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Preliminary communication

Synthesis of methyl 6-deoxy-4-*C*-(hydroxymethyl)-5-*O*-methyl-2,3-*O*-methylene-L-idonate

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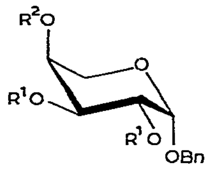
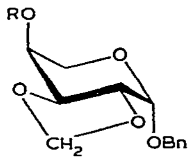
As a part of studies on branched-chain sugars, syntheses of such new, branched-chain sugars as D-evermicose[1], D-evalose[2], and L-evernitrose[3] (found in certain oligosaccharide antibiotics, the everninomycins[4]) have been reported from our laboratory. The structure of the remaining, branched-chain sugar lactone, which is linked by an acetal inter-linkage[5] at a terminal position of everninomycins B and D, was recently determined by Ganguly *et al.*[6] to be 6-deoxy-4-*C*-(hydroxymethyl)-5-*O*-methyl-2,3-*O*-methylene-L-idono-$1,4^1$-lactone having the (*R*) configuration at C-1. Because the branched-chain sugar lactone was chemically characterized[7] as the methyl ester (**20**) of the free acid, the synthesis of **20** from L-arabinose is described in this communication.

Treatment of benzyl 2,3-di-*O*-benzoyl-β-L-arabinopyranoside[8] (**1**) in acetic acid with dimethyl sulfoxide and acetic anhydride gave the corresponding 3-*O*-(methylthio)-methyl ether (**2**) as a syrup, $[\alpha]_D$ +176.8° (*c* 1.24, $CHCl_3$), in 86% yield; this was *O*-debenzoylated with sodium methoxide, to give benzyl 3-*O*-(methylthio)methyl-β-L-arabinopyranoside (**3**), m.p. 72–73°, $[\alpha]_D$ +193.9° (*c* 0.72, $CHCl_3$), in 57% yield. Treatment of **3** with an excess of dichloromethane and sodium hydride[9] gave the corresponding 2,3-*O*-methylene derivative (**4**) as a syrup, $[\alpha]_D$ +110° (*c* 1.0, $CHCl_3$), in 46% yield; this was *O*-de(methylthio)methylated with mercuric chloride in the presence of calcium carbonate, to give benzyl 2,3-*O*-methylene-β-L-arabinopyranoside (**5**) as a syrup, $[\alpha]_D$ +212° (*c* 1.6, $CHCl_3$), in 62% yield. The conformation of **5** was proved by its n.m.r. spectrum to be $^4C_1$ (L) [δ 7.28–7.40 (m, 5 H, Ph), 5.36 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 5.11 and 5.04 (each d, 2 H, J_{gem} 1.0 Hz, 2,3-*O*-methylene), 4.75 and 4.64 (ABq, 2 H, *J* 11.6 Hz, CH_2Ph), 4.30 (m, 1 H, H-4), 3.89 (q, 1 H, $J_{3,4}$ 1.0, $J_{2,3}$ 10.0 Hz, H-3), 3.79 (dd, 1 H, H-2), 3.73 (dd, 1 H, $J_{4,5e}$ 1.8, H-5*e*), 3.58 (dd, 1 H, $J_{4,5a}$ 2.0, $J_{5a,5e}$ 13.2 Hz, H-5*a*), and 3.22 (broad s, OH)].

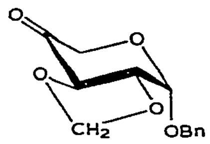
Oxidation of **5** with dimethyl sulfoxide–trifluoroacetic anhydride[10] gave benzyl 2,3-*O*-methylene-β-L-*threo*-pentopyranosid-4-ulose (**6**) in good yield. Compound **6** could not be completely purified, but the n.m.r. spectrum could be analyzed: δ 7.52–7.21 (m, 5 H, Ph), 5.50 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.20 and 5.10 (each d, J_{gem} 1.0 Hz, 2,3-*O*-methylene), 4.86 and 4.76 (ABq, *J* 11.5 Hz, CH_2Ph), 4.72 (dd, 1 H, $J_{3,5e}$ ~1.0 Hz, H-3), 4.02 (dd, 1 H, H-5*e*), 3.92 (d, 1 H, $J_{5a,5e}$ 15.0 Hz, H-5*a*), and 3.67 (dd, 1 H, $J_{2,3}$ 10.8 Hz, H-2).



