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A NEW, DOUBLY CONVERGENT SYNTHESIS OF ANTHRACYCLINONES. DIELS-ALDER ADDITIONS TO 2,3,5,6-TETRAKIS(METHYLENE)-7-OXANORBORNANE.

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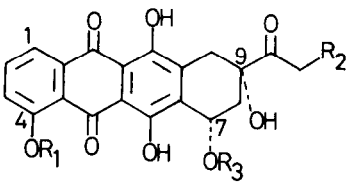
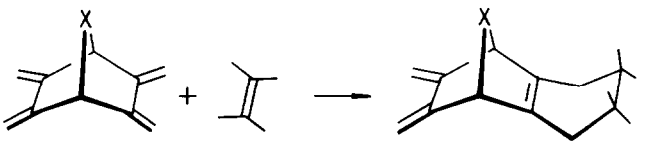
Summary: a new, highly versatile synthesis of polyfunctionalized, polycyclic systems is described; the preparation of a precursor of 1*-methoxydaunomycinone is presented.*

The anthracycline antibiotics daunorubicin[1] 1, carcinomycin[2] 2 and especially adriamycin[3] 3 have proved to be useful for the treatment of human cancers[4]. The activity of these compounds can be improved by structural modification of the aglycone (anthracyclinone) portion[4,5]. Unfortunately, these cytotoxic drugs display side effects like cardiotoxicity[6]. These facts have stimulated the development of several approaches to the synthesis of anthracyclinones[7]. We now wish to report a basically new, simple and, in principle, doubly convergent technique[8] for the preparation of polyfunctionalized, linearly condensed six-membered ring systems that should allow the preparation of a great number of modified anthracyclines.



$R_1 = CH_3$, $R_2 = H$: 1
$R_1 = R_2 = H$: 2
$R_1 = CH_3$, $R_2 = OH$: 3
R_3-OH = daunosamine

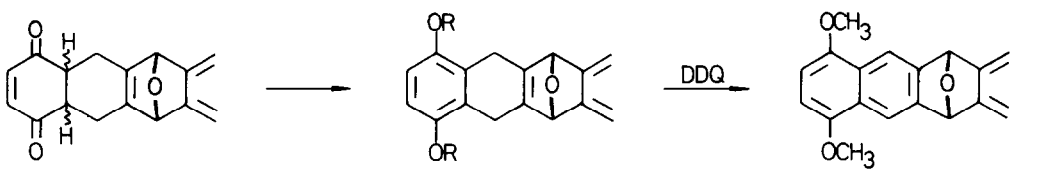
Our strategy uses a bifunctional starting material *A* into which two different reagents *B* and *C* can be added sequentially. If the two functions are the same, it requires the reaction *A + B → AB* to be faster (in practice > 10 times) than the reaction *B + AB → BAB*. This route has the advantage that the two functional groups in *A* can be generated at the same time (limited number of steps) and, therefore, can be readily prepared. We decided that the reactions *A + B → AB* and *C + AB → CAB* should be Diels-Alder additions because they can be carried out for a large variety of substituted reactants[9] and sometimes, regio- and/or stereoselectivity can be expected, even for remote substitution[10].



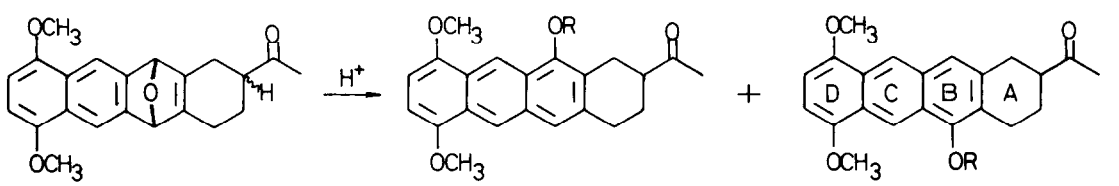
X = O : 4[11] → 9
= CH_2: 5[12] → 10
= CH=CH : 6[13] → 11
= CH-CH (O) : 7[14] → 12
= CH_2-CH_2 : 8[13] → 13

Kinetic studies on the addition of 2,3,5,6-tetrakis(methylene)-bicycloalkanes 4-7 to strong dienophiles showed that these tetraenes reacted faster than their corresponding monoadducts 9-12[13,14]. These polyenes belong, therefore, to the class of reagents *A* defined above. This was not the case for the system 8 which was observed to react practically as fast as its monoadducts 13 with some dienophiles[13,T4]. We show now how 2,3,5,6-tetrakis(methylene)-7-oxanorbornane (*A*=4)[11] can be engaged in the synthesis of the bis-acetate of (±)-7,9-bis(desoxy)-1-methoxydaunomycinone (25) when using benzoquinone (*B*) and methylvinylketone (*C*) as dienophiles.

