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Note

An improved synthesis of D-amicetose

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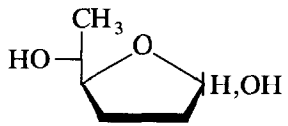
The structure of D-amicetose (2,3,6-trideoxy-D-*erythro*-hexose, **1**), a constituent of the antibiotic amicetin[1], was proved first by synthesis from D-glucal[2]. Since then, numerous syntheses of D-amicetose and related sugars have been described[3], and that by Bethell and Ferrier[4] is relevant to the work now reported.

The starting material for their synthesis[4] was 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) and the key step involved ethanethiolysis of **3** to give the tetrathio derivative **7** in a yield of ~40%. The postulated precursor of **7**, the acyclic D-*allo* intermediate **8**, was assumed on the basis of earlier work[5,6].

We now report on the acid-catalysed ethanethiolysis of 3,5-di-*O*-acetyl-6-*S*-acetyl-1,2-*O*-isopropylidene-6-thio-α-D-glucofuranose (**5**) and 3,5,6-tri-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose[7] (**6**). In parallel with the earlier work[5,6], **10** was main product (> 90% from **5**).



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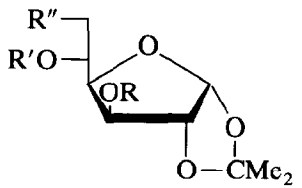

2 R = R′ = H, R″ = OH
4 R = R′ = Ac, R″ = OTs
5 R = R′ = Ac, R″ = SAc
6 R = R′ = Bz, R″ = OBz

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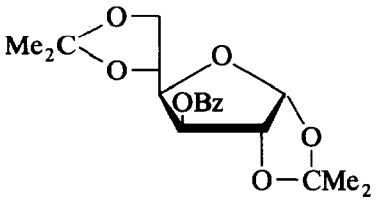

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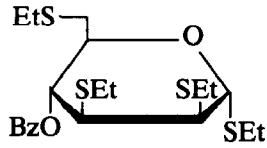

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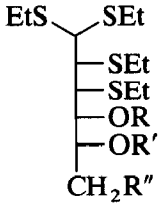
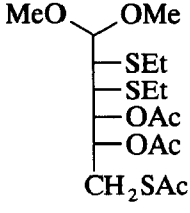
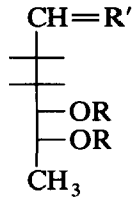


8 R = Bz, R′ = H, R″ = OH
9 R = R′ = Bz, R″ = OBz
10 R = R′ = Ac, R″ = SAc



11



12 R = Ac,
R′ = $(OMe)_2$
13 R = Ac,
R′ = $NNHC_6H_3(NO_2)_2$

The acetylated compound **5** was more reactive than the benzoylated compound **6**. At the same time, the product **10** was formed in a higher yield than the product **9**. Moreover, the reaction conditions (concd HCl, EtSH, room temperature) were more practical than those (CF_3CO_2H, EtSH–chloroform, room temperature) used earlier[4–6].

Treatment of **10** with *N*-bromosuccinimide in methanol[8] gave **11**, desulfation of which afforded D-amicetose dimethyl acetal (**12**), which was characterised as the known[1] 3,5-dinitrophenylhydrazone **13**.

Bethell and Ferrier[4] recorded an overall yield of 11% in the synthesis of D-amicetose from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**), whereas 33% was obtained by the route now reported. The starting compound **2** was obtained by a modified "one-pot" procedure.

The structure of **10** was confirmed by X-ray crystallography and the details will be published elsewhere.

EXPERIMENTAL

General procedures.–Melting points (Kofler apparatus) are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter and IR spectra with a Unicam SP-1100 spectrophotometer. ^1H NMR spectra were recorded for solutions in $CDCl_3$ (internal $MeSi_4$) with a Bruker AC 250 E spectrometer.

