CHEMISTRY LETTERS, pp. 1403-1406, 1977. Published by the Chemical Society of Japan

SYNTHESIS OF EVERNITROSE AND ITS ENANTIOMER

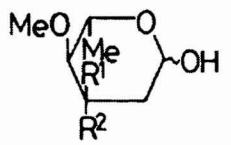
Juji YOSHIMURA, Masafumi MATSUZAWA, Ken-ichi SATO, and Masuo FUNABASHI
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

Evernitrose (1: 2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*arabino*-hexopyranose) and its enantiomer (17) were synthesized from methyl 2,6-dideoxy-4-*O*-methyl-α-L-*erythro*-hexopyranosid-3-ulose and methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose, respectively. In both cases, the unique nitro group attached to the tertiary branching carbon was introduced by oxidation of the corresponding amino derivatives prepared by Bourgeois's method.

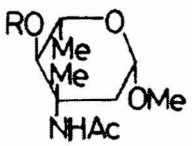
Evernitrose (1) is the first naturally occuring nitro-sugar found by Ganguly et al. in oligosaccharide antibiotics, everninomicin B, C and D.[1] The structure of 1 was previously deduced from spectroscopic evidences and chemical degradation[2] to be 2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*ribo*-hexopyranose (2), but it was recently revised to be L-*arabino* configuration by X-ray analysis of methyl β-glycoside of the corresponding 3-acetamido derivative (3).[3]

This communication describes the first synthesis of 1 and its enantiomer.

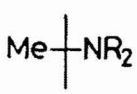
Nitroethane cyclization of dialdehydes is one applicable method for the construction of the characteristic tertiary nitrogen function (type A branching) in 1, and actually, 4-*epi*-vancosaminide (4) was synthesized from the corresponding cyclization product of the dialdehyde from methyl α-L-rhamnopyranoside.[4] In our plan, however, type B branching was introduced at first into uloses by the method of Bourgeois[5] presented in Scheme 1, and finally oxidized into type A.



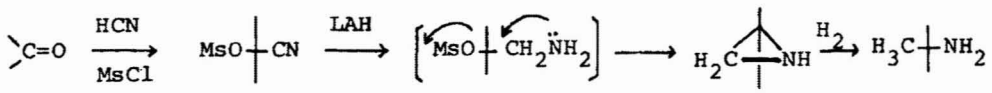
(1) R^1=Me, R^2=NO_2
(2) R^1=NO_2, R^2=Me



(3) R=Me
(4) R=Ac

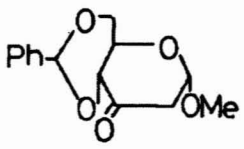


Type A: R=O
Type B: R=H

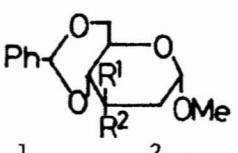


Scheme 1

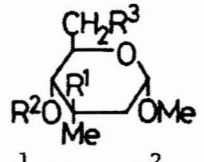
In order to examine the stereoselectivity of cyano-mesylation: the first step in Scheme 1, on a pyranosidulose, methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (5)[6] was used at first. Reaction of 5 and hydrogen cyanide in pyridine at 0°C overnight and subsequent mesylation with methanesulfonyl chloride gave the corresponding 3-*C*-cyano-3-*O*-mesyl derivative of D-*ribo* (6: mp 151-151.5°C, $[\alpha]_D$ +38°) and D-*arabino* (7: mp 156-159°C, $[\alpha]_D$ +102°) configuration in 64% and 3% yields, respectively. Reduction of 6 with lithium alminium hydride in ether at room temperature gave the corresponding spiro-aziridine (8) in 81% yield, which was characterized as the *N*-acetyl derivative (mp 112-113°C, $[\alpha]_D$ +35°). Further hydrogenation of 8 in the presence of Raney nickel gave the corresponding amino derivative (9) in 93% yield, which was also characterized as the *N*-acetyl derivative (10: amorphous, $[\alpha]_D$ +39°). Reaction of 10 with *N*-bromosuccinimide gave methyl 3-acetamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-3-*C*-methyl-α-D-*arabino*-hexopyranoside (11: mp 71-72°C, $[\alpha]_D$ +81°) in 60% yield, of which 6-bromo atom was hydrogenolized with Raney nickel to give sirupy (12). Attempted dehydrobromination of 11 under various conditions gave only a bicyclic pyrrolidine (13: mp 169-174°C, $[\alpha]_D$ -111°) quantitatively.[7] This conversion proved unambiguously the configuration at C-3 position of 9-12, and consequently, indicated that cyanide anions attacked to the carbohyl function of 5 from the upper side of pyranoside ring to give 6. Compound 12 was de-*O*-benzoylated and subsequently methylated with equimolar sodium hydride and methyl iodide to give 4-*O*-methyl derivative (14: mp 136-138°C, $[\alpha]_D$ +73°) in 93% yield. Treatment of 14 with potassium hydroxide in hot aqueous ethanol gave a sirupy de-*N*-acetyl derivative (15) in 52% yield. Oxidation of 15 with *m*-cholroper-



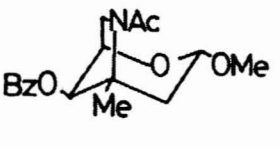
(5)



(6) R^1=CN, R^2=OMs
(7) R^1=OMs, R^2=CN
(9) R^1=NH_2, R^2=CH_3
(10) R^1=NHAc, R^2=CH_3



(11) R^1=NHAc, R^2=Bz, R^3=Br
(12) R^1=NHAc, R^2=Bz, R^3=H
(14) R^1=NHAc, R^2=Me, R^3=H
(15) R^1=NH_2, R^2=Me, R^3=H
(16) R^1=NO_2, R^2=Me, R^3=H



