Synthesis of a Trisaccharide related to the Antitumour Antibiotic, Aclacinomycin A

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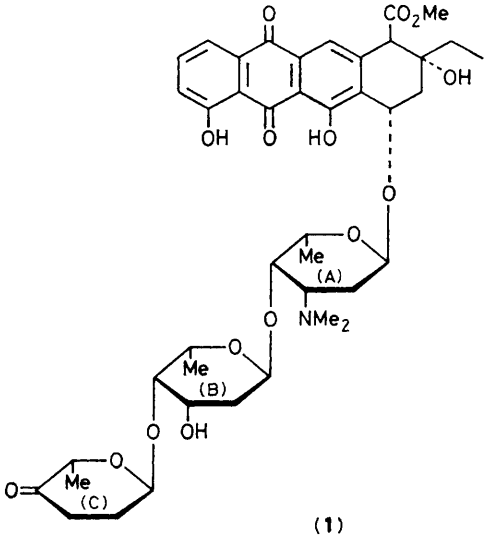
Trisaccharide (**14**), closely related to the trisaccharide moiety of aclacinomycin A has been synthesized stereoselectively by coupling (**3**) and (**5**) under Koenigs–Knorr conditions and then (**7**) and (**9**) in the presence of *N*-iodosuccinimide.

Among the new generation of anthracycline antitumour agents currently under clinical investigation, the most promising product is aclacinomycin A[1] (**1**), a trisaccharide class II anthracycline. Starting from the aglycone, aklavinone, the sugar sequence of its trisaccharide moiety is as follows: L-rhodosamine (A), 2-deoxy-L-fucose (B), and then L-cinerulose (C) with α-(1—4) interlinkages.

In the present synthesis of the closely related trisaccharide (**14**), the sugars used as the respective precursors of these three units were benzyl *N*-(trifluoroacetyl)-α-L-daunosaminide (**3**), 4-*O*-acetyl-3-*O*-benzyl-2-deoxy-α-L-fucosyl bromide (**5**), and 4-*O*-acetyl-L-amicetal (**7**). Compound (**3**), syrup, $[\alpha]_D$ −69°,† was synthesized in one step from methyl *N*-trifluoroacetyl-β-L-daunosaminide[3] (**2**) *via* a stereoselective transglycosylation reaction[4] ($PhCH_2OH$, p-$MeC_6H_4SO_3H$, n-hexane, reflux with a Dean–Stark apparatus) in 89% yield. Acetylation of methyl 3-*O*-benzyl-2-deoxy-β-L-fucoside[2] led to (**4**), m.p. 60 °C from ether, $[\alpha]_D$ −49°. Further treatment of (**4**) with bromotrimethylsilane[5] in benzene at room temperature gave the bromo-derivative (**5**) as a mixture with methyl 3-*O*-benzyl-2-deoxy-α-L-fucoside (**6**) and a small amount of unchanged starting material (**4**). As the instability of (**5**) did not permit purification, the crude reaction mixture was used in the coupling of (**5**) and (**3**) as follows.

Crude (**5**) (2 mol. equiv.) was treated with (**3**) (1 mol. equiv.) under Koenigs–Knorr conditions ($HgBr_2$, HgO yellow, powdered 4 Å molecular sieves, CH_2Cl_2) for 15 min at 0 °C and for 1 h at room temp. After chromatography on silica gel (hexane–acetone 4:1 and toluene–EtOAc 95:5), the desired disaccharide (**8**) was obtained as a crystalline compound, m.p. 127—128 °C from ether, $[\alpha]_D$ −167°, in 40% overall yield from (**3**). The anomeric configuration at the inter-sugar linkage was unambiguously assigned from the ^{1}H n.m.r. spectrum taken at 400 MHz ($CDCl_3$) δ 4.94 (2H, dd, J 4 and <1 Hz, 1-H and 1′-H).

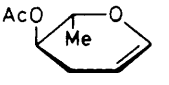
Treatment of (**8**) with NaOMe–MeOH in order to remove the acetyl group gave (**9**) quantitatively as a syrup, $[\alpha]_D$ −123°. Coupling of (**9**) with an excess of 4-*O*-acetyl-L-amicetal (**7**) (4 mol. equiv.) was performed in the presence of *N*-iodosuccinimide[6] (MeCN, 0 °C, 1 h) affording‡ the trisaccharide (**10**) stereospecifically in 68% yield after chromatography on silica gel (toluene–EtOAc, 95:5), syrup, $[\alpha]_D$ −148°. The α-linkage between the (B) and (C) units



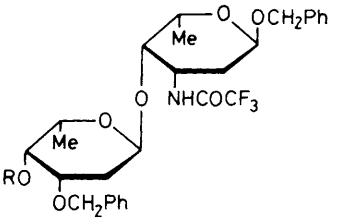
(**1**)

(**2**) R^1=H, R^2=OMe
(**3**) R^1=OCH_2Ph, R^2=H

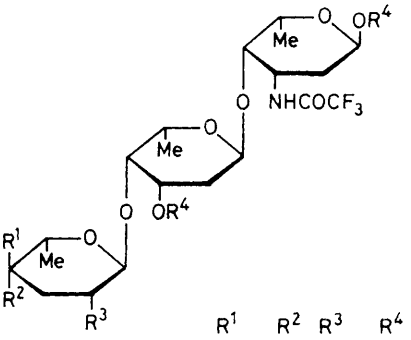
(**4**) R^1=H, R^2=OMe
(**5**) R^1=Br, R^2=H
(**6**) R^1=OMe, R^2=H



(**7**)



(**8**) R = Ac
(**9**) R = H



	R^1	R^2	R^3	R^4
(**10**)	OAc	H	I	CH_2Ph
(**11**)	OAc	H	H	CH_2Ph
(**12**)	OH	H	H	CH_2Ph
(**13**)	=O		H	CH_2Ph
(**14**)	=O		H	H

† All the optical rotations were determined in chloroform at 20 °C, c = 1.

‡ The 4-*O*-deacetyl derivative of (**4**) gave, as previously reported (ref. 2), a mixture of disaccharides with the α and β interlinkage in the ratio of 2.3:1.

was proved by a characteristic signal for 1″-H at δ 5.07 (br. s) in the ^{1}H n.m.r. spectrum.

Hydrogenolysis of (**10**) (Pd–C, Et_3N, EtOH) leading to (**11**), syrup, $[\alpha]_D$ −138°, was followed by deacetylation to give (**12**) quantitatively as a syrup, $[\alpha]_D$ −171°. Oxidation of (**12**) (pyridinium dichromate, 5 mol. equiv., dry CH_2Cl_2, 3 Å molecular sieves)[7] afforded (**13**), m.p. 115—116 °C from hexane–ether, $[\alpha]_D$ −213°, in 90% yield. Finally, hydrogenolysis of (**13**) (Pd–C, EtOAc, H_2) led to the reducing trisaccharide (**14**), syrup, $[\alpha]_D$ −202°. This trisaccharide can serve as a synthon for the preparation of (**1**). In this case, deprotection of 3-N followed by dimethylation must be achieved after glycosylation. However, another method would be to start from (**13**) so that the transformations can be effected before glycosylation.§

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§ Such a trisaccharide, obtained from the hydrogenolysis of (**1**), has recently been successfully coupled with aklavinone (ref. 8).

References

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