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POLYCYCLIC HYDROXYQUINONES—XIX[1]

REGIOSPECIFIC SYNTHESIS OF ANTHRACYCLINONES VIA THE DIELS–ALDER REACTION WITH DICHLORONAPHTHAZARINS

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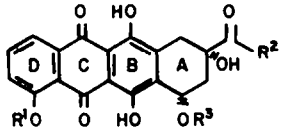
Abstract—A convenient route to the daunomycinone precursor **18** *via* a succession of Diels–Alder reactions from 2,7-dichloronaphthazarin (**9**) is described. In a similar manner, starting from 2,6-dichloronaphthazarin (**19**) compound **20**, a regioisomer of **18**, is synthesized. This methodology constitutes a regiospecific approach to (±)-daunomycinone and related anthracyclinones.

THE anthracyclines constitute a group of natural antibiotics isolated from cultures of various *Streptomyces*[2] spp., certain members of which possess significant antineoplastic activity. Among these, daunomycin (**1**) and adriamycin (**2**) have been the object of considerable interest in recent years because of their excellent therapeutic value in cancer chemotherapy[3] which was only limited because of their high degree of cardiotoxicity. The demonstrated efficacy of these anthracyclines in the treatment of cancer has stimulated the development of total synthesis of these compounds, thus allowing their preparation and the development of new analogues with improved chemotherapeutic properties.[3,4] The principal problem in their synthesis lies in the preparation of the



1, $R^1 = R^2 = Me$
R^3 = DAUNOSAMINYL

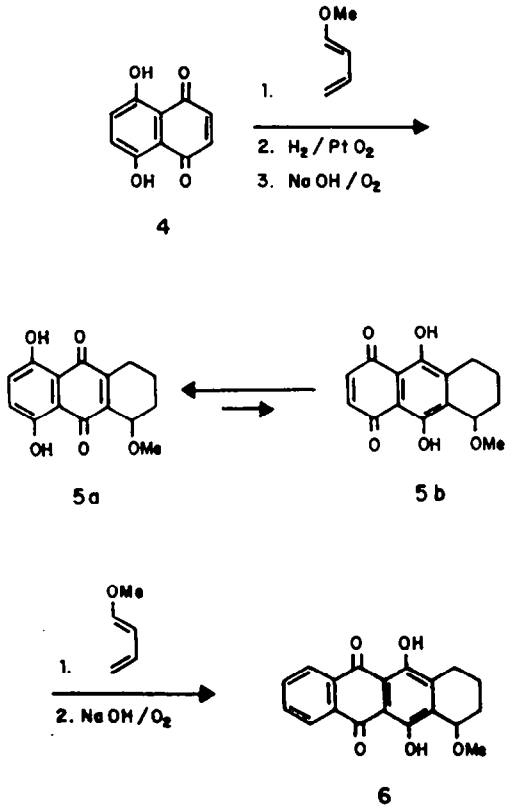
2, $R^1 = Me$, $R^2 = CH_2OH$
R^3 = DAUNOSAMINYL

3, $R^1 = R^2 = Me$, $R^3 = H$

corrresponding aglycones, the anthracyclinones, whose synthesis has been studied by many research groups.

Many different synthetic routes to anthracyclinones have been explored and these have been recently summarised in several reviews.[3b,c,e,4] As noted by Kelly,[4] the synthesis of an anthracyclinone such as daunomycinone (**3**), poses three types of problems: (a) the construction of the tetracyclic skeleton, (b) the introduction of the existing functionilization in the A ring and (c) the achievement of the correct regiochemical juxtaposition of the substituents in the A and D rings.

One of the most direct methods for construction of the tetracyclic skeleton utilizes the Diels–Alder reaction as a key step. A few years ago, we described[5] a simple route to the tetracyclic system of anthracyclinones using naphthazarin (**4**) as a BC synthon (Scheme 1). The Diels–Alder reaction with 1-methoxybutadiene, followed by hydrogenation and selective aromatization of the B ring, produces a tricyclic system **5a** containing the partially functionalised A ring. Compounds of type **5a** undergo a second Diels–Alder reaction, through the less stable tautomer **5b** and, using once again 1-methoxybutadiene cycloaddition leads to a mixture of



Scheme 1

regioisomeric adducts. When treated in alkaline solution, these adducts undergo aromatization of the D ring affording the tetracyclic compound **6**.

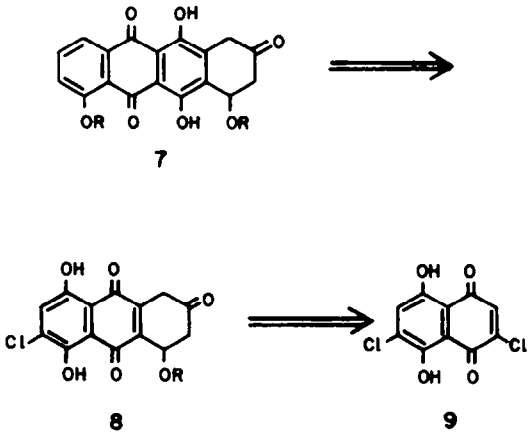
Later studies in our laboratory[6] and by Krohn *et al.*[7] have succeeded in introducing the suitable functionalization of the A ring in positions 7 and 9, by using suitable dienes such as 1-methoxy-3-trimethylsilyloxybuta-1,3-diene and 1,3-bis(trimethylsilyloxy)butadiene. In a related approach, Kelly *et al.*[8] have achieved an elegant regiospecific synthesis of (±)-daunomycinone (**3**) from a Diels–Alder reaction between a monoacylated naphthazarin and 1-methoxycyclohexa-1,3-diene.

