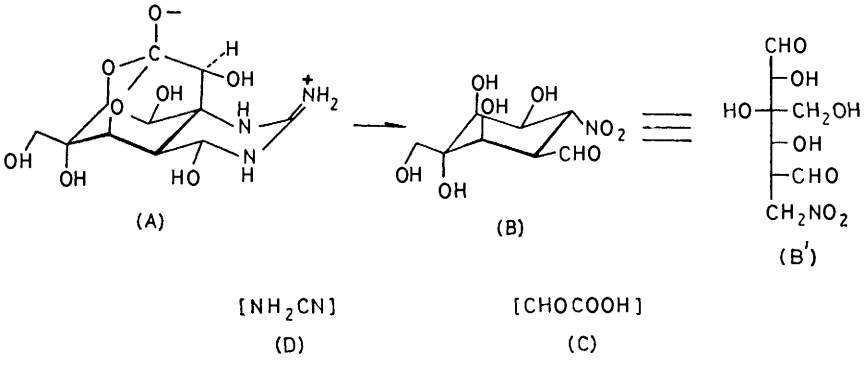
Branched-chain Sugars. Part 15.† Synthesis of 1L-(1,2,3',4,5/3,6)-3-Hydroxymethyl-4,5-*O*-isopropylidene-3,3'-*O*-methylene-6-nitro-2,3,4,5-tetrahydroxycyclohexenecarbaldehyde Dimethyl Acetal, a Potential Key Compound for Total Synthesis of Optically Active Tetrodotoxin

By **Masuo Funabashi,***‡ **Hiroo Wakai, Kenichi Sato,** and **Juji Yoshimura,** Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

The Michael addition of 2-lithio-1,3-dithian to 5,6-dideoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3,3'-*O*-methylene-6-nitro-α-D-*xylo*-hex-5-enofuranose (6) obtained in seven steps from 3-deoxy-1,2 : 5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose gave 5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3,3'-*O*-methylene-6-nitro-α-D-glucofuranose (7) and -β-L-idofuranose (8) [(7) : (8) = 5 : 4] in *ca.* 60% yield. Intramolecular cyclization of both compounds after removal of the isopropylidene group gave branched-chain cyclitols with the *muco*-configuration (9) [from (7)] and the *myo*-configuration (13) [from (8)] respectively. The cyclitol (9) was easily converted into the desired title compound (12) in excellent yield.

In natural product chemistry, the stereospecific synthesis of biologically active, complicated compounds with many chiral centres is making rapid progress. Interestingly, the recent successes of total syntheses of optically active biotin,[1] avenaciolide,[2] isoavenaciolide,[3] canadensolide,[4] thromboxane B2,[5] and tetrahydrocerulenine [6] as well as oxaprostaglandins [7] have depended heavily on the sophisticated application of carbohydrate stereochemistry.



Scheme 1

We have been studying the stereoselective introduction of a carbon-branch at the C-2, -3, or -5 positions of several hexoses [8] and we previously proposed [9] a simple procedure for the synthesis of branched-chain *muco*-inositol derivatives from 5,6-dideoxy-6-nitro-5-*C*-substituted-D-glucofuranose.

We have tried to apply our previous results to a synthesis of the title compound as a precursor of optically active tetrodotoxin, which is known to be one of the most toxic substances of animal origin. Though a synthesis of DL-tetrodotoxin in *ca.* 30 steps from *p*-toluhydroquinone has already been reported by Kishi *et al.*,[10] a total synthesis of optically active tetrodotoxin has not yet been achieved.

For the synthesis of polyfunctional compounds, monosaccharides are quite suitable, chiral starting materials, and we chose D-glucose. As shown in Scheme 1, tetrodotoxin (A) can be divided formally into three units, the *muco*-nitroinositol derivative (B), glyoxylic acid (C), and cyanamide (D). The success [11] of a model system of coupling 2-nitrocyclohexanol with (C) in a weakly basic medium drove us to prepare unit (B) as the first key target with six chiral centres, four of which are originally derived from D-glucose.

As unit (B) is essentially equivalent to 5,6-dideoxy-5-*C*-formyl-3-*C*-hydroxymethyl-6-nitro-D-glucose (B'), our plan can be summarized as follows: (1) introduction of a hydroxymethyl group into C-3, (2) introduction of formyl group into C-5, and (3) introduction of nitro group into C-6 of D-glucose, respectively.

The first problem was easily solved by stereoselective epoxidation [8b] of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose,[12] followed by ring-opening with 1N-sodium hydroxide in tetrahydrofuran to give 3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1) in a good yield. Direct oxidation [8a] of the 3-*C*-methylene derivative with potassium permanganate was not suitable for a large-scale reaction in terms of yield and handling.

