Total Synthesis of *C*-Glycoside Fragment of Nogalamycin

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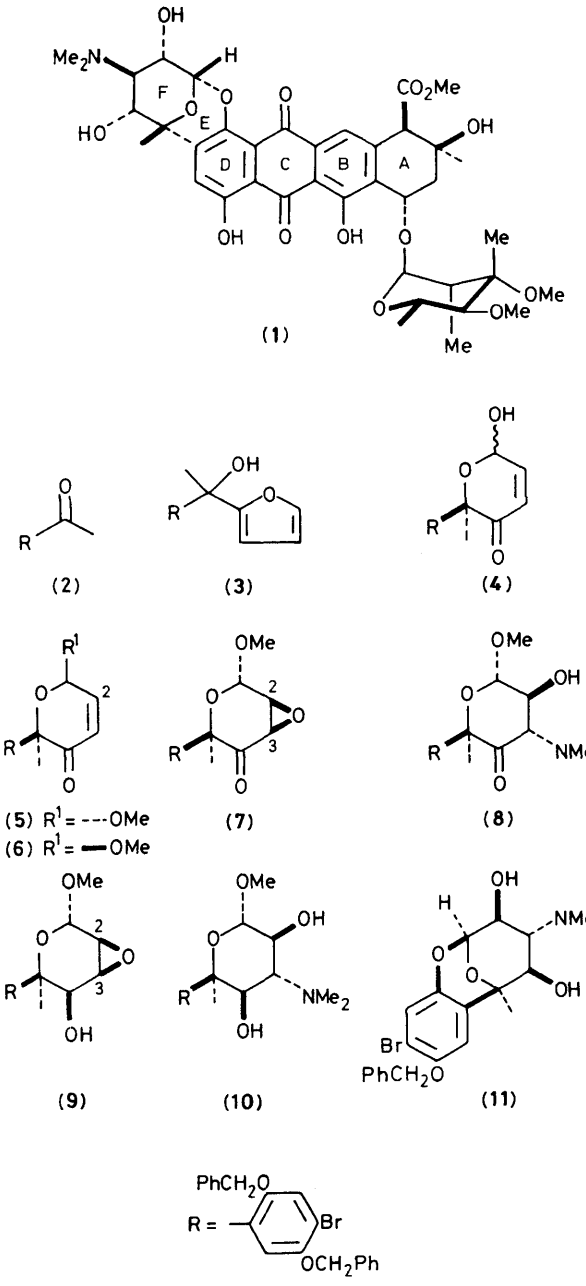
A versatile method for attaching *C*-glycoside precursors onto aromatic rings is described and exemplified by the preparation of the DEF ring system of nogalamycin.

Nogalamycin (**1**) is a member of the anthracyclinone antibiotic family and is notable in possessing reduced cardiotoxicity compared to daunomycin and related compounds.[1] Recent *X*-ray crystallographic studies[2] have confirmed the absolute stereochemistry depicted. Of note in the structure of nogalamycin is the presence of the amino-sugar unit fused to ring D as a *C*-glycoside. Herein we report a flexible method suitable both for the construction of this part of the natural product and for the preparation of a wide range of analogues.

Reaction of 4-bromo-2,5-dibenzyloxyacetophenone† (**2**), m.p. 107 °C, with 2-furyl-lithium[3] produced the alcohol (**3**), which was directly oxidised with *m*-chloroperoxybenzoic acid to yield the diastereoisomeric pyranuloses (**4**),‡ overall yield 75%. Methylation of the alcohols (**4**) with methyl iodide–silver oxide in acetone afforded the corresponding methyl acetals, separated by silica gel chromatography to give, as the major isomer, compound (**5**) (65%), m.p. 123—126 °C, in which the methoxy and aryl substituents are *trans*-oriented with respect to the pyranulose ring, together with some of the *cis*-substituted isomer (**6**) (10%), m.p. 132—134 °C. The relative con-

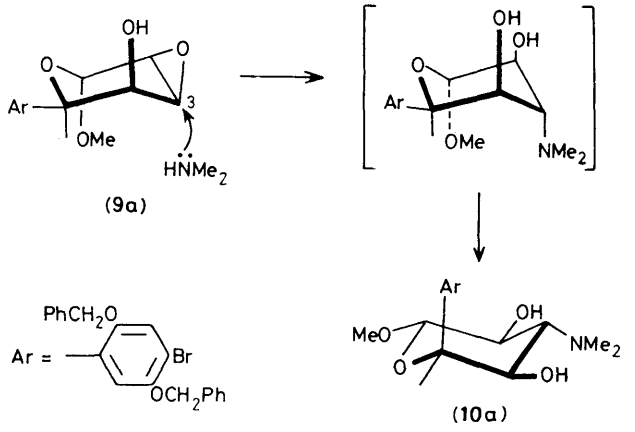
† Readily prepared from 4-bromo-2,5-dihydroxyacetophenone. All new compounds gave satisfactory microanalytical and/or mass spectroscopic data.

