THE SYNTHESIS OF TRIDEOXY SUGARS. A PREPARATION OF RHODINOSE (2,3,6-TRIDEOXY-L-*THREO*-HEXOSE) AND METHYL 2,3,6-TRIDEOXY-α-L-*ERYTHRO*-HEXOPYRANOSIDE[1]

A. H. HAINES
School of Chemical Sciences, University of East Anglia, Norwich, NOR 88C (Great Britain)
(Received July 16th, 1970; accepted for publication in revised form, July 9th, 1971)

ABSTRACT

A preparation of trideoxy sugars from L-rhamnose is described, which utilises, as the key step, the Corey–Winter olefin synthesis from vicinal diols. Application of this procedure to methyl 4-*O*-benzyl-6-deoxy-α-L-mannopyranoside, followed by reduction of the resulting olefin and hydrogenolysis of the benzyl ether group, gave methyl 2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (the methyl glycoside of the enantiomer of amicetose). Similar treatment of methyl 4-*O*-benzyl-6-deoxy-α-L-talopyranoside gave methyl 2,3,6-trideoxy-α-L-*threo*-hexopyranoside from which rhodinose was obtained on acid hydrolysis. This constitutes the first synthesis of natural rhodinose.

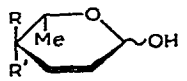
INTRODUCTION

The synthesis of trideoxy sugars is of interest in view of their occurrence in several antibiotics. Thus amicetin[2], rhodomycin[3], and streptolydigin[4] contain 2,3,6-trideoxyaldohexoses, and Stevens *et al.*[5] have synthesized 2,3,6-trideoxy-D-*erythro*-hexose (amicetose, the enantiomer of **1**) and 2,3,6-trideoxy-D-*threo*-hexose [the enantiomer of natural rhodinose (**2**)]. From work on the synthesis of olefinic sugars[6], it became apparent that, commencing with readily available 6-deoxy sugars, a new route to this type of compound was available. The present work describes the first synthesis of natural rhodinose and of the methyl glycoside of the enantiomer of amicetose, from 6-deoxy-L-mannose.

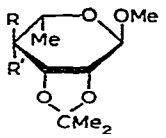
RESULTS AND DISCUSSION

The enantiomer of amicetose (**1**) may be formally derived from 6-deoxy-L-mannose (L-rhamnose) by replacement of HO-2 and HO-3 by hydrogen atoms. Derivation of rhodinose (**2**) from the same compound requires a similar replacement of these hydroxyl groups and inversion of the configuration at C-4. The synthesis described below achieves the former objective through the Corey–Winter olefin

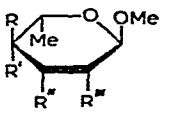
synthesis[7], and inversion at C-4 by means of sequential oxidation and reduction of a suitably substituted derivative of 6-deoxy-L-mannose[8].



1 R=OH, R′=H
2 R=H, R′=OH



3 R, R′=O=
4 R=OH, R′=H
5 R=H, R′=OH
6 R=OCH_2Ph, R′=H
7 R=H, R′=OCH_2Ph

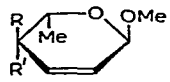


8 R=OCH_2Ph, R′=H, R″=R‴=OH
9 R=H, R′=OCH_2Ph, R″=R‴=OH
10 R=OCH_2Ph, R′=H, R″, R‴= 
11 R=H, R′=OCH_2Ph, R″, R‴ = 

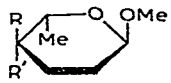
Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[9] (**4**) was benzylated to give the ether **6**, which was partially hydrolyzed to yield methyl 4-*O*-benzyl-6-deoxy-α-L-mannopyranoside (**8**). Conversion of this diol into the syrupy thionocarbonate **10**, by successive treatment with butyl-lithium, carbon disulphide, and methyl iodide (method *A*), was readily achieved, but purification by chromatography was required to remove starting diol. The thionocarbonate **10** was more easily prepared by reaction of the diol with bis(imidazol-1-yl)thione[10] (method *B*). Introduction of a double bond between C-2 and C-3 occurred in high yield on decomposition of the thionocarbonate[10] in refluxing trimethylphosphite, and the olefin **12** so obtained was readily reduced over platinum to yield methyl 4-*O*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (**14**). Hydrogenolysis of the benzyl group over palladium–charcoal gave methyl 2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (**16**) which is the methyl glycoside of the enantiomer of amicetose. Surprisingly, gas–liquid chromatography (g.l.c.) of **16** showed, in addition to the main component, 13% of a second substance having a slightly longer retention time. In an attempt to remove this minor component, the glycoside was converted into the crystalline 3,5-dinitrobenzoate **18**, but examination of the regenerated alcohol showed no alternation in the g.l.c. pattern. Exactly analogous observations were made in the case of the L-*threo* isomer (see below). The most likely explanation is that the second peak is due to the β-L-glycoside as a result of anomerization occurring in the injection block*. Experiments reported below confirm that in the L-*threo* case this second peak is due to the β-L-glycopyranoside. The trideoxy sugar was characterized as the 2,4-dinitrophenylhydrazone, which was formed from glycoside **16** in 84% yield. The physical constants of this derivative compared well with those of the D enantiomer[5,11].

