Tetrahedron Letters, Vol.22,No.46,pp 4635-4638,1981 0040-4039/81/464635-04$02.
Printed in Great Britain

CIS - OXYAMINATION ROUTES TO AMINO SUGARS: A SIMPLE SYNTHESIS OF HOLACOSAMINE

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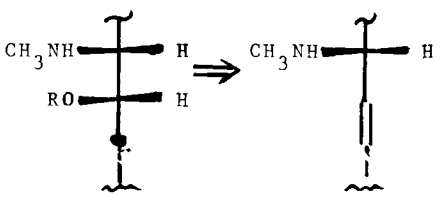
SUMMARY: *The known D-threo hex-2-enopyranoside 7a is converted into an N-methyl allyl amine, the methyl urethane of which undergoes electrophile-induced cyclisation to give the iodocyclic urethane 9. The cis relationship of H3 and H4 in the latter is confirmed by NMR spectroscopy. Reduction at C2 and C6 is done simultaneously and the cyclic urethane is hydrolysed. The amino group is then acetylated and the hydroxy group methylated.*

Holacosamine, 1, is a component of the glycosteroids holantiosine[2], holacurtin[3], holarosine[3] and mitiphylline[4] which are of some interest as cardiotonic agents[2]. There has been only one reported synthesis of this amino sugar which was undertaken primarily for reasons of structure proof[5] However, the demanding route pursued in this endeavor amply illustrates many of the problems associated with the syntheses of deoxyamino sugars. In this communication we report a simple route to 1 which promises to be of general applicability for the synthesis of a wide variety of deoxyamino sugars.



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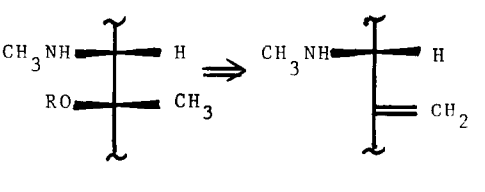
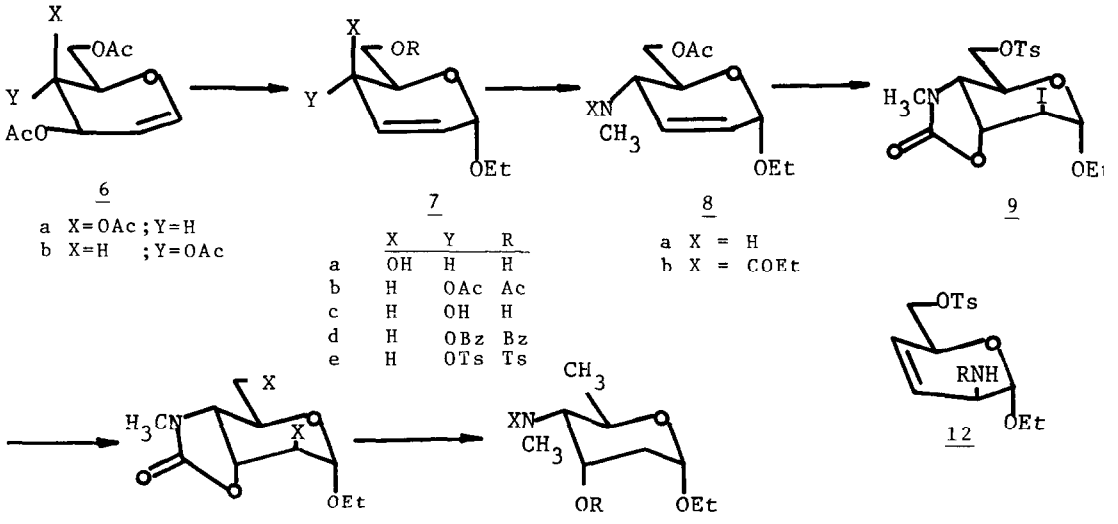


