A New Strategy for the Enantiocontrolled Synthesis of Anthracyclines resulting in a Practical Route to (+)-4-Demethoxydaunomycinone

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The Diels–Alder reaction of (*E*)-3-trimethylsilyloxybuta-1,3-dienyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside and 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetrone is subject to high diastereocontrol; the cycloadduct is converted into (+)-4-demethoxydaunomycinone by a six-step sequence.

There is considerable current interest in the anthracycline antibiotics because certain members, *e.g.* daunomycin (**1a**) and adriamycin (**1b**), are endowed with significant anticancer activity. Extensive studies, involving the synthesis and testing of analogues of the aforementioned compounds, have established that chemotherapeutic improvements are possible. Such analogues may incorporate modifications in the aglycone, *e.g.* 4-demethoxydaunomycin (**1c**), in the glycone, *e.g.* 4′-epiadriamycin, or in both moieties, *e.g.* 4-demethoxy-4′-epiadriamycin.[1]

To date, all syntheses of anthracyclines have relied upon the glycosidation of a sugar with an anthracyclinone.[2] We now report a new strategy for the elaboration of anthracyclines, in which the 6a,7- and 10,10a-bonds are constructed by a Diels–Alder reaction. Moreover, we illustrate the value of the method by describing a short practical synthesis of (+)-4-demethoxydaunomycinone (**2c**), the aglycone of 4-demethoxydaunomycin (**1c**), a synthetic anthracycline of emerging clinical importance.

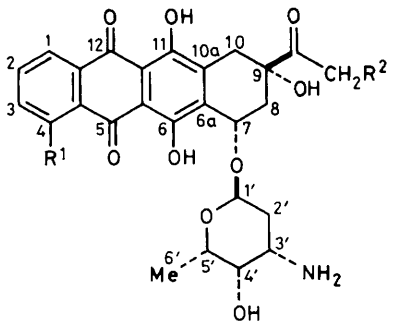
Recently, we reported[3] a diastereocontrolled synthesis of (±)-4-demethoxy-7-*O*-methyldaunomycinone (**2a**). The tetracycle (**3a**), which served as the precursor, was elaborated from the oxirane (**4**) and the diene (**5a**) by a cycloaddition reaction. With a view to adapting the procedure for the enantioselective synthesis of anthracyclines, it was decided to examine the behaviour of the diene (**5b**) towards the oxirane (**4**). It was expected that a mixture of the cycloadducts (**3b**) and (**6**) would result, from which, hopefully, the former cycloadduct would be separable.

When 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[4] was treated in dimethyl sulphoxide with the sodium salt of (*E*)-4-hydroxybut-3-en-2-one,[5] the glucoside (**7**), m.p. 149—150 °C, $[\alpha]_D$ −20° (EtOH), was obtained (35% yield after recrystallisation). Silylation of the enone (**7**), to give the diene (**5b**), m.p. 105—106 °C, $[\alpha]_D$ −19° (EtOH), was achieved (78% yield after recrystallisation) by using trimethylsilyl chloride, zinc chloride, and triethylamine in dry benzene.[6]

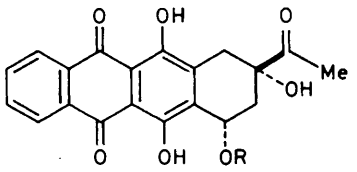
The diene (**5b**) reacted with the oxirane (**4**) in benzene to give a cycloadduct, which, after recrystallisation, showed m.p. 173—174 °C and $[\alpha]_D$ +92° (EtOH); the cycloadduct was assigned the stereostructure (**3b**) on the basis of subsequent transformations. Hydrolysis of the crude cycloadduct with dilute hydrochloric acid in tetrahydrofuran (THF) afforded the ketone (**8**), m.p. 215—220 °C, $[\alpha]_D$ −34° ($CHCl_3$), in 57% yield after recrystallisation [based upon the diene (**5b**)].

Reduction of the oxirane (**8**) with zinc in acetic acid afforded the compound (**9**) (72% yield after recrystallisation), m.p. 185—188 °C, $[\alpha]_D$ +134° (EtOH), which was converted by sequential reactions with ethynylmagnesium bromide in THF and lead(IV) acetate in acetic acid into the hydroxy-acetylene (**10a**) (77% yield after recrystallisation), m.p. 239—241 °C, $[\alpha]_D$ +201° (dioxane).