The synthetic route to rhodinose (**2**) involved inversion of the C-4 hydroxyl group of the *manno* sugar before introduction of the unsaturated linkage between C-2 and C-3. Thus, oxidation of the alcohol **4** with ruthenium dioxide–sodium metaperiodate[12] gave the oxo sugar **3**, but in the author's hands the reaction did not go to completion. However, separation of product and starting material was readily

*The author acknowledges a referee's suggestion of this possibility.



12 R = OCH_2Ph, R′ = H
13 R = H, R′ = OCH_2Ph



14 R = OCH_2Ph, R′ = H
15 R = H, R′ = OCH_2Ph
16 R = OH, R′ = H

17 R = H, R′ = OH
18 R = $OCO \cdot C_6H_3(NO_2)_2$, R′ = H
19 R = H, R′ = $OCO \cdot C_6H_3(NO_2)_2$

achieved by partition between water and carbon tetrachloride, the oxo sugar being much more soluble than the alcohol in the chlorinated solvent. Reduction of **3** with lithium aluminium hydride yielded alcohol **5**, with only a trace of alcohol **4**, as reported by Collins and Overend[8]. The crude reduction product was benzylated to give, in good yield, crystalline methyl 4-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**7**). Partial hydrolysis of this ether gave the vicinal diol **9**, which was converted by method *A* or, in better yield, by method *B* into the crystalline thionocarbonate **11**. Treatment of **11** with trimethylphosphite yielded the crystalline methyl 4-*O*-benzyl-2,3,6-trideoxy-α-L-*threo*-hexo-2-enopyranoside (**13**), which was hydrogenated over platinum to yield methyl 4-*O*-benzyl-2,3,6-trideoxy-α-L-*threo*-hexopyranoside (**15**). Hydrogenolysis of **15** (palladium–charcoal catalyst) removed the benzyl group to give, presumably, the methyl glycoside **17** of rhodinose which, although homogeneous by thin-layer chromatography (t.l.c.), did not give a correct elemental analysis. However, the crystalline 3,5-dinitrobenzoate **19** did analyse correctly.

Investigation of alcohol **17** by g.l.c. showed a major component with 8% of a minor component having a slightly longer retention time, this behaviour being similar to that observed for the *erythro* isomer **16** (see above). Attempted purification of **17** through its 3,5-dinitrobenzoate and regeneration of the alcohol yielded a product with unchanged properties on g.l.c. That the minor component was the β-L-glycopyranoside was shown as follows. A solution of the benzyl ether **15** in methanol was treated with an acidic ion-exchange resin to achieve equilibration of the α- and β-glycosides. The benzyl group was then removed by hydrogenolysis. G.l.c. of the resultant product showed two peaks having the same retention times as those obtained on chromatography of the alcohol **17**. The component with the longer retention time now formed 32% of the mixture. An examination (g.l.c.) of a methanolic solution of the alcohol **17** stored over an acidic ion-exchange resin showed that the amount of β-pyranoside increased immediately at the expense of the α-pyranoside but that two new peaks with shorter retention times (presumably the α- and β-furanosides) appeared with the passage of time.

The methyl glycoside **17** was hydrolyzed directly to yield rhodinose (**2**) having rotation and chromatographic properties in agreement with those reported for the sugar isolated from natural sources[3]. The glycoside **17** gave a 2,4-dinitrophenylhydrazone in 56% yield, which after further purification had m.p. 118–121°. Stevens and co-workers[5] reported m.p. 121–122° for the 2,4-dinitrophenylhydrazone of natural rhodinose derived from streptolydigin, and also for its synthetic enantiomer. The infrared spectrum of the hydrazone described in this work, when compared with the spectrum of the authentic derivative from natural rhodinose, showed four extra

peaks in the fingerprint region, and on electrophoresis was found to run identically with the derivative of the natural rhodinose but to contain a second, minor component*. The following points are pertinent in providing evidence that the minor component was not an impurity but most probably an isomer (as a result of geometrical, ring-chain, or α,β-isomerism[13]). Firstly, all intermediates in the final synthetic sequence leading to rhodinose were subjected to rigorous purification by preparative-layer chromatography (p.l.c.). Secondly, the exact melting point of the hydrazone was found to vary in an unsystematic manner on recrystallization, although slow crystallization from benzene yielded material (needles) of highest melting point; occasionally a small amount of a second crystal modification was apparent. Thirdly, t.l.c. (ether–pyridine) of the hydrazone revealed two components having R_F 0.41 and 0.32. Separation of these components by p.l.c. and rechromatography of each component again yielded, in both cases, the same two components. Fourthly, it was observed that the mass spectra of the hydrazone of rhodinose, and of that of the enantiomer of amicetose, were virtually identical.

