Syntheses of Methyl 2,3,6-Trideoxy-α-L-*erythro*-hexopyranoside (Methyl α-L-Amicetoside) and Methyl 2,3,4,6-Tetradeoxy-4-(dimethylamino)-α-L-*threo*-hexopyranoside (Methyl α-L-Ossaminide)

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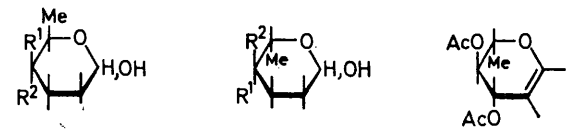
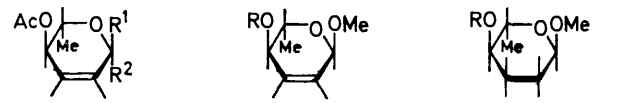
Methyl 2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (12), the free sugar of which is enantiomeric with a constituent of the antibiotic amicetin, has been synthesized in three steps from 3,4-di-*O*-acetyl-L-rhamnal (7) by its rearrangement to, *inter alia*, methyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (8) with boron trifluoride in dichloromethane–methanol. Deacetylation and hydrogenation of the latter compound gave the required product (12). Methyl 2,3,6-trideoxy-4-*O*-methylsulphonyl-α-L-*erythro*-hex-2-enopyranoside (15) underwent ready S_N2 displacement of the allylic sulphonate group to give the 4-azide (16), which on hydrogenation and *N*-dimethylation gave methyl 2,3,4,6-tetradeoxy-4-(dimethylamino)-α-L-*threo*-hexopyranoside (17). The free sugar liberated from the latter glycoside is enantiomeric with a sugar component of the spiramycin antibiotics.

RECENT years have seen the isolation of a number of antibiotic substances containing derivatives of 2,3,6-trideoxyhexoses as constituents; these include 2,3,6-trideoxy-D-*erythro*-hexose (amicetose) (1) from amicetin,[1] 2,3,6-trideoxy-L-*threo*-hexose (rhodinose) (2) from rhodomycin [2] and streptolydogin,[3] 2,3,4,6-tetradeoxy-4-(dimethylamino)-D-*erythro*-hexose (forosamine) (3) from the spiramycins,[4] 4-amino-2,3,4,6-tetradeoxy-L-*erythro*-hexose (tolyposamine) (4) from tolypomycin,[5] 2,3,4,6-tetradeoxy-4-(dimethylamino)-D-*threo*-hexose (ossamine) (5) from ossamycin,[6] and 2,3,6-trideoxy-L-*glycero*-hexopyranos-4-ulose (cinerulose A) (6) from cinerubin A.[7] Syntheses of most of the naturally occurring sugars [6,8–13] or their enantiomers [8–11] are either available or potentially so through modification of existing routes. Most of the syntheses reported have commenced from D-glucose.

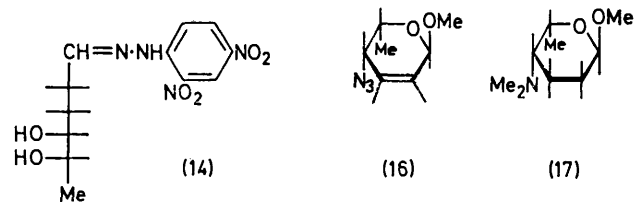
Investigations started in this laboratory several years ago were directed towards the synthesis of the foregoing antibiotic sugars from such readily available 6-deoxy-hexoses as L-rhamnose. The advantage of this approach is that it removes the need to introduce the 6-deoxy-function at some stage in the synthesis. Our first approach [14] was based upon the synthesis of 2,3-unsaturated sugars by the Corey–Winter procedure.[15] In this regard, our work essentially duplicates that recently reported by Haines,[11] and, as a consequence, will not be discussed further. However, in extending the work to syntheses of aminosugar derivatives [*e.g.* (3) and (4)], we encountered a number of practical difficulties in isolating the products after nucleophilic displacements on, for example, methyl 2,3,6-trideoxy-4-*O*-methylsulphonyl-α-L-*erythro*-hexopyranoside [*i.e.* the saturated derivative of (15)] when using sodium azide in dipolar, aprotic solvents such as *NN*-dimethylformamide. These difficulties seemed to stem from the fairly volatile nature of the product azides, which were removed with the solvent on concentrating



(1) R^1=H, R^2=OH (2) R^1=OH, R^2=H (7)
(3) R^1=H, R^2=NMe_2 (4) R^1=H, R^2=NH_2
(5) R^1=NMe_2, R^2=H (6) R^1, R^2=O



(8) R^1=OMe, R^2=H (10) R=H (12) R=H
(9) R^1=H, R^2=OMe (11) R=Bz (13) R=CO·$C_6H_3(NO_2)_2$
(15) R=Ms



(14) (16) (17)

the reaction solutions thereby reducing the yields to unacceptable levels. In an effort to overcome this problem, attention was directed towards the synthesis of the more reactive allylic sulphonates [*e.g.* (15)] in the hope that displacements could then be conducted in other

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solvents that could be removed at much lower temperatures. Ferrier and his colleagues [16] have shown that carbohydrate allylic sulphonates undergo S_N2 displacements very readily and no evidence was obtained for any rearrangements.