‡ All compounds were prepared as racemates; for convenience drawings depict only one enantiomer.

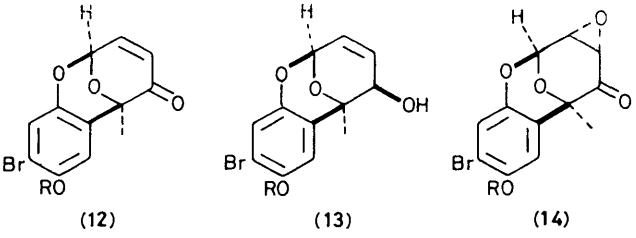


figurations of the methyl acetals were made on the basis of ^{1}H n.m.r. spectroscopic studies; shielding by the anomeric ring causes the anomeric proton to resonate at δ 4.90 for the *trans*-compound (**5**), as compared to the chemical shift of δ 5.25 observed for the anomeric proton in its isomer (**6**). An n.m.r. spectroscopic study on systems related to compound (**5**) shows that the pyranulose rings are conformationally mobile;[4] the coupling constants observed for compound (**5**) are consistent with this finding.

Treatment of the major acetal (**5**) with alkaline t-butyl hydroperoxide in benzene, produced a single epoxide (**7**), formed by initial attack of the reagent at position 2 of the ring on the side opposite to that bearing the adjacent methoxy group. The assigned stereochemistry of epoxide formation was confirmed by treating compound (**7**) with dimethylamine to produce the unstable keto-aminoalcohol (**8**) which showed axial–axial coupling between the ring protons ($J_{C-1,C-2}$ 7, $J_{C-2,C-3}$ 10 Hz). Attempted reduction of the keto-amino-



Scheme 1



alcohol (**8**), with sodium borohydride and related reagents, gave products other than the expected alcohol (**10**).

Reduction of the keto-epoxide (**7**) with sodium borohydride in propan-2-ol afforded the single alcohol (**9**), m.p. 159—160 °C, in 96% yield; this alcohol has the *cisoid*-epoxy-alcohol configuration, the adjacent aryl group directing hydride attack from the opposite side of the ring. Treatment of the epoxy-alcohol with dimethylamine[5] at 100 °C for 15 h gave the desired amine (**10**) (58%), m.p. 138—140 °C, resulting from axial attack at position C-3, presumably *via* the conformer (**9a**); preferential nucleophilic attack at position 3 of 2,3-epoxypyrans is precedented.[6] Once opened, the product undergoes a conformational flip to the more stable form in which the dimethylamino and alcohol groups adopt equatorial positions, as ascertained from the relevant ^{1}H n.m.r. coupling constants. Furthermore, the anomeric proton in (**10**) occurs at a very high field position, δ 4.00, owing to shielding by the now axially-oriented, aromatic ring, see Scheme 1, (**10a**). The substituents in the pyranose ring have the same relative configuration as in ring F of nogalamycin (**1**).[7]

Treatment of the methylglycoside (**10**) with trimethylsilyl iodide (2 equiv.) and trimethylsilyl chloride (2 equiv.) in acetonitrile,[8] in this case effects selective debenzylation, demethylation, and cyclisation to produce the required cyclic acetal (**11**) (40%), m.p. 54—57 °C, the *C*-glycoside protons of which showed similar coupling constants and chemical shifts to those exhibited by ring F of nogalamycin.[7]

Attempts to cyclise the pyranulose (**4**), followed by introduction of the appropriate functional groups have so far failed. Thus selective treatment of compound (**4**) with trimethylsilyl iodide produced the cyclic pyranulose (**12**) in 94% yield. Reduction of (**12**) with sodium borohydride afforded some of the allylic alcohol (**13**) but this could not be induced to form an epoxide with a variety of oxidants. The alternative process, involving treatment of the enone (**12**) with alkaline t-butyl hydroperoxide afforded an epoxide but one of the incorrect relative stereochemistry, determined as (**14**).

Presumably, for compound (**12**), the bridged phenolic ether ring shields the double bond from oxidative attack on the same face of the molecule.

Compound (**11**) and its precursors should prove to be useful intermediates in the synthesis of nogalamycin (**1**) and its derivatives.

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