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A NEW SYNTHESIS OF ANTHRACYCLINES

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ABSTRACT. Carminomycinone (1) has efficiently been synthesised in a five-stage sequence based on cycloaddition of a 1,3-dioxybutadiene to the 1,4-anthraquinone (3); (1) was then converted into daunomycinone (2), an established source of daunomycin, adriamycin and related antitumour anthracyclines.

This communication reports what we believe to be the shortest synthesis so far devised of (±)-carminomycinone (1) and describes an effective procedure for converting it to (±)-daunomycinone (2). Daunomycinone is an established precursor of the anthracyclines, daunomycin and adriamycin, used in cancer chemotherapy.[1]

The new synthesis is based on the 1,4-anthraquinone (3) derived in one step from the dyestuff 1,4,5-trihydroxyanthraquinone (86%).[2] Diels-Alder addition of (*E*)-1,3-bistrimethylsilyloxy-1,3-butadiene at room temperature followed by acidic hydrolysis during work-up gave the trione (4) as a single diastereoisomer (78%) (δ -0.25, s, $SiMe_3$; 2.57, 2.65 [J_{gem} 15.1 Hz] H8α, β; 2.39, 3.46 [J_{gem} 15.6 Hz] H10β, α; 3.53, 3.62 [J_{vic} 6.3 Hz] H6a, 10a; 10.14, 4-OH; 17.03, 5-OH); m.p. > 77° (dec.). Further hydrolysis of (4) with acidic hydrogen peroxide[3] gave the hydroxy trione (5) (85%); m.p. > 75° (dec.). The low decomposition points for both (4) and (5) reflect the ease with which such systems undergo oxidative aromatisation with elimination of the 7-oxy substituent. This seriously constrains methodology based on cycloadducts of 1,3-dioxy butadienes, in contrast to earlier work here, which developed analogous cycloaddition of 2-oxy butadienes in the course of synthesising 7-deoxyanthracyclines.[2] However, if a successful sequence based on 1,3-dioxy systems could be devised it should offer greater reactivity and selectivity of cycloaddition and greater convergence overall.[3,4]

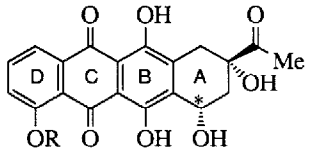
Addition of 2-trimethylsilylethynylcerium(III) chloride in tetrahydrofuran[5,6] occurred exclusively to the unconjugated carbonyl group of (5) giving the adduct (6) (52%) (δ 0.20, $SiMe_3$; 4.04, 9-OH; 4.45, 7-OH; 10.16, 4-OH; 17.15, 5-OH); m.p. 261-264°. This moderate yield, the lowest of the sequence, reflects both incomplete reaction even with a large excess of cerium reagent, and the apparent instability of the starting material (5) towards recovery under the work-up conditions. (For (6) and other 7,9-diols the 7-OH group resonated as a doublet, allowing it to be differentiated from the 9-OH.)

Attempted hydration of (6) under conventional mercuric catalysis, involving use of mineral acid,[3] gave varying degrees of decomposition and only poor yields of the acetyl dione (7). By contrast, hydration with mercury(II) trifluoroacetate in acetic acid gave (7) efficiently (84%) (δ 2.39, COMe; 4.14, 7-OH; 4.76, 9-OH; 10.18, 4-OH; 17.15, 5-OH; m.p. > 150° (dec.). However, the same catalyst in trifluoroacetic acid[7] gave a more spectacular outcome. Thus treatment of (6) in trifluoroacetic acid with mercury(II) trifluoroacetate (2.5 eq)

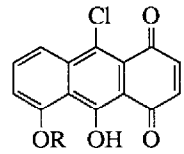
for 20 h at room temperature gave a mixture of (±)-carminomycinone (1) (78%), (δ 2.43, COMe; 12.18, 4-OH; 12.97, 6-OH; 13.48, 11-OH); and (±)-7-epicarminomycinone (8) (12%), (δ 2.41; 12.11; 13.25; 13.45). Preparative recycling of (8) by separate equilibration in trifluoroacetic acid gave a mixture of (1) and (8) (13:2),[8] thereby augmenting the effective yield of (1) to 88%. The work-up incorporated brief treatment with sodium hydrogen carbonate in aqueous methanol at room temperature, to hydrolyse O-trifluoroacetate intermediates. Compound (1) was identified by appropriate comparison with (+)-carminomycinone from hydrolysis of natural carminomycin.

