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Stereospecific and Stereoselective Reactions. IX.[1] Preparation of Ethyl (2*E*,7*R*)-7-Acetoxy-4-oxo-2-octenoate from D-Glucose

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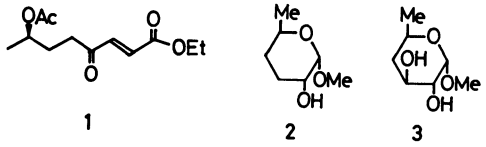
Reaction of methyl 2,3-anhydro-4,6-dideoxy-α-D-*ribo*-hexopyranoside with MgI_2 exclusively afforded methyl 3,4,6-trideoxy-3-iodo-α-D-*xylo*-hexopyranoside which was dehalogenated by treatment with $LiAlH_4$ to give methyl 3,4,6-trideoxy-α-D-*erythro*-hexopyranoside (**2**). Hydrolysis of **2** and subsequent treatment with ethoxycarbonylmethylenetriphenylphosphorane gave ethyl (2*E*, 4*R*, 7*R*)-4,7-dihydroxy-2-octenoate (**10**). Oxidation of **10** by active MnO_2 resulted in the formation of an equilibrium mixture of ethyl (2*E*, 7*R*)-7-hydroxy-4-oxo-2-octenoate (the carbon skeleton of pyrenophorin) and cyclic hemiacetal. On treatment with acetic anhydride, the mixture afforde dethyl (2*E*, 7*R*)-7-acetoxy-4-oxo-2-octenoate.

Carbohydrates have been utilized as potential starting materials for the construction of natural products having multiple centers of chirality.[2] In spite of many elegant approaches have been reported so far, there is still a need to develop convenient methods for stereospecific and regioselective transformation of a hydroxyl group of carbohydrates. 2,3-Anhydro sugars are attractive chiral intermediates for the transformation of carbohydrates. The opening of the oxirane ring on locked pyranosides system by nucleophiles has been much discussed and a clear pattern has emerged, while the reaction of flexible 2,3-anhydropyranosides with nucleophiles are more complicated and the factors determining the reaction site are not fully elucidated.[3]

We report here a simple synthesis of ethyl (2*E*,7*R*)-7-acetoxy-4-oxo-2-octenoate (**1**), the carbon skeleton of pyrenophorin, from methyl 3,4,6-trideoxy-α-D-*erythro*-hexopyranoside (**2**) which was obtained by a sequence of reactions involving regioselective oxirane ring-opening of readily available methyl 2,3-anhydro-4,6-dideoxy-α-D-*ribo*-hexopyranoside.[4]

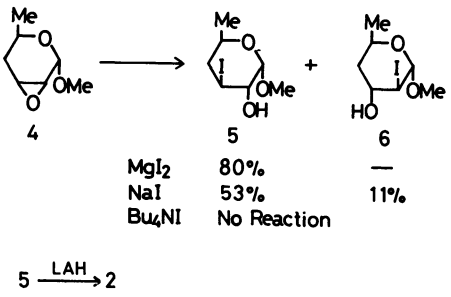


Scheme 1.

Reductive oxirane ring-opening of 2,3-anhydropyranoside has been reported.[5] Thus, methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside (**3**) was converted into methyl 2,3-anhydro-4,6-dideoxy-α-D-*ribo*-hexopyranoside (**4**) by the reaction with diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP).[6] It was found, however, that catalytic hydrogenation (Raney-Ni (W-2); 100—120 kg/cm² H_2, 80 °C) or $LiAlH_4$ reduction (−2—0 °C, ether) of **4** afforded the desired **2** in only 18% or 29% yields, respectively.

