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STEREOSPECIFIC ACCESS TO BRANCHED-CHAIN CARBOHYDRATE SYNTHONS.

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Abstract : Appropriate precursors for the synthesis of D-vancosamine and L-evernitrose have been stereospecifically obtained from methyl 4,6-O-benzylidene-2-deoxy-α- and β-D-threo-hexopyranosid-3-ulose.

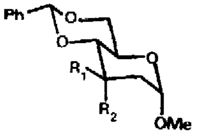
We have shown [1] that the addition of KCN to methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose 1 under conditions of thermodynamic control in CH_2Cl_2 solution in the presence of $NaHCO_3$ and water, followed by mesylation, furnished a product 3 belonging to the arabino-series.In contrast, the addition of HCN to 1 , under kinetic control in pyridine solution, followed by mesylation, has been shown by Yoshimura and al.[2] and by us [1] to afford a compound 2 with the ribo-configuration.

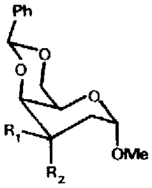
In an attempt to synthesize D-vancosamine 4 , the enantiomer of the branched-chain amino-sugar present in the glycopeptide antibiotic vancomycin [3] and L-evernitrose 5 , the naturally occurring nitro-sugar found in the oligosaccharide antibiotics everninomicin-B, C and D [4], methyl 4,6-O-benzylidene-2-deoxy-α-D-threo-hexopyranosid-3-ulose 6 [5] was submitted to the above mentioned reactions.Under conditions of thermodynamic control 6 afforded a single cyano-mesylate 7 , yield 78% [m.p. 97-99°C,$[\alpha]_D$ + 124° (c 0.7)] of unexpected configuration [1].Under conditions of kinetic control, again a single cyano-mesylate 8 was obtained, yield 73% [m.p. 128-130°C,$[\alpha]_D$ + 150° (c 1.3)] whose configuration at C-3 was also considered as surprising in the light of previous results [1,2].

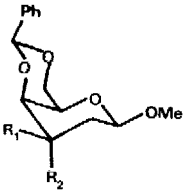
These observations have prompted us to investigate the influence of the anomeric configuration on the steric course of the reactions.Thus, methyl 4,6-O-benzylidene-2-deoxy-β-D-threo-hexopyranosid-3-ulose 9 [m.p. 177-178°C ,$[\alpha]_D$ - 29° (c 1.0)] prepared in

80% yield by CrO_3-pyridine oxidation of 10 was submitted to the cyanohydrin formation reactions.Each reaction afforded again a single cyano-mesylate.The technique which permitted to obtain 7 from 6 afforded 11 (yield 69%)[m.p. 140-141°C,$[\alpha]_D$ + 9°(c 1.3)] from 9 and the method which allowed the isolation of 8 from 6 gave 12 (yield 84%)[m.p. 127-128°C,$[\alpha]_D$ + 20°(c 1.3)] from 9.These results indicate that other factors than steric hindrance originating from the anomeric substituent are responsible for the stereochemistry at C-3 in the cyano-mesylates prepared.

Using the method of Bourgeois [7], compounds 7 and 8 were transformed into the amines 13 [oil,$[\alpha]_D$ + 100°(c 1.0)] and 14 [m.p. 76-79°C,$[\alpha]_D$ + 110°(c 0.7)] respectively with overall yields of 13% and 19%.In the same way, 11 and 12 were transformed into the amines 15[oil,$[\alpha]_D$ - 21°(c 1.0)] and 16 [oil,$[\alpha]_D$ - 22°(c 1.0)] respectively with overall yields of 18% and 32%.Compounds 13 and 15 on the one hand and compound 14 [6] on the other are appropriate precursors for the synthesis of the branched-chain sugars D-vancosamine 4 and L-evernitrose 5 respectively.



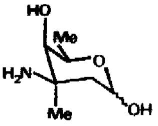




1 R_1R_2 = =O
2 R_1 = CN;R_2=OMs
3 R_1 = OMs;R_2=CN

6 R_1R_2 = =O
7 R_1 =CN;R_2=OMs
8 R_1 =OMs; R_2=CN
13 R_1 =NH_2; R_2=Me
14 R_1 =Me; R_2=NH_2
17 R_1 =OH ; R_2=Me
18 R_1 =Me ; R_2=OH
21 R_1R_2 = =CH_2

9 R_1R_2 = =O
10 R_1 =H; R_2=OH
11 R_1 =CN;R_2=OMs
12 R_1 =OMs;R_2=CN
15 R_1 =NH_2; R_2=Me
16 R_1 =Me; R_2=NH_2
19 R_1 =OH ; R_2=Me
20 R_1 =Me ; R_2=OH



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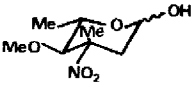

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^{13}C n.m.r. spectroscopy has been shown to be an excellent method to determine the configuration of substituents on quaternary centres [8] and this technique was used to establish the structure of all the new compounds.Carbon signal assignments for 7, 8, 11, 12, 13, 14, 15, 16 and for the models 17, 18, 19 and 20 are in the Table [9].Model 17 was prepared from 21 [10] by peracid treatment and $AlLiH_4$ reduction of the resulting two epoxides.The tertiary alcohols* 17 [oil,$[\alpha]_D$ + 91° (c 1.1)] and 18 [5] obtained in a ratio of 1 : 4 were separated by preparative thin layer chromatography.Models 19 and 20 were obtained in a ratio of 6 : 4 by a Grignard reaction from 9 with methyl magnesium iodide in ether.Attempts to separate them was unsuccessful and the spectral data shown in the Table result from an analysis of their mixture.