The one-pot transformation of (6) into the two diastereoisomers (1) and (8) involves protodesilylation, hydration, oxidation and displacement of chloride in an overall yield of 90%. The first two of these four stages are unexceptional, while the oxidation presumably was mediated by mercuric ion. The later stages have been separated but only at considerable cost to overall efficiency. Thus direct aerial oxidation of the dione (7) in a two-phase system of ether/aqueous K_2CO_3 gave the intermediate red quinone (9) but in poor yield (25%) (δ 2.40, COMe; 10.48, 4-OH; 17.44, 5-OH); m.p. 189-191°. The latter underwent standard displacement of chloride[2] in trifluoroacetic acid giving (1) (70%) and (8) (trace).

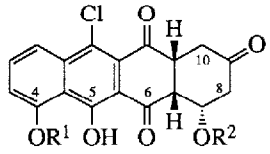
A similar approach to daunomycinone (2) was explored, by cycloaddition to the O-methyl dienophile (10).[2] Thus cycloadducts (11) (93%) and (12) (68%) were derived respectively from (*E*)-1-methoxy-3-trimethylsilyloxy- and (*E*)-1,3-bistrimethylsilyloxy-butadienes analogously to (4). However, the later stages of



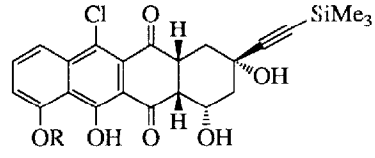
(1) R = H
(2) R = Me
(8) R = H; epimeric at *



(3) R = H
(10) R = Me



(4) R^1 = H, R^2 = $SiMe_3$
(5) R^1, R^2 = H
(11) R^1, R^2 = Me
(12) R^1 = Me, R^2 = H

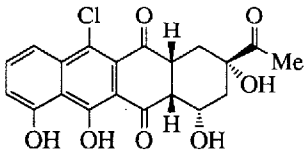


(6) R = H
(14) R = Me

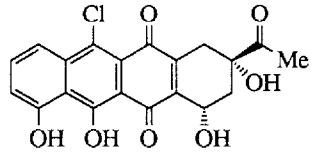
synthesis proved to be adversely affected by O-alkylation. Thus adduct (11) with 2-trimethylsilylethynylcerium(III) chloride gave chiefly the bisethynylated compound (13) (53%).[6] Adduct (12) gave the desired monoethynylated product (14) (36%), but subsequent conversion to daunomycinone (2) (mercury(II) trifluoroacetate/trifluoroacetic acid) proved unacceptably inefficient (8%).

The best route to (2) was found to involve methylation of carminomycinone (1). Direct methylation (1) —> (2) has been reported with diazomethane[9] but attempted repetition gave only the known 6-O-methyl ether (64%).[10] Methylation of (1) under more reactive conditions (methyl iodide/silver(I) oxide) was complicated by concomitant methylation of the benzylic alcohol. This was circumvented by prior protection of (1) as its benzeneboronate (15). When this protection step was carried out in trifluoroacetic acid[11] on the mixture of (1) and (8), derived from (6), it gave (15) as a single product (79%), efficiently recycling the unwanted epicarminomycinone (8) by acid-catalysed epimerisation through the *cis*-7,9-diol. Permethylation of (15) (methyl iodide/silver(I) oxide, reflux) then gave the trimethyl ether (16) (80%), (δ 2.57, COMe; 3.91, 4.01 4.22, 3 x OMe); m.p. 162-165°. Selective demethylation with boron trichloride,[12] followed by transboronation with 2,4-pentanediol, gave (±)-daunomycinone (2) (78%), identified by appropriate comparison with (+)-daunomycinone from hydrolysis of natural daunomycin.

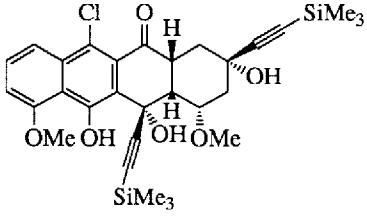
Carminomycinone (1) and daunomycinone (2) have thus been assembled regioselectively and with potential stereocontrol at C9 in 5 and 8 stages respectively from commercially available 1,4,5-trihydroxyanthraquinone and other readily obtainable reagents, in 26 and 13% overall yields. Extrapolation of this chemistry to an enantiocontrolled synthesis is currently under investigation, as is the synthesis of other anthracycline systems.



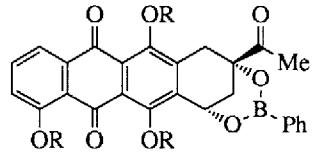
(7)



(9)



(13)



(15) R = H
(16) R = Me

All new compounds gave satisfactory analyses and spectroscopic data. We thank Farmitalia Carlo Erba and Bristol-Myers Company for natural anthracyclines, and Bayer AG for samples of dyestuffs. We acknowledge financial support from the Anti-Cancer Council of Victoria and an Australian Postgraduate Research Award (DGO'B).

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