Branched-chain Sugars. XXXIV. Synthesis of Methyl Dihydroeurekanate[1]

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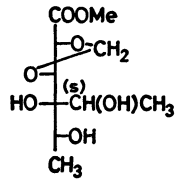
Synopsis. Methyl dihydroeurekanate; methyl 6-deoxy-4-*C*-[(*S*)-1-hydroxyethyl]-2,3-*O*-methylene-D-galactonate was synthesized from benzyl 6-deoxy-4-*C*-[(*S*)-1-hydroxyethyl]-2,3-*O*-methylene-D-galactopyranoside.

Up to the present, three branched-chain aldonolactones have been found in oligosaccharide antibiotics of orthothomycin family,[2] and they were characterized as their methyl aldonate. The structure of the first one in everninomicins[3] was determined to be 4-*C*-[(*S*)-1-methoxyethyl]-2,3-*O*-methylene-L-arabinono-1,5-lactone by X-ray analysis,[4] and the corresponding aldonate, methyl 6-deoxy-4-*C*-hydroxymethyl-5-*O*-methyl-2,3-*O*-methylene-L-idonate[5] was synthesized from L-arabinose *via* the introduction of equatorial 4-*C*-vinyl group by us.[6] The structure of methyl eurekanate obtained from flambamycin[2] and avilamycin A[7] was determined to be methyl 4-*C*-acetyl-6-deoxy-2,3-*O*-methylene-D-galactonate by a similar synthesis[8] and X-ray analysis.[7] D-*galacto* configuration of the remaining methyl dihydroeurekanate (**1**) from avialamycin C was proved by the fact that one of the epimers obtained by reduction of the 4-*C*-acetyl group of methyl eurekanate was identical with **1**,[9] but, the chirality of its 1-hydroxyethyl group was unknown. As was commonly observed in naturally occuring branched-chain sugars such as L-*γ*-octose[10] and D-aldgalose,[11] the chirality of 1-hydroxyethyl group of **1** was deduced to be (*S*), and in fact, it was recently proved by X-ray analysis.[12] This paper describes a simple preparation of **1** from benzyl 6-deoxy-4-*C*-[(*S*)-1-hydroxyethyl]-2,3-*O*-methylene-α-D-galactopyranoside [(1′*S*)-**2**].[13]



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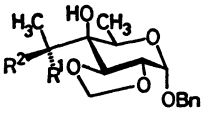
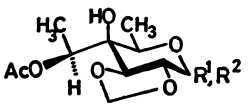
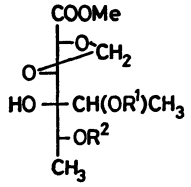


(1′R)-**2** R^1=OH, R^2=H
(1′S)-**2** R^1=H, R^2=OH
(1′R)-**3** R^1=OAc, R^2=H
(1′S)-**3** R^1=H, R^2=OAc



4 R^1,R^2=H, OH
5 R^1,R^2=O



6 R^1=Ac, R^2=H
7 R^1=H, R^2=Ac
8 R^1=R^2=Ac

Results and Discussion

In our previous report,[13] (1′*R*)-**2** and (1′*S*)-**2** obtained by reduction of (1′*R*)- and (1′*S*)-mixture of the corresponding 4-*C*-(oxiranyl) derivative were directly separated by silica-gel column chromatography, but, the separation proceeded more smoothly after the usual acetylation into (1′*R*)-**3** and (1′*S*)-**3**. The both epimers were thoroughly characterized by ^{1}H- and ^{13}C-NMR. However, the hydrogenolysis of (1′*S*)-**3** into **4** gave an unstable complex mixture which showed two acetyl signals in the ratio of 3:1 and aldehydic proton at *δ* 9.73 in ^{1}H-NMR spectrum. This fact indicates the presence of acyclic species and/or the occurrence of acetyl migration. Oxidation of crude **4** into **5** with bromine–water gave again a mixture which showed two acetyl signals. Therefore, crude **5** was converted into the corresponding methyl aldonate by treatment with diazomethane in methanol. ^{1}H-NMR spectrum of the product indicated the presence of two monoacetate (**6** and **7**) in the ratio of 1.5:1, indicating the acetyl migration during these conversions. Usual acetylation of the mixture gave diacetate (**8**) in fairly good yield. The ^{1}H NMR spectrum and the specific rotation of **8** shown in Table 1 revealed its structure. Deacetylation of **8** in methanol with catalytic amount of sodium methoxide gave **1** in 76% yield. ^{1}H-NMR and ^{13}C-NMR spectra shown in Table 2 together with that of **8** proved that **1** was identical with that obtained from avilamycin C.