This paper describes a new regiospecific synthesis of anthracyclinone derivatives *via* a succession of Diels–Alder reactions by the use of dichloronaphthazarins as BC synthons. The introduction of the halogens in the naphthazarin nucleus is to control regioselectivity in the initial Diels–Alder reaction (A ring formation) that, after HCl elimination, gives rise to an ABC synthon with a chloronaphthazarin system suitably positioned to control the orientation of the second Diels–Alder reaction (D ring formation). The use of chlorine atoms as directing substituents has been previously used by others[9] in regiospecific cycloadditions with chloronaphthoquinones and very recently by us[10] to control the orientation in Diels–Alder reaction with chloronaphthazarins.

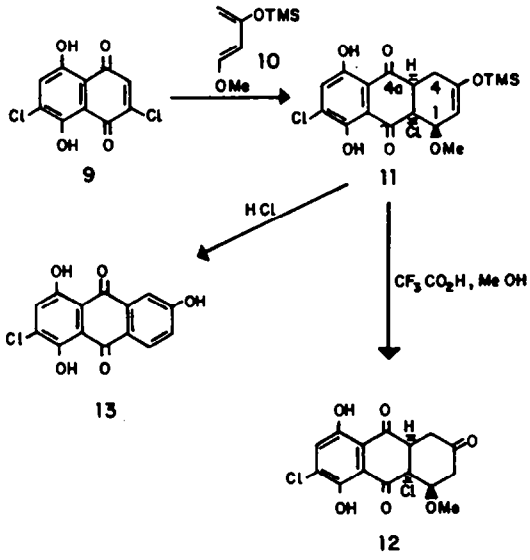
A retrosynthetic analysis of the synthon **7** (Scheme 2), from which the synthesis of daunomycinone has been achieved, indicates that the most suitable starting material is 2,7-dichloronaphthazarin (**9**), whereas the use of the 2,6-dichloroderivative would lead to an isomer of **7** with inversion of the regiochemistry.

To examine the feasibility of this scheme, we have previously studied[11] model reactions of (*E*)-1-methoxy-3-trimethylsilyloxybuta-1,3-diene (**10**) with chloronaphthoquinones which led regiospecifically to adducts in which the C-1 of the diene became attached to the carbon which supports the Cl in the quinone.

On the other hand, further model studies on the construction of the D ring by cycloaddition of suitable dienes with chloronaphthazarins showed[1] that the oxygen substituent of the diene, which ultimately remained at the C-4 in the D ring, also appeared attached to the adjacent carbon to that supporting the Cl atom.



Scheme 2



Scheme 3

We therefore decided to study the cycloaddition of the diene **10** with 2,7-dichlornaphthazarin (**9**). The reaction at 0°C in dichloromethane gave only one detectable adduct by TLC analysis. The formation of a single adduct was further evidenced by the ^{1}H-NMR spectrum of the crude reaction product which displayed two sharp singlets for the chelated hydroxy protons at δ 12.03 and 10.97.

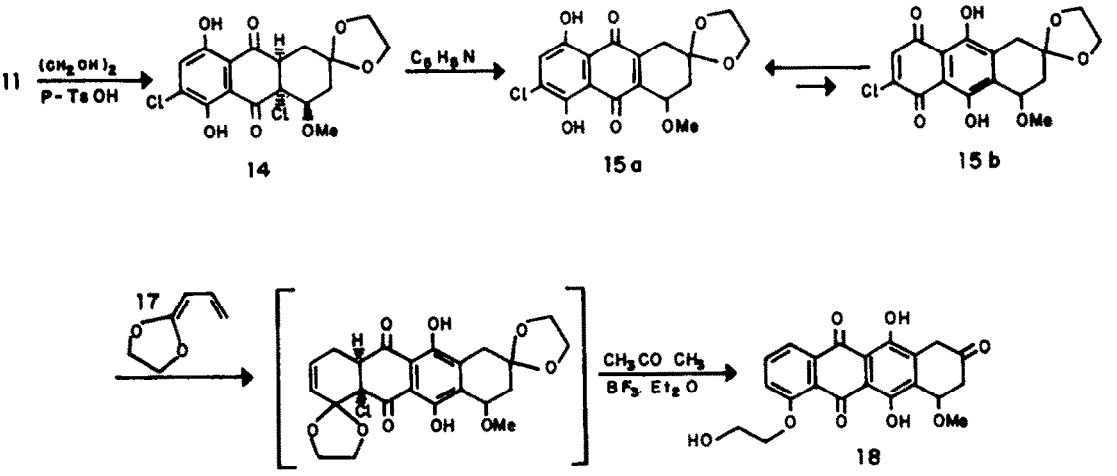
The crude adduct **11** was obtained in high yield (~ 97%). Moreover, this adduct is rather unstable and in an attempt to purify the crude reaction product, **11** was recovered in only 46% yield. From the mother liquors, by successive treatments with trifluoracetic acid in methanol–dichloromethane and acetic acid the ketone **12** and the aromatised derivative **13** were obtained in 27% and 24% yield respectively (Scheme 3).

The structure **11** was conclusively established by its ^{1}H-NMR spectrum, in which the methine proton on the carbon bearing the OMe (C-1) appeared as a doublet (δ 4.12) due to coupling with the olefin proton (J = 5.5 Hz). The angular proton at C-4a (δ 3.59) showed coupling of 7.1 Hz to one of the methylene protons at C-4. In addition, long-range couplings were observed between H-4a and H-1 and one of the protons at C-4. These data, conformed by decoupling experiments, are only consistent with structure **11**.

It was also found that the pure adduct **11** was readily converted into ketone **12** in excellent yield upon treatment with trifluoracetic acid in methanol. In contrast treatment of **11** with 1% hydrochloric acid produced the fully aromatic compound **13** in quantitative yield.

Adduct **11** and ketone **12** already possess suitable functions to be transformed into the substituents present in the A ring of the anthracyclinones. On the other hand, both products **11** and **12** by dehydrochlorination could afford a tricyclic synthon (ABC rings) with a naphthazarin structure, which can act as a dienophile in a second Diels–Alder reaction with subsequent formation of the D ring.

