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Preliminary communication

3-Azido-4-*C*-cyano-2,3,4,6-tetradeoxy-D-*arabino*-hexose trimethylene dithioacetal, a D-glucose-derived, "chiral template" for the total synthesis of thienamycin

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Thienamycin (**1**) is a highly potent, broad-spectrum, β-lactam antibiotic having the unique features of a 1-carbapen-2-em ring-system and a 6α-(1*R*-hydroxyethyl) side-chain[1]. Although several, total syntheses of **1** have been reported[2], not one has to date exploited the potentially powerful approach employing carbohydrate-derived "chiral templates" (ref. 3)*. Indeed, examination of the thienamycin structure (5*R*,6*S*,8*R* absolute stereochemistry[1b]) has led to the recognition of hidden D-glucose symmetry within the carbapenem molecule. Consequently, asymmetrical modification of D-glucose (**7**) in order to construct the chiral segment of **1** was investigated. Because the azetidinone aldehyde **2**, as its *N,O*-disilyl derivative, had already been shown to be convertible into thienamycin[2b], it was selected as the target for elaboration from the readily available, naturally occurring **7**.

The strategy devised for the synthesis of **2**, depicted retrosynthetically in Scheme 1, involved cyclization of β-amino acid **3** (ref. 2d) or β-amino ester **4** (refs. 2b, 2c, and 2e), which would be derived by hydrolysis (alcoholysis) and reduction of azidonitrile **5**, having the formyl group protected as its dithioacetal. Compound **5** would be obtained by functionalization of the 3- and 4-hydroxyl groups of 2,6-dideoxy-D-*arabino*-hexose (**6**) (in the form of its methyl α-pyranoside), with overall retention of configuration at the contiguous, chiral centers. Derivations of **6** from D-glucose (**7**) have been described[5,6]. The present communication reports the synthesis of the title compound **5** (see Scheme 1) as a key, chiral template in an enantiomerically specific route to thienamycin (**1**) from D-glucose (**7**).

Methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**8**) was readily prepared from D-glucose (**7**), as previously described[6]. Regioselective *p*-toluenesulfonylation of **8** afforded, in 69% yield, the 3-*p*-toluenesulfonate **9**†, m.p. 82.5–84.5°, $[\alpha]_D^{25}$ +106° (*c* 0.9, $CHCl_3$) {lit.[7], in the L series, m.p. 86.5–86.9°, $[\alpha]_D$ −116° ($CHCl_3$)}. Treatment of **9** with ethanolic sodium hydroxide generated the 3,4-epoxide, which was opened, without

*During the course of this work, progress on a related approach was reported[4].

†All compounds gave microanalyses, and exhibited n.m.r.- and mass-spectral characteristics, in agreement with their structures.

