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SYNTHESIS OF ANTHRACYCLINE C-GLYCOSYL ISOSTERES

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Summary: The C-glycosyl isostere of 4-demethoxy-9-desacetyldaunorubicin and its 7,9-diepi isomer have been synthesized via Diels-Alder reaction of a protected daunosaminyl-2,4-pentadiene with quinizarin quinone.

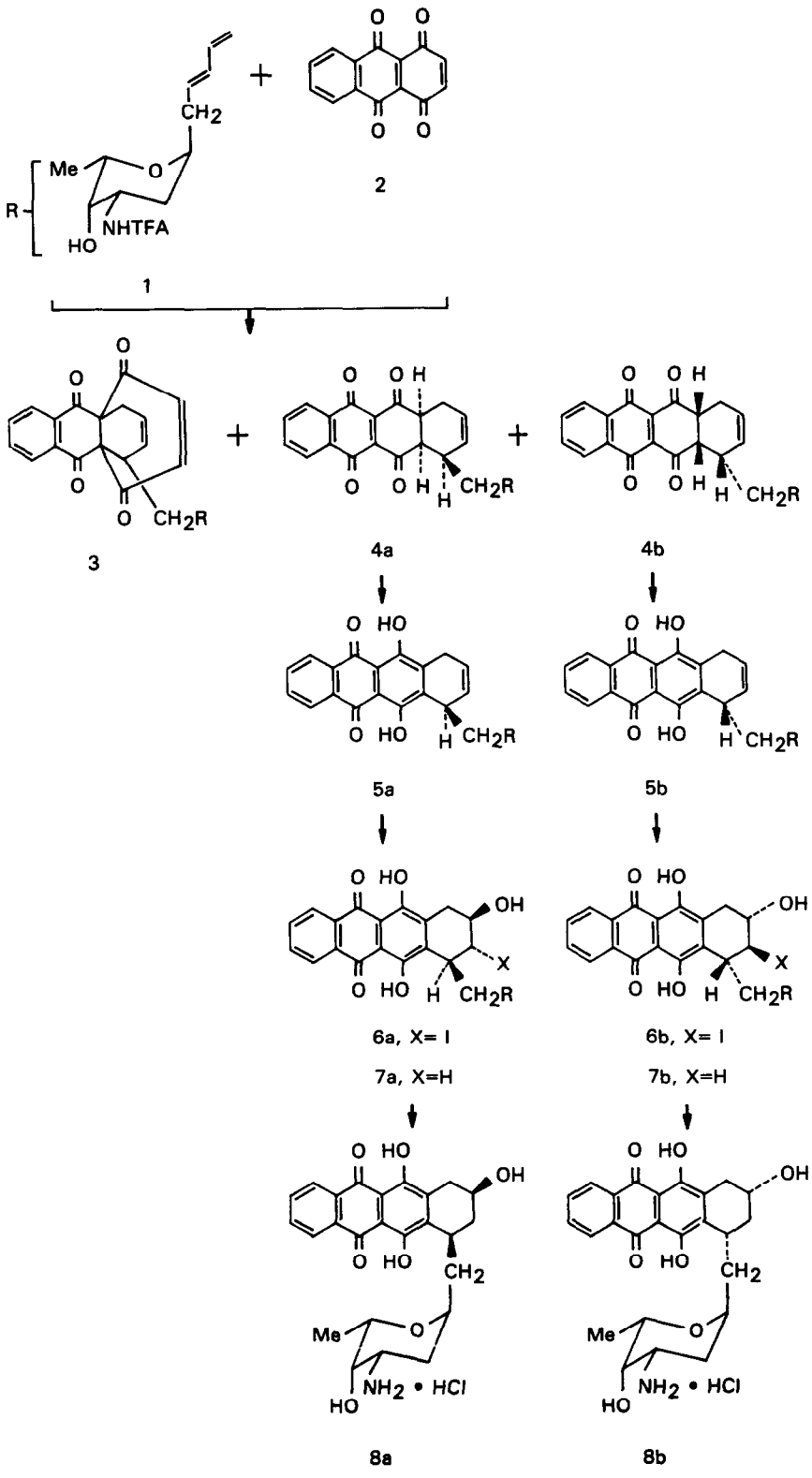
We recently synthesized[2] 1-(N-trifluoroacetyl-α-L-daunosaminyl)-(E)-2,4-pentadiene 1 as a key intermediate for the total synthesis of anthracyclinone C-glycosides by assembly of the A ring. We showed that 1 underwent[2] a facile Diels-Alder cycloaddition with quinizarin quinone (2) as the 4a,9a epoxide[3], which is used to block the internal double bond. In later steps, however, epoxide removal gave unstable intermediates or unidentified by-products, and completion of the synthesis proved difficult by this approach.