1 R^1 = Bz, R^2 = H
2 R^1 = Bz, R^2 = CH_2SMe
3 R^1 = H, R^2 = CH_2SMe



4 R = CH_2SMe
5 R = H



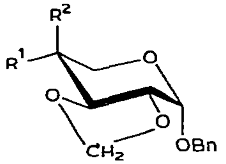
6

Bn = $PhCH_2$
Bz = PhCO

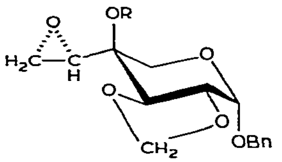
Reaction of **6** with vinylmagnesium bromide in oxolane gave a 4.1 : 1 mixture of benzyl 2,3-*O*-methylene-4-*C*-vinyl-β-L-arabinopyranoside (**7**), as a syrup {$[\alpha]_D$ +170° (*c* 1.2, $CHCl_3$); n.m.r.: δ 7.42–7.24 (m, 5 H, Ph), 5.86 (dd, 1 H, J_{cis} 10.0, J_{trans} 16.7 Hz, CH in vinyl group), 5.53 (dd, 1 H, J_{gem} 2.0 Hz, *trans*-H in CH_2 of vinyl group), 5.38 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 5.30 (dd, 1 H, *cis*-H in CH_2 of vinyl group), 5.15 and 5.07 (each d, 2 H, J_{gem} 1.0 Hz, 2.3-*O*-methylene), 4.79 and 4.67 (ABq, 2 H, *J* 12.2 Hz, CH_2Ph), 3.97 (d, 1 H, $J_{2,3}$ 9.4 Hz, H-3), 3.90 (dd, 1 H, H-2), 3.54 and 3.47 (ABq, 2 H, *J* 11.0 Hz, H-5*e*,5*a*), and 2.50 (broad s, OH)}, and its 4-epimer (**8**) (of the α-D-*xylo* configuration), as a syrup {$[\alpha]_D$ +137° (*c* 3.0, $CHCl_3$); n.m.r.: δ 7.41–7.20 (m, 5 H, Ph), 6.12 (dd, 1 H, J_{cis} 11.0, J_{trans} 17.6 Hz, CH in vinyl group), 5.52 (dd, 1 H, J_{gem} 1.8 Hz, *trans*-H in CH_2 of vinyl group), 5.32 (dd, 1 H, *cis*-H in CH_2 of vinyl group), 5.26 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 5.09 and 5.03 (each d, J_{gem} 1.0 Hz, 2,3-*O*-methylene), 4.76 and 4.63 (ABq, *J* 12.0 Hz, CH_2Ph), 4.01 (d, 1 H, $J_{2,3}$ 9.2 Hz, H-3), 3.62 and 3.56 (ABq, 2 H, *J* 10.8 Hz, H-5*e*,5*a*), 3.37 (dd, 1 H, H-2), and 2.96 (broad s, OH)}, in 59% yield; **7** was separated from **8** on a column of silica gel (eluant, 4 : 1 hexane–ethyl acetate). The configuration at the quarternary carbon atom was determined by comparison of the chemical shifts of the methine carbon atom of the vinyl group [**7**, δ 137.15 p.p.m. (from Me_4Si); **8**, δ 135.15 p.p.m.] in the ^{13}C-n.m.r. spectra[11]. Treatment of **7** with benzyl bromide and sodium hydride gave the corresponding 4-*O*-benzyl derivative (**9**) as a syrup, $[\alpha]_D$ +101° (*c* 1.8, $CHCl_3$), in 89% yield.

