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SYNTHESIS OF (±) 11-DEOXYDAUNOMYCINONE AND 4-DEMETHOXY ANALOGUE BY SEQUENTIAL DIELS-ALDER CYCLOADDITIONS

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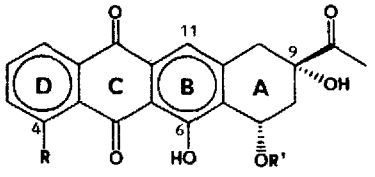
Summary : *Diketones **10a**, **10b**, key intermediates in the syntheses of title compounds were prepared in five steps from naphthoquinones **2a** and **2b** (49 % and 38 % yields respectively), by sequential Diels-Alder cycloadditions.*

The recognition of the efficacy of anthracycline antibiotics in the treatment of a broad spectrum of human cancers has captured the attention of the synthetic chemists [1]. Among the anthracyclines, the *11-deoxy* derivatives (*e.g.* 11-deoxydaunomycin **1c**) exhibit substantially improved chemotherapeutic properties when compared with the 11-oxy parent compounds, namely a reduced cardiotoxicity, often associated with a notable enhancement of the antineoplastic activity [2]. This remarkable feature has stimulated the development of new routes towards the corresponding aglycones, *11-deoxyanthracyclinones* [3,4].



1 **a** R = H R' = H
b R = OMe R' = H
c R = OMe R' = daunosaminyl

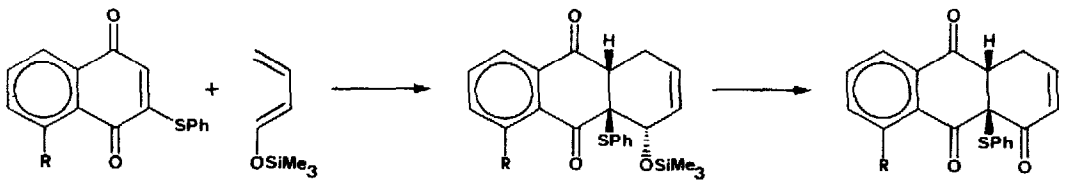
In this paper, we report an expeditious approach to the tetracyclic diones **10b** and **10a**, attractive key intermediates [4] in the synthesis of the anthracycline aglycones, 11-deoxydaunomycinone **1b** and 4-demethoxy analogue **1a**, by using sequential Diels-Alder cycloadditions.

Indeed, the Diels-Alder process offers *a priori* ideal possibilities for the construction of anthracyclinones, in view of the fact that their tetracyclic framework is constituted by a linearly fused pattern of six-membered carbocycles ; in the present strategy, an appropriately substituted naphthoquinone was chosen as the [CD] bicyclic starting subunit, from which the rings B and A were successively elaborated, each by a Diels-Alder cycloaddition reaction. One of the main advantages of this synthetic design is to solve the problem of the regioselective introduction of the C-6 and C-9 oxo-functions borne by the rings B and A in the final molecules **10**, both being created with the desired regiochemistry during the double annulation sequence.

Construction of the [BCD] segments.

The methodology we have used to build the present [BCD] segments **5** was, in fact, recently reported by Kraus and Walling,in an ingenious approach to anthracyclinones, based on the concept of "*blocked anthraquinone tautomer*" [5]. In this paper, these authors described, *inter alia*, the synthesis of tricyclic enone **5b**, through a Diels-Alder reaction involving 5-methoxy-3-phenylthio-1,4-naphthoquinone **2b** as dienophile. Remarkably, the phenylthio moiety of this quinone, not only secured the desired regiochemistry in the Diels-Alder process (**2b** + **3** → **4b**), but also prevented aromatization of the newly created ring in the subsequent adduct **5b**. Unfortunately, all attempts, made by these authors, to elaborate the ring A of anthracyclinones starting from enone **5b** were unsuccessful, a failure due to the great sensitivity of this molecule.

Tricyclic compounds **5** were thus prepared according to Kraus'methodology, except for the starting naphthoquinones **2**, obtained by using our own procedure [6]. Cycloaddition of quinones **2a** and **2b** with 1-trimethylsilyloxy-butadiene **3** (2.5 eq of diene, 1,2-dichloroethane, 90 °C, **2a** : 24 h, **2b** : 7 days) led regioselectively [7] to adducts **4**, which were then oxidized (Jones reagent, acetone, 0 °C) into *cis* enones **5a** and **5b** (70 % overall yields) [8].



2 **3** **4** **5**

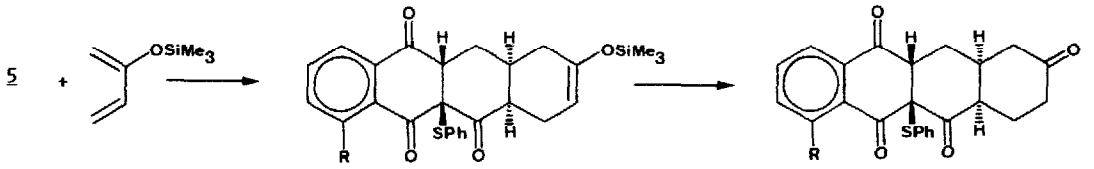
a R = H **b** R = OMe

Elaboration of the [ABCD] units, completion of the syntheses.