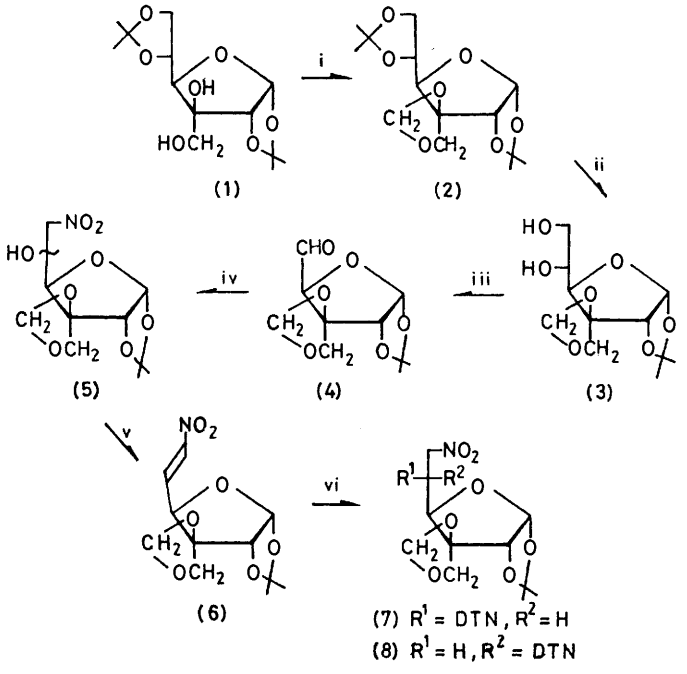
The protection of the free hydroxy groups of com-

† Part 14. ref. 9.

‡ *Present address,* College of Arts and Sciences, Chiba University, Yayoichō, Chiba 260, Japan.

pound (1) was effected with methylene bromide and sodium hydride in dry dimethylformamide (DMF) to give the syrupy 3,3′-*O*-methylene derivative (2) in 65% yield. The 5,6-*O*-isopropylidene group of (2) was then removed with 70% acetic acid at room temperature to give a crystalline 5,6-diol (3) in 90% yield.

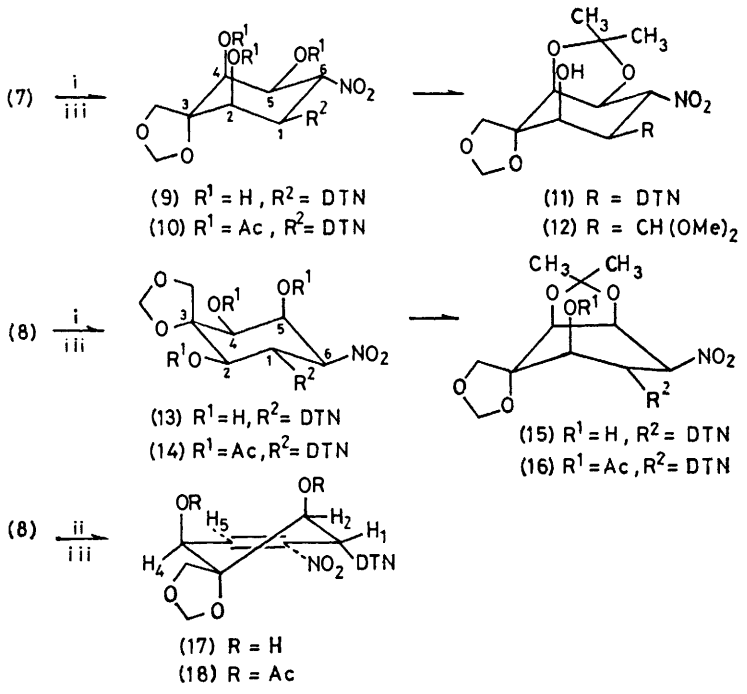
The second and third problems were solved by the method described previously [9] (Scheme 2). Oxidation of (3) with sodium metaperiodate in aqueous methanol gave a syrupy aldehyde (4), which was then condensed with nitromethane in methanol in the presence of sodium methoxide to give a nitroalcohol (5). Direct dehydration of (5) with 3 mol equiv. of methanesulphonyl chloride [13] in the presence of triethylamine



SCHEME 2 Reagents: i, CH_2Br_2–NaH; ii, 70% AcOH; iii, $NaIO_4$; iv, CH_3NO_2–CH_3ONa; v, MsCl–Et_3N; vi, 2-lithio-1,3-dithian

