

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.

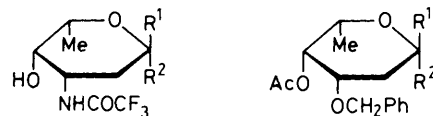
Among the new generation of anthracycline antitumour agents currently under clinical investigation, the most promising product is aclacinomycin A¹ (1), a trisaccharide class II anthracycline. Starting from the aglycone, aklavinone, the sugar sequence of its trisaccharide moiety is as follows: L-rhodamine (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, $[\alpha]_D^{20}$ -69° ,[†] was synthesized in one step from methyl *N*-trifluoroacetyl- β -L-daunosaminide² (2) via a stereoselective transglycosylation reaction¹ (PhCH₂OH, *p*-MeC₆H₄SO₃H, *n*-hexane, reflux with a Dean–Stark apparatus) in 89% yield. Acetylation of methyl 3-*O*-benzyl-2-deoxy- β -L-fucoside² led to (4), m.p. 60 °C from ether, $[\alpha]_D^{20}$ -49° . Further treatment of (4) with bromotrimethylsilane⁵ 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.

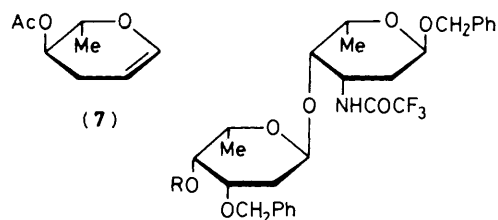
Crude (5) (2 mol. equiv.) was treated with (3) (1 mol. equiv.) under Koenigs–Knorr conditions (HgBr₂, HgO yellow, powdered 4 Å molecular sieves, CH₂Cl₂) for 15 min at 0 °C and for 1 h at room temp. After chromatography on silica gel (hexane–acetone 4:1 and toluene–EtOAc 95:5), the desired disaccharide (8) was obtained as a crystalline compound, m.p. 127–128 °C from ether, $[\alpha]_D^{20}$ -167° , in 40% overall yield from (3). The anomeric configuration at the inter-sugar linkage was unambiguously assigned from

the ¹H n.m.r. spectrum taken at 400 MHz (CDCl₃) δ 4.94 (2H, dd, *J* 4 and <1 Hz, 1-H and 1'-H).

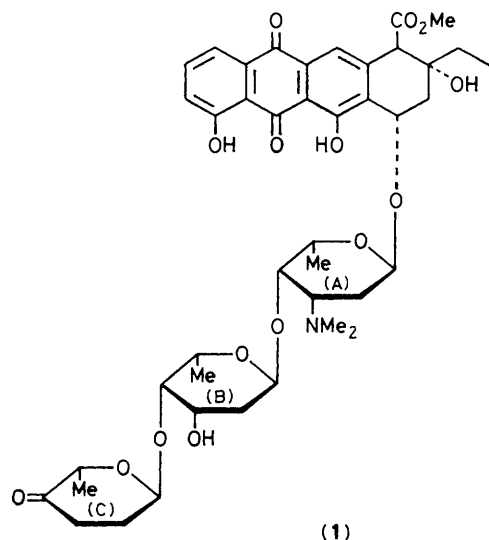
Treatment of (8) with NaOMe–MeOH in order to remove the acetyl group gave (9) quantitatively as a syrup, $[\alpha]_D^{20}$ -123° . Coupling of (9) with an excess of 4-*O*-acetyl-L-amicetal (7) (4 mol. equiv.) was performed in the presence of *N*-iodosuccinimide⁶ (MeCN, 0 °C, 1 h) affording[‡] the trisaccharide (10) stereospecifically in 68% yield after chromatography on silica gel (toluene–EtOAc, 95:5), syrup, $[\alpha]_D^{20}$ -148° . The α -linkage between the (B) and (C) units



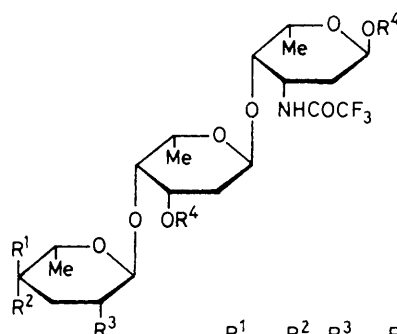
- (2) R¹=H, R²=OMe
 (3) R¹=OCH₂Ph, R²=H
 (4) R¹=H, R²=OMe
 (5) R¹=Br, R²=H
 (6) R¹=OMe, R²=H



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



(1)



- | | R ¹ | R ² | R ³ | R ⁴ |
|------|----------------|----------------|----------------|--------------------|
| (10) | OAc | H | I | CH ₂ Ph |
| (11) | OAc | H | H | CH ₂ Ph |
| (12) | OH | H | H | CH ₂ Ph |
| (13) | =O | H | H | CH ₂ Ph |
| (14) | =O | H | 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 ^1H n.m.r. spectrum.

Hydrogenolysis of (10) (Pd-C, Et_3N , EtOH) leading to (11), syrup, $[\alpha]_{\text{D}} -138^\circ$, was followed by deacetylation to give (12) quantitatively as a syrup, $[\alpha]_{\text{D}} -171^\circ$. 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, $[\alpha]_{\text{D}} -213^\circ$, in 90% yield. Finally, hydrogenolysis of (13) (Pd-C, EtOAc, H_2) led to the reducing trisaccharide (14), syrup, $[\alpha]_{\text{D}} -202^\circ$. 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. §

Received, 20th December 1982; Com. 1461

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

References

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