1,2-O-Isopropylidene-α-D-glucofuranose (**2**).—To ice-cooled dry acetone (150 mL) was added concd H_2SO_4 (3 mL) followed by powdered anhyd D-glucose (9 g, 50 mmol). The mixture was stirred at room temperature for 24 h, then filtered,

diluted with water (70 ml), stored for 30 min at room temperature, neutralised (solid $CaCO_3$), filtered, and concentrated. The syrupy residue was diluted with water and extracted with ether, the aqueous solution was concentrated, and the residue was crystallised from 2-propanol–EtOAc to give **2** (7 g, 63%), mp 159°, lit[9]. mp 160°.

3,5-Di-O-acetyl-1,2-O-isopropylidene-6-O-p-toluenesulfonyl-α-D-glucofuranose (**4**). —To a solution of **2** (4 g, 18 mmol) in anhyd pyridine (30 mL) at −10° was added *p*-toluenesulfonyl chloride (4 g, 21 mmol), and the mixture was stored overnight at −10°. Acetic anhydride (20 mL) was then added, and the mixture was stored at room temperature for 24 h, then poured into ice–water, and acidified with 5 M HCl to pH 2. After 3 h, the product was extracted with EtOAc, the extract was washed with aq $NaHCO_3$ and dried (Na_2SO_4), and the solvent was evaporated. The syrupy residue was crystallised from cyclohexane–CH_2Cl_2 to give **4** (7.1 g, 86%), mp 90–92°, lit[10] mp 94°.

Anal. Calcd for $C_{20}H_{26}O_{10}S$: C, 52.40; H, 5.67; S, 6.86. Found: C, 52.27; H, 5.75; S, 7.10.

3,5-Di-O-acetyl-6-S-acetyl-1,2-O-isopropylidene-6-thio-α-D-glucofuranose (**5**).—To a solution of **4** (4 g, 8.7 mmol) in *N*,*N*-dimethylformamide (25 mL) was added potassium thioacetate (4 g, 35 mmol). The mixture was stirred for 4 h at room temperature, then poured into water, and extracted with EtOAc, the extract was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. The syrupy residue was crystallised from hexane to afford **5** (2.8 g, 90%), mp 89–90°, $[\alpha]_D$ +37° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 1745, 1715, 1250, 1230 cm^{-1}. ^1H NMR data: δ 1.31 and 1.53 (2 s, 6 H, CMe_2), 1.97 and 2.06 (2 s, 6 H, OAc), 2.34 (s, 3 H, SAc), 3.04 (dd, 1 H, H-6b), 3.59 (dd, 1 H, H-6a), 4.34 (dd, 1 H, H-4), 4.47 (d, 1 H, H-2), 5.15–5.25 (m, 1 H, H-5), 5.32 (d, 1 H, H-3), 5.92 (d, 1 H, H-1).

Anal. Calcd for $C_{15}H_{22}O_8S$: C, 49.36; H, 6.15; S, 8.95. Found: C, 49.72; H, 6.02; S, 8.83.

4,5,6-Tri-O-benzoyl-2,3-di-S-ethyl-2,3-dithio-D-allose diethyl dithioacetal (**9**).—To a solution of **6**[7] (0.5 g, ~0.9 mmol) in ethanethiol (1.5 mL, 19.7 mmol) cooled in an ice–water bath was added precooled concd HCl (1.5 mL). The mixture was stirred at 0° for 3 h and then at room temperature for 20 h, neutralised with $PbCO_3$, filtered, and extracted with EtOAc. The extract was washed with brine, then dried (Na_2SO_4), and the solvent was evaporated. The crude product (0.9 g) was purified on a column (10 g) of silica gel, using light petroleum–EtOAc (8:1), to give **9** (0.45 g, 70%). Recrystallised from EtOH, it had mp 90–91°; lit[5]. mp 91–92°.