Since a sample of the authentic 2,4-dinitrophenylhydrazone of natural rhodinose was not available for direct comparison, the synthesis by Stevens and co-workers[5] of the 2,4-dinitrophenylhydrazone of the D enantiomer (which they have shown to be truly enantiomeric with the derivative of the natural sugar) was repeated. The material obtained (route *X*) was compared with the derivative described in the present work (route *Y*) and shown to have similar properties. Thus, the melting-point behaviour was capricious. When first isolated, the material had m.p. 109–112°, which was raised by further crystallization to 114–118° (material *A*). Two samples of *A* recrystallized separately gave *B*, m.p. 117–120°, and *C*, m.p. 108–109°. The infrared spectrum of *A* was superimposable on that of the enantiomeric hydrazone obtained by route *Y*. Material *B* showed a diminution in the intensities of the extra peaks (*i.e.* those found in the spectrum of the hydrazone prepared by route *Y* but not in Stevens' sample), but on further crystallization it gave *D*, m.p. 113–118°, in the infrared spectrum of which the "extra" peaks were restored to their former intensity as in *A*. Although crystallizations from several solvent systems were carried out, no systematic elevation of the melting point or simplification of the infrared spectrum was achieved. The material obtained by route *X* showed t.l.c. behaviour identical with that from route *Y*, in that two components were apparent, which on separation and rechromatography again gave the same two components. On electrophoresis in borate buffer, the two samples showed similar behaviour. Finally, the mass spectrum of the material from route *X* was virtually superimposable on that from route *Y*.

On this evidence, it would seem certain that the hydrazones of rhodinose and its enantiomer are displaying isomerism. Stevens and co-workers appear to have encountered only one form. The identity of the mass spectra of the derivative of rhodinose and the enantiomer of amicetose suggests that the isomerism is either of the *syn-anti* type in the acyclic form or of the α,β-type in cyclic form; ring-chain

*Personal communication from Professor C. L. Stevens. In later samples of the hydrazone, the author has been unable to confirm the presence of the minor component detected by electrophoresis.

tautomerism might be expected to lead to a significantly different breakdown pattern when compared to the amicetose hydrazone, which appears to exist in only one form.

N.m.r. spectra of the hex-2-enopyranosides **12** *and* **13**

Parameters obtained from a first-order analysis of the n.m.r. spectra of compounds **12** and **13** are recorded in Tables I and II, and assignments were supported by double-resonance experiments. The spectrum of the *threo* isomer **13** was amenable to a complete first-order analysis, since, in contrast to the *erythro* isomer **12**, the H-4 and H-5 resonances were well separated at 100 MHz. Both **12** and **13** showed a small splitting (*ca.* 2 Hz) of the anomeric proton signal, but they differed significantly in their olefinic proton signals. Both of the compounds showed simpler signals in this region of the spectrum than might be expected. For compound **12**, each peak of the

TABLE I

CHEMICAL SHIFT DATA[a] (τ VALUES) FOR SOLUTIONS OF **12** AND **13** IN CCl_4

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	OCH_3
12[b]	5.37d	4.42se	4.1d	complex		8.79d	6.7s
13[c]	5.33s	4.23q	4.06q	6.64q	6.07oc	8.77d	6.76s

[a]Peak multiplicities: d = doublet, q = quartet, s = singlet, se = sextet, oc = octet. [b]Also showed an AB quartet for benzyl methylene-H centred on 5.62 and Ar-H at 2.78. [c]Also showed an AB quartet for benzyl methylene-H centred on 5.75 and Ar-H at 2.85.

TABLE II

FIRST-ORDER COUPLING CONSTANTS (Hz) FROM 100-MHz SPECTRA OF **12** AND **13**

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,3}$	$J_{2,4}$
12	2.2	10.4	<1	8.6[a]	6.0	<1	2.2
13	2.3	10.1	4.8	2.7	6.7	<1	<1

[a]Approximate value because of second-order effects.

H-2 doublet ($J_{2,3}$ 10.4 Hz) was split into a triplet (*J ca.* 2 Hz). Double-resonance experiments with irradiation at H-1 caused a collapse of one of the splittings which was therefore assigned as $J_{1,2}$. The second, small splitting which remained was assigned as $J_{2,4}$. For compound **13**, each peak of the H-2 doublet ($J_{2,3}$ 10.1 Hz) showed a small splitting into a doublet, due to coupling with H-1 ($J_{1,2}$ 2.3 Hz). The two compounds differed also in their H-3 signals; each component of the H-3 doublet of **12** was unsplit although not sharp, but, for **13**, each component was split into a doublet ($J_{3,4}$ 4.8 Hz). Thus, the change in stereochemistry at C-4 is reflected in the coupling of H-4 to the olefinic protons, and the coupling constants are in quantitative agreement with those expected from a consideration of preferred conformations* and the known dependence of vicinal and allylic coupling constants on stereochemistry[14].

