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Pseudo-sugars. 5. Synthesis of DL-Validatol and DL-Deoxyvalidatol, and Their Epimers[1,2]

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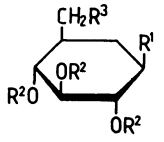
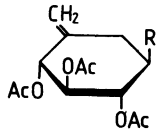
New cyclitols, validatol and deoxyvalidatol, derived by hydrogenolysis of antibiotic validamycin A, were synthesized as the racemates from readily available tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol.

In connection with a previous work,[3] we wish to report the first synthesis of racemic validatol and deoxyvalidatol, the degradation products of validamycin A,[4] from readily available tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**).[2]

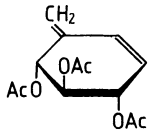
Treatment of **1** with 1.2 molar equivalent of silver fluoride in dry pyridine at ambient temperature overnight gave exclusively tri-*O*-acetyl-(1,3/2,4)-4-bromo-6-methylene-1,2,3-cyclohexanetriol (**2**) in 60% yield. The ^{1}H NMR spectrum showed the signals of C-5 methylene protons as a one-proton broad triplet (J=12 and 14 Hz) at δ 2.61 and a one-proton doublet of doublets (J=5 and 14 Hz) at δ 3.01, confirming the assigned structure. Debromination of **2** with tributyltin(IV) hydride in toluene in the presence of α,α'-azobisisobutyronitrile gave tri-*O*-acetyl-(1,3/2)-4-methylene-1,2,3-cyclohexanetriol (**3**) in 60% yield. On the other hand, exhaustive dehydrobromination of **1** was effected by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in toluene to give an exocyclic diolefin, tri-*O*-acetyl-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol (**4**)[5] in 45% yield, which was identical with the compound obtained from **2** in a similar way in 51% yield. Its structure was determined by the ^{1}H NMR spectrum, which revealed the signals of the exocyclic methylene protons as two broad singlets at δ 5.08 and 5.21. Compounds **2**, **3**, and **4** thus obtained might be useful intermediates for the preparation of unsaturated branched cyclitols.



	R^1	R^2	R^3
1	Br	Ac	Br
7	H	Ac	H
8	H	H	H
9	Br	Ac	OAc
10	H	Ac	OAc
11	H	H	OH



2 R=Br
3 R=H



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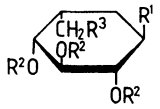

	R^1	R^2	R^3
5	H	Ac	H
6	H	H	H
12	Br	Ac	OAc
13	H	Ac	OAc
14	H	H	OH

Catalytic reduction of **3** or **4** in ethyl acetate with platinum oxide gave preferentially tri-*O*-acetyl-(1,3,4/2)-4-methyl-1,2,3-cyclohexanetriol (**5**) in a high yield, the ^{1}H NMR spectral data of which were identical with those of an optically active sample reported by Horii and Kameda.[6] A 4-epimer (**7**) of **5** was also prepared by hydrogenolysis of **1** with Raney nickel T-4[7] in ethyl acetate in the presence of Amberlite IR-45 (OH^-) in 92% yield. *O*-Deacetylation of **5** and **7** with methanolic sodium methoxide gave crystalline triol **6** (deoxyvalidatol) and **8**, respectively.

(1,3,4/2)-4-Hydroxymethyl-1,2,3-cyclohexanetriol (validatol) (**14**) was synthesized from **2** or **3** by hydroboration followed by the usual sequence of reactions. First, (1,3/2,4)-4-hydroxymethyl-1,2,3-cyclohexanetriol (**11**) was prepared from **1** as a reference compound. Tetra-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (**9**)[2] derived by treatment of **1** with sodium acetate in aqueous 2-methoxyethanol was hydrogenolyzed with Raney nickel in the usual way to give a crystalline tetraacetate (**10**) of **11** in 96% yield. *O*-Deacetylation gave a crystalline **11** in 97% yield.

Hydroboration of **2** with sodium borohydride and boron trifluoride in tetrahydrofuran (THF) followed by treatment with hydrogen peroxide[8] and successive acetylation gave, after purification on a silica-gel column, a homogeneous syrupy product in 30% yield. Comparison of the ^{1}H NMR spectrum with that of **9** showed that the product consists of **9** and tetra-*O*-acetyl-(1,3,6/2,4)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (**12**) in a 1:2 ratio. Without separation, the mixture was hydrogenolyzed in the usual way to give a syrup, which was found by ^{1}H NMR spectroscopy to consist of **10** and validatol tetraacetate (**13**) in a 1:2 ratio. Compound **3** was also subjected to hydroboration similarly followed by acetylation to give a 1:2.5 mixture of **10** and **13** in 29% yield. Since both compounds showed a similar mobility on TLC in various solvent systems, separation was carried out by converting them into tetrols **11** and **14**. *O*-Deacetylated mixture was successfully fractionated by chromatography on silica gel to give **11** as crystals and **14** as a homogeneous syrup. Acetylation of **14** gave a syrupy **13** whose