Table. ^{13}C chemical shifts [9], [a]

	7	8	11	12	13	14	15	16	17	18	19	20
C-1	95.9	97.3	97.2	99.0	99.2	99.7	100.9	99.9	99.0	99.7	100.9	99.9
C-2	32.6	34.1	36.3	36.0	39.1	36.9	41.2	39.6	39.1	35.8	41.3	39.4
C-3	74.2	74.6	77.6	76.4	48.8	49.2	54.2	52.0	70.0	68.9	71.4	69.7
C-4	72.3	73.4	71.9	72.8	80.0	80.5	79.1	78.8	78.9	78.4	78.2	77.8
C-5	58.0	60.7	64.7	65.4	61.4	59.6	66.2	65.8	61.7	59.9	66.0	65.6
C-6	69.1	69.5	69.3	69.3	70.3	70.5	69.8	70.3	70.0	70.3	69.7	70.1
C≡N	115.0	116.1	114.6	115.6	-	-	-	-	-	-	-	-
OMe	55.4	55.5	56.7	57.0	55.0	55.3	56.4	56.3	55.0	55.4	56.5	56.5
SMe	40.1	40.6	40.4	40.3	-	-	-	-	-	-	-	-
C-3-Me	-	-	-	-	26.1	26.8	24.1	29.6	24.9	25.3	23.3	26.8

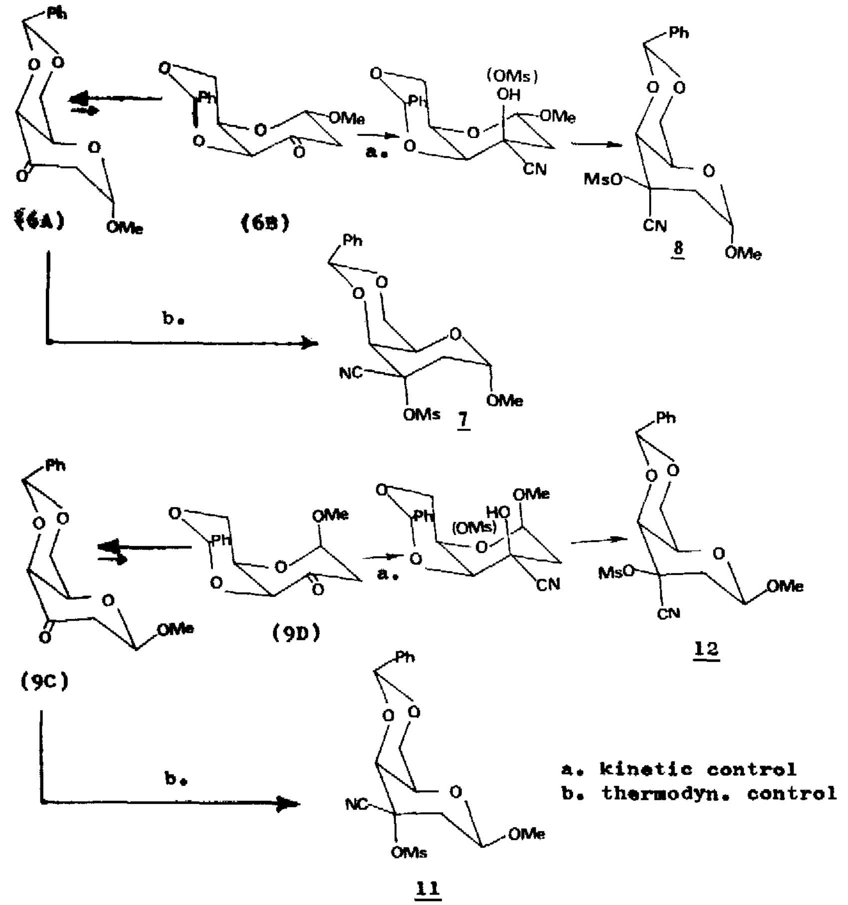
[a] benzylidene carbon signals appear for all compounds at 101.5 ± 0.5, 2 x 126.0 ± 0.2, 2 x 128.3 ± 0.2, 129.1 ± 0.2 and 136.5 ± 0.3.

Structural differentiation for the epimeric compounds was based on the diagnostic C-5 chemical shift in the case of the α-D-pyranosides and on the anomeric carbon shift for the β-D-pyranosides.It has been shown previously[1] that when C-5 bears an hydrogen atom situated 1,3-diaxially with respect to a C-3/O or C-3/N linkage, as in 7, 14 or 18, the chemical shift of C-5 is at higher field than in 8, 13 and 17, in which this hydrogen atom is 1,3-diaxially situated with respect to a C-3/CH$_3$ or C-3/CN bond.The same argument was extended to the anomeric carbon shifts in the case of the β-D-pyranosides 11, 12, 15, 16, 19 and 20.

In order to explain our apparently anomalous results under kinetic control, a conformational equilibrium between (6A) and (6B) was considered for the cis-decaline system. The equatorial approach of CN$^-$ would be then governed by the axial orientation of the C-5/C-6 bond of conformer (6B) affording after mesylation the kinetic product 8.In the case of 9, where the conformational equilibrium between (9C) and (9D) should be strongly in favour of the former, the axial configuration of the C-5/C-6 and C-1/O linkages on conformer (9D) directs the equatorial approach of CN$^-$ thus furnishing 12.

Under thermodynamic control, reaction of CN$^-$ on 6 and 9,followed by mesylation , permitted to isolate respectively 7 and 11 as the only stable compounds.Their stability may be related to the trans diaxially oriented two oxygen atoms attached to C-3 and C-4.

In the light of this interpretation, the structure of the products obtained in the cyanohydrin formation reactions from 1[1], 6 and 9 is well understood.



a. kinetic control
b. thermodyn. control

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