*A half-chair form of the six-membered ring, with the methoxyl group at C-1 axial, and the methyl group at C-5 equatorial, appears to give the best fit of n.m.r. data for both compounds **12** and **13**.

EXPERIMENTAL

T.l.c. was performed on Kieselgel G, with detection by sulphuric acid–vanillin[15], and p.l.c. on Kieselgel PF_{254}. G.l.c. was carried out on a Perkin–Elmer 452 instrument (2-m column, i.d. 0.5 cm, packed with polypropylene glycol on 800–100 mesh Chromosorb W; column temperature 125°; carrier gas, nitrogen at 15 lb.in.$^{-2}$; detection by flame ionization). N.m.r. spectra were determined at 100 MHz for solutions in carbon tetrachloride, with tetramethylsilane as internal standard. Optical rotations were determined in 1-dm tubes with a Perkin–Elmer 141 polarimeter. Mass spectra were determined on an MS9 AEI instrument. Routine identifications were based on infrared and n.m.r. spectroscopy, t.l.c. mobilities, and melting points. Melting points are uncorrected. Solutions were dried over anhydrous sodium sulphate.

Methyl 4-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-L-mannopyranoside (**6**). — Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[9] (**4**) (15.2 g) in benzyl chloride (60 ml) was stirred with powdered potassium hydroxide (30 g) for 5 h. Water (120 ml) was then added and the mixture extracted with chloroform (5 × 75 ml). Concentration of the combined extracts and distillation of the residue gave impure benzyl ether (22.4 g). T.l.c. in chloroform showed two spots, R_F 0.25 and 0.8 (minor component). A portion (1.3 g) of the impure ether was chromatographed on silica gel (100 g) using chloroform as eluent, which removed the faster-running compound. Elution with chloroform–methanol (9:1 v/v) yielded the slower-running component, which was distilled to yield **6**, b.p. 146–147°/0.8 mmHg, n_D^{24} 1.4936, $[\alpha]_D^{20}$ −62.6° (*c* 3.8, acetone) (Found: C, 65.85; H, 7.6. $C_{17}H_{24}O_5$ calc.: C, 66.2; H, 7.8%).

Methyl 4-O-benzyl-6-deoxy-α-L-mannopyranoside (**8**). — A mixture of **6** (4.4 g) and 50mM hydrochloric acid (40 ml) was heated under reflux, and enough ethanol (*ca.* 40 ml) was added to achieve dissolution. After 1 h, the solution was neutralized with sodium hydrogen carbonate, and most of the alcohol was then removed by distillation. The solution was extracted with light petroleum and then allowed to stand at 4°, when crystals deposited. These were recrystallized from ethyl acetate–light petroleum to yield **8** (2.9 g, 80%), m.p. 107–109°, $[\alpha]_D^{25}$ −68.3° (*c* 1.6, chloroform) (Found: C, 62.7; H, 7.8. $C_{14}H_{20}O_5$ calc.: C, 62.7; H, 7.5%).

Methyl 4-O-benzyl-6-deoxy-α-L-mannopyranoside 2,3-thionocarbonate (**10**). — The diol **8** (30.3 g) dissolved in tetrahydrofuran (250 ml) was treated successively with a hexane solution of butyl-lithium, carbon disulphide, and methyl iodide in the usual manner[6,7]. The reaction mixture was concentrated to 60 ml and then poured into ice–water (20 g). The aqueous mixture was extracted with chloroform (5 × 100 ml), and the combined extracts were washed with water (2 × 50 ml), dried, and concentrated. The residue was dissolved in hot benzene–light petroleum, and the starting diol crystallized on cooling. The mother liquor was concentrated and chromatographed on silica gel (1 kg), using benzene as initial eluent, when a fast-running, yellow impurity was removed. The thionocarbonate (15.4 g) was then eluted with chloroform–ether (4:1: v/v). A portion was treated with charcoal in light petroleum, to yield the analytical sample of **10** as an oil, $[\alpha]_D^{24}$ −50° (*c* 2.1, chloroform) (Found: C, 58.0; H, 5.8; S, 10.4. $C_{15}H_{18}O_5S$ calc.: C, 58.0; H, 5.8; S, 10.3%).

The thionocarbonate was also prepared in 81% yield by treatment of **8** with bis(imidazol-1-yl)thione[10].

*Methyl 4-O-benzyl-2,3,6-trideoxy-α-*L-erythro-*hex-2-enopyranoside* (**12**). — A solution of the thionocarbonate **10** (3.5 g) in trimethyl phosphite (40 ml) was heated under reflux in a nitrogen atmosphere for 3 days. The bulk of the solvent was then removed by distillation, and to the remainder was added sufficient 6M sodium hydroxide, such that the mixture remained alkaline on prolonged stirring. The solution was extracted with chloroform (5 × 40 ml), and the combined extracts were washed with water (2 × 15 ml), dried, and concentrated. Distillation of the residue yielded the title compound (2 g, 75%), b.p. 124–128°/0.8 mmHg, n_D^{25} 1.5092, $[\alpha]_D^{23}$ −168° (*c* 2.1, chloroform) (Found: C, 71.7; H, 7.7. $C_{14}H_{18}O_3$ calc.: C, 71.8; H, 7.7%). The product crystallized on storage at 4°.