4 5

The structural feature 2 represents the critical segment of holacasamine in which neighboring carbons bear cis-amino-hydroxy and deoxy functionalities. The usual routes to the cis-amino alcohol[6] involve (i) opening of an epoxide with a nitrogen nucleophile, followed by displacement of a sulfonate ester by an oxygen nucleophile, or (ii) displacement of a selectively activated hydroxyl in a vicinal trans-diol, by a nitrogen nucleophile. Both procedures obviously require several protection - deprotection episodes in order that only the desired hydroxyl group

becomes activated. Furthermore, since amines are not strong enough to displace secondary sulfonates on a sugar ring, azide ion is usually used, and even then, fairly drastic conditions must be employed. For example, in the earlier synthesis of 1 the azide displacement of a p-toluenesulfonate ester required heating in dimethylformamide at 150° for two hours[5].

In a recent synthesis of garosamine, we described a novel procedure for securing the vicinal cis-amino alcohol relationship in deoxyamino sugars[7]. In that study, the key structural feature was 4 which was obtained from an exocyclic methylene derivative represented here as 5. By comparison, the structural component 2 requires an allyl amine represented by 3. Such amines should be obtainable from readily available[8,9] unsaturated sugars, and we therefore decided to explore the application of our oxyamination procedure to the synthesis of holacosamine.



6

a X=OAc; Y=H
b X=H ; Y=OAc

7

	X	Y	R
a	OH	H	H
b	H	OAc	Ac
c	H	OH	H
d	H	OBz	Bz
e	H	OTs	Ts

8

a X = H
b X = COEt

9

10

a X = I
b X = H

11

a X=R=H
b X=Ac; R=H

12

1 X = Ac; R=OCH_3

The starting material for the synthesis was the known α-D-threo hex-2-enopyranoside, 7a, which can be obtained from commercially available D-galactal triacetate, 6a, by the Ferrier reaction[10]. However, the yields in this transformation are poor. We therefore utilized an indirect route beginning with D-glucal triacetate, 6b, since the α-D-erythro diacetate 7b is easily obtained as a crystalline material[11]. The C4 configuration of

the derived diol 7c was inverted by the Mitsunobu reaction[12], and the resulting dibenzoate 7d was processed in the usual way to give the ditosylate 7e. The overall yield from 6b to 7e is 51%.

Being allylic the C4 sulfonate of 7e is highly amenable to nucleophilic displacement and hence the desired amino functionality could be introduced directly instead of requiring the conventional procedure of azide displacement and subsequent processing. Thus, upon treatment of 7e with methylamine in dimethylsulfoxide at room temperature, the selective displacement occurred giving the amino sulfonate in 71% isolated yield. The structure of the latter was confirmed as 8a by comparing the ^{1}H NMR spectrum: (5.0 ppm (J_{12}=3Hz, H1), J_{34}=6Hz, J_{23}=9Hz) with the corresponding values for the diol 7c[11]. The product of S_N2' reaction, 12, was not detected. The urethane 8b was prepared directly in 80% yield by treatment of 8a with ethyl chloroformate in methylene chloride. The configuration at C4 was apparent from the ^{1}H NMR spectrum which showed H4 at 6.5 ppm with a coupling constant J_{56}=11Hz.

In a typical experiment the urethane 8b, (1.2g, 0.5 mmol) was dissolved in dry dioxane (15 ml) and the solution was brought to reflux. Iodonium dicollidine perchlorate[13] (3.5 equivalents) was added in three portions at 15 minute intervals and a total reaction time of 45 minutes was used. The solution was then evaporated to dryness and the residue redissolved in diethyl ether. After washing with dilute (0.5N) hydrochloric acid, sodium thiosulfate and water, the solution was dried and chromatographed to afford the cyclic urethane 9 (1.03g) in 71%. The structure of 9 was evident from its ^{1}H NMR spectrum which lacked olefinic absorptions, and showed an anomeric proton, H1, at 5.1 ppm with a coupling constant of 6Hz. The signal for H4 appeared at 4.7 ppm as a doublet of doublets with J_{45}=10Hz and J_{34}= 4Hz thereby confirming the axial orientation of the C3 oxygen.