However, selective aromatization of the B ring could not be carried out directly on the adduct **11** or the



Scheme 4

ketone **12**, because the basic conditions required to effect the dehydrochlorination produced a concomitant aromatization of the substrate under formation of **13**. Furthermore, introduction of the side chain present in the A ring of the anthracyclinones at this stage, by reaction with carbon nucleophiles, proved difficult because the basic reagent also caused the aromatization of the substrate.

In order to avoid the aromatization of the tricyclic system, it was necessary to first protect the 9-keto group as the ethylenedioxyderivative **14**, which was prepared from ketone **12** or from adduct **11** by treatment with an excess of ethylene glycol in the presence of *p*-toluenesulphonic acid. Thus, acetal **14** could be obtained directly from pure **11** in a single step in 82% yield. Dehydrochlorination of **14** to furnish the quinone **15** in quantitative yield was accomplished with pyridine in THF at room temperature (Scheme 4). These results indicate that the synthon **15** can be prepared from 2,7-dichloronaphthazarin (**9**) in 38% overall yield.

Quinone **15** can exist in an equilibrium between two main tautomeric forms **15a** ⇌ **15b**. The ^{1}H-NMR spectrum of the compound showed a singlet at δ 7.29 typical for a benzenoid proton, thus indicating that the predominant tautomer in solution was **15a**. This compound can, however, act as a dienophile through its less stable tautomer **15b**. The Cl atom in position 7 is intended to control the orientation of the second cycloaddition and to facilitate the subsequent aromatization by dehydrochlorination, keeping in D ring the oxygen substituent of the diene.

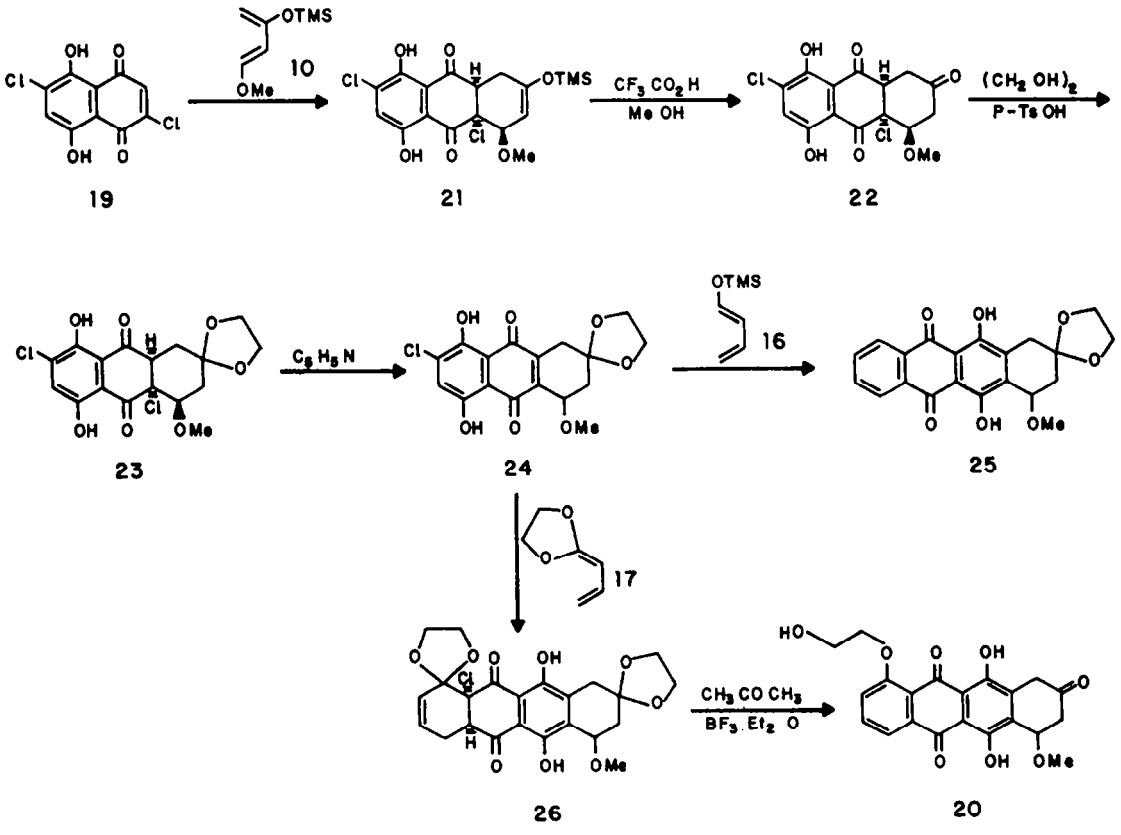
In previous model studies,[1] we have attempted to select OR substituted dienes suitable for the construction of the aromatic D ring, but maintaining the oxygen substituent. It was found that (*E*)-1-trimethylsilyloxybuta-1,3-diene (**16**) and 2-prop-2-enylidene-1,3-dioxolan (**17**) could be used for this purpose. In our particular case, however, the diene **17** gave better results. In fact, by using **16** a concomitant aromatization of the D ring was produced, with elimination of all the substituents.

Cycloaddition of the chloroquinone **15** with the diene **17** took place in dichloromethane, affording an adduct that easily decomposes in solution. The adduct was therefore not isolated and was directly treated with acetone and boron trifluoride etherate, by application of the previously developed transacetalisation procedure.[7b] Ketone **18** was obtained, in which the CO group has been deprotected and the aromatization of the D ring has been effected. The chloroquinone **15** was transformed as shown into ketone **18** in 37% overall yield.