gave the corresponding nitro-olefin (6) in excellent yield. The usual route to a nitro-olefin *via* a nitroacetate was also attempted, but the yield was a little lower. Finally, a formyl group was introduced at C-5 by the addition of 1.4 mol equiv. of 2-lithio-1,3-dithian to (6) in dry tetrahydrofuran, keeping the temperature at −45 to −50° for 30 min giving the syrupy 5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3,3′-*O*-methylene-6-nitro-α-D-glucofuranose (7) and a crystalline β-L-idofuranose derivative (8) in 60% yield. The ratio (7) : (8) was *ca.* 5 : 4 from n.m.r. analysis (comparison of the intensity of 5-H) of the crude mixture. Compounds (7) and (8) were separated by fractional crystallization and preparative t.l.c. The configuration of the new chiral carbon formed at C-5 was determined by converting them into the corresponding cyclitols in the manner described previously.[9] The 1,2-*O*-isopropylidene group of (7) was first removed by treating it either with 90% trifluoroacetic acid (at room temperature for 45 min) or with 85% acetic acid (at reflux for 90 min), and the resulting free sugar was then treated with 1.5 mol equiv. of sodium hydrogencarbonate or sodium carbonate in aqueous methanol to give a crystalline *muco*-inositol derivative, 1L-(1,2,3′,4,5/3,6)-3-hydroxymethyl-3,3′-*O*-methylene-6-nitro-2,3,4,5-tetrahydroxycyclohexanecarbaldehyde trimethylene dithioacetal (9) in a total yield of 45% from (7). Acetylation of (9) with acetic anhydride in the presence of toluene-*p*-sulphonic acid gave the corresponding triacetate (10) in good yield. The coupling constants of compound (10) ($J_{1,2}$ 2.5, $J_{4,5}$ 3.5, $J_{5,6} = J_{1,6} = 11.0$ Hz) as well as the chemical shifts of the three acetoxy groups (δ 1.95, 2.11, and 2.13; one equatorial and two axial) clearly demonstrate that it must be a *muco*-inositol derivative. Acetonation of (9) with acetone–2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid gave the 4,5-*O*-isopropylidene derivative (11) in 85% yield, and transformation of the trimethylene dithioacetal of (9) to the dimethyl acetal with mercury(II) chloride–mercury(II) oxide–boron trifluoride in dry methanol, followed by acetonation, gave the crystalline-title compound (12) in good yield.

On the other hand, a similar cyclization of (8) after removal of isopropylidene group was also carried out in the presence of sodium hydrogencarbonate in aqueous methanol to afford a *myo*-inositol derivative, 1D-(2,3′,4,5,6/1,3)-3-hydroxymethyl-3,3′-*O*-methylene-6-nitro-2,3,4,5-pentahydroxycyclohexanecarbaldehyde trimethylene dithioacetal (13) exclusively in good yield. Another possible isomer, the *scyllo*-inositol derivative, could not be detected. When the cyclization of (8) was carried out in the presence of sodium carbonate, a nitro-olefin (17) was isolated as the main product in addition to compound (13). The longer the reaction time, the more the yield of (13) decreased. Acetylation of (17) gave a crystalline diacetate (18). Acetylation of (13) as for (7), however, was difficult (a problem of solubility) and give the crystalline triacetate (14) in 30% yield, accompanied by an incompletely acetylated product. The coupling constants of (14) ($J_{1,2} = J_{1,6} = 10.0$, $J_{4,5} = J_{5,6} = 2.0$ Hz) and the chemical shifts of the three acetoxy groups (δ 1.98, 2.02, and 2.13; two equatorial and one axial) show that (13) is a *myo*-inositol derivative. Furthermore, acetonation of (13) with acetone–2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid gave the corresponding mono-*O*-isopropylidene derivative (15) in 80% yield. The n.m.r. parameters (see Experimental section) of the monoacetate (16) obtained from (15) clearly demonstrate that (16) must have a twist-boat conformation as reported for a similar *myo*-inositol derivative [9] derived from 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-6-nitro-L-idofuranose. It is surprising that an axially oriented 3-*C*-hydroxymethyl group fixed by a methylene bridge, seems to have no 1,3-nonbonded interaction with an axial hydroxy group at C-5 in the rigid chair conformation of (13).



SCHEME 3 Reagents: i, $NaHCO_3$–aq. MeOH; ii, Na_2CO_3– aq. MeOH; iii, Ac_2O–*p*-TsOH

EXPERIMENTAL

M.p.s were determined on a Yanagimoto micro apparatus and are uncorrected. Solvents were evaporated off *in vacuo* below 40°. N.m.r. spectra (100 MHz) were recorded with a JNM-PS-100 spectrometer in solutions of [^{2}H]chloroform containing tetramethylsilane as internal reference. Optical rotations were measured with a Carl Zeiss LEP A1 spectrophotometer using a 0.5 dm tube. I.r. spectra were recorded with a Hitachi EPI-G2 spectrometer. T.l.c. and preparative t.l.c. were effected on silica gel plates (Merck type 60) with the solvent systems A, 2 : 1 and B, 8 : 1 (v/v) benzene–ethyl acetate.

Modified Preparation of 3-C-*Hydroxymethyl*-1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose* [8a] (1).—3,3′-Anhydro-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (70 g, 0.26 mol) prepared as reported [8b] was dissolved in a mixture of tetrahydrofuran (100 ml) and 1N-sodium hydroxide (300 ml). The suspension (two layers) was heated for 4 h on a water-bath (90°) with stirring. The cooled suspension was extracted with hexane (100 ml × 3), and then chloroform (150 ml × 3). The chloroform layer was washed with brine, dried ($MgSO_4$), and concentrated to a syrup (65 g). The syrup was triturated with hexane (100 ml) to give crystals (60 g) which were used without further purification.