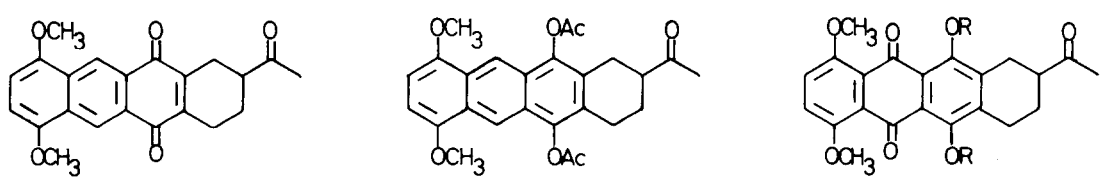
When 4 (2 g) was heated, under N_2, with 1 mol eq. of benzoquinone in $CHCl_3$(10 ml) to 80° for 5 h, it yielded the monoadduct 14 (m.p. 147°(dec.), 95 %)[15]. Only one isomer was observed whose stereochemistry has not yet been established rigourously. 14 was aromatized into 15 in presence of a trace of acid or base. When heated to 80°, under N_2, with 10 mol. equiv. of CH_3I and



14 R = H : 15 R = CH_3 : 16 17



18 R = H : 19 R = Ac : 21 R = H : 20 R = Ac : 22



23 24 R = Ac : 25

K_2CO_3 in dry acetone for 12-15 h, 14 furnished directly the dimethoxybenzene 16 (m.p. 177-8°, 92%). 16 was readily oxidized into 17 (m.p. 205-6°, 98%) with 1.1 equiv. of 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ)(20°, ½ h). When heated to 90°, under N_2, for 24 h in freshly distilled methylvinylketone, 17 gave the adduct 18 (m.p. 167-8°, 93%, after crystallisation from THF:CH_2Cl_2:hexane 3:3:5). Only one isomer was observed (by tlc, ^{13}C-NMR) whose stereochemistry has not yet been determined unambigously. In the presence of CF_3COOH (2%, 20°, ½ h), the oxanorbornadiene 18 (20% in $CHCl_3$ or benzene, under N_2) was isomerized into a mixture of phenols 19 + 20.

Aerial oxidation of 19 + 20 led to both phenolic coupling and quinone 23. However oxidation with PbO_2 (2 mol. equiv., AcOH, 20°, 2 h, under N_2) yielded only the deep-red quinone 23 (m.p. 198-9°, 72 % based on 18). Zinc dust reduction of 23 in Ac_2O (110°, ½ h) gave the yellow diacetate 24 (m.p. 232-3°, 90 %). 24 was obtained more readily in 45-50 % yield by treatment of 19 + 20 with 5 mol. equiv. of $Tl(OAc)_3 \cdot 1\frac{1}{2} H_2O$ in Ac_2O (20°, 1 h) followed by addition of 5 mol. equiv. of pyridine and stirring for 1 h at 20°. Oxidative acetylation of the aromatic rings C and D seemed to be slow reactions under these conditions. The acetates 21 + 22 (obtained by isomerization of 18 in Ac_2O + 2 % CF_3COOH (20°, ½ h, 98 %) did not react with $Tl(OAc)_3 \cdot 1\frac{1}{2} H_2O$ in Ac_2O at 20°. A complex mixture of oxidized products was formed with $Tl(CF_3COO)_3$ in CF_3COOH. Oxidation of 24 with CrO_3 (3 mol equiv.) in 95 % AcOH in H_2O (20°, 1 h, under N_2) gave 25 (m.p. 146°(dec.), 15-50 % yield)[16].