The regiochemistry of the cycloaddition was assigned on the basis of results of previous model studies[1] using diene **17** and 2,6- and 2,7-dichloronaphthazarins, indicating that it was a regiospecific process in which the carbon supporting the chlorine atom became attached to the substituted C-1 of the diene.

The structure of the ketone **18** was assigned on the basis of spectroscopic data. The ^{1}H-NMR spectrum showed two signals corresponding to chelated protons at δ 13.79 and 13.28. In the region between δ 7.3 and 8.0 there appeared three signals assigned to the aromatic protons, whose coupling constants (J = 8.0 and J = 1.5 Hz) are typical for the D ring substitution pattern of the daunomycinone derivatives. The appearance of two multiplets centred at δ 4.2 and 4.0 integrating for 4 protons indicated the presence of the C-4 hydroxyethoxy substituent. The methylene protons at C-10 formed an AB system (J = 18.0 Hz), and the methine proton at C-7 and the methylene protons at C-8 formed an ABX system (J_{AB} = 14.8, J_{AX} = 3.2, J_{BX} = 6.5 Hz). This pattern was in full agreement with the substitution in A ring. The IR spectrum showed a broad band at 3580-3420 cm^{-1}, and a characteristic carbonyl absorption at 1733 cm^{-1} corresponding to the OH of the C-4 substituent and CO group at C-9, respectively. The mass spectrum showed the molecular ion at *m/e* 398 and the mass spectral fragmentation was also in agreement with the structure **18**.

The preparation of **18** from the starting 2,7-dichloronaphthazarin affords an overall yield of 14%. Since the complete functionalisation of position 9 in the anthracyclinones from their 9-oxoderivatives has previously been accomplished by other workers,[3,4] and there exist suitable methods for the cleavage of ethers in this type of compounds,[3,4] the route we have described might be considered as a regiospecific approach to (±)-daunomycinone.



Scheme 5

By using an analogous reaction sequence, 2,6-dichloronaphthazarin (**19**) was converted to the ketone **20**, the undesired regioisomer of **18** (Scheme 5). In this case the cycloaddition is practically quantitative, although the pure adduct **21** was isolated in only 60% yield. Its high resolution ^{1}H-NMR spectrum was indicative of the presence of a single regioisomer. The regiochemistry of **21** was also confirmed from its ^{1}H-NMR spectrum, by analogy to that of **11**. In fact, the H-1 (δ 4.12) couples only to the olefinic H-2 and the angular proton H-4a (δ 3.58) appears as a doublet due to coupling with one of the methylene protons; similar long-range couplings are also observed in this case.

The adduct **21** undergoes the same transformations as its regioisomer **11**, under similar conditions. It was readily transformed into the ketone **22** and the dioxolane **23**. Dehydrochlorination of **23** quantitatively yielded the quinone **24**.

The construction of the substituted D ring from the chloroquinone **24** was also attempted using the (*E*)-1-trimethylsilyloxybuta-1,3-diene (**16**). In fact, the model studies mentioned above[1] demonstrated that this diene reacted regiospecifically with chloroquinones. Moreover mild hydrolysis of the OTMS group on the adduct and subsequent oxidation with PCC permitted the retention of the oxygen substituent of the diene. The cyloaddition of **24** with the diene **16** occurred readily at room temperature in dichloromethane. However, after chromatography, only the partially aromatized product **25** was isolated in which the substituent has been removed. The physical and spectral data of the product **25** were identical with those previously described.[6,7] These results indicated that **16** was not the most suitable diene for our purposes.

In contrast, the reaction of **24** with diene **17** at room temperature afforded the corresponding adduct **26**, which could not be isolated, and by treatment with BF_3-etherate/acetone was directly converted into the pure **20** in 13% yield from **24**. A ^{1}H-NMR spectrum of **20** could not be obtained due to its insolubility. Its structure was inferred from the IR and mass spectra. The IR spectrum showed a broad OH band at 3500–3200 cm^{-1} and a characteristic absorption at 1730 cm^{-1} corresponding to the carbonyl group in the 9-position. The mass spectrum showed an intense ion at *m/e* 322 indicative of the elimination of methanol and of the presence of the hydroxyethyl chain (elimination of C_2H_4O) from the molecular ion which appeared, as expected, at *m/e* 398.

The foregoing results confirm the utility of the halogenated naphthazarins to control the orientation of remote substituents in the elaboration of tetracyclic systems by cycloaddition reactions. Furthermore, the strategy described herein may be applicable to the regiospecific synthesis of daunomycinone and related anthracyclinones, thus allowing the preparation of new analogues with modified pharmacological properties.

EXPERIMENTAL

Mps are uncorrected. IR spectra were obtained on a Unicam SP-1100 spectrophotometer for Nujol mulls, unless otherwise stated. ^{1}H-NMR spectra were recorded on Hitachi

Perkin-Elmer R-24A (60 MHz), Varian XL-100 (100 MHz) and Brucker WM-200-SY (200 MHz) instruments. If not stated otherwise, spectra were run at 60 MHz for $CDCl_3$ solns. Chemical shifts are reported in ppm (δ) downfield from internal Me_4Si. UV-vis spectra were determined on a Perkin-Elmer 124 instrument for EtOH solns. Mass spectra were recorded on Hitachi Perkin-Elmer RMU-6MG and Hewlett-Packard 5995 instruments. Analytical TLC and column chromatography were carried out on deactivated silica gel (DSG) prepared with 0.05 M KH_2PO_4 instead of water[12] (silica gel Merck G and Merck 60, 70–230 mesh respectively). The preparative TLC was carried out on silica gel Merck F-254.

