

## 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.

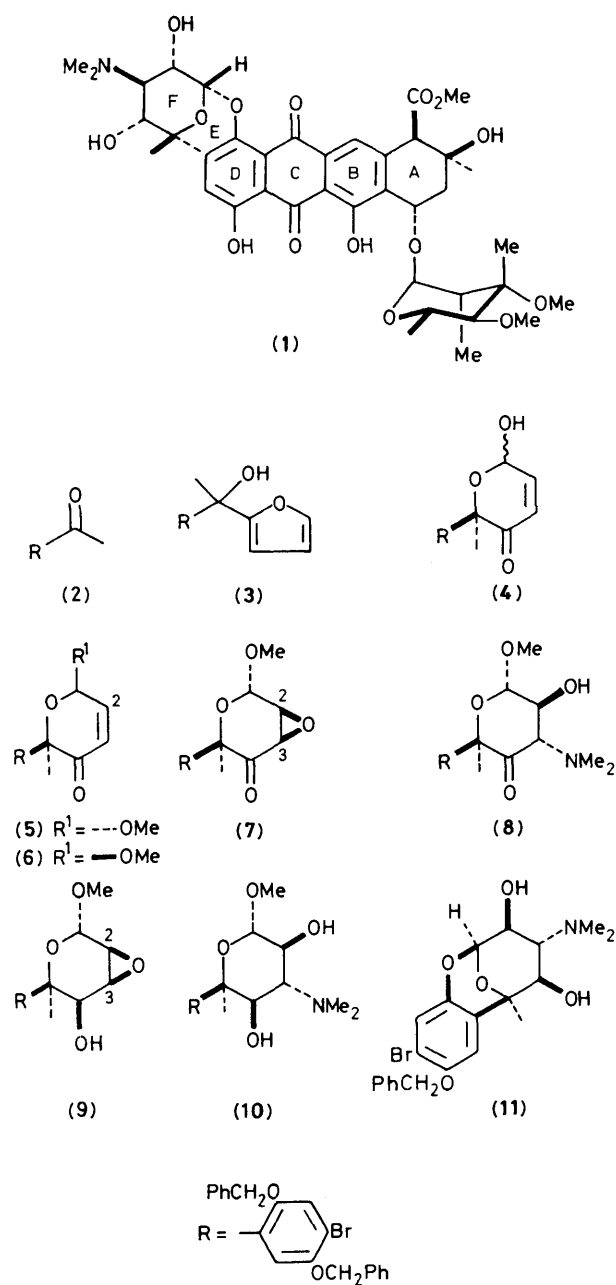
Nogalamycin (**1**) is a member of the anthracyclinone antibiotic family and is notable in possessing reduced cardiotoxicity compared to daunomycin and related compounds.<sup>1</sup> Recent X-ray crystallographic studies<sup>2</sup> have confirmed the absolute stereochemistry depicted. Of note in the 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-dibenzoyloxyacetophenone† (**2**),

m.p. 107 °C, with 2-furyl-lithium<sup>3</sup> 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.

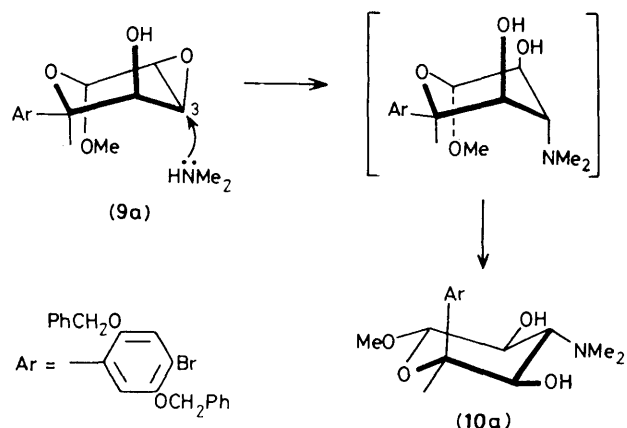
‡ All compounds were prepared as racemates; for convenience drawings depict only one enantiomer.



Scheme 1

figures of the methyl acetals were made on the basis of  $^1\text{H}$  n.m.r. spectroscopic studies; shielding by the anomeric ring causes the anomeric proton to resonate at  $\delta$  4.90 for the *trans*-compound (5), as compared to the chemical shift of  $\delta$  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;<sup>4</sup> 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 ( $J_{\text{C-1,C-2}}$  7,  $J_{\text{C-2,C-3}}$  10 Hz). Attempted reduction of the keto-amino-



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<sup>5</sup> 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-epoxy-pyrans is precedented.<sup>6</sup> 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  $^1\text{H}$  n.m.r. coupling constants. Furthermore, the anomeric proton in (10) occurs at a very high field position,  $\delta$  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).<sup>7</sup>

Treatment of the methylglycoside (10) with trimethylsilyl iodide (2 equiv.) and trimethylsilyl chloride (2 equiv.) in acetonitrile,<sup>8</sup> in this case effects selective debenylation, 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.<sup>7</sup>

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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