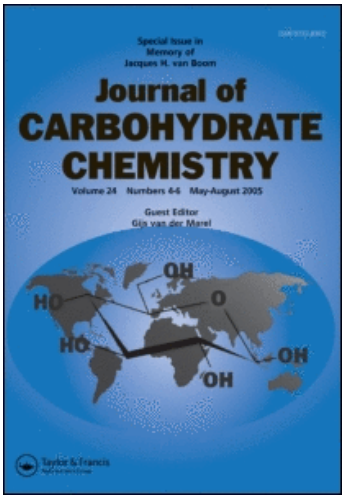

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COMMUNICATION

A STEREOCONTROLLED SYNTHESIS OF A LINCOSAMINE PRECURSOR.[a]

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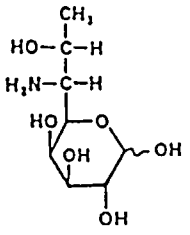
We report the first stereocontrolled synthesis of the protected lincosamine 2d, the sugar moiety of the clinically important antibiotic lyncomycine.[1] To achieve the synthesis of 1, the key structural problem to be solved is the formation of the chiral center C-6 in the D-*glycero* configuration. In the numerous previous attempts made from D-galactose,[2] very little success was obtained as far as stereocontrol is concerned. A fully synthetic route to (±)-methyl-β-lincosaminide was also reported.[3]

A structure of type 2 was chosen as the target molecule because the reduction of the keto-group in diversely protected aminoketones 2a[4] and 2b was already shown to afford the correct configuration at C-7 for lincosamine as the major product.

Since a D-*galacto* pyranose subunit is present in the target molecule, the protected dialdosugar derivative 3 was employed as starting material and the ethynyl group was used to introduce two carbon atoms and a masked methyl ketone.

[a] Chain-extension of Carbohydrates, IV.



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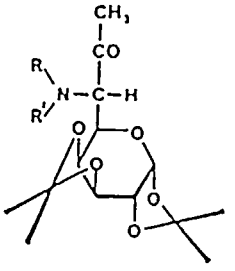
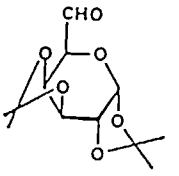


2a (R= H, R'= $PhCH_2$)

2b (R= H, R'= Ac)

2c (R= Ac, R'= $PhCH_2$)

2d (R= $PhCH_2$, R'= $PhCH_2OCO$)

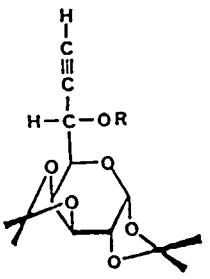


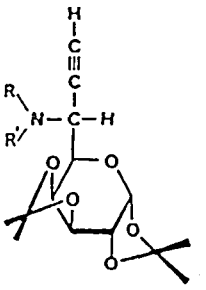
3

Compound 3 was smoothly ethynylated with complete stereocontrol by the Grignard reagent of trimethylsilylacetylene in the presence of an excess of magnesium bromide in ether.[5] Desilylation of the crude adduct (Et_3N, 3HF ; CH_3CN, R.T.) afforded 4 (mp 135-7°C) which was isolated in 73% yield from 3 by recrystallization (dichloromethane-petroleum ether). Absence of the D-*glycero* epimer in the obtained product was verified by GLC analysis.

Activation of the hydroxyl group of 4 was achieved with trifluoromethanesulfonyl anhydride (pyridine, 1,2-dichloroethane, R.T.). Subjection of 5 to benzylamine in the same pot (5 days, R.T.) gave 6a, mp 83-5°C[6], in 76% yield from 4a.

Hydration of the triple bond in 6a was not possible under standard acidic conditions. When the reaction was carried out under mild and strictly anhydrous conditions ($Hg(OAc)_2$/AcOEt then H_2S)[7] the *N*-acetyl, *N*-benzyl amino ketone 2c, was obtained in 68% yield (37.7% overall yield from 3 ; mp 38°C).[6] Examination of the 250 MHz ^1H NMR spectrum of 2c clearly indicated that no epimerization occurred during this step. Although in a less efficient way (7% overall yield), compound 2c was previously prepared from 3[2e] and transformed into protected 1 after debenzylation [2e] and reduction.[2b]





4 R= H

5 R= SO_2CF_3

6a (R= H, R'= $PhCH_2$)

6b (R= $PhCH_2OCO$, R'= $PhCH_2$)

Alternatively, the amino function of 6a was protected as its carbobenzyloxy derivative 6b ($PhCH_2OCOCl/Et_2O$, Na_2CO_3/H_2O, R.T., 87%) which was transformed into the amino-ketone 2d as above (65%).[6] The *N*-benzylaminoketone 2a, resulting from hydrogenolysis of the carbobenzyloxy group has previously been transformed into protected 1.[4]

Taking account of previous results [2b,4] related to the reduction of these protected aminoketones (*vide supra*), this approach constitutes the first fully stereocontrolled synthesis of lincosamine by the chain extension of D-galactose.

REFERENCES and NOTES

1. Lincomycin is a copyrighted trademark of the Upjohn Co. Kalamazoo, MI. For an excellent review of the chemistry of lincomycin see B. J. Magerlein, in "*Structure-Activity Relationships Among the Semisynthetic Antibiotics*" ;E. Pearlman, Ed.; Academic Press, New-York, 1977,pp. 601-650.

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6. All isolated compounds gave satisfactory elemental analysis and spectroscopic data (IR and 250 MHz ^{1}H NMR) in agreement with their structure.

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