The route used for the preparation of methyl 2,3,6-trideoxy-4-*O*-methylsulphonyl-α-L-*erythro*-hex-2-enopyranoside (15) commenced from 3,4-di-*O*-acetyl-L-rhamnal (7), which was prepared from L-rhamnose according to the literature procedure.[17] Brief treatment of the unsaturated sugar (7) with the boron trifluoride–ether complex in dichloromethane–methanol, as recommended [18] for the corresponding unsaturated dibenzoate, afforded a mixture of rearrangement products containing principally the anomeric methyl 4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hex-2-enopyranosides (8) and (9), in which the α-anomer predominated. These compounds were separated by preparative chromatography on silica gel. The structures of the anomeric glycosides were allocated initially from elemental analyses and n.m.r. and optical data, but that of the α-glycoside (8) was established unequivocally by its subsequent conversion into derivatives of known configuration.

Catalytic deacetylation of the α-glycoside (8) gave methyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (10), which was converted into the crystalline monobenzoate (11) for characterization; the physical constants of this derivative were in reasonable agreement with those reported by Pedersen *et al.*[18] for a product resulting from boron-trifluoride-catalysed rearrangement of 3,4-di-*O*-benzoyl-L-rhamnal. Platinum-catalysed hydrogenation of the unsaturated alcohol (10) afforded methyl 2,3,6-trideoxy-α-L-*erythro*-hexopyranoside (methyl α-L-amicetoside) (12) having physical constants in good agreement with literature values.[9,11] This identity was confirmed by further transformations of (12) into the crystalline 3,5-dinitrobenzoate (13) and, after acid hydrolysis, into the 2,4-dinitrophenylhydrazone (14) of the free sugar. Both derivatives exhibited physical constants in accord with literature values.[8-11]

The foregoing sequence of reactions provides an acceptable, alternative synthesis of derivatives of L-amicetose from readily available percursors.

Treatment of the unsaturated alcohol (10) with methanesulphonyl chloride in pyridine yielded a rather unstable methanesulphonate (15). Displacement of the allylic sulphonate group of (15) with azide ion was readily accomplished in aqueous acetone at room temperature to give methyl 4-azido-2,3,4,6-tetradeoxy-α-L-*threo*-hex-2-enopyranoside (16). In this instance, the fairly volatile unsaturated azide (16) was isolated, in reasonable yield, following removal of the solvents and preparative chromatography on silica gel. Hydrogenation of the olefinic linkage and azido-group of (16), with ensuing reductive *N*-dimethylation of the intermediate amine, was effected with hydrogen and formaldehyde over Raney nickel to give methyl 2,3,4,6-tetradeoxy-4-(dimethylamino)-α-L-*threo*-hexopyranoside (methyl α-L-ossaminide) (17). The physical constants and n.m.r. spectrum of compound (17) showed the expected agreement with those reported for the D-enantiomer, whose conversion into the naturally occurring free D-sugar has been described already by Albano and Horton.[13]

The foregoing route leading to derivatives of L-amicetose and L-ossamine should be capable of extension to other isomeric 2,3,6-trideoxyhexose derivatives either by using other acetylated glycals as percursors, or, by effecting configurational inversion at C-4 of the allylic methanesulphonate (15) with such nucleophiles as benzoate and acetate. Such investigations are being actively pursued.

EXPERIMENTAL

Kieselgel G (Merck) was used for t.l.c.; spots were detected with vanillin–sulphuric acid.[19] N.m.r. spectra were measured on a Perkin-Elmer R-10 spectrometer, and i.r. spectra were recorded for either Nujol mulls or liquid films with a Perkin-Elmer ' Infracord ' spectrometer. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter. Light petroleum refers to the fraction having b.p. 40—60°. Routine identifications were based on i.r. and n.m.r. spectroscopy, t.l.c. mobilities, and m.p.s.

