The total synthesis of (±)-4-demethoxy-10-nordaunomycinone

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4-Demethoxy-10-nordaunomycinone (**4**) is synthesized starting with 4,7-dimethoxy-1-indanone (**8**). Nucleophilic addition of ethynyl magnesium bromide to **8** followed by mercuric acetate oxidation and iron pentacarbonyl – tri-*n*-butyltin hydride reduction gave 4,7-dimethoxy-1-acetylindane (**16**). Condensation of **16** with phthalic anhydride followed by methylation with dimethylsulfate and oxidation gave **22**, which was epimerized to **24** by 2,2-dimethoxypropane and trifluoroacetic acid. Demethylation of **24** with aluminum chloride gave the 4-demethoxy-10-nordaunomycinone (**4**).

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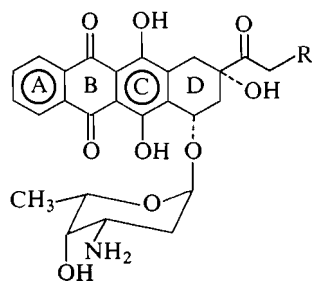
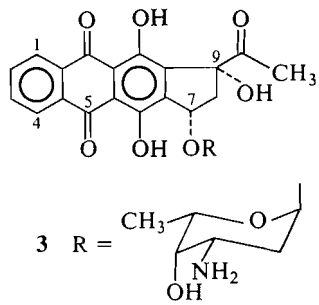
On a synthétisé la déméthoxy-4 nor-10 daunomycinone (**4**) à partir de la diméthoxy-4,7 indanone-1 (**8**). L'addition nucléophile du bromure d'éthynylmagnésium à la cétone **8**, suivie d'une oxydation par l'acétate mercurique et d'une réduction par l'hydrure de tri-*n*-butylétain/pentacarbonyle de fer, conduit au diméthoxy-4,7 acétyl-1 indane (**16**). La condensation de **16** avec l'anhydride phtalique, suivie d'une méthylation par le sulfate de méthyle et d'une oxydation, conduit au composé **22** que l'on a épimérisé en **24** par le diméthoxy-2,2 propane et l'acide trifluoroacétique. La déméthylation de **24** par le chlorure d'aluminium fournit la déméthoxy-4 nor-10 daunomycinone (**4**).

[Traduit par la revue]

Discovery of the antitumor properties of anthracyclines daunomycin (**1**) and adriamycin (**2**) and their subsequent successful clinical application raised interest in anthracycline research internationally (1–3). The study of the nature of their cardiotoxicity (4) and structure–activity relationship remains one of the most active areas of research into cancer chemotherapy. The challenge can be met, at least partially, by a new molecular structure, which exhibits stronger activity against a broader neoplastic syndrome and is much less toxic than daunomycin or adriamycin. Structure modification through partial or total synthesis or by mutant microorganism transformation has afforded a large number of new anthracycline derivatives, several of which have shown very encouraging results in terms of activity and toxicity (5–9). Of these numerous new anthracycline derivatives, no practical or biologically active example involving modification of the basic aglycone skeleton has been reported (3, 10), except the heteroanthracyclines, their aglycones (11–14), and the two recently reported syntheses of 4-demethoxy-8-nordaunomycinone (**4***a*) (16) and its dimethyl ether derivative. However, these elegantly designed syntheses were more laborious and meandering than anticipated and the juxtaposition of the C-7 and C-8 substitutions would eventually hinder the ensuing glycosidation process. All other syntheses involved functional group modification or substitution derivatives of daunomycin, adriamycin, aclacinomycins, and rhodomycins (3, 10, 15). In light of these considerations and of the fact that 4-demethoxydaunomycin is several times more potent than daunomycin and adriamycin (5), we would like to report the total synthesis of (±)-4-demethoxy-10-nordaunomycinone (**4**) and its C-7 epimer **25**.

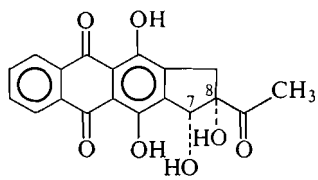


1 R = H
2 R = OH

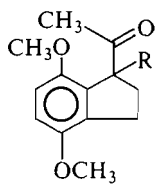


3 R =

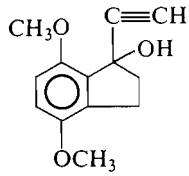
4 R = H



4*a*



5 R = OH
6 R = OAc
16 R = H



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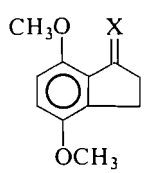