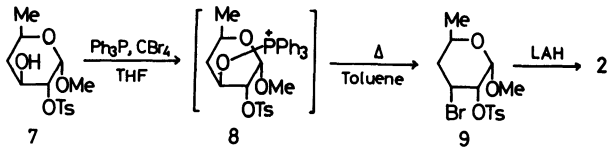
Next, a two-step procedure was examined. When **4** was allowed to react with MgI_2 in tetrahydrofuran (THF), methyl 3,4,6-trideoxy-3-iodo-α-D-*xylo*-hexopyranoside (**5**) was obtained in 80% yield without any detectable formation of 2-iodo isomer (**6**).[7] The sequence thus allowed net replacement of the 3-hydroxyl group of **3** by iodo substituent with retention of configuration. The reaction of **4** with NaI in the presence of sodium acetate and acetic acid in acetone gave **5** and **6** in 53 and 11% yields, respectively. It is noteworthy that no reaction occurred when **4** was treated with tetrabutylammonium iodide under the similar conditions (THF, refluxed for 6 h). Thus these results suggest that metal cations play an important role in the cleavage of the oxirane-ring of **4**.[8]

Compound **5** reacted smoothly with $LiAlH_4$ to give **2** in 95% yield.



Scheme 2.

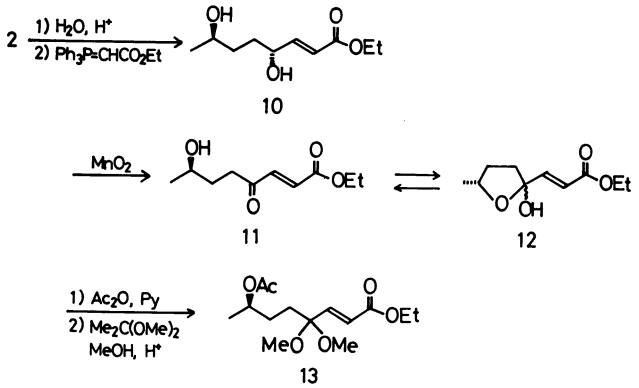
An alternative route to **2** was also examined. Methyl 4,6-dideoxy-2-*O*-*p*-tosyl-α-D-*xylo*-hexopyranoside (**7**) was allowed to react with carbon tetrabromide and TPP in THF at room temperature for 24 h giving an oily product which was assumed to be an alkoxyphosphonium bromide (**8**). The solvent was then replaced by toluene and the resulting mixture was refluxed for 2 h affording methyl 3-bromo-3,4,6-trideoxy-2-*O*-*p*-tosyl-α-D-*ribo*-hexopyranoside (**9**) in 54% yield. Although the configuration at the 3-position could not be determined, in view of the nature of the bromination reaction, D-*ribo*-configuration was tentatively assigned.[9] By treatment with $LiAlH_4$, **9** gave **2** in 73% yield.



Scheme 3.

Acid hydrolysis of **2** gave free sugar (83% yield) which was converted into ethyl (2*E*,4*R*,7*R*)-4,7-dihy-

droxy-2-octenoate (**10**) by the reaction with ethoxycarbonylmethylenetriphenylphosphorane in 75% yield. Selective oxidation of the 4-hydroxyl group of **10** could be accomplished by the reaction with active MnO_2.[10] As indicated by ^{1}H-NMR spectrum, however, the product is an about 1 : 1 mixture of desired ethyl (2*E*,7*R*)-7-hydroxy-4-oxo-2-octenoate (**11**) and cyclic hemiacetal (**12**; 74% total yield). In order to displace the equilibrium to the open chain compound, the mixture was treated with acetic anhydride in pyridine affording the expected ethyl (2*E*,7*R*)-7-acetoxy-4-oxo-2-octenoate (**1**) in 78% yield. Acetalization of **1** afforded ethyl (2*E*,7*R*)-7-acetoxy-4,4-dimethoxy-2-octenoate (**13**) in 91% yield.



Scheme 4.

