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A HIGH-YIELDING ENANTIOSPECIFIC SYNTHESIS OF (-)-7-DEOXYDAUNOMYCINONE*

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ABSTRACT: A comparison is made between two regiospecific modes of base-catalysed condensation of 4 (or 7)-methoxy-3-phenylsulfonyl phthalides with chiral bicyclic quinone monoketals, one of which occurs in 95% yield and forms the basis of the first enantiospecific total synthesis of (-)-7-deoxydaunomycinone (3).

The total synthesis of optically pure (+)-daunomycin (1), its aglycone or its analogues presents special mechanistic challenges not encountered in the preparation of the racemic materials. This is highlighted by the recent report by Terashima and his coworkers[1] on the chiral deficiency of the Friedel-Crafts bisacylation route to the aglycone (+)4-demethoxydaunomycinone (2). In this case the use of Lewis acids or strong protic acids, hallmarks of the Friedel-Crafts reaction, cause partial racemisation to occur under the reaction conditions. The subtleties in the reaction pathway to (2) which cause this phenomenon were only evident using the chiral centre of the AB synthon as probe.[2] This result, combined with the recognised lack of regiospecificity in the Friedel-Crafts bisacylation approach,[3] highlights the deficiencies of this method for the synthesis of optically pure (+)-daunomycin or its aglycone.[4] Several other routes to racemic daunomycin have been reported,[5] for which no chiral integrity data are available. We have chosen to evaluate, at the chiral level, our phthalide anion/quinone monoketal condensation[6] which has been used by Swenton[7] and others[8] to prepare racemic daunomycinone.

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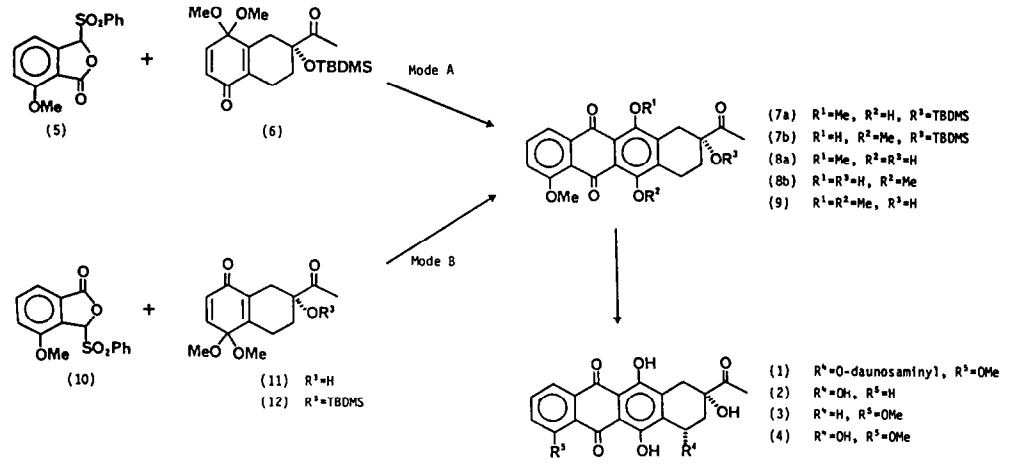
*Anthracycline Part IX: for Part VII see J.Chem.Soc.,Chem.Commun., 1983, 994.

Scheme 1. Condensations and conversion to (-)-7-deoxydaunomycinone.



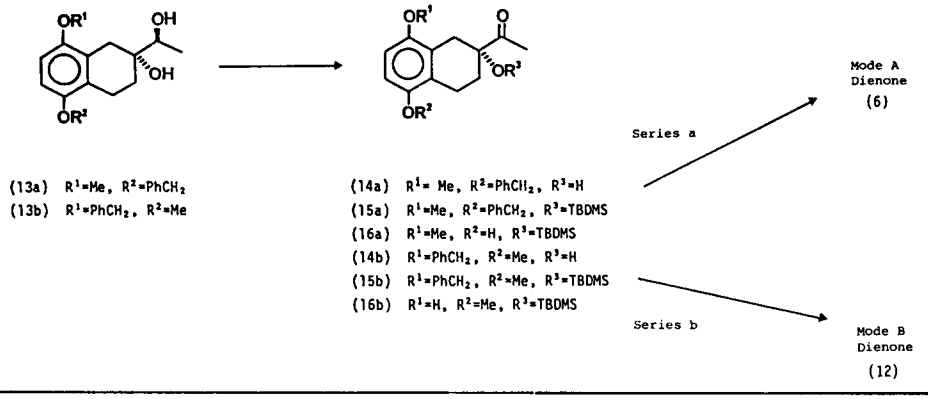
Physical Properties: {mp. °C, $[\alpha]_D$ °(conc.)} (6), syrup, +52.9; (7a), 158-9, + 69.5 (1.04); (7b), 131-3; (8a) 220-1, -121.1 (0.56); (8b), 213-215; (9), 117-9, -52.4 (1.00); (12), syrup, + 10.8 (3.56).

We now report that the phthalide anion/quinone ketal method can be applied to chiral quinone monoketals and proceeds with complete chiral integrity. We illustrated this by reporting the first totally regio- and enantiospecific synthesis of (-)-7-deoxydaunomycinone (3).