3-C-*Hydroxymethyl*-1,2:5,6-*di*-O-*isopropylidene*-3,3′-O-*methylene*-α-D-*glucofuranose* (2).—To a solution of (1) (7.5 g, 26 mmol) in dry DMF (20 ml) was gradually added a suspension of sodium hydride (4.0 g) in dry DMF (20 ml). Methylene bromide (20 ml) was then rapidly added to the above mixture, and vigorous stirring was continued for 1 h. The mixture was poured into ice–water, extracted with chloroform, washed with brine, dried ($MgSO_4$), and evaporated to a syrup (7.5 g), which was placed on a column of silica gel (Wako-gel C-200; 80 g), and eluted with benzene to give the pure *syrup* (2) (5.1 g, 65%), $[\alpha]_D^{23}$ +25° (*c* 1.0, methanol); δ_H 1.30, 1.31, 1.37, and 1.46 (12 H, s, isopropyl), 3.93—4.27 (5 H, m, H-4, -5, -6, and CCH_2O), 4.34 (1 H, d, $J_{1,2}$ 3.0 Hz, H-2), 5.03 (2 H, d, OCH_2O), and 5.85 (1 H, d, H-1) (Found: C, 55.85; H, 7.4. $C_{14}H_{22}O_7$ requires C, 55.6; H, 7.35%).

3-C-*Hydroxymethyl*-1,2-O-*isopropylidene*-3,3′-O-*methylene*-α-D-*glucofuranose* (3).—A solution of compound (2) (15.8 g, 52 mmol) in 70% acetic acid (80 ml) was allowed to stand overnight at room temperature, and concentrated to a syrup. The syrup was then treated with hexane to give *crystals* (12.5 g), which were recrystallized from ether–hexane (1 : 1), m.p. 88—89°; $[\alpha]_D^{23}$ +30° (*c* 1.1, chloroform) (Found: C, 50.55; H, 7.0. $C_{11}H_{18}O_7$ requires C, 50.35; H, 6.9%).

Periodate Oxidation of (3) *and Reaction of the Aldehyde* (4) *with Nitromethane*.—To a cooled (5—10°) solution of the 5,6-diol (3) (11 g, 42 mmol) in water (25 ml) and methanol (75 ml) was gradually added a solution of sodium metaperiodate (9.1 g, 42.5 mmol) in water (90 ml). The mixture was stirred for 30 min in an ice–water bath and for another 30 min at room temperature. The precipitate was filtered off and washed with methanol. The filtrate and washing were evaporated to a residue, which was re-extracted several times with methanol. The methanol extracts were concentrated to a clear syrup (9.3 g). A part of the syrup (100 mg) was converted into a crystalline 2,4-*dinitrophenylhydrazone* having m.p. 184—185°, $[\alpha]_D^{20}$ +10.2° (*c* 0.63, chloroform) (Found: C, 46.9; H, 4.45; N, 13.7. $C_{16}H_{18}N_4O_9$ requires C, 46.85; H, 4.4; N, 13.65%).

The syrup (9.2 g) was dissolved in methanol (30 ml) and nitromethane (20 ml), and a solution of sodium methoxide prepared from sodium (0.95 g) in methanol (40 ml) was added. The solution was stirred for 30 min at room temperature, acidified with acetic acid (2.7 ml), and concentrated to a residue. The residue was dissolved in chloroform, washed with brine, dried ($MgSO_4$), and concentrated to a pale brown syrup (11.3 g), which gradually crystallized. Recrystallization from ether–hexane (1 : 1) gave (5) as fine

needles (9.7 g, 82%), m.p. 91—92°, $[\alpha]_D^{23}$ +32° (*c* 1.1, chloroform) (Found: C, 45.65; H, 5.9; N, 4.7. $C_{11}H_{17}NO_8$ requires C, 45.35; H, 5.9; N, 4.8%); $\nu_{max.}$ 3 430 (OH) and 1 540 cm^{-1} (NO_2).

5,6-*Dideoxy*-3-C-*hydroxymethyl*-1,2-O-*isopropylidene*-3,3′-O-*methylene*-6-*nitro*-α-D-xylo-*hex*-5-*enofuranose* (6).—(a). A solution of the nitro-alcohol (5) (8.4 g, 0.029 mol) and a catalytic amount of toluene-*p*-sulphonic acid monohydrate (*p*-TsOH·H_2O) in acetic anhydride (35 ml) was kept for 3 h at room temperature, and then poured into ice–water containing aqueous sodium hydrogencarbonate, extracted with chloroform, washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and evaporated to a syrup (9.5 g). A solution of the syrup in dry benzene (30 ml) was then refluxed for 2 h in the presence of potassium carbonate (2.3 g). Inorganic materials were filtered off, and the filtrate was concentrated to a syrup (7.3 g), which was placed on a column of silica gel, and eluted with benzene to give the clear *syrup* (6) (5.8 g, 74%), $[\alpha]_D^{23}$ +19° (*c* 1.6, chloroform); $\nu_{max.}$ 1 650, 1 520, and 1 348 cm^{-1} (nitro-olefin); δ_H 1.37 and 1.52 (6 H, s, isopropyl), 3.90 (1 H, d, $J_{3,3'}$ 10 Hz, H-3′a), 4.29 (1 H, d, H-3′b), 4.50 (1 H, d, $J_{1,2}$ 3.7 Hz, H-2), 4.80 (1 H, d, $J_{4,5}$ 2.5 Hz, H-4), 4.98 (2 H, s, OCH_2O), 6.03 (1 H, d, H-1), and 7.09—7.40 (2 H, m, $J_{5,6}$ 15 Hz, H-5 and -6) (Found: C, 48.1; H, 5.8; N, 5.1. $C_{11}H_{15}NO_7$ requires C, 48.35; H, 5.55; N, 5.15%).