Bakuzis *et al.* have reported the synthesis of *dl*-pyrenophorine from ethyl *dl*-7-acetoxy-4,4-ethylenedioxy-2-octenoate by the use of DEAD and TPP in the cyclization step.[11] Since the lactonization using DEAD and TPP has been shown to proceed through inversion of configuration at the reaction site of the alcoholic component,[4,12] the synthesis of **13** indicates a relay approach to (*S*,*S*)-pyrenophorin.

Experimental

Nuclear magnetic resonance (NMR) spectra were measured on Hitachi R-20 spectrometer (60 MHz) using tetramethylsilane as an internal standard. Optical rotations were measured on JASCO DIP-4 digital polarimeter using a 1-dm cell in the solvent indicated. Preparative thin layer chromatography (PLC) and column chromatography were performed on Merck Kieselgel 60 PF_{254} (20 cm × 20 cm or 20 cm × 30 cm plate) and Kieselgel 60 (70—230 mesh), respectively. All evaporations were performed under reduced pressure. For distillation of small amount of product, Kugelrohr (Büchi) apparatus was used and oven temperature is indicated.

*Preparation of Methyl 2,3-Anhydro-4,6-dideoxy-α-*D*-ribo-hexopyranoside (**4**) from Methyl 4,6-Dideoxy-α-*D*-xylo-hexopyranoside (**3**).* *a) Two-step Procedure*: *p*-Tosyl chloride (35 g, 184 mmol) was added to a suspension of **3** (11.8 g, 73 mmol)[13] in pyridine (150 ml) at 0 °C. After the mixture had been stirred for 80 h at room temperature, chloroform (150 ml) was added. The mixture was washed successively with 10% H_2SO_4 and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was crystallized from methanol, affording methyl 4,6-dideoxy-2,3-di-*O*-*p*-tosyl-α-D-*xylo*-hexopyranoside (29.7 g, 86%, mp 110—112 °C). NMR ($CDCl_3$ δ=1.15 (d, H-6), 1.45—2.4 (m, H-4), 2.45 (s, $C\underline{H}_3$–C_6H_4–), 3.30 (s, CH_3O–), 3.5—4.15 (m, H-5), 4.2—4.5 (dd, H-2), 4.65—5.2 (m, H-3), 4.83 (d, H-1). Found: C, 53.54; H, 5.58%. Calcd for $C_{21}H_{26}S_2O_8$: C, 53.60; H, 5.57%.

Sodium methoxide in methanol (prepared from 0.87 g of sodium and 20 ml of methanol) was added to a suspension of the ditosylate (6.31 g, 13.4 mmol) in methanol (30 ml) at room temperature. The mixture was refluxed for 6 h with stirring, and then evaporated. Water was added to the residue and extracted with dichloromethane and ether. The organic layer was dried ($MgSO_4$) and evaporated. Methanol was added to the residue and evaporated to a small volume. Unreacted ditosylate was filtered off (1.18 g, 19% recovery). The filtrate was evaporated and the residue was chromatographed (benzene–ethyl acetate=5 : 1) to give **4** (1.11 g, 57%). $[\alpha]_D^{20}$ +61.7° (*c* 0.3, $CHCl_3$). NMR ($CDCl_3$) δ=1.1 (d, H-6), 1.2—2.2 (m, H-4), 3.2—4.2 (m, H-2,3,5), 3.3 (s, CH_3O–), 4.78 (d, H-1, $J_{1,2}$=2.8 Hz). Found: C, 58.65; H, 8.53%. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39%.

b) One-step Procedure: A solution of diethyl azodicarboxylate (1.04 g, 6 mmol) in benzene (2 ml) was added dropwise to a mixture of **3** (0.649 g, 4 mmol) and triphenylphosphine (1.57 g, 6 mmol) in benzene (7 ml) at room temperature. The mixture was refluxed for 2 h, allowed to cool to room temperature, and evaporated. Ether was added to the residue to precipitate triphenylphosphine oxide and diethyl hydrazinedicarboxylate which were filtered off. The filtrate was concentrated and the residue was distilled giving **4** [oven temperature 80—120 °C/22 Torr (1 Torr=133.322 Pa)]. The distillate was contaminated with a small amount of diethyl hydrazinedicarboxylate which was removed by passing through silica-gel column (benzene–ethyl acetate=1 : 5). The yield of **4** was 75% (431 mg). Thin layer chromatography of the crude reaction mixture indicated the presence of a trace of methyl 2,3-anhydro-4,6-dideoxy-α-D-*lyxo*-hexopyranoside. However, the isomer could not be isolated.