7,9a-*Dichloro*-5,8-*dihydroxy*-1-*methoxy*-3-*trimethylsilyloxy*-1,4,4a,9a-*tetrahydro*-9,10-*anthraquinone* **11**

Compound **9**[11] (350 mg) was dissolved in CH_2Cl_2 (6 ml) and (*E*) **10** (600 mg) was added at 0°. The mixture was stirred for 30 min at 0° and the solvent was evaporated *in vacuo* at 10°. The crude product was triturated with light petroleum and filtered to give 270 mg (46%) of practically pure **11**, m.p. 86–88° (solidifies and melts definitively at 258–262°); IR 1672, 1653 and 1581 cm^{-1}; ^{1}H-NMR (200 MHz) 12.03 (s, 1H, OH), 10.97 (s, 1H, OH), 7.37 (s, 1H, C-6), 5.08 (dt, 1H, C-2, J = 5.5, J = 1.5 Hz; collapses to a triplet by irradiation at δ 4.12), 4.12 (d, 1H, C-1, J = 5.5 Hz; collapses to a singlet by irradiation at δ 5.08), 3.59 (br d, 1H, C-4a, J = 7.1 Hz; transformed to a dd by irradiation at δ 4.12, J = 1.0 Hz, transformed to a dt by irradiation at δ 5.08, J = 1.1 Hz), 3.00 (s, 3H, OMe), 3.25 (br d, 1H, C-4, J = 18 Hz, transformed to a dd by irradiation at δ 5.08, J = 1.2 Hz), 2.66 (ddt, 1H, C-4, J = 18.1, J = 7.1 and J = 1.3 Hz; collapses to a ddd by irradiation at δ 5.08, J = 0.9 Hz; collapses to a dd by irradiation at δ 4.12, J = 1.6 Hz), 0.29 (s, 9H, OTMS); *m/e* 430 (M^+) (1.3) 432 (0.6), 398 (0.6), 362 (98), 347 (100), 290 (29).

The mother liquors were concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (2 ml) and MeOH (0.5 ml) and two drops of trifluoracetic acid was added. The solvent was then evaporated *in vacuo* at 25° and the residue was triturated with ethyl ether and filtered to give 130 mg (27%) of ketone **12** identical with the product described below. The mother liquors of the methanolysis were concentrated *in vacuo* and the residue was dissolved in AcOH (13 ml) and was stirred for 15 min at room temp. The mixture was poured into water (50 ml) and the ppt was collected, washed with water and dried to give 94 mg (24%) of the fully aromatized **13**, identical with the product described below.

7,9a-*Dichloro*-5,8-*dihydroxy*-1-*methoxy*-3-*oxo*-1,2,3,4,4a,9a-*hexahydro*-9,10-*anthraquinone* **12**

To a soln of adduct **11** (240 mg) in CH_2Cl_2-MeOH 3:1 (4 ml) was added two drops of trifluoracetic acid. The mixture was concentrated *in vacuo* at 20–22° and the residue was triturated with light petroleum to give 195 mg (97%) of **12**, m.p. 99–101° (dec); IR 1730, 1658–1641 and 1580 cm^{-1}; ^{1}H-NMR 12.43 (s, 1H, OH), 11.42 (s, 1H, OH), 7.41 (s, 1H, C-6), 4.11 (m, 1H, C-1), 3.81 (m, 1H, C-4a), 3.36 (m, 1H, C-4), 3.03 (s, 3H, OMe), 3.0–2.8 (m, 3H, C-4 and C-2); *m/e* 326 ($M^+ - 32$) (2.0), 290 (100), 292 (35), 255 (14).

2-*Chloro*-1,4,6-*trihydroxy*-9,10-*anthraquinone* **13**

To a 1% soln of conc HCl in THF—H_2O 9:1 (15 ml) was added the adduct **11** (290 mg). The mixture was stirred at room temp for 1 hr. The ppt formed was collected, washed with water and dried to give 195 mg (100%) of **13**, m.p. 282–283° (pyridine); IR 3370, 1633, 1593 and 1578 cm^{-1}; ^{1}H-NMR (100 MHz) 13.56 (s, 1H, OH), 12.69 (s, 1H, OH), 8.21 (d, 1H, C-8, J = 9.0 Hz), 7.65 (d, 1H, C-5, J = 3 Hz), 7.2 (2H, C-3 and C-7); UV-vis 278 (4.36), 303 sh (4.15), 467 (3.96); *m/e* 290 (M^+) (100), 292 (35), 262 (4), 255 (14), m* 224, 237.5. (Found: C, 57.49; H, 2.61; Cl 12.21. Calc for $C_{14}H_7O_5Cl$: C, 57.85; H, 2.42; Cl 12.20).

7,9a-*Dichloro*-3,3-*ethylenedioxy*-5,8-*dihydroxy*-1-*methoxy*-1,2,3,4,4a,9a-*hexahydro*-9,10-*anthraquinone* **14**

Method A. A stirred mixture of adduct **11** (300 mg), ethylene glycol (300 mg) and *p*-toluenesulphonic acid (20 mg) in CH_2Cl_2 (6 ml) was refluxed for 2 hr. After being cooled to room temp, the mixture was diluted with CH_2Cl_2 (10 ml), washed with water (3 × 25 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was triturated with MeOH to give 230 mg (82%) of **14**, m.p. 170–173° (dec); IR 1655 and 1591 cm^{-1}; ^{1}H-NMR 12.22 (s, 1H, OH), 12.00 (s, 1H, OH), 7.37 (s, 1H, C-6), 3.96 (br s, 4H, OCH_2CH_2O), 3.9–3.4 (m, 2H, C-1 and C-4), 3.36 (s, 3H, OMe), 2.10 (m, 4H, C-2 and C-4); *m/e* 402 (M^+) (5), 404 (3), 366 (3), 334 (43), 304 (73), 290 (68), 280 (100), 265 (32), 262 (39), 234 (18).

Method B. A stirred mixture of ketone **12** (295 mg), ethylene glycol (350 mg) and *p*-toluenesulphonic acid (20 mg) in dichloromethane (7 ml) was refluxed for 4 hr. The mixture was cooled at room temp and diluted with CH_2Cl_2 (10 ml), washed with water (4 × 20 ml), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was triturated with ethyl ether to give 255 mg (77%) of **14**, identical with the product described above.