The synthesis of (-)-7-deoxydaunomycinone required the use of chiral quinone ketals (6) or (12) since the synthesis could be approached in two ways according to the relative substitution pattern of the AB and CD partners. These are designated Mode A or Mode B as illustrated in Scheme 1.

The chiral bicyclic quinone monoketal (6) required for the Mode A condensation was prepared in four steps from the bicyclic diol (13a)[9] (Scheme 2). Reaction of dienone (6) with 7-methoxy-3-phenylsulfonylphthalide anion (5) in the Mode A type condensation was carried out[12] using equimolar ratios of (5) and (6) and yielded the tetracyclic quinone (7a) in 45% yield, together with unreacted dienone (6). Increasing the proportion of the phthalide anion (5) threefold[13] raised the isolated yield of quinone (7a) to 95%, m.p. 158-9°C; $[\alpha]_D$ + 69.5 (c = 1.04, $CHCl_3$)[14]. Desilylation of (7a) (CsF/DMF/r.t.) to alcohol (8a), followed by selective dealkylation ($BCl_3/CH_2Cl_2/-78°C$)[15] of the phenolic methoxy group at C 11

Scheme 2. Preparation of quinone monoketals.

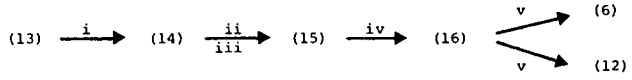


(13a) R^1=Me, R^2=$PhCH_2$
(13b) R^1=$PhCH_2$, R^2=Me

(14a) R^1= Me, R^2=$PhCH_2$, R^3=H
(15a) R^1=Me, R^2=$PhCH_2$, R^3=TBDMS
(16a) R^1=Me, R^2=H, R^3=TBDMS
(14b) R^1=$PhCH_2$, R^2=Me, R^3=H
(15b) R^1=$PhCH_2$, R^2=Me, R^3=TBDMS
(16b) R^1=H, R^2=Me, R^3=TBDMS

Physical Properties: {mp.°C; $[\alpha]_D$ °(conc.)} (13a), 148-150, -34.4 (1.02; (13b), 178-9, -38.6 (1.40); (14a), 109-110, -34.1 (1.06); (14b), 86-7, -24.3 (1.11); (15a), syrup, + 1.4 (0.99); (15b), 93-4, -13.0 (1.23); (16a), syrup, -13.8 (0.98); (16b), syrup, -3.3 (1.10).

Reagents and Yields



Reagents: i, Ag_2CO_3 - Celite/C_6H_6/reflux; ii, TBDMS triflate/lutidine/CH_2Cl_2/rt; iii, H^+resin/MeOH; iv, H_2/Pd-C/HOAc-EtOAc; v, $Tl(NO_3)_3.3H_2O$/$NaHCO_3$/$(MeO)_3CH$/THF/MeOH /0°.

Yields %: (6), 95; (12), 93; (14a), 80; (14b), 96; (15a), 93; (15b), 96; (16a), 99; (16b), 99.

afforded the natural isomer of (-)-7-deoxydaunomycinone (3), m.p. 247-8°C, $[\alpha]_D$ -83° (c = 0.089, $CHCl_3$)[14,16] in a two-step yield of 82%. The synthetic product was identical in all respects with material prepared from natural daunomycin[17]. As procedures exist for converting (3) to (4) and (4) to (1),[3] our synthesis constitutes a formal regiospecific and enantiospecific route to (+)-daunomycin.

Mode B condensations using the isomeric phthalide anion (10) and the previously reported[18] chiral dienone ketal (11) gave poor yields (less than 15%) of the regiospecific condensation product (8b). The related t-butyldimethylsilyl derivative (12) also gave poor yields of (7b) on condensation with (10). In the latter case, increasing the molar ratio of the anion (10) raised the yield of condensed product (7b) to around 60%.

These results clearly show the superiority of the Mode A type of condensation[18] and have already influenced our approach to the synthesis of analogues of (3)[20]. Since these

condensations occur with complete regioselectivity and without loss of chiral integrity, this method must presently be the method of choice for the synthesis of anthracycline antibiotics related to (1).

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9. The key chiral diols (13a) and (13b) were prepared respectively from 3-acetyl-8-benzyloxy-5-methoxy-1,2-dihydronaphthalene and 3-acetyl-5-benzyloxy-8-methoxy-1,2-dihydronaphthalene[10] by a method similar to that described by Terashima.[1,11] Ketones (14a) and (14b) were homogeneous by HPLC on a Baker-bond chiral phase column, and hence of confirmed optical purity.
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12. Condensations were conducted at -78° using LDA in THF (cf. ref. 6). The temperature was optimised for the dienone (6), but not for related dienones.
13. The use of excess LDA with 1 mole of phthalide does not increase the yield since LDA destroys the dienone.
14. The significance of specific rotations in assessing the optical purity of anthracyclinones is discussed in a subsequent communication. Rotations reported in this paper were determined in ethanol-free chloroform.
15. $AlCl_3$ is less satisfactory and leads to partial racemisation. Reversal of the desilylation/dealkylation procedure also lowers the yields.
16. The related dimethyl ether (9) has m.p. 117°C $[\alpha]_D$ - 52.4° (c = 1.00, $CHCl_3$)[14].
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19. Hauser[19] has observed a similar but less dramatic difference in reactivity between anion (5) and (10) with 5-ethoxy-2-furanone. No such difference was observed[7] with monocyclic quinone monoketals.
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