We now report a more successful approach via the cycloaddition of 1 with 2 (90-100°, 18 hr, anhydrous toluene) despite the expected formation of both end and internal adducts. The product (> 100% of theory) of this reaction was obtained by precipitation with hexane and showed the presence of four constituents, which we assumed to be two disastereoiso-meric internal adducts depicted as 3[4] (20%, HPLC 60:40, 8.7 min; and 15%, 10.8 min) and the two end adducts 4a (26%, 6.5 min) and 4b (29%, 7.1 min)[6]. Partial precipitation by chilling the reaction mixture to 0° alternatively gave a fraction (30% yield) containing 75% of 4a (^{1}H NMR δ 1.21 d for sugar C-CH_3) and 15% of 4b; adding hexane then gave a precipitate containing 3% of 4a, 37% of 4b, and 44% of 3. Silicic acid chromatography of these fractions, in attempts at purification, gave losses and decomposition. Purifications were best accomplished after enolization (HCl-MeOH, 20°,

18 hr; followed by reprotection with TFAA-Et_2O, MeOH) to form the more stable anthracycline 8,9-olefin. Thus, the sample of 4a was converted to 5a (15% from 1), homogeneous[7] after crystallization from MeOH (HPLC 40:60, 12.9 min); δ 6.13 ddd (H-8), 6.01 ddd (H-9), 4.22 q (H-5'), 1.30 d (CH_3). Similar treatment of the mixture of 4a, 4b, and 3 (adding the mother liquor from 5) was followed by column chromatography (silicic acid; $CHCl_3$-MeOH, 98:2) to yield a mixture of 5a/5b (20%) and a pure sample of 5b[7] (4% from 1; HPLC 13.5 min) after crystallization from CH_3CN, 6.03 dddd (H-9), δ 5.92 dddd (H-8), 3.57 q (H-5'), 0.83 d (CH_3). The separation between CH_3's (1.30 and 0.83) was unexpected. Circular dichroism curves were nearly equal and opposite (troughs at 295-7 nm) as expected for 7-epimers, with 5a positive (as in the unnatural configuration) and 5b negative (similar to daunomycin and daunomycinone[8]).

Functionalization of the A ring was achieved by treatment with $AgOOCCF_3/I_2$ (CH_2Cl_2, rm. temp., 18 hr; followed by MeOH to cleave the OTFA). Pure 5a regio- and stereospecifically yielded a single iodohydrin assigned as 6a[7] (72%, crystallized from $CHCl_3$; HPLC 45:55, 10.9 min). On purely steric grounds, we assume that initial I^+ attack of the olefin was from the face opposite to the sugar, and then CF_3COO^- attack was syn to the sugar but at the more remote carbon, placing the OH at C-9 and cis to the sugar at C-7, as in the anthracycline series. Consistent with this was the absence of any trans diaxial proton splitting in the ^1H NMR; δ 4.83 dd (H-8), 4.57 ddd (H-9), 4.17 q (H-5'), 1.33 d (CH_3), $J_{8,9}$ = 5.0 Hz. An identical sample of 6a (16%) was obtained from a mixture (1:4) of 5a and 5b, after column chromatography on silicic acid (CH_2Cl_2-MeOH, 99:1), along with 6b[7] (42%; HPLC, 9.9 min), δ 4.68 dd (H-8), 4.48 dd (H-9), 3.81 q (H-5'), 1.09 d (CH_3), $J_{8,9}$ = 5.6 Hz.

Reductive cleavage of the 8-I with Bu_3SnH[9] (toluene, 75-80°, 19 hr) required UV irradiation (100 watt lamp, 466 nm). Product purification by preparative TLC ($CHCl_3$-MeOH, 9:1, silicic acid) yielded 7a[7] (25% from 6a, after crystallization from MeOH; HPLC 50:50, 5.7 min), δ 4.3 m (H-9), 4.25 q (H-5'), 2.11 dddd and 1.94 ddd (2 H-8), 1.29 d (CH_3), $J_{8,9}$ = 3.5 Hz, $J_{8,9}$ = 8.0 Hz; and 7b[7] (56% from 6b, after crystallization from CH_3CN; HPLC, 5.6


Me
O
CH2
R
NHTFA
HO
1
2
3
4a
4b
5a
5b
6a, X= I
6b, X= I
7a, X=H
7b, X=H
8a
8b
OH
X
NH2 • HCl

min), δ 4.25 m (H-9), 3.87 q (H-5'), 2.34 ddd and 2.25 ddd (2 H-8), 1.14 d (CH_3). Assignment of position and orientation of 9-OH in 7a and 7b were supported by mechanistic arguments and by the NMR analyses. Cleavage of the N-TFA groups with refluxing HCl-MeOH for 18 hr gave 8a precipitated from MeOH-ether; HPLC 70:30, 5.9 min); and the isostere 8b[7] of 4-demethoxy-9-desacetyldaunorubicin (52% from 7b, recrystallized from EtOH; HPLC, 4.56 min). A CD comparison of 8a and 8b verified the epimeric configurations assigned at C-7. Both 8a and 8b showed cytotoxic effects in a preliminary test vs L1210 cells in culture (ED_{50}'s = 4-5 μM). The further elaboration of these structures is being pursued.

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4. Formation of 3 was suggested by presence in the ^1H NMR of more vinyl protons than the 2 required for 4.
5. Reverse-phase, using Waters Radial-Pak Nova C-18 5- μm column in 0.1 M NaH_2PO_4-CH_3CN; eluent ratios given with the retention times.
6. We again assume[1] a Diels-Alder endo transition state, forming only the products with cis H's at 6a, 7, and 10a (as drawn for 4a and 4b), and hence only 2 of 4 possible diastereoisomers for either 3 or 4.
7. The compounds were homogeneous to HPLC[5] and gave acceptable elemental analyses. MS consistently showed M^+ and M - (N-trifluroacetyl-daunosaminyl-CH_2). Structure assignments from ^1H NMR (δ) at 400 MHz ($CDCl_3$) were supported by proton-proton decoupling.
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