Experimental

Specific rotations were measured with JASCO DIP-4 polarimeter in chloroform. ^{1}H- and ^{13}C-NMR were recorded in chloroform-*d* with JEOL PS-100 and JEOL FX-100 spectrometers, respectively. Chemical shifts and Coupling constants were recorded in *δ* (ppm) and Hz units, respectively.

*Isolation of (1′*R*)-3 and (1′*S*)-3.* The mixture of (1′*R*)-**1** and (1′*S*)-**1** (3.2 g, 10.3 mmol) in pyridine (25 ml) was acetylated in the usual procedure to give a syrupy product which was separated on a silica-gel (WAKO C-200) column (1:2 ethyl acetate–hexane). (1′*R*)-**3** (R_f 0.28) and (1′*S*)-**3** (R_f 0.41) were obtained in 49% (1.79 g) and 34% (1.23 g) yields, respectively.

(1′*R*)-**3**: $[\alpha]_D$ +167° (*c* 1.0), ^{1}H-NMR (*δ*): 7.41 (s, 5H, Ph), 5.36 (d, $J_{1,2}$ 3.0, H-1), 5.14 and 5.24 (ABq, 2H, *J* 1.4, OCH_2O), 5.00 (q, $J_{1',2'}$ 6.8, H-1′), 4.79 (s, 2H, CH_2Ph), 4.03 (d, $J_{2,3}$ 9.8, H-3), 3.92 (dd, H-2), 3.70 (q, $J_{5,6}$ 6.8, H-5), 2.85 (bs, OH), 2.14 (s, 3H, OAc), 1.28 (d, 3H, H-2′), 1.19 (d, 3H, H-6); ^{13}C-NMR (ppm): 13.4 and 15.7 (each q, C-6,2′), 21.3 (q, CH_3CO), 68.1, 73.2, 73.3 and 73.6 (each d, C-2,3,5,1′), 70.1 (t, CH_2Ph), 76.6 (s, C-4), 96.4 (t, OCH_2O), 96.7 (d, C-1), 127.9 and 128.5 (each d, Ph), 137.3 (s, Ph), 171.2 (s, C=O).

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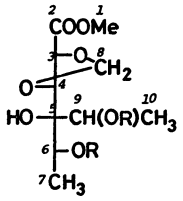
Table 1. Comparison of physical properties for **1** and **8** with those reported for samples obtained from avilamycin C

	$[\alpha]_D$ (in $CHCl_3$)	Chemical shift (δ) and coupling constant (Hz)									
		H-2 ($J_{2,3}$)	H-3	H-5 ($J_{5,6}$)	H-6	H-1′ ($J_{1',2'}$)	H-2′	OCH_2O	CO_2Me	OH	OAc
1	—	4.26 d (5.5)	4.88 d	3.7—4.3 m (6.6)	1.28 d	3.7—4.3 m (6.6)	1.32 d	4.90 s 5.23 s	3.79 s	2.02 s 2.23 s	—
(Reported)	−36.9°	4.38 d (5.5)	4.88 d	3.8—4.3 m (6.5)	1.30 d	3.8—4.3 m (6.5)	1.32 d	4.90 s 5.22 s	3.78 s	2.52 d 2.70 d 3.18 s	—
8	−48°	4.36 d (4.8)	4.92 d	5.30 q (7.0)	1.30 d	5.16 q (7.0)	1.32 d	4.91 s 5.20 s	3.80 s	2.80 s	2.03 s 2.07 s
(Reported)	−50°	4.35 d (5.2)	4.92 d	5.30 q (7.1)	1.30 d	5.16 q (7.1)	1.31 d	4.90 s 5.18 s	3.75 s	2.73 s	2.00 s 2.04 s