Epoxidation of the double bond in **7** with *m*-chloroperoxybenzoic acid in dichloromethane gave a 4.5 : 1 mixture of benzyl 2,3-*O*-methylene-4-*C*-[(*S*)-oxiran-2-yl]-β-L-arabinopyranoside (**11**) as a syrup, $[\alpha]_D$ +182° (*c* 0.9, $CHCl_3$), and the corresponding (*R*) isomer (**10**) as a syrup, $[\alpha]_D$ +183.2° (*c* 1.1, $CHCl_3$), in 52% yield. Similar oxidation of **9** gave the corresponding *R* epoxide (**12**) as a syrup {$[\alpha]_D$ +114.6° (*c* 1.1, $CHCl_3$); n.m.r.: δ 7.48–7.10 (m, 5 H, Ph), 5.39 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 5.14 and 5.07 (each d, 2 H, J_{gem} 1.0 Hz, 2,3-*O*-methylene), 4.82 and 4.78 (ABq, 2 H, *J* 15.2 Hz, 4-*O*-CH_2Ph), 4.78 and 4.68 (ABq, 2 H, *J* 11.6 Hz, 1-*O*-CH_2Ph), 4.10–3.98 (m, 2 H, H-2,3), 3.95 and 3.58 (ABq, *J* 12.2 Hz, H-5*e*,5*a*), and 3.16, 2.90, and 2.79 (each dd, 3 H, *J* 3.0, 4.0, and 5.0 Hz, epoxy H)}, and the (*S*) epoxide (**13**) as a syrup {$[\alpha]_D$ +114.7° (*c* 1.1, $CHCl_3$), n.m.r.: δ 7.50–7.12 (m, 5 H, Ph), 5.34 (d, 1 H, $J_{1,2}$ 2.6 Hz, H-1), 5.08 and 5.04 (each d, 2 H, J_{gem} 0.8 Hz, 2,3-*O*-methylene), 4.94 and 4.85 (ABq, 2 H, *J* 11.6 Hz, 4-*O*-CH_2Ph), 4.77 and 4.66 (ABq, 2 H, *J*

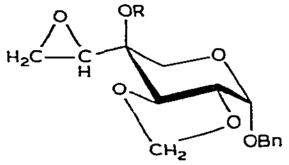
12.4 Hz, 1-*O*-CH_2Ph), 4.00 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 3.93 (d, 1 H, H-3), 3.78 and 3.66 (ABq, 2 H, *J* 12.5 Hz, H-5*e*,5*a*), and 3.11, 3.04, and 2.83 (each dd, 3 H, *J* 2.9, 4.2, and 5.0 Hz, epoxy-H)} in the ratio of 1 : 1, in 65% yield. The difference in the ratio of isomers, as between the products from **7** and **9**, indicates the effect of the tertiary hydroxyl group on C-4, as had been observed for 2-cyclohexen-1-ol derivatives[12]. The configurations of the epoxides were deduced by comparison of the ratio with that of the products obtained by similar oxidation of the 2,3-di-*O*-benzyl analog of **7**; unexpectedly, their absolute configurations could be determined by a chemical method.*



