Tetrahedron Letters,Vol.30,No.15,pp 1993-1996,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

β,γ-UNSATURATED α-AMINO ACID δ-LACTONES; PRECURSORS FOR POLYHYDROXY AMINO ACIDS

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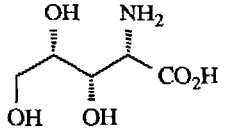
Enantiocomplementary routes to (R)- and (S)- Z-2-amino-5-hydroxy-pent-3-enoic acid lactones are described, starting from D-xylose.

Polyhydroxy α-amino acids such as polyoxamic acid (1) are of considerable current interest [1] because of the problems associated with the stereocontrolled construction of polyfunctional acyclic amino acids. We therefore report a chiral route to β,γ-unsaturated α-amino acid δ-lactones which should afford flexible access to a range of such structural variants.

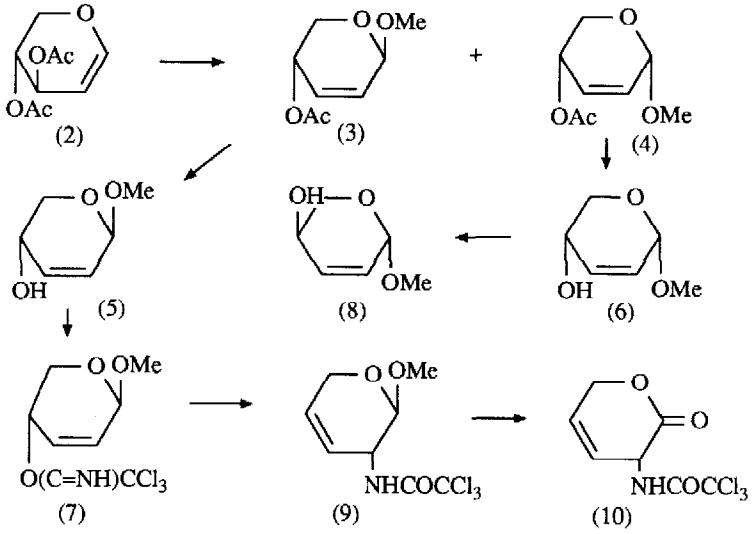


(1)

Triacetyl D-xylosyl bromide was converted into the diacetyl xylal (2) by a modification of the original method[2] (Zn-Cu/AcOH). Rearrangement to the 2,3-unsaturated 4-xylals (3) and (4) can be achieved with $BF_3.Et_2O$-MeOH[3], or $SnCl_4$-MeOH[4], or $PdCl_2$-MEOH[5], in good yield and giving an easily separable mixture of the two anomers, each being optically pure.

The subsequent synthetic steps will be described for anomer (3), but it is of importance to note that anomer (4) can be converted in good yields into the alcohol (6) (K_2CO_3-MeOH) which was inverted by the Mitsunobu reaction [6] (DEAD-PPh_3,$PhCO_2H$) hydrolysed (MeOH-NaOH) to give (8), which is the enantiomer of (5)[7]. No competitive S_n2^1 displacement or dehydration occurred.

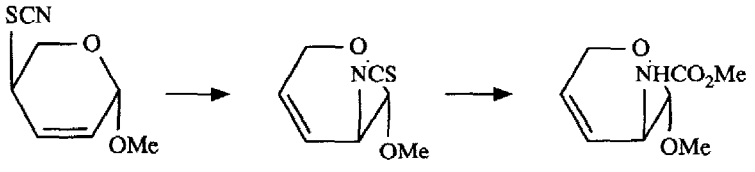
The Overman rearrangement[8], which to our knowledge has not been employed in the synthesis of α-amino acids, was used to introduce the amino group stereospecifically to the 3α-position of the carbohydrate. Thus, allylic alcohol (5) was transformed into the 5α-trichloromethylimidate (7) (Cl_3CCN, NaH) which rearranged smoothly in refluxing xylene to the trichloromethyl amide (9)[9,10] (80%).



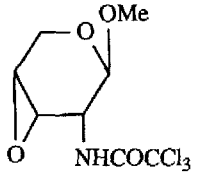
Hydrolysis of the glycosidic group (2M HCl) was followed by oxidation, best achieved by DMSO-Ac_2O[11], giving unsaturated lactone (10) (77%).