(b) To a cooled (0°) solution of nitro-alcohol (5) (11 g, 38 mmol) in dry methylene chloride (100 ml) was added methanesulphonyl chloride (13 g, 114 mmol). Triethylamine (15 g, 152 mmol) was then gradually added to the above solution, and the reaction solution was kept for 30 min at 0°. Methylene chloride (60 ml) was added, washed with aqueous sodium hydrogencarbonate, brine, and water, dried ($MgSO_4$), and concentrated *in vacuo* (1 Torr) to a syrup. The syrup was finally purified on a column of silica gel to give the pure nitro-olefin (6) (9.3 g, 90%).

5,6-*Dideoxy*-5-C-(1,3-*dithian*-2-*yl*)-3-C-*hydroxymethyl*-1,2-O-*isopropylidene*-3,3′-O-*methylene*-6-*nitro*-α-D-*glucofuranose* (7) and -β-L-*idofuranose* (8).—To a cooled (−45 to −50°) solution of (6) (7.2 g, 26.5 mmol) in dry tetrahydrofuran (THF) (40 ml) was added at once a solution of 2-lithio-1,3-dithian prepared from 1,3-dithian (5.2 g, 43 mmol) and butyl-lithium (10% hexane solution; 25 ml; 37.5 mmol) in dry THF (20 ml). The mixture was kept for 30 min at the same temperature, and then acidified with acetic acid. The gelatinous mixture was dissolved in methanol and concentrated to a residue, which was treated with chloroform and brine. The chloroform layer was washed with water, dried ($MgSO_4$), and evaporated to a syrup (11.9 g). The syrup was placed on a column of silica gel (Wako gel C-200; 120 g), and an excess of 1,3-dithian was removed by eluting with hexane. Benzene to benzene–ethyl acetate (10 : 1) fractions gave a syrupy mixture of (7) and (8) (6.6 g). The syrup was repeatedly triturated with ethanol to give crystals (2.7 g) of (8). Recrystallization from ethanol gave fine *needles*, m.p. 129—130°; $[\alpha]_D^{24}$ −10.5° (*c* 1.0, chloroform); δ_H 1.32 and 1.48 (6 H, s, isopropyl), 1.8—2.2 (2 H, m, $SCH_2CH_2CH_2S$), 2.5—3.0 (4 H, m, $SCH_2CH_2CH_2S$), 3.53 (1 H, m, H-5), 4.12 (2 H, s, CCH_2O), 4.23—5.13 (not fully assigned), and 5.91 (1 H, d, $J_{1,2}$ 3.7 Hz) (Found: C, 45.65; H, 5.95; N, 3.5. $C_{15}H_{23}NO_7S_2$ requires C, 45.8; H, 5.9; N, 3.55%).

From the filtrate, a syrup (3.6 g) contaminated with a little (8) was obtained. A part of the syrup was purified by repeated preparative t.l.c. (solvent B) to give the *syrup* (7), $[\alpha]_D^{27}$ −8.3° (*c* 1.26, acetone); δ_H 1.32 and 1.47 (6 H, s, isopropyl), 1.8—2.2 (2 H, m, $SCH_2CH_2CH_2S$), 2.5—3.0 (4 H, m, $SCH_2CH_2CH_2S$), 3.15 (1 H, m, H-5), 3.85—5.09 (not fully assigned), and 5.90 (1 H, d, $J_{1,2}$ 3.2 Hz) (Found: C, 45.8; H, 5.8; N, 3.3%).

1L-(1,2,3′,4,5/3,6)-3-*Hydroxymethyl*-3,3′-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (9).—A solution of compound (7) [contaminated with a little (8)] (640 mg, 1.63 mmol) in 90% trifluoroacetic acid (12 ml) was kept for 45 min at room temperature and concentrated to a syrup. The syrup was then dissolved in a mixture of methanol (20 ml) and aqueous sodium hydrogencarbonate (270 mg) in water (14 ml). The mixture was kept for 15 h at room temperature, neutralized with IR-120 (H^+), and concentrated to a syrup which was placed on a column of silica gel (10 g). Concentration of the benzene–ethyl acetate (2 : 1) fractions gave a crystalline *mass* (360 mg), which was recrystallized from ethanol, m.p. 195—196°; $[\alpha]_D^{20}$ +22.3° (*c* 1.51, acetone) (Found: C, 41.0; H, 5.45; N, 4.0. $C_{12}H_{19}O_7NS_2$ requires C, 40.7; H, 5.4; N, 3.95%).