The enone moiety in compounds **5** is suitably positioned to control the desired regiochemical orientation of the second Diels-Alder process (**5** + **6** → **7**). However, this crucial cycloaddition step was severely hindered by the notoriously poor (cyclohexenone-like) dienophilic properties of enones **5**, combined with the exceptionally high sensitivity of these dienophiles and of the expected adducts **7**. Thus, not surprinsingly, various attempts of cycloaddition of compounds **5** with 2-trimethylsilyloxy-butadiene **6**, under thermal or catalyzed (Ph_3CSnCl_5) [9] conditions, invariably gave mainly anthraquinones, the result of the aromatization of compounds **5**.

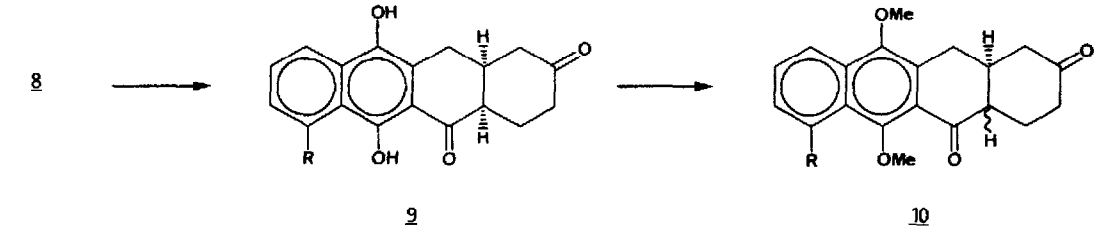
Activation by high pressure was then attempted, since we have demonstrated, in a closely related work, the usefulness of this technique for the obtention of highly sensitive Diels-Alder adducts [10]. As expected, in such activation conditions (2.5 eq of diene, CH_2Cl_2, 15 kbar, 50 °C, 60 h), the cycloaddition of reactant partners **5** +**6** proceeded efficiently, leading to the desired tetracyclic adducts **7a** and **7b**. These were not purified, but directly hydrolyzed (0.01 N aqueous HCl/THF : 1/4, 0 °C, 30 min) into tetrones **8a** and **8b**, each isola-

ted as the single *cis*, *anti*, *cis* isomer (analytical HPLC, ^{1}H and ^{13}C NMR data), with 75 % and 65 % overall yields, respectively [11].



a R = H b R = OMe

With the tetracyclic units **8** in hand, we then proceeded with their transformation into target molecules **10**. For this purpose, the reductive elimination of the phenylthio group was first performed smoothly, using zinc powder (10 eq Zn, AcOH/THF : 1/4, 0 °C), providing the hydroquinones **9a** and **9b** with 97 % and 98 % yields, respectively, each isolated as the single *cis* isomer (^{1}H and ^{13}C NMR data) [12]. Finally, double methylation of hydroquinones **9** (K_2CO_3, Me_2SO_4, acetone, reflux, **9a** : 14 h, **9b** : 5 days) led to our synthetic goals **10a** and **10b**, each obtained as a 2.3:1 mixture of diastereoisomers at the AB ring junction, with 97 % and 85 % yields, respectively. Base-promoted epimerization therefore took place during the methylation process, the *trans* isomer ultimately becoming the major component. The *cis*, *trans* geometric relationship implied in this epimerization was confirmed by HPLC separating and then equilibrating (DBU, THF, 20 °C) the individual isomers to identical mixtures (*trans/cis*: 4/1) [13,14,15].



a R = H b R = OMe

Since compound **10b** has previously been efficiently converted into 11-deoxydaunomycinone **1b** [4a], the present approaches constitute formal syntheses of the target anthracyclinones **1a** and **1b**.

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8 **5a** : no definite mp. **5b** : mp 135-137 °C (dec).

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11 **8a** : mp 248-249 °C (dec). **8b** : mp 198 °C (dec) ; IR (KBr) : 1725, 1715, 1690, 1680, 1585 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) : 1.67 (dddd, 1H, J=16, 16, 4, 4 Hz), 1.98 (ddd, 1H, J = 14, 4, 2 Hz), 2.14-2.35 (m, 3H), 2.43 (ddd, 1H, J = 14, 14, 4 Hz), 2.62-2.80 (m, 3H), 3.20 (b.t., 1H, J = 5 Hz), 3.49 (dd, 1H, J = 14, 4 Hz), 3.73 (s, 3H), 7.1-7.3 (m, 6H), 7.65-7.80 (m, 2H) ; ^{13}C NMR (63 MHz, $CDCl_3$) : 24.9 (t), 33.3 (t), 37.3 (t), 39.8 (d), 43.2 (t), 47.1 (d), 53.2 (d), 56.2 (q), 73.7 (s), 118.1 (d), 119.2 (d), 121.0 (s), 128.5 (d), 128.9 (s), 129.4 (d), 133.3 (s), 135.8 (d), 136.5 (d), 159.7 (s), 190.0 (s), 193.0 (s), 202.0 (s), 209.1 (s).