*Reaction of Methyl 2,3-Anhydro-4,6-dideoxy-α-*D*-ribo-hexopyranoside (**4**) with Iodide.* *a) Reaction with MgI_2*: MgI_2 was prepared by the reaction of activated magnesium[14] with I_2. After a mixture of potassium (2.54 g, 65 mmol) and $MgCl_2$ (3.22 g, 34 mmol) in THF (20 ml) had been refluxed with stirring under N_2 for 2 h, a solution of I_2 (8.21 g, 32 mmol) in THF (20 ml) was added, followed by a solution of **4** (2.15 g, 15 mmol) in THF (15 ml). The mixture was heated under reflux for 6 h. Saturated aqueous NH_4Cl (10 ml) was added to the cooled reaction mixture and filtered through Hyflosupercel. The filtrate was evaporated, the residue being extracted with chloroform. The organic layer was washed with aqueous sodium thiosulfate, dried ($MgSO_4$), and evaporated affording chromatographically (TLC) pure methyl 3,4,6-trideoxy-3-iodo-α-D-*xylo*-hexopyranoside (**5**; 3.94 g, 97%). Purification by means of PLC (ether–chloroform=1 : 20) afforded pure **5** (80% yield) which was recrystallized from hexane, mp 57—59 °C. $[\alpha]_D^{21}$ +140° (*c* 1.08, $CHCl_3$). NMR ($CDCl_3$) δ=1.16 (d, H-6), 1.9—2.7 (m, H-4, OH), 3.4 (s, CH_3O–), 3.5—4.6 (m, H-2,3,5), 4.66 (d, H-1, $J_{1,2}$=*ca.* 3.5 Hz). Found: C, 31.17; H, 4.95%. Calcd for $C_7H_{13}O_3I$: C, 30.91; H, 4.81%.

b) Reaction with NaI: A mixture of **4** (0.309 g, 2.14 mmol), NaI (1.61 g, 10.7 mmol), sodium acetate (0.0882 g, 1.08 mmol), and acetic acid (2.5 ml) in acetone (10.5 ml) was refluxed with stirring for 2 h. After the solvent had been removed, chloroform was added, washed successively with saturated aqueous $NaHCO_3$ and aqueous sodium thiosulfate, and dried ($MgSO_4$). Solvent was removed and the residue was separated by PLC (ethyl acetate–chloroform=1 : 20) giving **5** (0.309 g, 53%) and **6** (0.0662 g, 11%). NMR for **6** ($CDCl_3$) δ=1.27 (d, H-6), 3.4 (s, CH_3O–), 5.12 (br s, H-1).

c) Reaction with Tetrabutylammonium Iodide: A mixture of **4** (0.144 mg, 1 mmol) and tetrabutylammonium iodide (1.85 g, 5 mmol) in THF (60 ml) was refluxed with stirring for 6 h. The mixture was allowed to cool to room temperature. The precipitated tetrabutylammonium iodide was recovered by filtration (96%). From the filtrate, 76% of **4** was recovered by means of PLC (benzene–ethyl acetate=5 : 1).