1L-(1,2,3′,4,5/3,6)-2,4,5-*Tri*-O-*acetyl*-3-*hydroxymethyl*-3,3′-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (10).—A solution of (9) (100 mg, 0.28 mmol) in acetic anhydride (5 ml) containing a catalytic amount of *p*-TsOH·H_2O was kept overnight at room temperature. The solution was then poured into ice–water containing $NaHCO_3$, extracted with chloroform, washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to a crystalline residue, which was recrystallized from ethanol, m.p. 173—175°; $[\alpha]_D^{24}$ +66° (*c* 1.05, chloroform); δ_H 1.95, 2.11, and 2.13 (3 H × 3, s, acetyl), 2.6—3.0 (m, trimethylene), 3.21 (1 H, octet, $J_{1,2}$ 2.5, $J_{1,1'}$ 4.0, $J_{1,6}$ 11 Hz, H-1), 3.75 (2 H, dd, J_{gem} 9.5 Hz, OCH_2C), 4.15 (1 H, d, H-1′), 5.34 (2 H, s, OCH_2O), 5.33 (1 H, t, $J_{5,6}$ 11 Hz, H-6), 5.37 (1 H, q, $J_{4,5}$ 3.5, $J_{2,4}$ 10 Hz, H-4), 5.51 (1 H, q, H-2), and 5.68 (1 H, q, H-5).

1L-(1,2,3′,4,5/3,6)-3-*Hydroxymethyl*-4,5-O-*isopropylidene*-3,3′-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (11).—A suspension of (9) (310 mg, 0.87 mmol) and copper(II) sulphate (100 mg) in dry acetone (5 ml) and 2,2-dimethoxypropane (2 ml) was stirred for 20 h at room temperature in the presence of *p*-TsOH·H_2O. The inorganic material was filtered off, and the solution concentrated to a pale brown syrup, which was immediately treated with chloroform and aqueous $NaHCO_3$. The chloroform layer was washed with brine and dried ($MgSO_4$), and concentrated to a crystalline *mass* (340 mg), which was crystallized from ethanol, m.p. 192—193°; $[\alpha]_D^{20}$ −67° (*c* 1.0, chloroform); δ_H 1.36 and 1.58 (6 H, s, isopropylidene), 1.7—2.3, 2.5—3.0 (m, trimethylene), 4.1—4.3 (4 H, m, H-1′, -2, and OCH_2C), 4.66 (1 H, q, $J_{4,5}$ 5.0, $J_{5,6}$ 8.5 Hz, H-5), 4.98 (1 H, d, H-4), 5.00 (2 H, s, OCH_2C), 5.10 (1 H, q, $J_{1,6}$ 12.5 Hz, H-6) (Found: C, 45.8; H, 5.95; N, 3.6. $C_{15}H_{23}NO_7S_2$ requires C, 45.8; H, 5.9; N, 3.55%).

1L-(1,2,3′,4,5/3,6)-3-*Hydroxymethyl*-4,5-O-*isopropylidene*-3,3′-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Dimethyl Acetal* (12).—A suspension of (9) (1.0 g, 2.83 mmol), mercury(II) oxide (0.97 g, 4.49 mmol) and mercury(II) chloride (1.21 g, 4.46 mmol) in absolute methanol (20 ml) and trimethoxymethane (10 ml) containing boron trifluoride–ether (100 mg) was stirred for 24 h at room temperature. The precipitate was filtered off and the filtrate was evaporated to a syrup, which was dissolved in a mixture of acetone (10 ml) and 2,2-dimethoxypropane (10

ml) containing *p*-TsOH·H_2O (20 mg) and anhydrous copper(II) sulphate (500 mg). The suspension was stirred for 2 h at room temperature. After filtration of inorganic material, the filtrate was evaporated to a pale brown syrup, which was immediately treated with chloroform and aqueous $NaHCO_3$. The chloroform layer was washed with brine, dried ($MgSO_4$), and evaporated to a syrup (0.91 g), which gradually crystallized. Recrystallization from ether–hexane (1 : 1) gave fine *needles*, m.p. 135—136°; $[\alpha]_D^{20}$ −77° (*c* 1.13, chloroform); δ_H 1.36 and 1.56 (6 H, s, isopropyl), 2.62 (1 H, octet, $J_{1,1'}$ 4.7, $J_{1,2}$ 1.9, $J_{1,6}$ 12.5 Hz, H-1), 3.08 (1 H, d, *J* 3.8 Hz, OH), 3.37 and 3.42 (6 H, s, OCH_3 × 2), 4.05—4.23 (4 H, m, H-2, -4, and OCH_2C), 4.35 (1 H, d, H-1'), 4.68 (1 H, dd, $J_{4,5}$ 4.5, $J_{5,6}$ 8.8 Hz, H-5), 4.90 (1 H, dd, H-6) (Found: C, 48.0; H, 6.65; N, 4.05. $C_{14}H_{23}NO_9$ requires C, 48.15; H, 6.65; N, 4.0%).