12 **9a** : yellow solid, mp 202 °C (dec) : MS (70 eV) : 296 (M^+), 278, 238, 105 ; IR (KBr) : 3600-3200, 1700, 1620, 1390 cm^{-1} ; ^1H NMR (250 MHz, DMSO d_6) : 1.82-1.98 (m, 1H), 2.20-2.55 (m, 5H), 2.77-2.95 (m, 2H), 3.05-3.28 (m, 2H), 7.55 (ddd, 1H, J = 8, 8, 1 Hz), 7.71 (ddd, 1H, J = 8, 8, 1 Hz), 8.17 (b d , 1H, J = 8 Hz), 8.30 (b d , 1H, J = 8 Hz), 8.81 (1H, OH), 14.00 (s, 1H, OH) ; ^{13}C NMR (63 MHz, DMSO d_6) : 24.5 (t), 26.5 (t), 35.2 (d), 38.3 (t), 44.0 (t), 45.4 (d), 109.5 (s), 117.7 (s), 121.9 (d), 123.2 (s), 123.5 (d), 125.4 (d), 129.7 (d), 130.8 (s), 140.5 (s), 156.1 (s), 205.7 (s), 209.3 (s).
9b : yellow solid, mp 192-193 °C (dec).

13 Somewhat surprisingly, none of the three aforementioned groups (ref. **4**) discussed the stereochemistry of compound **10b**.

14 **10a *cis*** : oil ; MS (70 eV) : 324 (M^+), 309, 149, 86, 84 ; IR ($CDCl_3$) : 1710, 1680, 1335 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) : 1.99 (m, 1H), 2.28-2.55 (m, 4H), 2.66 (dddd, 1H, J = 12, 6, 6, 5 Hz), 2.89 (ddddd, 1H, J = 10, 6, 5, 5, 5 Hz), 3.03 (ddd, 1H, J = 5, 5, 5 Hz), 3.12 (dd, 1H, J = 17, 6 Hz) , 3.29 (dd, 1H, J = 17, 5 Hz), 3.89 (s, 3H), 4.01 (s, 3H), 7.55 (ddd, 1H, J = 8, 8, 1 Hz), 7.65 (ddd, 1H, J = 8, 8, 1 Hz), 8.06 (dd, 1H, J = 8, 1 Hz), 8.34 (dd, 1H, J = 8, 1 Hz) ; ^{13}C NMR (63 MHz, $CDCl_3$) : 25.5 (t), 27.4 (t), 36.3 (d), 38.8 (t), 44.5 (t), 48.2 (d), 61.2 (q), 62.9 (q), 120.5 (s), 121.9 (d), 124.8 (d), 126.4 (d), 127.5 (s), 128.8 (s), 129.3 (d), 131.6 (s), 149.3 (s), 155.9 (s), 197.3 (s), 210.0 (s). **10a *trans*** : mp 193 °C ; MS (70 eV) : 324 (M^+), 309, 295, 86, 84, IR (KBr) : 1710, 1680, 1355 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) : 1.79 (dddd, 1H, J = 13, 13, 11, 5 Hz), 2.27 (ddddd, 1H, J = 12, 12, 12, 4, 4 Hz), 2.37-2.80 (m, 7H), 3.45 (dd, 1H, J = 16, 4 Hz), 3.90 (s, 3H), 4.00 (s, 3H), 7.53 (ddd, 1H, J = 8, 8, 1 Hz), 7.64 (ddd, 1H, J = 8, 8, 1 Hz), 8.06 (dd, 1H, J = 8, 1 Hz), 8.31 (dd, 1H, J = 8, 1 Hz) ; ^{13}C NMR (63 MHz, $CDCl_3$) : 26.5 (t), 31.4 (t), 38.9 (d), 40.3 (t), 47.5 (t), 51.3 (d), 61.6 (q), 62.9 (q), 121.2 (s), 121.8 (d), 124.7 (d), 126.3 (d), 128.5 (s), 128.7 (s), 129.1 (d), 131.2 (s), 148.3 (s), 155.5 (s), 196.6 (s), 208.9 (s).

15 Recrystallization of a mixture of ***cis-trans* 10b** in methanol afforded pure ***trans* 10b** mp 217 °C (lit. : mp 218-220 °C **4a** , 217-218 °C **4b** ; see ref. **13**).

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