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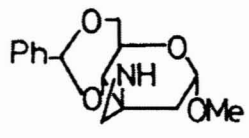

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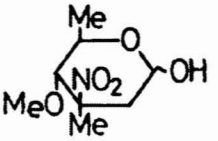

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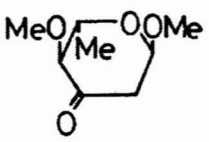

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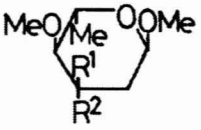
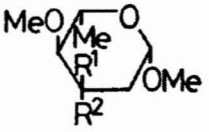


(19) R^1=OMe, R^2=CN

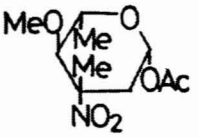
(22) R^1=CH_3, R^2=NHAc

(23) R^1=CH_3, R^2=NO_2



(20) R^1=OMs, R^2=CN

(21) R^1=CN, R^2=OMs



(24)

benzoic acid[8] in dichloromethane gave successfully the 3-nitro derivative (16: sirup, $[\alpha]_D$ +95°) in 77% yield, which was then hydrolyzed with 0.05M sulfuric acid to give D-evernitrose (17: mp 84-88°C, $[\alpha]_D$ +34°) in 72% yield.

From the stereoselectivity of the cyano-mesylation mentioned above, methyl 2,6-dideoxy-4-*O*-methyl-α-L-*erythro*-hexopyranosid-3-ulose (18)[9] was deduced to be the most suitable starting material for the synthesis of 1, and actually, the reaction of 18 gave exclusively the product (19: mp 105-106°C, $[\alpha]_D$ -134°) having the desired configuration in 80% yield. While, the examination of the product of the same cyano-mesylation of the β-anomer[10] of 18 with NMR spectrum showed the formation of desired (20) and undesired (21: mp 97-99°C, $[\alpha]_D$ -2.1°) compounds in the ratio of 1 to 2,[11] indicating that the stereoselectivity of the reaction is mainly controlled by the steric hindrance of the axial C_1-methoxyl group. Compound 19 was converted into the corresponding 3-amino derivative *via* the 3-spiro-aziridine, which was characterized as 3-*N*-acetyl derivative (22: mp 140-141°C, $[\alpha]_D$ -75°), the enantiomer of 14. Oxidation of the 3-amino derivative with *m*-chloroperbenzoic acid in chloroform gave the corresponding 3-nitro derivative (23: sirup, $[\alpha]_D$ -103°) in 45% yield, which was then hydrolyzed into 1 (mp 85-89°C, $[\alpha]_D$ -34°, lit.[2]: mp 88-93°C, $[\alpha]_D$ -19.4°). For comparison, 1-*O*-acetate of 1 (24: sirup, $[\alpha]_D$ -19°, lit.[2]: mp 58-59°C, $[\alpha]_D$ -20.5°) was also synthesized. It is worthy to note that the crude 24 was composed of almost pure β-anomer due to the steric effect of the axial C_3-methyl group.

Although the physical constants of synthesized 1 are slightly different from those reported, NMR data shown in Table 1 supported our results. Each pair of 3-acetamido (14 and 22) and 3-nitro (16 and 23) enantiomers showed almost the same parameters, and C_3-methyl signal in the latter markedly shifted to a lower field than the former due to electron-withdrawing charactor of the nitro group. Parameters of 24 also strongly supported the structure, though little deviations from those reported are observed in the chemical shifts of a few protons.

All compounds described here gave satisfactory elemental analyses.

Table 1. NMR Data of Derivatives of Evernitrose and Its Enantiomer

Compounds	Chemical Shifts (δ) and Coupling Constants (Hz)									
	H_1 ($J_{1,2e}$)	H_{2e} ($J_{1,2a}$)	H_{2a} ($J_{2e,2a}$)	H_4 ($J_{4,5}$)	H_5 ($J_{5,6}$)	H_6	OMe	NAc	C_3-Me	NH
14	4.68	1.77	2.97	3.90	3.64	1.28	3.49	1.94	1.35	5.36
	(0)	(4.5)	(13.6)	(10.0)	(5.9)		3.28			
22	4.69	1.77	2.98	3.90	3.65	1.29	3.50	1.94	1.35	5.34
	(0)	(4.5)	(13.2)	(10.0)	(6.0)		3.29			
16	4.74	2.14	2.46	3.78	3.64	1.34	3.40		1.95	
	(1.5)	(4.5)	(13.5)	(9.5)	(5.4)		3.31			
23	4.74	2.13	2.45	3.77	3.62	1.34	3.39		1.94	
	(1.5)	(4.5)	(13.5)	(9.7)	(5.3)		3.29			
24[a)]	5.76	2.18	2.44	3.77	3.58	1.38	3.43		1.73	
	(3.0)	(10.0)	(13.0)	(9.5)	(6.0)					

a) The chemical shift of C_1-acetoxy signal was 2.10. The chemical shifts of H_4, OMe and OAc were reported to be 3.38, 3.88 and 1.95, respectively.[2)]

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9) D. M. Clode, D. Horton, and W. Weckerle, *Carbohyd. Res.*, 44, 227 (1975).

10) The synthesis of the β-anomer of 18 from methyl 2,3-*O*-benzylidene-4-*O*-methyl-α-L-rhamnopyranoside will be reported elsewhere.

11) This ratio was also confirmed after the conversion of the mixture into the 3-acetamido derivatives.

(Received September 29, 1977)