1D-(2,3',4,5,6/1,3)-3-*Hydroxymethyl*-3,3'-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (13).—A solution of (8) (200 mg, 0.51 mmol) in 90% trifluoroacetic acid (6 ml) was kept for 40 min at room temperature, and evaporated to a syrup, which was dissolved in methanol (6 ml) and water (4 ml) containing $NaHCO_3$ (84 mg, 1 mmol). The mixture was stirred overnight at room temperature, neutralized with IR-120 (H^+), and concentrated in the presence of ethanol to an almost pure crystalline *residue* (170 mg, 95%), which was recrystallized from ethanol, m.p. 237° (decomp.), $[\alpha]_D^{20}$ −28° (*c* 0.67, acetone) (Found: C, 41 0; H, 5 45; N, 3.95. $C_{12}H_{19}NO_7S_2$ requires C, 40.8; H, 5.4; N, 3.95%).

1D-(2,3',4,5,6/1,3)-2,4,5-*Tri*-O-*acetyl*-3-*hydroxymethyl*-3,3'-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (14).—A suspension of (13) (170 mg, 0.48 mmol) in acetic anhydride (3 ml) and isopropenyl acetate (1 ml) containing a catalytic amount of *p*-TsOH·H_2O was stirred for 5 h at room temperature, poured into ice–water containing $NaHCO_3$, washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to a syrup, which showed two spots on t.l.c. (solvent A). The syrup was subjected to preparative t.l.c. (solvent A) to give a less polar crystalline triacetate (14) (70 mg) and a more polar syrupy diacetate (80 mg). The triacetate was recrystallized from ethanol, m.p. 213—215°, $[\alpha]_D^{24}$ −2.8° (*c* 1.0, chloroform), δ_H 1.98, 2.02, 2.13 (9 H, s, $COCH_3$ × 3), 2.6—2.9 (m, H-1 and trimethylene), 4.00 (1 H, d, $J_{1,1'}$ 3.0 Hz, H-1'), 4.13 (2 H, s, OCH_2C), 4.85 (2 H, d, OCH_2O), 5.00 (1 H, q, $J_{1,6}$ 10, $J_{5,6}$ 2.0 Hz, H-6), and 5.43 (1 H, d, $J_{1,2}$ 10 Hz, H-2).

1D-(2,3',4,5,6/1,3)-3-*Hydroxymethyl*-4,5-O-*isopropylidene*-3,3'-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (15).—A suspension of (13) (100 mg, 0.28 mmol) in dry acetone (5 ml) and 2,2-dimethoxypropane (4 ml) containing *p*-TsOH·H_2O and copper(II) sulphate (100 mg) was stirred for 48 h at room temperature. Inorganic material was filtered off and concentrated to a pale brown syrup, which was immediately treated with chloroform and aqueous $NaHCO_3$. The chloroform layer was washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to a syrup (100 mg), which gradually crystallized. Recrystallization from ethanol gave pure *crystals* (80 mg, 72%), m.p. 190—191°; $[\alpha]_D^{20}$ −92° (*c* 1.4, chloroform) (Found: C, 45.6; H, 5.95; N, 3.55. $C_{15}H_{23}NO_7S_2$ requires C, 45.8; H, 5.9; N, 3.55%).

1D-(2,3',4,5,6/1,3)-2-O-*Acetyl*-3-*hydroxymethyl*-4,5-O-*isopropylidene*-3,3'-O-*methylene*-6-*nitro*-2,3,4,5-*tetrahydroxycyclohexanecarbaldehyde Trimethylene Dithioacetal* (16).—A solution of (15) (100 mg, 0.23 mmol) in acetic anhydride (3 ml) containing a catalytic amount of *p*-TsOH·H_2O was kept overnight at room temperature. The solution was then poured into ice–water containing $NaHCO_3$, extracted with chloroform, washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to a crystalline residue, which was recrystallized from ethanol to give pure *crystals* (83 mg, 75%), m.p. 269—270°; $[\alpha]_D^{20}$ −47° (*c* 0.74, chloroform); δ_H 1.28 and 1.52 (6 H, s, isopropyl), 2.05 (3 H, s, $COCH_3$), 2.6—2.9 (6 H, m, trimethylene), 3.20 (1 H, td, $J_{1,1'} = J_{1,2}$ = 4.0, $J_{1,6}$ 12 Hz, H-1), 3.92 (2 H, dd, J_{gem} 8.8 Hz, OCH_2C), 4.30 (1 H, dd, $J_{2,4}$ 1.9, $J_{4,5}$ 7.5 Hz, H-4), 4.32 (1 H, d, H-1'), 4.91 (1 H, dd, $J_{5,6}$ 3.2 Hz, H-5), 5.01 (2 H, d, OCH_2O), 5.21 (1 H, dd, H-6), and 5.50 (1 H, q, H-5) (Found: C, 46.7; H, 5.85; N, 3.55. $C_{17}H_{25}NO_8S_2$ requires C, 46.9; H, 5.8; N, 3.2%).