Methyl 4-O-Acetyl-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranoside (8).—To a solution of 3,4-di-*O*-acetyl-L-rhamnal [17] (7) (43 g) in dry dichloromethane (600 ml) was added a mixture of boron trifluoride–ether complex, methanol, and dichloromethane (1 : 1 : 8; 162·5 ml), and the solution was set aside for 20 min at room temperature. During this period, the colour of the solution changed from orange to red and then to purple. T.l.c. (hexane–acetone, 6 : 1) showed that at least three products had been formed. The solution was diluted with dichloromethane, washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Removal of the solvents yielded an oil (42·7 g), which after distillation at 64—70° (bath) and 1 mmHg was chromatographed on silica gel (elution with hexane–acetone, 6 : 1) to give firstly the *unsaturated α-glycoside* (8) (18·3 g, 49%), b.p. 52—54° (bath) at *ca.* 0·1 mmHg, $[\alpha]_D$ −187° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 1730 cm^{-1} (OAc) (Found: C, 57·4; H, 8·1. $C_9H_{14}O_4$ requires C, 58·0; H, 7·5%); τ (CCl_4) 6·62 (3H, s, OMe), 7·97 (3H, s, OAc), and 8·82 (3H, d, $J_{5,6}$ 6 Hz, CMe).

Continued elution yielded *methyl 4-O-acetyl-2,3,6-trideoxy-β-L-erythro-hex-2-enopyranoside* (9) (1·7 g, 4·5%), b.p. 65—72° (bath) at *ca.* 0·1 mmHg, $[\alpha]_D$ −85° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ (film) 1733 cm^{-1} (OAc) (Found: C, 58·6; H, 7·3%); τ (CCl_4) 6·64 (3H, s, OMe), 7·97 (3H, s, OAc), and 8·72 (3H, d, $J_{5,6}$ 6 Hz, CMe). No attempt was made to separate and identify the other component(s) present.

Methyl 2,3,6-Trideoxy-α-L-erythro-hex-2-enopyranoside (10).—To a solution of the 4-acetate (8) (15·8 g) in dry methanol (100 ml) was added a small piece of sodium, and the solution was set aside for 30 min at room temperature, after which time deacetylation was completed. The solution was carefully concentrated at room temperature, the

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residual oil was taken up in ether (100 ml), and the extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil (11·3 g), which on distillation afforded the *unsaturated alcohol* (10) (10·6 g, 87%), b.p. 96—98° (bath) at *ca.* 15 mmHg, $[\alpha]_D$ −94° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 3400 cm^{-1} (OH) (Found: C, 58·0; H, 8·6. $C_7H_{12}O_3$ requires C, 58·3; H, 8·3%); τ (CCl_4) 6·64 (3H, s, OMe) and 8·76 (3H, d, $J_{5,6}$ 6 Hz, CMe).

Benzoylation of the unsaturated alcohol (10) in the usual way, gave methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (11), m.p. 53—54·5° (from ether–light petroleum), $[\alpha]_D$ −225° (*c* 1 in $CHCl_3$). The n.m.r. spectrum of this derivative appeared to be identical with that recorded by Bock, Christiansen, and Pedersen,[18] who used an alternative method of preparation; the compound obtained by these workers had m.p. 43—45°, $[\alpha]_D$ −215° (*c* 1·5 in $CHCl_3$).

Methyl 2,3,6-*Trideoxy*-α-L-erythro-*hexopyranoside* (*Methyl* α-L-*Amicetoside*) (12).—A solution of the unsaturated alcohol (10) (2 g)in methanol (50 ml) containing Adams catalyst (0·15 g) was hydrogenated with a slight overpressure of hydrogen for 16 h at room temperature, during which time complete reaction occurred. The catalyst was filtered off, the filtrate was concentrated, and the residual oil was distilled to give *methyl* α-L-*amicetoside* (12) (1·7 g, 81%), b.p. 94—96° (bath) at *ca.* 15 mmHg, $[\alpha]_D$ −139° ± 1° (*c* 1·3 in $CHCl_3$) {lit.,[11] b.p. 97—99° at 12 mmHg, $[\alpha]_D^{20}$ −144° (*c* 0·23 in $CHCl_3$); D-enantiomer,[9] b.p. 50° (bath) at 1 mmHg, $[\alpha]_D$ +142° (*c* 1·2 in H_2O)}.