Further flexibility in this approach comes from use of thiocyanates such as (11), obtained Sn2 displacement on the mesylate derived from (6), with no allylic rearrangement. Suprafacial rearrangement to the isothiocyanate (12) occurred (80%) in refluxing toluene. Hydrolysis of (12) (AcOH-NaOAc) gave the 2β-acetamide (13) (61%).

Subsequent transformations of these systems are illustrated by the epoxidation of aminoglycoside (9) and aminolactone (10). The former was stereoselective, whereas the latter gave both α-and β-epoxides. Treatment of (8) with MCPBA gave, interestingly, only the α-epoxide (14)[13]. Further stereoselective conversions of (9) and (10) are in progress and will be reported.



(11) (12) (13)



(14)

Thus, we have observed a range of stereospecific transformations from the key precusor (5). Its enantiomer (8) is available as described, and enantiocomplementary reactions are therefore accessible. Additional manipulations in the thiocyanate-isothiocyanate series add further flexibility.

Acknowledgements

We thank ICI Agrochemicals for financial support, SERC for a studentship (R.J.O.) and for a grant towards high field NMR.

1. M. Hirama, H. Hioki and S. Ito, *Tetrahedron Letters*, 1988, 3125, and refs. cited therein.

2. B. Helferlich, E.H. Mulcahy and H. Ziegler, *Chem. Ber.*, 1954, 87, 233; M. Barczai-Martos and F. Korosy, *Nature*, 1950, 369.

3. R.J. Ferrier and N. Vethaviyaser, *J. Chem. Soc* (C), 1970, 1385.

4. G. Grynkiewcz, W. Priebe and A. Zamojski, *Carb. Res.*, 1979, 68, 33; P. Phate, D. Horton and W. Priebe, *Carb. Res.*, 1985, 144, 331.

5. L.V. Dunkerton, K.T. Brady and F. Mohamed, *Tetrahedron Letters*, 1982, 23, 599.

6. O. Mitsunobu, *Synthesis*, 1981, 1.

7. The NMR spectra of (6) and (7) were superimposable, and the $[\alpha]_D$ values were reversed

8. L.E. Overman, *J. Amer. Chem. Soc.*, 1976, 98, 2901.

9. m.p. 91.0-91.5°; $[\alpha]_D$ ($CDCl_3$)-216° (c. 12 mg/ml); Found: C, 35.0; H, 3.6; N, 5.1. $C_8H_{10}NO_3Cl_{13}$ requires C, 35.0; H, 3.7; N, 5.0; υ_{max} ($CDCl_3$) 3400 and 1710 cm^{-1}; δ_H ($CDCl_3$ 6.9 (1H, br., NH), 6.08 (1H, m, =CH), 5.82 (1H, m, =CH), 4.71 (1H, s, 1-H), 4.29-4.07 (3H, m, 2-H and 5β-H) and 3.50 (3H, s, OMe); δ_C ($CDCl_3$) 161.4 (CO), 131.0, 120.0 (2x=CH), 98.9 (1-C), 92.3 (Cl_3), 58.9 (5-C), 56.1 (2-C) and 47.1 (OMe); CIMS 274 (M+1).

10. The trichloromethylimidate derived from the α-methoxy anomer (6) rearranged much more slowly because of steric congestion in the transition state.

11. A.J. Mancuso and D. Swern, *Synthesis*, 1981, 165.

12. m.p. 81.83°; $[\alpha]_D$ ($CDCl_3$) - 5.6° (c. 8.7 g/ml); Found: C 48.9 H, 5.7; N, 8.2. $C_7H_{10}NO_4$ requires C, 49.2; H, 5.3; N 8.2%); υ_{max} (CD_2Cl_2) 3420, 1750 and 1725 cm^{-1}; δ_H ($CDCl_3$ 6.12-6.06 (1H, m, =CH), 6.05-5.98 (1H, dt, J 9.5, 2 Hz =CH), 5.62 (1H, br., NH exch), 5.04-4.8 (2H, m, 5α-H and 5p-H), 4.76 (1H, m, 2-H), and 3.74 (3H, s, OMe); δ_C ($CDCl_3$) 177.9 (lactone CO), 168 (CO), 127.9, 123.8 (each, = CH), 68.2 (5-C), 526. (2-C) and 49.9 (OMe); CIMS, 172 (M+1).

13. X-ray crystallographic structure. For relevant studies of diastereoselectivity in allylic amide epoxidations see; W.R. Roush, J.A. Straub and R.J. Brown, *J. Org. Chem.*, 1987, 52, 5127.

(Received in UK 22 February 1989)