4,5-Di-O-acetyl-6-S-acetyl-2,3-di-S-ethyl-2,3,6-trithio-D-allose diethyl dithioacetal (**10**).—To a solution of **5** (3.6 g, 10 mmol) in ethanethiol (11 mL, 145 mmol) cooled in an ice–water bath was added concd HCl (11 mL). The mixture was stirred at 0° for 3 h and then at room temperature for 20 h, neutralised with $PbCO_3$, filtered, and extracted with EtOAc. The extract was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. Recrystallisation of the residue from MeOH gave

10 (4.5 g, 85%), mp 78–80°, $[\alpha]_D$ +27° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 1750, 1710, 1240, 1210 cm^{-1}. [1] NMR data: δ 1.20–1.30 (m, 12 H, 4 SCH_2CH_3), 2.02 and 2.11 (2 s, 6 H, 2 OAc), 2.34 (s, 3 H, SAc), 2.50–3.00 (m, 8 H, 4 SCH_2CH_3), 3.05–3.09 (m, 2 H, H-2, 6b), 3.38–3.54 (m, 2 H, H-3,6a), 4.38 (d, 1 H, H-1), 5.49 (m, 1 H, H-5), 5.78 (t, 1 H, H-4).

Anal. Calcd for $C_{20}H_{36}O_5S_5$: C, 46.53; H, 6.98; S, 31.01. Found: C, 46.86; H, 6.85; S, 31.32.

*4,5-Di-*O*-acetyl-6-*S*-acetyl-2,3-di-*S*-ethyl-2,3,6-trithio-*D*-allose dimethyl acetal* (**11**). —A solution of **10** (2.5 g, 5 mmol) in dry MeOH (40 mL), cooled in an ice–water bath, was treated with *N*-bromosuccinimide (2.5 g, 14 mmol) during 2 min at 0°. After further 10 min, sodium thiosulphate and $NaHCO_3$ (10 g, 1:1) were added, and stirring was continued for 60 min. The mixture was poured into water, then extracted with EtOAc, the extract was washed with brine and dried (Na_2SO_4), and the solvent was evaporated. Column chromatography (20 g of silica gel, hexane–EtOAc, 6:1) gave **11** (1.9 g, 85%), isolated as a colourless syrup, $[\alpha]_D$ +44° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 1750, 1710 cm^{-1}. ^1H NMR data: δ 1.23–1.33 (m, 6 H, 2 SCH_2CH_3), 1.59 (s, 1 H, H-2), 2.01 and 2.10 (2 s, 6 H, 2 OAc), 2.34 (s, 3 H, SAc), 2.70–2.81 (m, 4 H, 2 SCH_2CH_3), 3.08 (m, 3 H, H-2,3,6b), 3.35 (dd, 1 H, H-6a), 3,43 and 3.50 (2 s, 6 H, 2 OMe), 4.52–4.55 (d, 1 H, H-1), 5.40 (m, 2 H, H-4,5).

*4,5-Di-*O*-acetyl-2,3,6-trideoxy-*D*-erythro-hexose dimethyl acetal* (**12**).—To a solution of **11** (1.8 g, 4 mmol) in dioxane (15 mL) was added a slurry of freshly prepared Raney nickel (30 g) in 95% EtOH (20 mL). The mixture was boiled under reflux for 90 min, then filtered, the catalyst was washed with hot 95% EtOH, and the filtrate and washings were combined and concentrated to dryness. Column chromatography (10 g of silica gel, cyclohexane–EtOAc, 5:1) of the residue gave **12**, isolated as a colourless oil (0.65 g, 65%), $[\alpha]_D$ −1.7° (*c* 1.0, $CHCl_3$); ν_{rmax}^{KB} 1750, 1250 cm^{-1}. ^1H NMR data: δ 1.20–1.22 (d, 3 H, Me), 1.61 (m, 4 H, CH_2CH_2), 2.03 and 2.06 (2 s, 6 H, 2 OAc), 3.32 (s, 6 H, 2 OMe), 4.52–4.56 (d, 1 H, H-1), 5.38–5.44 (m, 2 H, H-4,5).

Treatment of **12** (80 mg, 0.3 mmol) with a hot solution of 2,4-dinitrophenylhydrazine hydrochloride (150 mg) in 2 M HCl (15 mL), with recrystallisation of the product from ether–light petroleum, gave the 2,4-dinitrophenylhydrazone **12**, mp 95°; lit[1]. mp 95–96°.

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