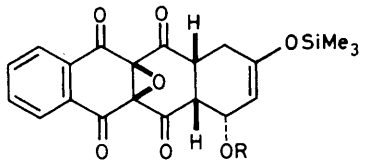
Hydration of the acetylenic linkage of the compound (**10a**) was achieved without glycosidic hydrolysis by using mercury(II)



(1) a; R^1 = MeO, R^2 = H
b; R^1 = MeO, R^2 = HO
c; R^1 = R^2 = H



(2) a; R = Me
b; R = Z
c; R = H



(3) a; R = Me
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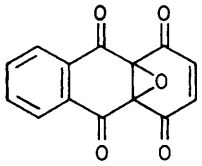
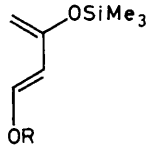
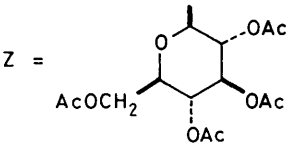


(4)



(5) a; R = Me
b; R = Z

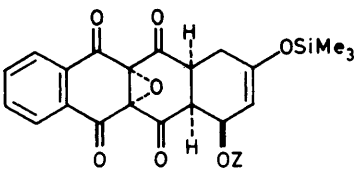


Z =

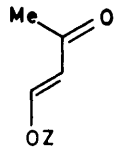
oxide in a 1:1 mixture of acetone and 7% sulphuric acid. The derived methyl ketone (**2b**) (88% yield after recrystallisation), m.p. 240—242 °C, $[\alpha]_D$ +165° (dioxane), was identical to one of the products obtained† from the reaction of (+)-4-demethoxydaunomycinone (**2c**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide.

Acidic hydrolysis of the anthracycline (**10a**) afforded the anthracyclinone (**10b**) (89% yield after recrystallisation), m.p.

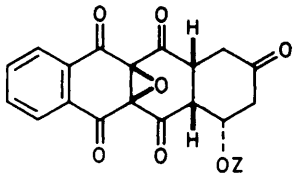
† We are grateful to Dr. M. J. Broadhurst, of Roche Products, for this information. See M. J. Broadhurst, C. H. Hassall, and G. T. Thomas, *J. Chem. Soc., Perkin Trans.* 1, 1982, 2249.



(6)



(7)



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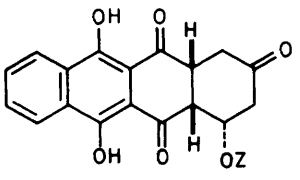
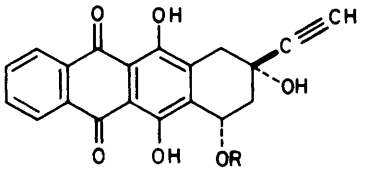
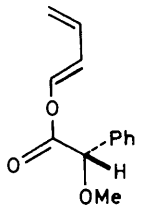


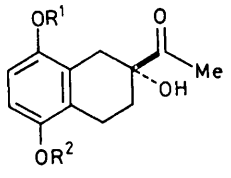
(9)



(10) a; R = Z
b; R = H



(11)



(12) a; R^1 = R^2 = Me
b; R^1 = R^2 = H
c; R^1 = $PhCH_2$, R^2 = Me

215—218 °C, $[\alpha]_D$ +161° (dioxane), which was transformed into (+)-4-demethoxydaunomycinone (**2c**) (77% yield after recrystallisation), m.p. 175—178 °C (lit.[7] 184—186 °C), $[\alpha]_D$ +160° (dioxane) [lit.[7] + 170° (dioxane)] in the presence of mercury(II) oxide and sulphuric acid.

The foregoing results are significant in several respects. First, they show that the Diels–Alder strategy involving the construction of the 6a,7- and 10,10a-bonds, which hitherto has played an important role in the elaboration of anthracyclinones,[3,8] can be used for the synthesis of anthracyclines. Second, they disclose a practical route to (+)-4-demethoxydaunomycinone (**2c**), which is exceptional in that no resolution step‡ or chromatography is involved. Third, the ketone (**9**) has obvious potential as a precursor of novel chiral anthracyclines. Fourth, the diastereoselection observed in the cycloaddition of the diene (**5b**) with the oxirane (**4**) is interesting. With some exceptions,[9,10] particularly Trost's diene (**11**), chiral dienes have had only a modest record of diastereodifferentiation.[11] Finally,

‡ Asymmetric syntheses of the (+)-4-demethoxydaunomycinone precursors (**12a**—**c**), have been reported [S.-S. Jew, S. Terashima, and K. Koga, *Chem. Pharm. Bull. (Tokyo)*, 1979, **27**, 2351; S. Terashima, N. Tanno, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 2753; R. N. Warrener, P. S. Gee, and R. A. Russell, *J. Chem. Soc., Chem. Commun.*, 1981, 1100].

in view of the versatility of Danishefsky's diene (**5a**),[12] the diene (**5b**) would appear to have a promising future in organic synthesis.

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