester protective group was hydrolized using barium hydroxide to give **10**. Attempted removal of the *O*-benzyl protective groups by catalytic hydrogenation using palladium on charcoal in acetic acid resulted in the formation of lactone **12** as well as the expected acid **11** in approximately equal amount. **12** can be transformed into **11** by hydrolysis with base. In the IR spectra of compounds **9**, **10** and **11** containing two C-H bonds in diaxial positions to the lone pair of the nitrogen, so called Bohlmann bands[12] could be observed in the region of 2600-2900 cm^{-1}.

Thus, it has been demonstrated that the cyclic nitrone approach is a valuable tool for the diastereoselective synthesis of polyhydroxylated indolizidines. Further study of this method is under way in our laboratory. Biological assay of the end-products will be reported elsewhere.

Acknowledgments: This work has been supported by the Hungarian Academy of Sciences through a grant OTKA 1181.

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11. All new compounds were characterized with satisfactory elemental analyses and/or spectral data. Selected physical data: **4**: $[\alpha]_D$= -3 (c= 0.77, $CHCl_3$); MS: m/z= 580 (M^+). ^{1}H-NMR: δ ($CDCl_3$): 6.10 (dd, 1H, H-2, $J_{2,3}$= 16 Hz). **5**: $[\alpha]_D$= +2 (c= 0.71, $CHCl_3$). ^{1}H-NMR: δ ($CDCl_3$): 9.65 (d, 1H, -CHO). **6**: MS: m/z= 489 (M^+). **7**: m.p. 103-105°, $[\alpha]_D$= -22 (c= 1.5, $CHCl_3$). MS: m/z= 575 (M^+). **8**: m.p. 103-104°, $[\alpha]_D$= -74 (c= 1.57, $CHCl_3$). MS: m/z= 546 (M^+). **9**: $[\alpha]_D$= -52 (c= 2.7, $CHCl_3$). MS: m/z= 532 (MH^+). **10**: m.p. 153°, $[\alpha]_D$= -44 (c= 0.7, $CHCl_3$). MS: m/z= 517 (M^+). **11**: m.p. 158°, $[\alpha]_D$= -53 (c= 0.3, MeOH). ^{1}H-NMR: δ (D_2O): 1.47 (ddd, 1H, H-1', $J_{1,1'}$= 12.5 Hz, $J_{1',8a}$= 8.2 Hz, $J_{1',2}$= 4.0 Hz); 2.32 (dd, 1H, H-5", $J_{5,5''}$= 4.5 Hz); 2.42 (dd, 1H, H-5', $J_{5',5''}$= 15 Hz, $J_{5,5'}$= 6.5 Hz); 2.54 (ddd, 1H, H-1); 2.63 (dd, 1H, H-8a, $J_{1,8a}$= 6 Hz); 2.77 (dd, 1H, H-3', $J_{3,3'}$= 10.5 Hz); 2.88 (dd, 1H, H-3); 3.31 (dd, 1H, H-8, $J_{8,8a}$= 9 Hz); 3.39 (dd, 1H, H-7, $J_{7,8}$= 8.6 Hz); 3.74 (m, 1H, H-5); 3.79 (dd, 1H, H-6, $J_{6,7}$ = 8.6 Hz); 4.41 (m, 1H, H-2, $J_{1,2}$= 5 Hz, $J_{2,3}$= 4 Hz, $J_{2,3'}$= 2 Hz). **12**: m.p. 184°, $[\alpha]_D$= -16 (c= 0.71, MeOH). MS: m/z= 229 (M^+). ^{1}H-NMR: δ (D_2O): 1.59 (ddd, 1H, H-1', $J_{1',8a}$= 8 Hz, $J_{1',2}$= 4 Hz); 2.54 (ddd, 1H, H-1, $J_{1,1'}$= 13 Hz, $J_{1,2}$= 7.5 Hz, $J_{1,8a}$= 7.5 Hz); 2.69 (dd, 1H, H-8a); 2.80 (dd, 1H, H-3', $J_{3,3'}$= 10 Hz); 2.90 (dd, 1H, H-3); 3.41 (dd, 1H, H-8, $J_{8,8a}$= 9 Hz); 3.60 (dd, 1H, H-7, $J_{7,8}$ = 9.5 Hz); 4.14 (dd, 1H, H-6, $J_{5,6}$= 7.5 Hz, $J_{6,7}$= 7.5 Hz); 4.18 (m, 1H, H-5); 4.45 (m, 1H, H-2, $J_{2,3}$= 7 Hz, $J_{2,3'}$= 2 Hz).
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(Received in UK 1 December 1992)