7-*Chloro*-3,3-*ethylenedioxy*-5,8-*dihydroxy*-1-*methoxy*-1,2,3,4-*tetrahydro*-9,10-*anthraquinone* **15**

To a soln of **14** (155 mg) in THF (7 ml) was added pyridine (50 mg) and the mixture was stirred at room temp for 15 min. The mixture was then concentrated under reduced pressure to 1/2 of its volume, filtered, diluted with CH_2Cl_2 (20 ml), washed with water (5 × 20 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give 141 mg (100%) of **15**, m.p. 141–142° (CCl_4); IR 1627 and 1588 cm^{-1}; ^{1}H-NMR 12.83 (s, 1H, OH), 12.21 (s, 1H, OH), 7.29 (s, 1H, C-6), 4.73 (m, 1H, C-1), 4.01 (br s, 4H, OCH_2CH_2O), 3.54 (s, 3H, OMe), 2.95 (d, 1H, C-4, J = 17 Hz), 2.86 (d, 1H, C-4, J = 17 Hz), 2.19 (m, 2H, C-2); UV-vis 280 (3.87), 499 (3.74); *m/e* 366 (M^+) (2.4), 368 (1), 334 (33), 304 (7), 300 (4), 290 (23), 280 (100), 265 (31), 262 (30), 246 (9), 234 (13). (Found: C, 55.14; H, 3.74; Cl, 10.16. Calc for $C_{17}H_{15}O_7Cl$: C, 55.67, H, 4.12; Cl 9.67).

6,11-*Dihydroxy*-4-(2'-*hydroxyethoxy*)-7-*methoxy*-9-*oxo*-7,8,9,10-*tetrahydronaphthacene*-5,12-*dione* **18**

To a soln of **15** (47 mg) in CH_2Cl_2 (5 ml) was added **17**[13] (crude, *ca* 10 equiv). The mixture was stirred at room temp for 15 min. The solvent was evaporated *in vacuo* and the residue was dissolved in acetone (5 ml) and two drops of $BF_3 \cdot Et_2O$ were added. After stirring the soln at room temp for 1 hr, CH_2Cl_2 was added (15 ml), and the mixture was washed with water (6 × 20 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was chromatographed by preparative TLC (toluene-EtOAc 1:1), to give 19 mg (37%) of **18**, m.p. > 340° (dec); IR(KBr) 3580, 3420, 1733, 1626, 1590 and 1150–1125 cm^{-1}; ^{1}H-NMR (100 MHz) 13.79 (s, 1H, OH), 13.28 (s, 1H, OH), 7.99 (dd, 1H, C-1, J = 8.0, J = 1.5 Hz), 7.72 (t, 1H, C-2, J = 8.0 Hz), 7.30 (d, 1H, C-3, J = 8.0 Hz), 4.88 (part X system ABX, 1H, C-7), 4.2 (m, 2H, C-1'), 4.2–4.0 (m, 1H, OH), 4.0 (m, 2H, C-2'), 3.49 (s, 3H, OMe), 3.24 (part A system AB, 1H, C-10, J = 18.0 Hz), 2.89 (part B system AB, 1H, C-10, J = 18.0 Hz), 2.40 (part A system ABX, 1H, C-8β, J_{AB} = 14.8, J_{AX} = 3.2, J^4 = 1.0 Hz), 2.14 (part B system ABX, C-8α, J_{AB} = 14.8, J_{BX} = 6.5 Hz); UV-vis 253 (3.90), 472 (3.42), 488 (3.44), 497 (3.45), 533 (3.29); *m/e* 398 (M^+) (2), 397 (2), 396 (2), 380 (3), 370 (3), 366 (15), 356 (100), 355 (3), 352 (2), 348 (3), 338 (34), 336 (22), 327 (5), 326 (11), 324 (12), 322 (14).

6,9a-*Dichloro*-5,8-*dihydroxy*-1-*methoxy*-3-*trimethylsilyloxy*-1,4,4a,9a-*tetrahydro*-9,10-*anthraquinone* **21**

To a stirred suspension of **19**[11] (140 mg) in CH_2Cl_2 (3 ml) at 0° was added a soln of (*E*)- **10** (300 mg) in CH_2Cl_2 (1 ml). The mixture was stirred at 0° for 1 hr. The solvent was evaporated *in vacuo* (10°) and the residue was triturated with light petroleum to give 140 mg (60%) of pure **21**, m.p. 119–120° (dec) (solidifies and melts at 245–250°); IR 1658 and 1643 cm^{-1}; ^{1}H-

NMR (200 MHz) 11.80 (s, 1H, OH), 11.73 (s, 1H, OH), 7.34 (s, 1H, C-7), 5.08 (d, 1H, C-2, J = 5.5 Hz; collapses to a singlet by irradiation at δ 4.10), 4.10 (d, 1H, C-1, J = 5.5 Hz, collapses to a singlet by irradiation at δ 5.08), 3.59 (d, 1H, C-4a, J = 6.9 Hz; collapses to a singlet by irradiation at δ 2.46), 3.20 (d, 1H, C-4, J = 18 Hz), 2.99 (s, 3H, OMe), 2.46 (dd, 1H, C-4, J = 18 Hz, J = 6.6 Hz), 0.29 (s, 9H, OTMS); *m/e* 430 (M^+) (0.2), 432 (0.1), 398 (0.7), 362 (93), 347 (100), 290 (10).