Table 2. ^{13}C-NMR data of **1** and **8**

Position[a]	**1**	Reported **1**	**8**[b]
1	52.6(q)	52.6(q)	52.5(q)
2	172.3(s)	172.1(s)	171.5(s)
3	82.4(d)	82.1(d)	80.9(d)
4	74.6(d)	74.5(d)	74.8(d)
5	76.2(s)	76.1(s)	76.2(s)
6	69.6(d)**[c]	69.6(d)**	71.9(d)**
7	17.6(q)*	18.0(q)*	15.4(q)*
8	95.6(t)	95.6(t)	95.6(t)
9	69.9(d)**	69.9(d)**	71.9(d)**
10	18.1(q)*	18.2(q)*	15.5(q)*

a) The numbering of carbon atoms is shown below.
b) **8** showed additional signals of acetyl carbons: 21.2 (q, 2×C), 170.0 and 174.8 (each s, 2×C=O) ppm.
c) Each pairs of marked assignments may be reversed although those given here are preferred.



(1′*S*)-**3**: $[\alpha]_D$ +116° (*c* 0.64); ^{1}H-NMR (δ): 7.42 (s, 5H, Ph), 5.36 (d, $J_{1,2}$ 3.6, H-1), 5.15 and 5.24 (ABq, 2H, *J* 1.0, OCH_2O), 5.07 (q, $J_{1',2'}$ 6.6, H-1′), 4.78 (s, 2H, CH_2Ph), 4.17 (d, $J_{2,3}$ 10.0, H-3), 3.85 (dd, H-2), 3.78 (q, $J_{5,6}$ 6.6, H-5), 2.36 (bs, OH), 2.04 (s, 3H, OAc), 1.38 (d, 3H, H-2′), 1.16 (d, 3H, H-6); ^{13}C-NMR (ppm): 13.4 and 15.7 (each q, C-6,2′), 21.3 (q, CH_3CO), 68.1, 73.2, 73.3 and 73.6 (each d, C-2,3,5,1′), 70.1 (t, CH_2Ph), 76.6 (s, C-4), 96.4 (t, OCH_2O), 96.7 (d, C-1), 127.9 and 128.5 (each d, Ph), 137.3 (s, Ph), 171.2 (s, CO). Found for (1′*R*)-**3**: C, 60.97; H, 6.79 and for (1′*S*)-**3**: C, 60.96; H, 6.88%. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86%.

Conversion of (1′S)-3 into 6 and 7. A suspension of (1′*S*)-**3** (540 mg, 1.46 mmol) and palladium–carbon (10%, 500 mg) in ethanol (100 ml) containing 1 M HCl (2 ml) was hydrogenolyzed in an autoclave under hydrogen atmosphere (60 kg/cm^2) for 7 h at room temperature. The usual work-up of the reaction mixture gave crude **4** in 76% (292 mg) yield. To a suspension of the above **4** (241 mg, 0.92 mmol) and trilead (II) dicarbonate dihydroxide (2.84 g) in water (5 ml) was added bromine (94.9 μl) and the mixture was shaken in dark for 12 h at room temperature. After aeration the mixture was filtered, and the filtrate was passed through IR 120 (H^+) column and then evaporated to give a syrupy **5** in 95% (194 mg) yield. This syrup was esterified with diazomethane in the usual manner gave a mixture of **6** and **7**. The predominant product showed the following ^{1}H-NMR data: 5.40 (q, $J_{1',2'}$ 7.0, H-1′), 5.20 (q, $J_{5,6}$ 6.4, H-5), 5.19 and 5.00 (each s, 2H, OCH_2O), 4.88 (d, $J_{2,3}$ 4.4, H-3), 4.72 (d, H-2), 3.83 (s, 3H, MeO), 2.14 (s, 3H, OAc), 1.51 (d, 3H, H-2′), 1.32 (d, 3H, H-6).

Methyl Dihydroeurekanate Diacetate (8). The mixture of **6** and **7** (58 mg, 0.199 mmol) in pyridine (0.5 ml) was acetylated by the usual manner to give syrupy **8** in 66% (42 mg) yield, which was purified by a preparative TLC (2:3 acetone–hexane). Found: C, 50.01; H, 6.72%. Calcd for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63%.

Methyl Dihydroeurekanate (1). A solution of **8** (23 mg, 0.1 mmol) in methanol (1 ml) containing catalytic amount of sodium methoxide was kept at room temperature for 6 h, passed through a IR 120 (H^+) column, evaporated, to give a sirup which was purified on a preparative TLC (1:1 acetone–hexane). Yield, 76% (15 mg).

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