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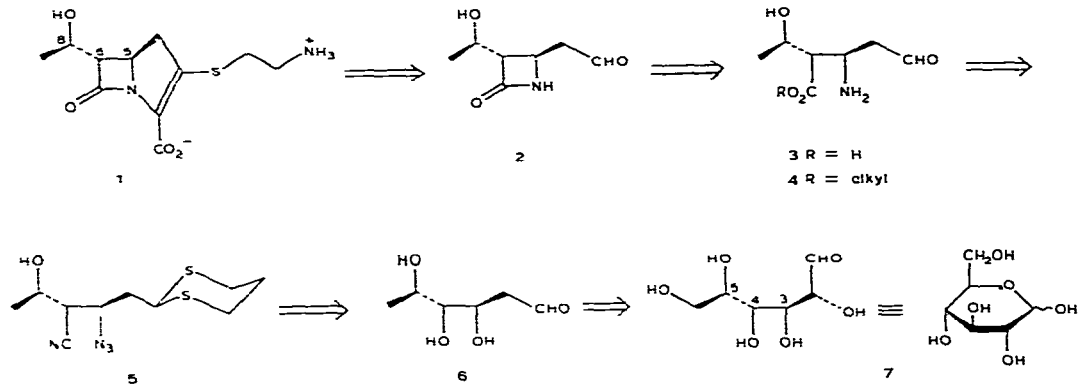
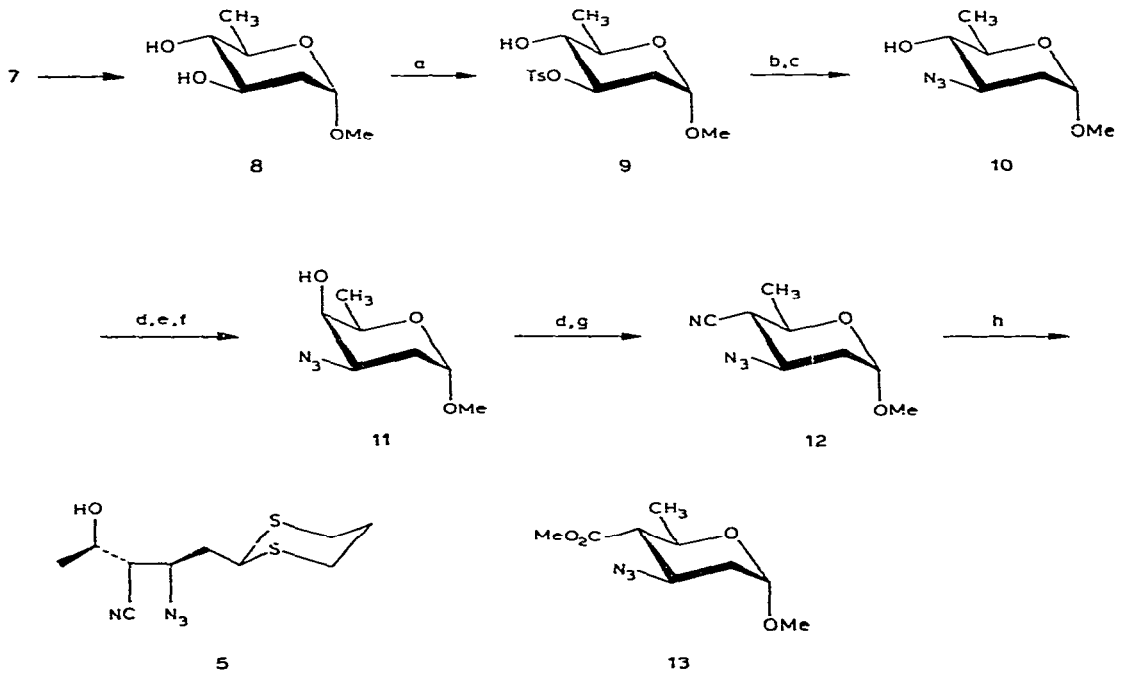


Scheme 1



(a) 1.03 equiv. TsCl, C_5H_5N, 8d at 0°; (b) NaOH, EtOH, 60°; (c) NaN_3, NH_4Cl; (d) 1.1 equiv. of Tf_2O, C_5H_5N, CH_2Cl_2, −10°; (e) 1.9 equiv. of Bu_4NOAc, MeCN, 30 min at 40°; (f) MeONa, MeOH; (g) 2 equiv. of Bu_4NCN, MeCN, 5 min at 30°; (h) conc. HCl, HS⌒⌒SH, MeOH.