7 R^1 = CH=CH$_2$, R^2 = OH
8 R^1 = OH, R^2 = CH=CH$_2$
9 R^1 = CH=CH$_2$, R^2 = OBn



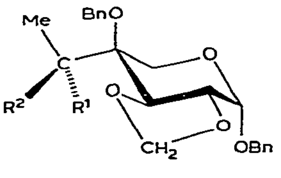
10 R = H
12 R = Bn



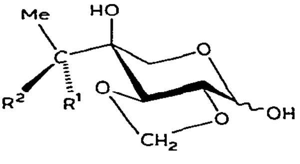
11 R = H
13 R = Bn

Reduction of **12** and **13** in oxolane with lithium aluminum hydride gave the corresponding alcohols, which were characterized as the *O*-methyl derivatives: **14**, a syrup, $[\alpha]_D$ +123.9° (*c* 0.8, $CHCl_3$), 74%; and **15**, a syrup, $[\alpha]_D$ +114.5° (*c* 0.9, $CHCl_3$), 69%. Hydrogenation of **14** and **15** in the presence of palladium-on-charcoal gave 4-*C*-[(*R*)-1-methoxyethyl]-(**16**), a syrup, $[\alpha]_D$ −28.7° (*c* 3.3, EtOH), and 4-*C*-[(*S*)-1-methoxyethyl]-2,3-*O*-methylene-L-arabinose (**17**), m.p. 53–57°, $[\alpha]_D$ −44.7° (*c* 1.9, EtOH), in 93 and 83% yield, respectively.

Oxidation of **16** in 85% aqueous methanol with bromine, treatment with silver oxide, and separation of the products by preparative t.l.c., gave methyl 6-deoxy-4-*C*-(hydroxymethyl)-5-*O*-methyl-2,3-*O*-methylene-D-gluconate (**18**) as a syrup (see Table I), together with the dimethyl acetal (**19**) of **16** as a syrup {$[\alpha]_D$ −23.7° (*c* 2.2, $CHCl_3$); n.m.r.: δ 5.07 and 4.93 (each s, 2 H, 2,3-*O*-methylene), 4.44 (d, 1 H, H-1), 4.35 (t, 1 H, $J_{1,2} = J_{2,3}$ =



14 R^1 = OMe, R^2 = H
15 R^1 = H, R^2 = OMe



16 R^1 = OMe, R^2 = H
17 R^1 = H, R^2 = OMe

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*For the 2,3-di-*O*-benzyl derivatives, the absolute configuration of the 4-*C*-(oxiran-2-yl) derivatives was determined by comparison of the corresponding, reduced products with that of those obtained by the epoxidation of the corresponding (*Z*)- and (*E*)-4-*C*-ethylene derivatives followed by alkaline cleavage of the epoxide ring.

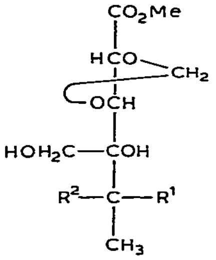
TABLE I

COMPARISON OF ROTATIONAL VALUES AND N.M.R. PARAMETERS

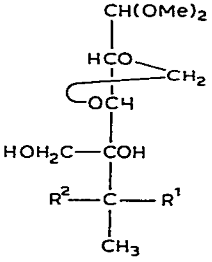
	$[\alpha]_D$ in $CHCl_3$ (degrees)	*Chemical shifts (δ) and coupling constants (Hz)*								
		H-2	*H-3*	*H-4'*	*H-5*	*H-6*	*OCH_2O*	*OMe*	*CO_2Me*	*OH*
18	−70.0	4.74d	4.41d	3.60 ABq 3.78	3.67q	1.28d	4.96s 5.21s	3.38	3.81	3.00
		$J_{2,3}$ 5.0		J 12.4	$J_{5,6}$ 6.5					
20	−26.1	4.85d	4.17d	3.59 ABq 3.78	3.69q	1.26d	4.98s 5.23s	3.40	3.80	2.66
		$J_{2,3}$ 5.0		J 12.2	$J_{5,6}$ 6.5					
20 (reported[7])	−28	4.85d	4.19d	3.6–3.9m		1.25d	5.0s 5.21s	3.35	3.81	—
		$J_{2,3}$ 5.0			$J_{5,6}$ 6.5					