In principle, our approach to the synthesis of anthracyclinones should be a very versatile one since a wide variety of substituted tetraenes *A* and dienophiles *B* and *C* can be used. Preliminary studies on the cycloadditions of dehydrobenzenes, 3-trimethylsilyloxybut-3-en-2-one and acrylic esters to 4 and to their monoadducts of type 9 (and derivatives 15-17)[17] confirm this statement. The possibility of isolating linearly condensed aromatic systems with varying oxidation levels, as well as the stereoselectivity observed with the cycloadditions of tetraene 4 and the dienes of type 9, 17 will add another dimension to the versatility of our technique.

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15. All the new compounds gave satisfactory elemental analyses and IR, UV, ^{1}H, ^{13}C-NMR and MS spectra in accord with the structures proposed; the yield have not been optimized. Spectral characteristics of:

    14 : ^{1}H-NMR($CDCl_3$): 6.65(2H, s), 5.2(2H, s), 5.0(2H, s), 4.88(2H, br.s), 3.25-1.9(6H, m); IR(KBr): 1680, 1610 cm^{-1}; MS(70 eV): 254(64 %), 225(100);

    16 : ^{1}H-NMR($CDCl_3$): 6.6(2H, s), 5.15(2H, s), 4.9(2H, br.s), 3.8(6H, s), 3.35(4H, m); UV(dioxane): 291(sh, logε = 3.72), 285(3.75), 255(sh, 3.88), 228(4.34); IR($CHCl_3$): 3010, 2960, 1480, 1465, 1440, 1105, 1080 cm^{-1}; MS(70 eV): 282(19 %), 281(100);

    17 : ^{1}H-NMR($CDCl_3$): 8.08(2H, s), 6.6(2H, s), 5.7(2H, br.s), 5.25(2H, s), 5.1(2H, s), 3.87 (6H, s); UV(EtOH 96 %): 336(3.70), 322(3.67), 226(4.73), 208(5.26); IR($CHCl_3$): 3010, 2960, 1620, 1465, 1430, 1140 cm^{-1}; MS(70 eV): 280(100), 265(29);

    18 : ^{1}H-NMR($CDCl_3$): 7.9(2H, s), 6.65(2H, s), 5.45(2H, br.s), 3.9(6H, s), 2.0(3H, s), 2.65-1.6(7H, m); UV(EtOH 96 %): 340(3.63), 325(3.67), 300(3.74), 260(4.57), 220(4.58); IR (KBr): 3000, 2940, 2920, 1705, 1615, 1475, 1440 cm^{-1}; MS(70 eV): 350(100), 335(31), 307(24), 289(10);

    23 : ^{1}H-NMR($CDCl_3$): 8.6(2H, s), 6.62(2H, s), 3.9(6H, s), 2.2(3H, s), 3.2-2.5(7H, m); IR(KBr): 3000, 2870, 1710, 1660, 1620, 1470 cm^{-1}; MS(70 eV): 366(100), 364(93), 356(55), 351(22), 345(43), 321(32); UV(EtOH 96 %): 476(3.72), 255(4.78);

    24 : ^{1}H-NMR($CDCl_3$): 8.55(2H, s), 6.5(2H, s), 3.95(6H, s), 2.56(3H, s), 2.55(3H, s), 2.25(3H, s), 3.0-2.0(7H, m); IR(KBr): 2950, 2930, 1780, 1760, 1715, 1635 cm^{-1}; SM(70 eV): 450 (49), 408(40), 392(12), 375(100);

    25 : ^{1}H-NMR($CDCl_3$): 8.15(2H, s), 3.9(6H, s), 2.56(3H, s), 2.55(3H, s), 2.25(3H, s), 3.0-2.0 (7H, m); IR(KBr): 3000, 2960, 1780, 1730, 1720, 1440, 1370, 1180, 1070 cm^{-1}; MS(70 eV): not volatile, dec.

16. Yield of this oxidation was very sensitive to the concentration of H_2O and to traces of air. Work is under way to find a better technique for the transformation of 24 into 25.

17. P.A. Carrupt, Y. Thomas-Bessière, J. Tamariz and P. Vogel, *in preparation.*

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