Scheme 2

isolation, with azide anion to give a 77% yield of azidoalcohol **10***; $[\alpha]_D^{25}$ +125° (*c* 1, $CHCl_3$) {lit.[9] in the L series, $[\alpha]_D^{25}$ −131.8° (*c* 0.5, $CHCl_3$)}. Although conversion of alcohol **10** into the corresponding nitrile **12** by a double-inversion process involving SN2 reaction of 4-deoxy-4-halo-D-*lyxo*-hexopyranosides** (axial halogen) with cyanide did not appear promising, a more circuitous route, which took advantage of the excellent nucleofugality[10] of the trifluoromethanesulfonate (triflate) group† and enhanced nucleophilicity of cyanide anion in the form of its tetraalkylammonium salts[12], allowed the successful introduction of the cyano group at the secondary, C-4 atom of the pyranoid-ring system. The desired azido alcohol **11**, having an axial 4-hydroxyl group, was obtained in 88% overall yield from **10** by sequential triflation, displacement with acetate anion, and deacetylation (see Scheme 2); for **11**, m.p. 39–40°, $[\alpha]_D^{25}$ +150° (*c* 1, $CHCl_3$) {lit.[8] $[\alpha]_D^{22}$ +150.0° (*c* 0.8, MeOH)}; n.m.r. (200-MHz, $CDCl_3$): δ 1.27 (d, C-CH_3), 1.89 (m, H-2*e*, $J_{2e,3}$ 5.1 Hz), 2.10 (td, H-2*a*, $J_{1,2a}$ 3.7 Hz), 3.35 (s, OCH_3), 3.67 (bs, H-4), 3.88 (bq, H-5), and 4.85 (bd, H-1). Conversion of alcohol **11** into its triflic ester, and SN2 reaction thereof with tetrabutylammonium cyanide afforded the cyclic azido-nitrile **12**†† in 21% yield (based on **11**) as an oil; $[\alpha]_D^{25}$ +135° (*c* 1, $CHCl_3$); n.m.r. (300-MHz, $CDCl_3$): δ 1.42 (d, C-CH_3), 1.61 (td, H-2*a*, $J_{1,2a}$ 3.6 Hz), 2.22 (o, H-2*e*, $J_{1,2e}$ 1.3, $J_{2e,3}$ 4.9 Hz), 2.27 (t, H-4, $J_{3,4} = J_{4,5}$ = 10.9 Hz), 3.36 (s, OCH_3), 3.93–4.06 (m, H-3,5), and 4.85 (bd, H-1).

Finally, 3-azido-4-*C*-cyano-2,3,4,6-tetradeoxy-D-*arabino*-hexose trimethylene dithioacetal (**5**), having the requisite chirality (3*R*,4*S*,5*R*) and functionality for conversion into thienamycin (**1**), was isolated in 86% yield by treatment of **12** with conc. hydrochloric acid in the presence of 1,3-propanedithiol; m.p. 118–119°, $[\alpha]_{365}^{25}$ +4.8° (*c* 1, $CHCl_3$); n.m.r. (300-MHz, $CDCl_3$ after CD_3OD "exchange"): δ 1.35 (d, C-CH_3), 1.78–1.96 (m, dithiane 1 H and H-2), 2.04–2.20 (m, dithiane 1 H and H-2'), 2.59 (dd, H-4, *J* 2.9 and 9 Hz), 2.76–2.94 (m, dithiane 4 H), 4.00 (m, H-5), 4.15 (dd, H-1, *J* 5.2 and 9.7 Hz), and 4.28 (m, H-3).

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*An alternative, 9-step synthesis of **10** from D-glucose (**7**) has been reported[8]; however, no physical data for the compound were provided.

Methyl 3-azido-4-chloro-2,3,4,6-tetradeoxy-α-D-*arabino*-hexopyranoside was obtained by treatment of **10 with sulfuryl chloride; the corresponding bromide and iodide were prepared by reaction of the triflic ester of **10** with tetrabutylammonium bromide and iodide, respectively, in acetonitrile.

†Triflic esters for effecting SN2 reactions under mild conditions have been used in other carbohydrate systems; see, *e.g.*, ref. 11.

††Methyl 3-azido-2,3,4,6-tetradeoxy-4-*C*-(methoxycarbonyl)-α-D-*arabino*-hexopyranoside (**13**) was isolated from the reaction of **12** with methanolic sodium methoxide; n.m.r. (300-MHz, $CDCl_3$): δ 1.18 (d, C-CH_3), 1.64 (td, H-2*a*, $J_{1,2a}$ 3.4, $J_{2e,2a} = J_{2a,3}$ = 12.8 Hz), 2.08 (t, H-4, $J_{3,4} = J_{4,5}$ = 10.8 Hz), 2.16 (o, H-2*e*, $J_{1,2e}$ 1.2, $J_{2e,3}$ 5.0 Hz), 3.36 (s, OCH_3), 3.76 (s, CO_2CH_3), 3.92 (m, H-5), 4.03 (td, H-3), and 4.83 (bd, H-1).

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