*Methyl 4-O-benzyl-2,3,6-trideoxy-α-*L-erythro-*hexopyranoside* (**14**). — A solution of the olefin **12** (2.65 g) in methanol (25 ml) was added to a suspension of prereduced Adam's catalyst (0.1 g) in methanol (25 ml), and the mixture was shaken under a slight overpressure of hydrogen. After 3 h, uptake (250 ml) ceased, and filtration of the catalyst followed by concentration of the filtrate yielded an oil which was distilled to yield **14** (2.1 g, 86%), b.p. 114–115°/0.5 mmHg, $[\alpha]_D^{26}$ −175° (*c* 2.2, chloroform) (Found: C, 71.2; H, 8.5. $C_{14}H_{20}O_3$ calc.: C, 71.15; H, 8.5%).

*Methyl 2,3,6-trideoxy-α-*L-erythro-*hexopyranoside* (**16**). — A solution of the benzyl ether **14** (2.5 g) in methanol (40 ml) was subjected to hydrogenolysis with palladium–charcoal (0.16 g) as catalyst. After removal of the catalyst, the solution was concentrated and distilled to yield the title compound (1.4 g, 85%), b.p. 97–99°/12 mmHg, $[\alpha]_D^{20}$ −144° (*c* 0.23, chloroform); lit.[11], for the enantiomer, b.p. 50°/1 mmHg, $[\alpha]_D^{18}$ +142° (*c* 1.2, water) (Found: C, 57.75; H, 9.4. $C_7H_{14}O_3$ calc.: C, 57.5; H, 9.65%).

G.l.c. showed one major component, with 13% of a material having a slightly longer retention time. Purification of **16** as its 3,5-dinitrobenzoate **18** (see below), and then regeneration of the alcohol, yielded exactly the same mixture (g.l.c.).

Treatment of **16** with 3,5-dinitrobenzoyl chloride in pyridine yielded, after two crystallizations from methanol, the 3,5-dinitrobenzoate **18**, m.p. 96–98° $[\alpha]_D^{20}$ −131° (*c* 0.97, chloroform); lit.[11] for the enantiomer, m.p. 100–101°, $[\alpha]_D^{20}$ +134° (*c* 0.4, chloroform) (Found: C, 49.6; H, 4.7; N, 8.4. $C_{14}H_{16}N_2O_8$ calc.: C, 49.4; H, 4.7; N, 8.2%). The infrared spectrum (Nujol) was identical to that of the D isomer, m.p. 97–99°, $[\alpha]_D^{20}$ +136° (*c* 0.3, chloroform), prepared in this laboratory by the published method[11].

*2,4-Dinitrophenylhydrazone of 2,3,6-trideoxy-α-*L-erythro-*hexopyranose.* — Methyl 2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (**16**, 40 mg) dissolved in water (3 ml) was added to a hot solution of 2,4-dinitrophenylhydrazine (55 mg) in 2M hydrochloric acid (8 ml). The yellow precipitate which formed immediately was collected after 2 h, washed with water, and dried over P_2O_5 *in vacuo* to give, after crystallization from methanol–benzene, the title compound (72 mg, 84%), m.p. 154–156°, $[\alpha]_D^{20}$ +11.3° (*c* 0.23, pyridine); lit. for the enantiomer, m.p. 156–157°, $[\alpha]_D^{25}$ −10° (*c* 0.9, pyridine)

(Ref. 5); m.p. 154–155.5°, $[\alpha]_D^{19}$ −9.8° (*c* 0.4, pyridine) (Ref. 11) (Found: C, 46.2; H, 5.3; N, 18.0. $C_{12}H_{16}N_4O_6$ calc.: C, 46.15; H, 5.2; N, 17.9%).

Methyl 4-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-L-talopyranoside (**7**). — A solution of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[9] (**4**, 14.9 g) was oxidized in carbon tetrachloride (250 ml) with the ruthenium dioxide–sodium metaperiodate reagent[12]. Investigation of the carbon tetrachloride solution (infrared spectroscopy) showed that oxidation was not complete. The alcohol and ketone were readily separable by partition between water and carbon tetrachloride, and concentration of the latter extracts yielded methyl 2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**3**) (9.6 g) (C=O, ν_{max} 1740 cm^{-1}; no OH band near 3500 cm^{-1}). From the aqueous extracts, unchanged starting alcohol **4** (4.5 g) was extracted with chloroform.