^{1}H NMR spectrum was superimposable on that of an authentic optically active sample reported.[4b]

Experimental

Melting points were determined in a capillary in a silicone bath and are uncorrected. Solutions were evaporated under reduced pressure at 40—50 °C. Unless otherwise stated, the ^{1}H NMR spectra were taken on a Varian EM 360A (60 MHz) or HA 100D (100 MHz) in deuteriochloroform ($CDCl_3$) with reference to tetramethylsilane as an internal standard, the peak positions being given in terms of δ-values. Values given for coupling constants are of first-order. TLC was performed on pre-coated silica gel 60 F-254 plaques (Merck, Darmstadt; 0.25 mm thickness). Silica gel (Wakogel C-300, Wako Pure Chemical Industries, Ltd.) was used for column chromatography.

Tri-O-acetyl-(1,3/2,4)-4-bromo-6-methylene-1,2,3-cyclohexanetriol (2). A mixture of tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**)[2] (1 g) and silver fluoride (0.36 g, 1.2 molar equiv.) in dry pyridine (20 ml) was stirred at ambient temperature for 20 h. The brown reaction mixture was diluted with ether (100 ml) and the precipitates were removed by filtration. The filtrate was evaporated and the product purified by passage through a short column of alumina with chloroform. The eluate was evaporated and the residue was crystallized from ethanol to give **2** (0.49 g, 60%) as needles: mp 124—125 °C: ^{1}H NMR (60 MHz) δ 2.00 (3H, s), 2.05 (3H, s), and 2.10 (3H, s) (OAc), 2.61 (1H, broad t, $J_{4,5ax}=12$ Hz, $J_{5gem}=14$ Hz, H-5ax), 3.01 (1H, dd, $J_{4,5eq}=5$ Hz, H-5eq), 3.80 (1H, ddd, $J_{3,4}=9.5$ Hz, H-4), 4.7—5.5 (5H, m, H-1, H-2, H-3, and exocyclic methylene).

Found: C, 44.43; H, 4.87; Br, 23.12%. Calcd for $C_{13}H_{17}O_6Br$: C, 44.71; H, 4.91; Br, 22.88%.

Tri-O-acetyl-(1,3/2)-4-methylene-1,2,3-cyclohexanetriol (3). A solution of **2** (1.65 g) in dry toluene (50 ml) was treated with tributyltin(IV) hydride (1.6 ml) in the presence of a trace of α,α'-azobisisobutyronitrile at 80 °C for 30 min under a nitrogen stream. The reaction mixture was then evaporated and the residue was crystallized from ligroin to give **3** (0.76 g, 60%) as prisms: mp 69—71 °C; ^{1}H NMR (60 MHz) δ 1.15 (4H, m, ring methylene), 2.00 (3H, s), 2.01 (3H, s), and 2.10 (3H, s) (OAc), 4.7—5.5 (5H, m, H-1, H-2, H-3, and exocyclic methylene).

Found: C, 57.56; H, 6.71%. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.

Tri-O-acetyl-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol (4). a) A solution of **1** (1 g) and DBU (1.8 ml, 5 molar equiv.) in toluene (10 ml) was refluxed for 30 min. After cooling, the precipitates were removed by decantation. The solution was evaporated and the residue dissolved in ethyl acetate (50 ml). The solution was washed with 0.2 M hydrochloric acid, aqueous saturated sodium hydrogencarbonate, and water, successively, dried over anhydrous sodium sulfate, and filtered through a short column of alumina. The filtrate was evaporated and the residue was crystallized from ethanol to give **4** (0.28 g, 45%) as needles: mp 67—68 °C; ^{1}H NMR (100 MHz) δ 2.06 (3H, s), 2.08 (3H, s), and 2.15 (3H, s) (OAc), 5.08 (1H, broad s) and 5.21 (1H, broad s) (exocyclic methylene), 5.28 (1H, dd, $J=7.5$ Hz, $J=10.5$ Hz, H-2), 5.6—5.8 (3H, m, H-1, H-3, and H-5), 6.31 (1H, m, H-6).

Found: C, 57.97; H, 5.96%. Calcd for $C_{13}H_{16}O_6$: C, 58.26; H, 6.01%.

b) A solution of **2** (1 g) and DBU (0.52 ml, 1.2 molar equiv.) in toluene (20 ml) was refluxed for 6 h. After cooling, the precipitates were removed by filtration and the filtrate was treated as described above. Crystallization of the crude product from ethanol gave **4** (0.4 g, 51%): mp 66—67.5 °C, identical with the compound obtained above.