1D-(2,3',4/1,3)-2,4-*Di*-O-*acetyl*-3-*hydroxymethyl*-3,3'-O-*methylene*-6-*nitro*-2,3,4-*trihydroxycyclohex*-5-*enecarbaldehyde Trimethylene Dithioacetal* (18).—A solution of (8) (300 mg, 0.76 mmol) in 90% trifluoroacetic acid (6 ml) was kept for 45 min at room temperature and concentrated to a syrup, which was then dissolved in methanol (10 ml) and water (6 ml) containing Na_2CO_3 (120 mg, 1.14 mmol). The mixture was kept for 20 h at room temperature, neutralized with IR-120 (H^+), and concentrated to a syrup with two components, $\nu_{max.}$ 1 650, 1 560, and 1 520 cm^{-1}. Preparative t.l.c. (solvent A) of the syrup gave a less polar nitro-olefin (17) (80 mg) as the main component and a more polar crystalline nitro-alcohol (13) (60 mg).

The nitro-olefin (80 mg) was acetylated as described for (10) and gave a gum, which was subjected to a silica gel column chromatography. Evaporation of benzene–ethyl acetate (10 : 1) fractions gave *needles* of (18) (60 mg), m.p. 172—173°; $[\alpha]_D^{30}$ −10° (*c* 0.97, acetone); δ_H 2.10, 2.22 (6 H, s, acetyl), 2.0 and 2.4—3.2 (6 H, m, trimethylene), 3.92 2 H, q, J_{gem} 10 Hz, OCH_2C), 4.04 (1 H, octet, $J_{1,2}$ 4.0, $J_{1,4}$ 1.0, $J_{1,1'}$ 9.0 Hz, H-1), 4.23 (1 H, d, H-1'), 4.92 and 5.04 (2 H, s, OCH_2O), 5.66 (1 H, q, $J_{4,5}$ 3.2 Hz, H-4), 5.82 (1 H, d, H-2), and 6.17 (d, H-5) (Found: C, 46.15; H, 5.1; N, 3.3. $C_{16}H_{21}NO_8S_2$ requires C, 45.8; H, 5.0; N, 3.3%).

[8/1896 *Received*, 31*st October*, 1978]

REFERENCES

[1] (*a*) H. Ohrui and S. Emoto, *Tetrahedron Letters*, 1975, 2765; (*b*) T. Ogawa, T. Kawana, and M. Matsui, *Carbohydrate Res.*, 1977, **57**, C32.

[2] (*a*) R. C. Anderson and B. Fraser-Reid, *J. Amer. Chem. Soc.*, 1975, **97**, 3870; (*b*) H. Ohrui and S. Emoto, *Tetrahedron Letters*, 1975, 3657.

[3] R. C. Anderson and B. Fraser-Reid, *Tetrahedron Letters*, 1977, 2865.

[4] R. C. Anderson and B. Fraser-Reid, *Tetrahedron Letters*, 1978, 3233.

[5] (*a*) S. Hanessian and P. Lavallee, *Canad. J. Chem.*, 1977, **55**, 562; (*b*) E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Letters*, 1977, 1625; (*c*) O. Hernandez, *ibid.*, 1978, 219.

[6] (*a*) H. Ohrui and S. Emoto, *Tetrahedron Letters*, 1978, 2095; (*b*) J.-R. Pougy and P. Sinäy, *ibid.*, p. 3301.

[7] (*a*) S. Hanessian, P. Dextraze, A. Fougerousse, and Y. Guindon, *Tetrahedron Letters*, 1974, 3983; (*b*) G. J. Lourens and J. M. Koekemoer, *ibid.*, 1975, 3715, 3719.

[8] (*a*) J. Yoshimura, K. Kobayashi, K. Sato, and M. Funabashi, *Bull. Chem. Soc. Japan*, 1972, **45**, 1806; (*b*) M. Funabashi, H. Sato, and J. Yoshimura, *ibid.*, 1976, **49**, 788; (*c*) J. Yoshimura, K. Mikami, K. Sato, and C. Shin, *ibid.*, p. 1686.

[9] M. Funabashi and J. Yoshimura, *J.C.S. Perkin I*, 1979, 1425.

[10] Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Amer. Chem. Soc.*, 1972, **94**, 9217, 9219.
[11] J. Yoshimura, T. Iida, and M. Funabashi, *Bull. Chem. Soc. Japan*, 1970, **43**, 3887.
[12] (*a*) W. A. Szarek, J. S. Jewell, I. Szczerek, and J. K. N. Jones, *Canad. J. Chem.*, 1969, **47**, 4473; (*b*) A. Rosenthal and M. Sprinzl, *ibid.*, 1969, **47**, 4477.
[13] J. Melton and J. E. McMurry, *J. Org. Chem.*, 1975, **40**, 2139.