A solution of **3** (9.6 g) in ether (150 ml) was reduced[8] by a suspension of lithium aluminium hydride (1.5 g) in ether (400 ml) for 3 h. Excess hydride was destroyed by addition of ethyl acetate (8 ml) and then water (2.8 ml). After filtration the reaction mixture was dried and concentrated to a syrup (8.9 g) (OH, ν_{max} 3480 cm^{-1}; no C=O band at 1740 cm^{-1}). T.l.c. of the reaction product in methanol–chloroform (1:18 v/v) showed one main spot (R_F 0.75) for methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**5**), and only a trace of the starting *manno* isomer (R_F 0.6). Collins and Overend reported[8] the preponderant formation of the L-*talo* isomer in this reduction.

Unpurified material from the above reduction (1.3 g) dissolved in tetrahydrofuran (15 ml) was treated with sodium hydride (0.33 g of a 50% dispersion in oil), and then benzyl bromide (1.1 g) was added. After being heated under reflux for 31 h, the mixture was filtered through Kieselguhr and concentrated to a syrup which crystallized from light petroleum to yield **7** (1.4 g, 76%), m.p. 68–70°, $[\alpha]_D^{20}$ −5.3° (*c* 4.2, chloroform) (Found: C, 66.3; H, 7.8. $C_{17}H_{24}O_5$ calc.: C, 66.2; H, 7.8%).

Methyl 4-O-benzyl-6-deoxy-α-L-talopyranoside (**9**). — The benzyl ether **7** (10.3 g) was dissolved in ethanol (50 ml), and 50mM hydrochloric acid (90 ml) was added. The mixture was maintained at its boiling point for 15 min and then neutralized with sodium carbonate. After removal of ethanol by distillation, the mixture was extracted with chloroform (6 × 50 ml), and the combined extracts were dried and concentrated. Crystallization of the residue from ethyl acetate–light petroleum yielded the diol **9** (8.0 g, 89%), m.p. 63–64°, $[\alpha]_D^{18}$ −97° (*c* 2.3, chloroform) (Found: C, 62.55; H, 7.6. $C_{14}H_{20}O_5$ calc.: C, 62.7; H, 7.5%).

Methyl 4-O-benzyl-6-deoxy-α-L-talopyranoside 2,3-thionocarbonate (**11**). — The diol **9** (7.7 g) was treated successively with butyl-lithium in hexane, carbon disulphide, and methyl iodide in the usual manner[6,7]. The reaction product was purified by chromatography on silica gel (500 g), and the required compound (4.5 g) was eluted with chloroform–ether (4:1; v/v). Recrystallization from ethanol afforded **11** (2.7, g 31%), m.p. 88–90°, $[\alpha]_D^{20}$ +4.8° (*c* 1.6, chloroform) (Found: C, 57.9; H, 5.95; S, 10.2. $C_{15}H_{18}O_5S$ calc.: C, 58.0; H, 5.8; S, 10.3%). The thionocarbonate **11** was more conveniently prepared, in 80% yield, by treatment of **9** with bis(imidazol-1-yl)thione[10].

Methyl 4-O-benzyl-2,3,6-trideoxy-α-L-threo-hex-2-enopyranoside (**13**). — The

thionocarbonate **11** (3.2 g) was treated with trimethyl phosphite (30 ml), and the mixture was worked up, as described for the *erythro* isomer, to yield, after distillation, the olefin **13** (1.9 g, 81%), b.p. 115°/0.3 mmHg, $[\alpha]_D^{29}$ +172° (*c* 1.2, chloroform). Crystallization of the distillate from light petroleum yielded the analytical sample, m.p. 34–36° (Found: C, 71.8; H, 7.9. $C_{14}H_{18}O_3$ calc.: C, 71.8; H, 7.7%). In other preparations, t.l.c. of the distilled material showed trace contaminants which were removed by p.l.c.

*Methyl 4-O-benzyl-2,3,6-trideoxy-α-*L-threo-*hexopyranoside* (**15**). — The olefin **13** (1.13 g) dissolved in absolute methanol (20 ml) was reduced with hydrogen in the presence of Adam's catalyst. On t.l.c., the product had an R_F value similar to that of the starting material, but had a different colour response. N.m.r. confirmed the disappearance of olefinic protons. The product was separated from a small amount of a faster-running contaminant by p.l.c. in chloroform, and distilled to yield the title compound (0.87 g, 77%), b.p. 98–100°/0.1 mmHg, $[\alpha]_D^{21}$ −42.4° (*c* 0.7, chloroform) (Found: C, 71.1; H, 8.4. $C_{14}H_{20}O_3$ calc.: C, 71.15; H, 8.5%).