The key iodosulfonate 9 was converted into the diiodide 10a by refluxing for two hours with sodium iodide in acetone. Reduction with tri-n-butyl tin hydride then led to the 2,6-dideoxy derivative 10b obtained as a crystalline material mp 68°, ($C_{10}H_{17}NO_4$: Calcd C 55.80, H. 7.96, N 6.51; Found C 55.58, H 7.98, N. 6.54). ^{1}H NMR, 60 MHz ($CDCl_3$, TMS): 4.8 (d,1,J_{12}=5.0, H1), 2.15 (m,2,H2,H2'), 4.5 (m,1,H3).

With this key intermediate in hand all that remained were some simple adjustments of the functionalities at C3 and C4. Thus, the cyclic urethane 10b was hydrolyzed with 5% potassium hydroxide in ethanol and the resulting oily amine 11a was treated with acetic anhydride in methanol. The resulting amide 11b upon treatment with sodium hydride, methyl iodide and

the tetra-n-butyl ammonium iodide gave the protected holacosamine 1 in 80% yield as a crystalline material[14] mp 83-84°. $[\alpha]_D$ = +6.29° (c, 0.035 in $CHCl_3$). $C_{12}H_{23}N\,O_4$: Calcd C 58.78, H 9.38, N 5.71; Found C 58.84, H 9.50, N 5.92. ^1H NMR, 200 MHz ($CDCl_3$. TMS): 4.86 (d,1,$J_{1,2a}$=4.0,H1). 4.32-4.52 (m,2,H4,H5); 3.70 (m,1,$J_{2e,3}$=2.5, $J_{2a,3}$=3.5, H3), 2.26 (td, 1, $J_{2a,2e}$=15, H2e), 1.95, (dt. 1, H2a). The NMR resonances for the acetyl, O-CH_3 and N-CH_3 groups all show up as double signals indicating the two geometric forms of the amide.

ACKNOWLEDGEMENTS: We are grateful to Professor Donald MacKay (University of Waterloo) for many helpful discussions.

REFERENCES

1. Financial support for the work in Canada was obtained from the Natura Sciences and Engineering Research Council, and in the United States from the National Cancer Institute (CA 28193).
2. H. Brockmann, Progr. Chem. Org. Natural Prods., 1963, 21, 121.
3. M.M. Janot, Ph. Devissaguet, Q. Khuong-Huu, J. Parello, N.G. Bisset and R. Goutarel, C.R. Acad. Sci., Ser. C., 1968, 266, 388.
4. M.M. Janot, M. Leboeuf, A. Cave. R.O.B. Wijesekera and R. Goutarel, ibid. Ser. C., 1968, 267, 1050.
5. J. Hildesheim, S.D. Gero, Q. Khuong-Huu and C. Monnoret, Tetranedron Letters, 1969, 2849.
6. D. Horton, In "The Amino Sugars" volume IA, R. Jeanloz, Ed., Academic Press, New York, 1969.
7. H.W. Pauls and B. Fraser-Reid, J. Am. Chem. Soc., 1980, 102, 3956.
8. R.J. Ferrier, Advan. Carbohyd. Chem. Biochem., 1965, 20 67; 1969, 24, 199.
9. B. Fraser-Reid, Accts. Chem. Research, 1975, 8, 192.
10. D.M. Ciment and R.J. Ferrier, J. Chem. Soc., C 1966, 441.
11. R.J. Ferrier and N. Prasad, ibid., 1969, 570.
12. O. Mitsunobo, Synthesis, 1981, 1.
13. R.U. Lemieux and A.R. Morgan, Can. J. Chem., 1965, 43, 2199.
14. We were unable to obtain from Drs. Gero or Monneret a sample or a spectrum of the material prepared twleve years ago which was the methyl αβ, anomeric mixture corresponding to 1. The elemental analysis and high resolution ^1H NMR spectrum confirm the structure of our product.

(Received in USA 27 July 1981)