The filtrate was evaporated *in vacuo* at 10° and the residue was dissolved in CH_2Cl_2 (20 ml) and then one drop of trifluoracetic acid in MeOH (0.5 ml) was added. The solvent was evaporated *in vacuo* (30°) and the residue was triturated with ethyl ether–light petroleum and collected to give 35 mg (18%) of **22**, identical with the product described below. The mother liquors of the methanolysis were concentrated *in vacuo* and the residue was dissolved in AcOH (10 ml) and was stirred at room temp for 10 min. The mixture was poured into water (60 ml) and the ppt was collected to give 35 mg (22%) of the fully aromatic product **27**, m.p. 247–249° (HOAc), identical with the product described below.

6,9a-*Dichloro*-5,8-*dihydroxy*-1-*methoxy*-3-*oxo*-1,2,3,4,4a,9a-*hexahydro*-9,10-*anthraquinone* **22**

To a stirred soln of pure adduct **21** (110 mg) in CH_2Cl_2-MeOH 3:1 (4 ml) at room temp were added two drops of trifluoracetic acid. The mixture was then concentrated *in vacuo* at 18–20°, and the residue was triturated with light petroleum to give 80 mg (87%) of **22**, m.p. 173–176° (dec) (solidifies and melts at 247–250°); IR 1728, 1653–1640 and 1581 cm^{-1}; ^{1}H-NMR 11.67 (s, 1H, OH), 11.62 (s, 1H, OH), 7.35 (s, 1H, C-7), 4.10 (m, 1H, C-1), 3.85 (m, 1H, C-4a), 3.7–2.6 (m, 2H, C-2 and C-4), 3.02 (s, 3H, OMe), 3.0–2.9 (m, 2H, C-2 and C-4); *m/e* 290 ($M^+ - 68$) (100), 292 (35), 255 (14).

3-*Chloro*-1,4,6-*trihydroxy*-9,10-*anthraquinone* **27**

To a 1% soln of conc HCl in THF—H_2O 9:1 (40 ml) was added the adduct **21** (830 mg). The mixture was stirred 1 hr at room temp. The ppt formed was collected, washed with water and dried to give 560 mg (100%) of **27**, m.p. 247–249° (HOAc); IR 3420, 1635, 1598 and 1582 cm^{-1}; ^{1}H-NMR (100 MHz) 12.89 (s, 1H, OH), 12.67 (s, 1H, OH), 8.22 (dd, 1H, C-8, J = 9.0 Hz, J = 1.0 Hz), 7.65 (d, 1H, C-5, J = 3.0 Hz), 7.2 (2H, C-2 and C-7); UV-vis 229 (4.46), 278 (4.39), 302 sh (4.12), 467 (3.99), 482 (3.96), 516 (3.72); *m/e* 290 (100), 292 (35), 262 (5), 255 (15), m* 224, 237.5. (Found: C, 55.05; H, 2.32; Cl, 10.65. Calc for $C_{14}H_7O_5Cl \cdot HOAc$: C, 54.79; H, 3.16; Cl 10.11).

6,9a-*Dichloro*-3,3-*ethylenedioxy*-5,8-*dihydroxy*-1-*methoxy*-1,2,3,4,4a,9a-*hexahydro*-9,10-*anthraquinone* **23**

Method A. A stirred mixture of adduct **21** (340 mg), ethylene glycol (350 mg) and *p*-toluenesulphonic acid (15 mg) in CH_2Cl_2 (25 ml) was refluxed for 3 hr. After cooling to room temp, the mixture was washed with water (3 × 50 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was triturated with ethyl ether–light petroleum to give 210 mg (66%) of **23**, mp. 142–144° (dec); IR 1651 and 1586 cm^{-1}; ^{1}H-NMR 12.07 (s, 1H, OH), 11.29 (s, 1H, OH), 7.37 (s, 1H, C-7), 3.98 (br s, 4H, OCH_2CH_2O), 3.9–3.4 (m, 2H, C-1 and C-4a), 3.38 (s, 3H, OMe), 2.16 (m, 4H, C-2 and C-4); *m/e* 402 (M^+) (3), 404 (3), 366 (5), 334 (49), 304 (2), 290 (50), 280 (100), 265 (35), 262 (40), 234 (15).

Method B. A stirred mixture of **22** (220 mg), ethylene glycol (250 mg) and *p*-toluenesulphonic acid (15 mg) in CH_2Cl_2 (20 ml) was refluxed for 2.5 hr. The mixture was cooled to room temp, washed with water (3 × 50 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was triturated with ethyl ether–light petroleum to give 170 mg (69%) of **23**, m.p. 142–144° (dec), identical with the product described above.

6-*Chloro*-3,3-*ethylenedioxy*-5,8-*dihydroxy*-1-*methoxy*-1,2,3,4-*tetrahydro*-9,10-*anthraquinone* **24**

To a soln of **23** (109 mg) in THF (10 ml) was added pyridine (24 mg). The mixture was stirred at room temp for 10 min and then concentrated *in vacuo* at 1/2 of its volume, filtered, diluted with CH_2Cl_2 (10 ml), washed with water (5 × 20 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 100 mg (100%) of **24**, m.p. 160–161° (cyclohexane); IR 1651 cm^{-1}; ^{1}H-NMR 12.66 (s, 1H, OH), 12.39 (s, 1H, OH), 7.32 (s, 1H, C-7), 4.70 (m, 1H, C-1), 4.00 (br s, 4H, OCH_2CH_2O), 3.53 (s, 3H, OMe), 2.94 (d, 1H, C-4, J = 17.0 Hz), 2.85 (d, 1H, C-4, J = 17.0 Hz), 2.19 (m, 2H, C-2); UV-vis 281 (3.86), 498 (3.70); *m/e* 366 (M^+) (4), 368 (2), 304 (10), 300 (11), 290 (61), 280 (100), 265 (24), 262 (31), 246 (20), m* 252. (Found: C, 55.73; H, 4.17; Cl, 9.86 Calc for $C_{17}H_{15}O_7Cl$: C, 55.67; H, 4.12; Cl 9.67).