*2,3,6-Trideoxy-*L-threo-*hexose* (*rhodinose*) (**2**). — Methyl 4-*O*-benzyl-2,3,6-trideoxy-α-L-*threo*-hexopyranoside (**15**, 1.4 g) dissolved in methanol (20 ml) was shaken with hydrogen in the presence of palladium–charcoal catalyst (0.1 g), when 1 mole equivalent of hydrogen was absorbed. Concentration of the solution, followed by distillation of the residue, yielded chromatographically homogeneous material, presumably methyl 2,3,6-trideoxy-α-L-*threo*-hexopyranoside (**17**) (0.76 g, 87%), on which an acceptable analysis could not be obtained (OH, ν_{max} 3450 cm^{-1}; no Ar-H stretch at 3100–3000 cm^{-1}). It gave a 3,5-dinitrobenzoate, m.p. 135–136°, $[\alpha]_D^{24}$ −48° (*c* 0.23, chloroform) (Found: C, 49.2; H, 5.0; N, 8.3. $C_{14}H_{16}N_2O_8$ calc.: C, 49.4; H, 4.7; N, 8.2%). G.l.c. of the glycoside **17** showed one main peak and a second minor component (8%) having a slightly longer retention time. Glycoside **17**, which had been formed by regeneration from its rigorously purified (p.l.c.) 3,5-dinitrobenzoate, showed an exactly similar g.l.c. pattern.

The glycoside **17** (0.51 g) was dissolved in 0.1M hydrochloric acid (25 ml). After 4 h, the solution was neutralized with sodium hydrogen carbonate and continuously extracted with chloroform for 24 h. The extract was concentrated, and the residue was chromatographed on alumina (50 g) with chloroform as initial eluent. Minor traces of two impurities and some unhydrolyzed glycoside were eluted first. Further elution with chloroform–methanol (19:1; v/v) yielded the free sugar (0.32 g, 70%) which was distilled to yield the analytical sample of rhodinose, b.p. 90–105° (bath)/0.5 mmHg, $[\alpha]_D^{27}$ −6.7° (*c* 1.1, acetone); lit.[3] $[\alpha]_D^{20}$ −11° (acetone); lit.[5], for the enantiomer, b.p. 60–65° (bath)/0.1 mmHg, $[\alpha]_D^{26}$ +10.2° (*c* 1.1, acetone) (Found: C, 54.75; H, 9.1. $C_6H_{12}O_3$ calc.: C, 54.5; H, 9.15%).

The synthetic rhodinose was subjected to t.l.c. [with digitoxose (Dig) as a reference compound] in chloroform–acetone (1:7; v/v) and showed R_{Dig} 1.18 (lit[3]. 1.16). Paper chromatography using butyl alcohol–acetic acid–water (4:4:1) gave R_{Dig} 1.22 (lit.[3] 1.27).

2,4-Dinitrophenylhydrazone of rhodinose. — Methyl 2,3,6-trideoxy-α-L-*threo*-

hexopyranoside (0.153 g), obtained by hydrogenolysis of the corresponding benzyl ether as described above, and purified by p.l.c., was dissolved in 2M hydrochloric acid (3 ml). 2,4-Dinitrophenylhydrazine (0.21 g) in 2M hydrochloric acid (11 ml) was added to the glycoside solution, and the yellow precipitate which formed immediately was collected after 24 h to yield the crude product (0.184 g, 56%), m.p. 105–108°. Chromatography on alumina (activity I), using chloroform–methanol (19:1; v/v), removed minor impurities and the material in the major band was crystallized from benzene to yield a product (0.1 g), m.p. 114–118°. The analytical sample, obtained by a further crystallization from benzene–methanol, had m.p. 118–121°, $[\alpha]_D^{20}$ −17.7° (*c* 0.6, pyridine); lit.[5] m.p. 121–122°, $[\alpha]_D^{25}$ −14.9° (*c* 0.5, pyridine) (Found: C, 46.3; H, 5.1; N, 17.4. $C_{13}H_{16}N_4O_6$ calc.: C, 46.15; H, 5.2; N, 17.9%) (data on molecular ion reported below).

Isomerism of the 2,4-dinitrophenylhydrazone of rhodinose. — Crystallization of the purified hydrazone on separate occasions gave material of variable melting point, and a second crystal modification (rosettes) was noticed in small amounts amongst the usual needles. T.l.c. (ether–pyridine, 9:1, v/v) of the hydrazone gave two spots R_F 0.41 and 0.32. These two components were separated by p.l.c., but on re-examination of the isolated products, each was found to consist of the same two components, suggesting facile interconversion. A sample of relatively high m.p. contained a greater proportion of the slower-running component. Identical chromatographic behaviour was shown by a sample of the D isomer prepared by the method of Stevens and coworkers[5].

Infrared spectrum and electrophoresis of the 2,4-dinitrophenylhydrazone of rhodinose. — The infrared spectrum (KBr) of material having m.p. 118–121° was nearly identical with that of a sample of the hydrazone, m.p. 121–122°, derived from natural sources by the hydrolysis of streptolydigin, but contained four extra, small peaks in the fingerprint region[16]. It was identical with the spectrum of a sample of the 2,4-dinitrophenylhydrazone of 2,3,6-trideoxy-D-*erythro*-hexose, m.p. 114–118°, prepared in this laboratory by the published procedure[5].

