Tetrahedron Letters No. 13, pp 1153 - 1156. 0040-4039/79/0322-1153$02.00/0

SYNTHESIS OF NOGALOSE , A COMPONENT OF THE ANTITUMOR ANTIBIOTIC NOGALAMYCIN.

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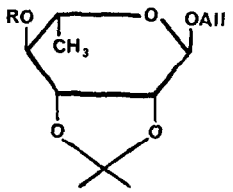
Four naturally occurring 3-C-branched-chain monosaccharides are known in which the configuration of the substituent at C-2 in the most favoured conformation is axial : nogalose (21)[1], vinelose [2], evalose [3] and sibirosamine [4].A synthesis of vinelose has already been reported [14,15].We have recently developed a general method applicable for the preparation of all the four monosaccharides and wish to report here as an example the synthesis of nogalose (21) (2,3,4-tri-O-methyl-3-C-methyl-L-rhamnopyranose) a constituent of the antitumor antibiotic nogalamycin [5].

Benzyl 4-O-methyl-α-L-rhamnopyranoside (2)(oil,$[\alpha]_D$ -55.2°) was readily prepared from benzyl α-L-rhamnopyranoside (1)[6] using a procedure applied to the synthesis of a compound closely related to (2)[7].Partial benzoylation of (2) in pyridine solution at - 45°C afforded in 80% yield a mixture of monobenzoates in which unexpectedly [8] the undesired compound (3)(mp. 144-145°,$[\alpha]_D$ -43.4°)(65%) predominated; the desired (4) (oil,$[\alpha]_D$ -44.3°) constituted only 35% of the mixture.

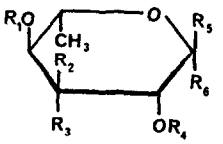
This result prompted us to explore the possibility of the selective protection of the C-3 hydroxy group by another technique.Dibutylstannylene derivatives formed in the reaction between di-n-butyltin oxide and cyclohexanoid axial-equatorial vicinal diols were reported [9] to open in the presence of alkylating or acylating agents with total regioselectivity.The treatment of dibutylstannylene derivatives with halides constitutes an efficient method of acylation or alkylation of the equatorial hydroxy group in an equatorial-axial pair [9].However, it is well known that the case of the dibutylstannylene derivative of methyl 4,6-O-benzylidene-α-D-mannopyranoside is an exception [9].While the mannoside derivative yielded exclusively the 3-O-benzyl ether with benzyl bromide, a mixture of the corresponding 3-O-benzoate and 2-O-benzoate was obtained with benzoyl chloride [9].Based on this result the synthesis of nogalose (21) could be completed in the following way :

Allyl α-L-rhamnopyranoside (5) (oil,$[\alpha]_D$ -56°) could be prepared in much higher yield (92%) than benzyl α-L-rhamnopyranoside (1)[6].Allyl 4-O-methyl-α-L-rhamnopyranoside (6)(oil,$[\alpha]_D$ -81°) was obtained in quantitative yield from (5) through allyl 2,3-isopropylidene-α-L-rhamnopyranoside (7)(oil,$[\alpha]_D$-32°), methylation (8)(oil,$[\alpha]_D$-55°) and acid hydrolysis of the isopropylidene group.Reaction of (6) with di-n-butyltin

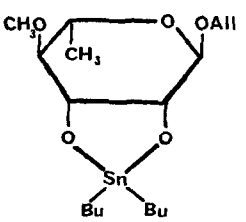
oxide [9] in methanol afforded (9) which in the presence of an excess of benzyl bromide in DMF solution under reflux gave allyl 3-O-benzyl-4-O-methyl-α-L-rhamnopyranoside (10) (oil, $[\alpha]_D$ -5°) in 94% yield. Isomerisation of the allyl group of (10) into a propenyl group proceeded only after protection of its C-2 hydroxy function. The di-propenyl compound (12)(oil, $[\alpha]_D$ -29°) was readily prepared from (11)(oil, $[\alpha]_D$ -44°) by potassium t-butoxide treatment in DMSO solution [10]. Depropenylation of (12) was instantaneous in the presence of mercuric chloride [11] affording 3-O-benzyl-4-O-methyl-L-rhamnopyranose (13) with an overall yield of 85% from (10). Treatment of (13) with 1,1-dimethoxy cyclohexane in DMF solution at 55°/15 mm in the presence of a catalytic amount of p-toluene sulfonic acid gave 3-O-benzyl-1,2-O-cyclohexylidene-4-O-methyl-β-L-rhamnopyranose (14)(mp. 78-80°, $[\alpha]_D$ +27°) in 68% yield.