*Methyl 3,4,6-Trideoxy-α-*D*-erythro-hexopyranoside (2).*

*a) From Methyl 3,4,6-Trideoxy-3-iodo-α-*D*-xylo-hexopyranoside (5)*: A solution of **5** (4.42 g, 16.3 mmol) in THF (30 ml) was added to a suspension of $LiAlH_4$ (0.679 g, 17.9 mmol) in THF (20 ml) with stirring at room temperature, and then refluxed with stirring for 6 h. The mixture was allowed to cool to room temperature, quenched by water (15 ml), filtered through Hyflosupercel, and concentrated. The residue was extracted with dichloromethane. The extracts were washed with water, dried ($MgSO_4$), and evaporated giving **2** (2.27 g, 95%), which was practically pure as indicated by GLC (Carbowax 20M, 1 m, 100 °C). The product could be purified by distillation (oven temperature 60—80 °C/14 Torr) or column chromatography (benzene–ethyl acetate=1 : 5). $[\alpha]_D^{20}+142°$ (*c* 1.08, $CHCl_3$). NMR (CCl_4) δ=1.05 (d, H-6), 1.1—2.0 (m, H-3,4), 3.3—4.0 (m, H-2,5), 3.34 (s, CH_3O–), 4.46 (d, H-1). Found: C, 56.95; H, 9.68%. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65%.

*b) From Methyl 4,6-Dideoxy-2-*O*-p-tosyl-α-*D*-xylo-hexopyranoside (7)*: A solution of carbon tetrabromide (1.68 g, 5.06 mmol) in THF (2 ml) was added dropwise to a solution of **7** (949 mg, 3 mmol)[15] and TPP (917 mg, 3.5 mmol) in THF (8 ml) at room temperature with stirring. After the mixture had been stirred for 24 h at room temperature, the solvent was removed. Toluene (10 ml) was added to the residue and refluxed for 2 h. The resulting mixture was concentrated and separated by PLC (ether–petroleum ether=2 : 1) to give methyl 3-bromo-3,4,6-trideoxy-2-*O*-*p*-tosyl-α-D-*ribo*-hexopyranoside as an oil (**9**; 615 mg, 54%) and 8.5% of **7** was recovered. The **9** was used in the next step without further purification. NMR for **9** (CCl_4) δ=1.12 (d, H-6), 1.85—2.25 (m, H-4), 2.4 (s, CH_3–C_6H_4–), 3.2 (s, CH_3O–), 3.85—4.4 (m, H-3,5), 4.12 (d, H-1,2, $J_{1,2}$=*ca.* 2.5 Hz).

A mixture of **9** (570 mg, 1.5 mmol) in THF (5 ml) was added to $LiAlH_4$ (379 mg, 10 mmol) in THF (10 ml) at room temperature and heated under reflux for 20 h. After the addition of water (10 ml) and 2 M (1 M=1 mol dm^{-3}) H_2SO_4 (30 ml), the mixture was extracted with chloroform (120 ml). The organic layer was washed with 2 M Na_2CO_3 and water, dried, and concentrated. The residue was chromatographed (benzene–ethyl acetate=1 : 5) to give **2** (160 mg, 73%) and 20% of **9** was recovered.

*Ethyl (2*E*,4*R*,7*R*)-4,7-Dihydroxy-2-octenoate (10).* A mixture of **2**, (1.99 g, 13.6 mmol) and Dowex 50 (H^+) (3.50 g) in water (50 ml) was refluxed with stirring for 4.5 h. After filtration, the filtrate was concentrated to a small volume and extracted with chloroform. The aqueous layer was evaporated to dryness giving 3,4,6-trideoxy-D-*erythro*-hexopyranose (1.30 g, 72%; mp 47—53 °C) which was used in the next step without purification.