Electrophoresis of the hydrazone in 83mM sodium tetraborate buffer solution at 400 volts showed one component migrating to the anode. An earlier sample, m.p. 117–119°, migrated identically with the hydrazone of natural rhodinose but contained a minor impurity[16]. The 2,4-dinitrophenylhydrazone of the D enantiomer migrated similarly to the derivative of synthetic rhodinose.

2,4-Dinitrophenylhydrazone of 2,3,6-trideoxy-D-threo-*hexose.* — Ethyl 2,3,6-trideoxy-α-D-*threo*-hexopyranoside {$[\alpha]_D^{25}$ +83° (*c* 0.33, water); n_D^{25} 1.4488; lit.[5] $[\alpha]_D^{25}$ +88.5° (*c* 0.7, water); n_D^{25} 1.4474; lit.[17] $[\alpha]_D^{25}$ +98° (*c* 0.8, water)} (75 mg) was treated with a solution of 2,4-dinitrophenylhydrazine (93 mg) in 2M hydrochloric acid (5 ml). After removal of minor impurities in the crude product by chromatography on alumina, the product was crystallized from benzene–methanol to yield the hydrazone (42 mg), m.p. 109–112°. Further crystallization gave material having m.p. 114–118°. Two samples of this material, when recrystallized separately under similar conditions, gave materials having m.p. 117–120° and 108–109°, respectively.

The higher-melting form, on further recrystallization, gave material having m.p. 113–118° (lit.[5] m.p. 121–122°). The hydrazone showed a molecular ion at *m/e* 312.1065 (calc.: 312.1070), and its mass spectrum was virtually indistinguishable from that of the hydrazone of synthetic rhodinose. Comparative infrared spectral data are reported in the Discussion.

*Preparation of methyl 2,3,6-trideoxy-αβ-*L-threo-*hexopyranoside mixture for g.l.c. studies.* — A solution of the benzyl ether **15** (0.1 g) in methanol (5 ml) was stirred with Amberlite IR-120 (H^+) resin (*ca.* 0.1 g) for 48 h at room temperature. The resin was removed, and triethylamine (0.1 ml) was added to the filtrate. Palladium–charcoal catalyst (0.1 g) was added, and the suspension was shaken under a slight overpressure of hydrogen. When subjected to g.l.c., the product showed two components having retention times identical to those of the components observed on chromatography of the alcohol **17**. The component having the longer retention time formed 32% of the mixture.

Treatment of alcohol **17** with acidic resin in dry methanol resulted in an immediate increase (g.l.c.) in the component having the longer retention time. Two new components, with shorter retention times, were detected when further time elapsed.

Mass spectra. — The mass spectra of the 2,4-dinitrophenylhydrazones of 2,3,6-trideoxy-L-*threo*-hexose (rhodinose) and the *erythro* isomer were virtually identical. They gave molecular ions, with *m/e* 312.1066 and 312.1065, respectively (calc.: 312.1070).

ACKNOWLEDGMENTS

The author is indebted to Professor C. L. Stevens for comparing the synthetic hydrazone with natural material, and thanks CIBA Laboratories, Ltd., Horsham for financial support of part of this work.

REFERENCES

1 Preliminary communication: A. H. Haines, *Carbohyd. Res.*, 10 (1969) 466.
2 C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, 27 (1962) 2991.
3 H. Brockmann and T. Waehneldt, *Naturwissenschaften*, 50 (1963) 43.
4 K. L. Rinehart, Jr., and D. B. Borders, *J. Amer. Chem. Soc.*, 85 (1963) 4037.
5 C. L. Stevens, P. Blumbergs, and D. L. Wood, *J. Amer. Chem. Soc.*, 86 (1964) 3592.
6 A. H. Haines, *Carbohyd. Res.*, 1 (1965) 214.
7 E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, 85 (1963) 2677.
8 P. M. Collins and W. G. Overend, *J. Chem. Soc.*, (1965) 1912.
9 J. Jarý, K. Čapek, and J. Kovář, *Collect. Czech. Chem. Commun.*, 28 (1963) 2171.
10 H. A. Staab and G. Walther, *Ann.*, 657 (1962) 98.
11 E. L. Albano and D. Horton, *J. Org. Chem.*, 34 (1969) 3519.
12 V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, 43 (1965) 3452.
13 J. Buckingham, *Quart. Rev. Chem. Soc.*, 23 (1969) 37.
14 S. Sternhell, *Quart. Rev. Chem. Soc.*, 23 (1969) 236.
15 *Chromatography*, E. Merck A.G., Darmstadt, 2nd edn., p. 30.
16 C. L. Stevens, personal communication.
17 A. B. Foster, R. Harrison, J. Lehmann, and J. M. Webber, *J. Chem. Soc.*, (1963) 4471.