Treatment of the glycoside (12) with 3,5-dinitrobenzoyl chloride in pyridine afforded the 3,5-dinitrobenzoate (13), m.p. 97—99° (from methanol), $[\alpha]_D$ −130° (*c* 0·5 in $CHCl_3$) (Found: C, 49·5; H, 5·0; N, 8·2. $C_{14}H_{16}N_2O_8$ requires C, 49·4; H, 4·7; N, 8·2%) {lit.,[11] m.p. 96—98°, $[\alpha]_D^{20}$ −131° (*c* 0·97 in $CHCl_3$); D-enantiomer,[9] m.p. 100—101°, $[\alpha]_D^{20}$ +134 ± 1° (*c* 0·4 in $CHCl_3$)}.

2,3,6-*Trideoxy*-L-erythro-*hexose* 2,4-*Dinitrophenylhydrazone* (14).—The glycoside (12) (80 mg) in water (6 ml) was treated with a hot solution of 2,4-dinitrophenylhydrazine (110 mg) in 2M-hydrochloric acid (16 ml). After 2 h, the solution was concentrated and the precipitate deposited was filtered off, washed with water, and dried *in vacuo* (P_2O_5). Two recrystallisations from methanol–benzene gave the *hydrazone* (14) (0·11 g), m.p. 154—156°, $[\alpha]_D$ +12° (*c* 0·4 in pyridine) {lit.,[11] m.p. 154—156°, $[\alpha]_D^{20}$ +11·3° (*c* 0·23 in pyridine); D-enantiomer, m.p. 156—157°, $[\alpha]_D^{25}$ −10° (*c* 0·9 in pyridine) (ref. 8); m.p. 154—155·5°, $[\alpha]_D^{19}$ −9·8 ± 1° (*c* 0·4 in pyridine) (ref. 9)}.

Methyl 2,3,6-*Trideoxy*-4-O-*methylsulphonyl*-α-L-erythro-*hex*-2-*enopyranoside* (15).—Compound (15) (52%), obtained by methylsulphonylation of the alcohol (10) in the usual way, had m.p. 47—49° (from ether—hexane), $[\alpha]_D$ −149° (*c* 0·9 in $CHCl_3$); τ (CCl_4) 6·65 (3H, s, OMe), 7·03 (3H, s, OMs), and 8·70 (3H, d, $J_{5,6}$ 6 Hz, CMe) (Found: C, 43·5; H, 6·8. $C_8H_{14}O_5S$ requires C, 43·6; H, 6·4%). This material gradually decomposed.

Methyl 4-*Azido*-2,3,4,6-*tetradeoxy*-α-L-threo-*hex*-2-*enopyranoside* (16).—A slightly impure sample of the methanesulphonate (15) (2·7 g) in acetone (30 ml) containing sodium azide (0·7 g) (previously dissolved in the minimum quantity of water) was left for 16 h at room temperature, after which time the reaction was essentially complete. The solvents were carefully removed, the residue was extracted with ether (50 ml), and the extract was dried (Na_2SO_4) and evaporated. The residual oil (2 g; containing a small proportion of starting material) was chromatographed on silica gel (elution with hexane–acetone, 6 : 1) to give the 4-*azide* (16) (1·1 g, 54%), $[\alpha]_D$ +33 ± 2° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 2100 cm^{-1} (N_3), as a colourless oil, τ ($CDCl_3$) 6·65 (3H, s, OMe) and 8·73 (3H, d, CMe). A satisfactory elemental analysis could not be obtained and severe losses occurred when attempts were made to distil this material.

Methyl 2,3,4,6-*Tetradeoxy*-4-(*dimethylamino*)-α-L-threo-*hexopyranoside* (*Methyl* α-L-*ossaminide*) (17).—An aqueous solution of formaldehyde (37·2%; 1·5 ml), sodium acetate (0·1 g), and Raney nickel [20] (3 g) were added to a solution of the azide (16) (0·67 g) in ethanol (80 ml), and the mixture was hydrogenated for 16 h at room temperature at 50 lb in^{-2}. The catalyst was filtered off and the solvent was removed. The residue was dissolved in aqueous 2% ammonium hydroxide (50 ml), the solution was extracted with dichloromethane (3 × 25 ml), and the combined extracts were dried (Na_2SO_4) and evaporated. The residual oil was distilled to give *methyl* α-L-*ossaminide* (17) (0·26 g, 38%), b.p. 80—85° (bath) at 15 mmHg, $[\alpha]_D$ −50 ± 2° (*c* 1 in $CHCl_3$), $\nu_{max.}$ (film) 2500 cm^{-1} (NMe) {lit. (D-enantiomer),[13] b.p. 40—45° (bath) at 0·5 mmHg, $[\alpha]_D^{25}$ +55·2 ± 1° (*c* 0·72 in $CHCl_3$)}. The n.m.r. spectrum of this glycoside showed the absence of an olefinic linkage and was identical with that reported [13] for the D-isomer.

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