Tri-O-acetyl-(1,3,4/2)-4-methyl-1,2,3-cyclohexanetriol (Deoxyvalidatol) (5). a) A solution of **3** (0.1 g) in ethyl acetate (10 ml) was hydrogenated in a Parr shaker apparatus in the presence of platinum oxide (10 mg) under an initial hydrogen pressure of 3 kg cm^{-2} at ambient temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to give **5** (77 mg, 76%) as a chromatographically homogeneous syrup: ^{1}H NMR (100 MHz) δ 1.05 (3H, d, $J=7$ Hz, methyl), 1.1—1.9 (4H, m, two ring methylene), 2.01 (6H, s) and 2.05 (3H, s) (OAc), 2.21 (1H, m, H-4), 4.83 (1H, dd, $J_{2,3}=9$ Hz, $J_{3,4}=5$ Hz, H-3), 5.23 (1H, t, $J_{1,2}=9$ Hz, H-2). The ^{1}H NMR spectral data were almost identical with those of an optically active sample reported,[6] showing that **5** contains a trace of its 4-epimer (**7**). (Found: C, 56.75; H, 7.31%).

b) Compound **4** (65 mg) was hydrogenated in ethyl acetate (5 ml) in a similar way to that described above to give a syrupy mixture (56 mg, 85%) of **5** and **7** in the ratio of 3: 1.

(1,3,4/2)-4-Methyl-1,2,3-cyclohexanetriol (Deoxyvalidatol) (6). A solution of crude **5** (0.1 g) in methanol (10 ml) was treated with 1 M methanolic sodium methoxide (0.2 ml) and allowed to stand at ambient temperature overnight. The mixture was then treated with Amberlite IR-120 (H^+) and concentrated to give a crystalline residue. Recrystallization from ethanol–ether gave **6** (46 mg, 86%) as colorless crystals: mp 109.5 °C (after melting partly at 93 °C). ^{1}H NMR (60 MHz in D_2O with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as an internal standard) δ 0.92 (3H, d, $J=7$ Hz, methyl), 1.12—2.27 (5H, m, two ring methylene and H-4), 3.06—3.76 (3H, m, H-1, H-2, and H-3).

Found: C, 57.23; H, 9.44%. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65%.

Tri-O-acetyl-(1,3/2,4)-4-methyl-1,2,3-cyclohexanetriol (7). A solution of **1** (0.5 g) in ethyl acetate (10 ml) was hydrogenated in a Parr shaker apparatus in the presence of Raney nickel T-4[7] (5 ml) and Amberlite IR-45 (OH^-) (7 ml) under an initial hydrogen pressure of 3 kg cm^{-2} at ambient temperature overnight. The catalyst and resin were removed by filtration and the filtrate was evaporated to give a crystalline residue, which was recrystallized from ethanol to give **7** (0.29 g, 92%) as feathers: mp 92—93.5 °C; ^{1}H NMR (60 MHz) δ 0.92 (3H, d, $J=6$ Hz, methyl), 1.98 (6H, s) and 2.00 (3H, s) (OAc), 4.54—5.18 (3H, m, H-1, H-2, and H-3).

Found: C, 57.07; H, 7.22%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

(1,3/2,4)-4-Methyl-1,2,3-cyclohexanetriol (8). Compound **7** (0.1 g) was treated with methanolic sodium methoxide in the same way as in the preparation of **6**. The crude product was recrystallized from ethanol–ether to give **8** (53 mg, 99%) as colorless crystals: mp 120.5—121 °C. ^{1}H NMR (60 MHz in D_2O) δ 0.93 (3H, d, $J=5.5$ Hz, methyl), 1.09—2.04 (5H, m, two ring methylene and H-4), 2.64—3.66 (3H, m, H-1, H-2, and H-3).

Found: C, 57.27; H, 9.46%. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65%.

Tetra-O-acetyl-(1,3/2,4)-4-hydroxymethyl-1,2,3-cyclohexanetriol (10). A solution of tetra-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (**9**)[2] (0.5 g) in ethyl acetate (10 ml) was hydrogenolyzed as in the preparation of **7**. Crystallization of a crude product from ethanol gave **10** (0.39 g, 96%) as prisms: mp 99.5—100 °C; ^{1}H NMR (60 MHz) δ 2.00 (9H, s) and 2.03 (3H, s) (OAc), 1.2—2.3 (5H, m, ring methylene and H-4), 3.83—4.03 (2H, AB-quartet, H-7 and H-7'), 4.62—5.12 (3H, m, H-1, H-2, and H-3).