4.8 Hz, H-2), 4.27 (d, 1 H, H-3), 3.68 (q, 1 H, $J_{5,6}$ 6.4 Hz, H-5), ~3.6 (m, 2 H, 4'-CH_2), 3.50, 3.47, and 3.36 (each s, 3 OMe), 2.81 (broad s, 2 OH), and 1.26 (d, 3 H, H-6)}, in 10 and 13% yield, respectively. Similar oxidation of **17** gave the C-5 epimer (**20**) of **18** as a syrup (see Table I), and the dimethyl acetal (**21**) of **17** as a syrup {$[\alpha]_D$ +3.8° (*c* 2.3, $CHCl_3$); n.m.r.: δ 5.10 and 4.98 (each d, 2 H, J_{gem} 0.8 Hz, 2,3-*O*-methylene), 4.50–4.36 (m, 2 H, H-1,3), 4.05 (dd, 1 H, *J* 1.2 and 3.0 Hz, H-2), 3.71 (q, 1 H, $J_{5,6}$ 6.0 Hz, H-5), 3.68 and 3.54 (ABq, 2 H, *J* 12.4 Hz, 4'-CH_2), 3.51, 3.49, and 3.42 (each s, 3 OMe), 3.02 (broad s, 2 OH), and 1.28 (d, 3 H, H-6)}, in 8 and 6% yield, respectively.

Comparison of the rotational value and n.m.r. parameters (see Table I) of **18** and **20** with those reported[7] indicated that the determination and deduction of the configuration of C-4 and of the α-carbon atom in the branch chain were correct. Thus, synthesis of all of the new, branched-chain sugars found in the everninomycins is now complete.



18 $R^1 = OMe, R^2 = H$
20 $R^1 = H, R^2 = OMe$



19 $R^1 = OMe, R^2 = H$
21 $R^1 = H, R^2 = OMe$

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REFERENCES

1 M. Funabashi, N. Hong, H. Kodama, and J. Yoshimura, *Carbohydr. Res.*, 67 (1978) 139–145.
2 J. Yoshimura, N. Hong, and K. Sato, *Chem. Lett.*, (1979) 1263–1264.
3 J. Yoshimura, M. Matsuzawa, K. Sato, and Y. Nagasawa, *Carbohydr. Res.*, 76 (1979) 67–78.
4 A. K. Ganguly, "Oligosaccharide Antibiotics", in P. G. Sammes (Ed.), *Topics in Antibiotic Chemistry*, Vol. 2, Wiley, New York, 1978, pp. 59–98.
5 J. Yoshimura and M. Tamaru, *Carbohydr. Res.*, 72 (1979) C9–C11.
6 A. K. Ganguly, O. Z. Sarre, A. T. McPhall, and R. W. Miller, *J. Chem. Soc. Chem. Commun.*, (1979) 22–24.
7 A. K. Ganguly, O. Z. Sarre, D. Greeves, and J. Morton, *J. Am. Chem. Soc.*, 97 (1975) 1982–1985.
8 T. Sivakumaran and J. K. N. Jones, *Can. J. Chem.*, 45 (1967) 2493–2500.
9 J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *J. Chem. Soc., C*, (1967) 2404–2407.
10 J. Yoshimura, K. Sato, and H. Hashimoto, *Chem. Lett.*, (1977) 1327–1330.
11 (*a*) M. Miljkovic, M. Gligorijevic, T. Satoh, D. Glisin, and R. D. Pitcher, *J. Org. Chem.*, 39 (1974) 3847–3850; (*b*) P. M. Collins and V. R. N. Munasinghe, *Carbohydr. Res.*, 62 (1978) 19–26; (*c*) K. Sato, M. Matsuzawa, K. Ajisaka, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 53 (1980) 189–191.
12 (*a*) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, (1957) 1958–1965; (*b*) H. B. Henbest, B. Nicholls, W. R. Jackson, R. A. L. Wilson, and N. S. McElhinney, *Bull. Soc. Chim. Fr.*, (1960) 1365–1368.