9,9-*Ethylenedioxy*-6,11-*dihydroxy*-7-*methoxy*-7,8,9,10-*tetrahydronaphthacene*-5,12-*dione* **25**

A soln of **24** and (*E*)-**16** (100 mg) in CH_2Cl_2 (5 ml) was stirred for 4 hr at room temp. The solvent was removed *in vacuo* and the residue was purified by column chromatography using CH_2Cl_2 as eluant, to give 15 mg (62%) of **25**, m.p. 190–191° (MeOH–$CHCl_3$ 2:1) (lit.[7] 198–199°); IR 1630 and 1590 cm^{-1}; ^{1}H-NMR (100 MHz) 13.58 (s, 1H, OH), 13.36 (s, 1H, OH), 8.3 (m, 2H, C-1 and C-4), 7.8 (m, 2H, C-2 and C-3), 4.87 (part X system ABX, 1H, C-7), 4.01 (m, 4H, OCH_2CH_2O), 3.50 (s, 3H, OMe), 3.13 (part A system AB, 1H, C-10, J = 18.0 Hz), 2.97 (part B system AB, 1H, C-10, J = 18.0 Hz), 2.40 (part A system ABX, 1H, C-8, J_{AB} = 15.0, J_{AX} = 6.0 Hz), 2.20 (part B system ABX, 1H, C-8, J_{AB} = 15.0, J_{BX} = 3.0 Hz); UV-vis 252 (4.58), 257 sh (4.55), 285 (3.91), 458 sh (3.95), 485 (4.00), 518 (3.80); *m/e* 382 (M^+) (6), 352 (19), 350 (31), 306 (22), 296 (100), 278 (12).

6,11-*Dihydroxy*-1-(2'-*hydroxyethoxy*)-7-*methoxy*-9-*oxo*-7,8,9,10-*tetrahydronaphthacene*-5,12-*dione* **20**

To a soln of **24** (18 mg) in CH_2Cl_2 (1 ml) was added **17**[13] (crude, *ca* 10 eq). The mixture was stirred for 5 min at room temp. The solvent was removed *in vacuo* and the residue was dissolved in acetone (5 ml) and one drop of $BF_3 \cdot Et_2O$ was added. The soln was stirred for 2.5 hr at room temp and then diluted with CH_2Cl_2 (10 ml), washed with water (7 × 10 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was chromatographed in column using EtOAc–light petroleum 2:1 as eluant, to give 2.5 mg (13%) of **20**, m.p. 248–250°; IR 3500–3200, 1730 and 1575 cm^{-1}; UV-vis 224, 250, 276, 468, 497, 532; *m/e* 398 (M^+) (10), 397 (11), 396 (11), 380 (11), 370 (45), 366 (11), 356 (21), 355 (51), 352 (11), 348 (12), 338 (19), 336 (14), 327 (24), 326 (30), 324 (62), 322 (100).

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REFERENCES

[1] Part XVIII, A. Echavarren, F. Fariña and P. Prados, *J. Chem. Res.* to be published.

[2] H. Brockmann, *Fortschr. Chem. Org. Naturst.* **21**, 121 (1963).

[3] [a]J. R. Brown, *Prog. Med. Chem.* **15**, 125 (1978); [b]F. Arcamone *Topics in Antibiotic Chemistry* (Edited by P. G. Sammes) Vol. 2, p. 102; Halsted Press, New York (1978); [c]W. A. Remers, *The Chemistry of Antitumor Antibiotics* Vol. 1, p. 63; Wiley Interscience, New York (1979), [d]*Anthracyclines: Current Status and New Developments*, (Edited by S. T. Crooke and S. D. Reich) Academic Press, New York (1980); [e]F. Arcamone, *Doxorubicin*. Academic Press, New York (1981); [f]*Anthracycline Antibiotics*, (Edited by H. S. El Khadem), Academic Press, New York (1982).

[4] T. R. Kelly, *Annu. Rep. Med. Chem.* **14**, 288 (1979).

[5] F. Fariña and J. C. Vega, *Tetrahedron Lett.* 1655 (1972).

[6] [a]F. Fariña and P. Prados, *Tetrahderon Lett.* 477 (1979); [b]F. Fariña, P. Prados and J. C. Vega, *An. Quim.* **78C**, 344 (1982); [c]F. Fariña, P. Prados and J. C. Vega, *An. Quim.* **78C**, 354, (1982).

[7] [a]K. Krohn and K. Tolkiehn, *Tetrahedron Lett.* 4023 (1978); [b]K. Krohn and K. Tolkiehn, *Chem. Ber.* **112**, 3453 (1979).

[8] T. R. Kelly, J. Vaya and L. Ananthasubramanian, *J. Am. Chem. Soc.* **102**, 5983 (1980).

[9] [a]L. Boisvert and P. Brassard, *Tetrahedron Lett.* **24**, 2453 (1983) and references cited therein; [b]D. W. Cameron, G. I.

Feutrill and P. G. McKay, *Tetrahedron Lett.* **22**, 701 (1981); [c]J. P. Gesson, J. C. Jacquesy and M. Mondon, *Tetrahedron Lett.* **22**, 1337 (1981) and references cited therein: [d]R. A. Russell, E. G. Vikingur and R. N. Warrener, *Aus. J. Chem.* **34**, 131 (1981).

[10] P. Cano, A. Echavarren, F. Fariña and P. Prados, *J. Org. Chem.* **48**, 5373 (1983).

[11] A. Echavarren, F. Fariña and P. Prados, *J. Chem. Res.*, to be published.

[12] W. W. Lee, A. P. Martinez, T. H. Smith and D. W. Henry, *J. Org. Chem.* **41**, 2296 (1976).

[13] D. H. R. Barton, S. V. Ley, W. L. Mitchell and T. V. Radhakrishnan, *J. Chem. Soc.* Perkin I, 1582 (1981).