A solution of 3,4,6-trideoxy-D-*erythro*-hexopyranose (779 mg, 5.9 mmol), ethoxycarbonylmethylenetriphenylphosphorane (2.222 g, 6.4 mmol), and benzoic acid (30 mg, 0.25 mmol) in benzene (20 ml) was refluxed with stirring for 8 h. After evaporation, ether was added to precipitate triphenylphosphine oxide which was filtered off. The filtrate was evaporated and the residue was separated by chromatography (ethyl acetate) giving about 2 : 1 mixture of desired **10** and triphenylphosphine oxide. The yield of **10** was estimated to be 75% from the integration of the signal of NMR spectrum. The mixture was used in the next step. NMR (CCl_4) δ=1.15 (t, C<u>H</u>$_3$CH$_2$O–), 1.58 (d, H-8), 1.1—2.0 (br one peak, H-5,6), 3.25—5.25 (m, H-4,7 and two OH), 4.08 (q, CH$_3$C<u>H</u>$_2$O–), 5.96 (dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=1.5 Hz), 6.88 (dd, H-3, $J_{3,4}$=4 Hz).

*Ethyl (2*E*,7*R*)-7-Acetoxy-4-oxo-2-octenoate (1).* A 2 : 1 mixture of ethyl (2*E*,4*R*,7*R*)-4,7-dihydroxy-2-octenoate (**10**) and triphenylphosphine oxide (containing 4.37 mmol of **10**) was stirred with active MnO_2 (3.00 g)[16] in chloroform (50 ml) for 7 h at room temperature. After filtration, the filtrate was evaporated. The residue was chromatographed (benzene–ethyl acetate=1 : 1), giving about 1 : 1 mixture of ethyl (2*E*,7*R*)-7-hydroxy-4-oxo-2-octanoate (**11**) and cyclic hemiacetal (**12**) in 74% (649 mg) yield. The ratio was determined from the integration of the signal of NMR spectrum.

Acetic anhydride (0.1 ml) was added to a solution of the mixture (105 mg, 0.525 mmol) in pyridine (2 ml) at room temperature. After the solution had been stirred for 22 h at room temperature, water (1 ml) was added. The resulting mixture was evaporated and distilled to give **1** (99 mg, 72%, oven temperature 100—120 °C/0.4 Torr). NMR (CCl_4) δ=1.24 (d, H-8), 1.31 (t, C<u>H</u>$_3$CH$_2$O–), 1.54—2.1 (m, H-6), 1.95 (s, CH_3CO), 2.68 (t, H-5), 4.24 (q, C<u>H</u>$_3$CH$_2$O–), 4.87 (sext, H-7), 6.55 and 7.02 (AB q, olefin, J=16 Hz).

*Ethyl (2*E*, 7*R*)-7-Acetoxy-4,4-dimethoxy-2-octenoate (13).* Acetalization was performed by the analogous procedure reported by Hase *et al.*[17] A solution of 2,2-dimethoxypropane (122 mg, 1.17 mmol) in methanol (1 ml) was added to anhydrous *p*-toluenesulfonic acid (6 mg) at −70 °C, followed by ethyl (2*E*,7*R*)-7-acetoxy-4-oxo-2-octenoate (**1**, 49 mg, 0.202 mmol) in methanol (5 ml). The mixture was stirred for 4 h at −50 °C and then for 18 h at room temperature. The mixture was diluted with ether (5 ml), neutralized (3% $NaHCO_3$), and evaporated. The residue was extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated giving practically pure **13** (53 mg, 91%). Purification by PLC (ether–hexane=2 : 3) gave **13** in 60% yield. $[\alpha]_D^{19}$ +7.9° (*c* 1.53, $CHCl_3$). NMR (CCl_4) δ=1.18 (d, H-8), 1.31 (t, C<u>H</u>$_3$CH$_2$O–), 1.3—2.0 (m, H-5,6), 1.96 (s, CH_3CO), 3.13 (s, two CH_3O–), 4.25 (q, CH$_3$C<u>H</u>$_2$O–), 4.85 (sextet, H-7), 6.03 and 6.56 (AB q, olefin, J=15.6 Hz). An analytical sample was obtained by distillation (oven temperature 125—128 °C/0.4 Torr). Found: C, 58.08; H, 8.27%. Calcd for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39%.

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