(7) R=H
(8) R=CH_3



(1) R_1=R_2=R_4=R_6=H; R_3=OH; R_5=OBn
(2) R_2=R_4=R_6=H; R_1=CH_3; R_3=OH; R_5=OBn
(3) R_2=R_6=H; R_1=CH_3; R_3=OH; R_4=Bz; R_5=OBn
(4) R_2=R_4=R_6=H; R_1=CH_3; R_3=OBz; R_5=OBn
(5) R_1=R_2=R_4=R_6=H; R_3=OH; R_5=OAll
(6) R_2=R_4=R_6=H; R_1=CH_3; R_3=OH; R_5=OAll
(10) R_2=R_4=R_6=H; R_1=CH_3; R_3=OBn; R_5=OAll
(11) R_2=R_6=H; R_1=CH_3; R_3=OBn; R_4=All; R_5=OAll
(12) R_2=R_6=H; R_1=CH_3; R_3=OBn; R_4=Prop; R_5=OProp
(19) R_6=H; R_1=R_2=R_4=CH_3; R_3=R_5=OCH_3
(20) R_5=H; R_1=R_2=R_4=CH_3; R_3=R_6=OCH_3

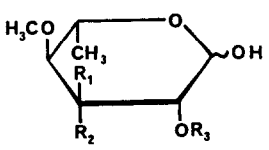


(9)

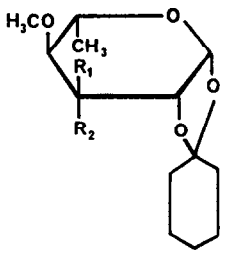
All = Allyl; Bn = Benzyl; Bz = Benzoyl; Prop = Propenyl; Bu = Butyl

Compound (14) was of great importance for the completion of the synthesis of nogalose (21). The substituent at C-2 of (14) and of nogalose (21) is of axial orientation. This substituent of (14) being involved in a cyclohexylidene group, the preparation of the ketone (16), a prerequisite for the construction of the branched-chain of (21), became possible without the risk of isomerisation at C-2 to the more stable equatorial configuration [12]. Furthermore, the presence of a bulky cyclohexylidene protecting group in (14) ensured (vide infra) the predominant upper-face attack of the Grignard reagent on the ketone (16).

Debenzylation of (14) proceeded smoothly affording (15)(oil, $[\alpha]_D \sim 0°$) which was oxidized with DMSO-$(Ac)_2O$ in 95% yield to the ketone (16). Reaction of (16) with methyl-



(13) R_1=R_3=H ; R_2 = OBn
(21) R_1=R_3=CH_3; R_2= OCH_3



(14) R_1=H ; R_2= OBn
(15) R_1=H ; R_2= OH
(16) R_1R_2 = =O
(17) R_1=CH_3 ; R_2= OH
(18) R_1=OH ; R_2= CH_3

magnesium iodide in ether furnished in 60% yield two alcohols (17)(oil,$[\alpha]_D$ -13°)(70%) and (18)(oil,$[\alpha]_D$ -15.5°)(30%) which were separated by preparative thin layer chromatography and their structures unambiguously assigned by ^{13}C n.m.r. spectroscopy.Mild acid hydrolysis of the cyclohexylidene group of (17) followed by methylation, first with methanolic hydrochloric acid, then with methyl iodide in DMF in the presence of sodium hydride gave in almost quantitative yield a mixture of methyl α-L-nogaloside (19)(methyl 2,3,4-tri-O-methyl-3-C-methyl-α-L-rhamnopyranoside)(mp. 39-41°,$[\alpha]_D$ -52.7°,(c=1 , CH_3OH),lit.[1]: mp. 41-43°,$[\alpha]_D$ -48.4°,(c=1 , CH_3OH) and methyl β-L-nogaloside (20)(methyl 2,3,4-tri-O-methyl-3-C-methyl-β-L-rhamnopyranoside)(oil,$[\alpha]_D$ + 23.7°).Our synthetic sample (19) and methyl α-L-nogaloside prepared from natural nogalose (21) gave absolutely identical ^1H n.m.r. spectra [1] at 250 MHz in $CDCl_3$ and at 90 MHz in C_6D_6 solution. Acid hydrolysis of methyl α-L-nogaloside (19) afforded in quantitative yield the desired nogalose (21) [13].

The authors thank Dr. B. Bannister, The Upjohn Company, for a sample of nogalose. L.E.S. Barata is indebted to the FAPESP, Brazil, for a postdoctoral fellowship.

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(Received in UK 15 November 1978)