Found: C, 54.71; H, 6.68%. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71%.

(1,3/2,4)-4-Hydroxymethyl-1,2,3-cyclohexanetriol (11). Compound **10** (0.22 g) was *O*-deacetylated with methanolic sodium methoxide as in the preparation of **6**. The crude product was recrystallized from ethanol to give **11** (0.11 g, 97%) as prisms: mp 126.5—127 °C.

Found: C, 51.93; H, 8.56%. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70%.

(1,3,4/2)-4-Hydroxymethyl-1.2,3-cyclohexanetriol (Validatol) (14) and Its Tetraacetate (13). a) To a stirred solution of **2** (0.5 g) and sodium borohydride (0.24 g) in THF (15 ml) was added dropwise a solution of 47% boron trifluoride etherate (2.4 ml) in THF (4.8 ml) at ambient temperature over a period of 1 h. After the reaction mixture had been set aside at ambient temperature overnight, an excess of sodium borohydride was destroyed by addition of 50% aqueous THF (5 ml). The reaction mixture was then treated with a mixture of 3 M aqueous sodium hydroxide (6 ml) and 30% hydrogen peroxide (3 ml). The resulting mixture was evaporated and the residue was treated with acetic anhydride (10 ml) and pyridine (10 ml) at ambient temperature overnight. Insoluble substance was removed by filtration and the filtrate was evaporated to give a syrup, which was purified by fractionation on a silica-gel column (50 g) with butanone–toluene (1: 10, v/v). A major product was obtained as a homogeneous syrup, 0.17 g (30%), whose ^{1}H NMR (60 MHz) spectrum showed that the product consists of **9** and tetra-*O*-acetyl-(1,3,6/2,4)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (**12**) in a 1: 2 ratio. Without further fractionation, the mixture was hydrogenolyzed as in the preparation of **7** to give a syrup (0.12 g, 85%). The ^{1}H NMR (60 MHz) spectrum showed that the product consists of **10** and **13** in a 1: 2 ratio. Since **10** and **13** showed a similar mobility on TLC in various solvent systems, attempts were made to separate them by converting them into tetrols **11** and **14**. The mixture (0.29 g) was treated with 1 M methanolic sodium methoxide in methanol (20 ml) at ambient temperature overnight. After treatment with Amberlite IR-120 (H^+), the reaction mixture was evaporated to give a syrup (0.13 g, 90%), which was shown by TLC [benzene–ethanol (3: 2, v/v)] to contain two components (R_f 0.46 and 0.32). The product was fractionated on a silica-gel column (7 g) with ethanol–toluene (2: 3, v/v) as an eluent. Fractions showing a single spot at R_f 0.46 were combined and evaporated to give **14** (55 mg) as a homogeneous syrup.

Found: C, 51.93; H, 8.50%. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70%.

Compound **14** was acetylated in the usual way to give **13** as a homogeneous syrup, whose ^{1}H NMR (100 MHz) spectrum was superimposable on that of an authentic optically active sample.[4b]

Fractions showing a single spot at R_f 0.32 were combined and evaporated to give **11** (30 mg) as crystals: mp 126—127 °C, identical with the compound obtained by hydrogenolysis of **10** followed by *O*-deacetylation.

b) Compound **3** (0.5 g) was hydroborated and subsequently worked up as described above. The acetylated product was chromatographed on a silica-gel column (50 g) with butanone–toluene (1: 10, v/v) to give a homogeneous syrup (0.18 g, 29%), which was shown by ^{1}H NMR (60 MHz) spectrum to consist of **10** and **13** in a 1: 2.5 ratio.

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References

1) All the compounds described in this paper are racemic. All the formulas depict one enantiomer of the respective racemates. The nomenclature is based on the IUPAC-IUB Tentative Cyclitol Nomenclature Rule [*J. Biol. Chem.*, **22**, 5809 (1968)].

2) For the previous paper in this series, S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, **52**, 1174 (1979).

3) T. Suami, S. Ogawa, K. Nakamoto, and I. Kasahara, *Carbohydr. Res.*, **58**, 240 (1977).

4) a) S. Horii, T. Iwasa, and Y. Kameda, *J. Antibiot.*, **24**, 57 (1971); b) S. Horii, T. Iwasa, E. Mizuta, and Y. Kameda, *ibid.*, **24**, 59 (1971).

5) When **1** was treated with sodium acetate in aqueous 2-methoxyethanol followed by acetylation, **9** was mainly obtained in 72% yield, and **2** and **4** could be isolated in very low yields from the mother liquor of **9** by silica gel chromatography.

6) S. Horii and Y. Kameda, *J. Chem. Soc., Chem. Commun.*, **1972**, 747.

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