8 X = O
9 X = H_2

Results and discussion

A logical approach to the tetracyclic skeleton would be the Friedel–Crafts condensation of 4,7-dimethoxy-1-hydroxy-1-acetylindane (**5**) with phthalic anhydride, analogous to our early synthesis of 7-*O*-methyl-4-demethoxydaunomycinone (17). However, it was observed that **5** was not stable under acidic conditions. The compound decomposed in the presence of strong Lewis acids. Polymeric unidentifiable amorphous foam was the major product recovered from all reactions involving strong acids. Attempts to condense the corresponding acetoxy compound 4,7-dimethoxy-1-acetoxy-1-acetylindane (**6**) with phthalic anhydride were equally futile. The precursor, 4,7-dimethoxy-1-hydroxy-1-ethynyl-indane (**7**), was also very

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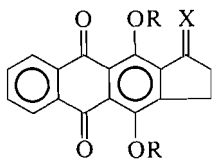
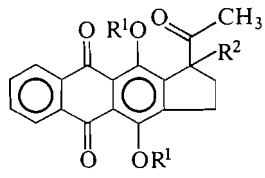
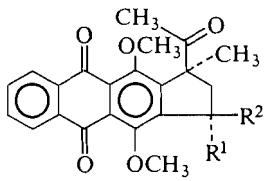


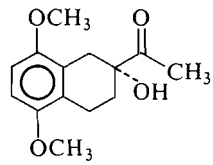
10 R = H, X = H_2
11 R = CH_3, X = H_2
12 R = CH_3, X = O
13 R = CH_3, X = OH, C≡CH



14 R^1 = CH_3, R^2 = OH
17 R^1 = R^2 = H
18 R^1 = CH_3, R^2 = H



19 R^1 = R^2 = H
20 R^1 = OH, R^2 = H
21 R^1 = H, R^2 = OH



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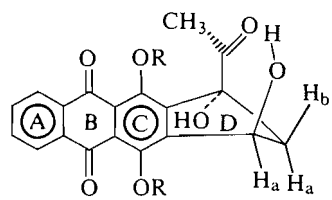
unstable in the presence of strong acids or bases. It regenerated the starting indanone **8**, which was inactive toward all Friedel–Crafts reactions. However, **9**, prepared by reduction of **8** by triethylsilane in trifluoroacetic acid solution, underwent the condensation with phthalic anhydride smoothly, forming the tetracyclic quinone **10** whose methyl ether **11** can be oxidized in good yield to **12** by chromium trioxide – acetic anhydride and converted to the fragile hydroxy acetylene **13** by excess lithium acetylide. Following the lithium acetylide nucleophilic addition process, it was observed that the quinone chromophore disappeared initially, and the D-ring carbonyl group remained practically unaffected until most of the quinone chromophore disappeared. Further reaction with excess lithium acetylide led to an unstable crude product, which displayed only very weak quinone absorption in the infrared spectrum and could not be characterized. But on standing, the quinone carbonyl group was regenerated at a rate faster than the regeneration of the D-ring carbonyl group. This allowed the isolation of **13**, albeit in poor yield. The acetylene group was converted to the acetyl group by mercuric acetate in aqueous acetic acid solution to form the stable intermediate **14**. The low yield of the acetylide addition necessitated a modification of our approach to this compound.

The disparate properties of **5** and its homologue **15** (17) very likely stemmed from the benzylic hydroxyl function, and its removal may facilitate the acylation process with phthalic anhydride. Dehydroxylation, however, proved to be more difficult than anticipated. The yield of **16** from either **5** or **6** under various conditions for dehydroxylation or deacetoxylation of α-hydroxy and α-acetoxyketones or benzylic alcohols was poor, and when reactions were carried out in acidic medium the product contained an unidentifiable polymeric solid as the major component. The small amount of **16** so accumulated did give excellent yield of **17** when it was allowed to react with phthalic anhydride in the presence of aluminium chloride. Thus allylic reduction by a free radical process in nonacidic medium is essential. Eventually, **16** was obtained in good yield when **6** was allowed to react with iron pentacarbonyl and tributylin hydride in xylene solution.

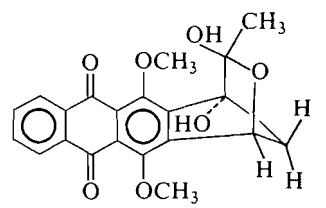
Attempts to methylate **17** by iodomethane under various basic conditions invariably gave **19** as the only methylated product. A 3H singlet at δ 1.55 showed unequivocally the presence of a methyl group, and oxidation of **19** by molecular oxygen in *tert*-butyl alcohol, potassium *tert*-butoxide, and dimethylformamide solution gave a mixture of two compounds whose ^{1}H nmr spectrum revealed the presence of two methyl singlets at δ 1.55 and 1.65 ppm, and four methoxy singlets at δ 3.87, 3.96, 4.05, and 4.08 ppm. Together with a molecular ion M^+ = 380 in the mass spectrum, it is very likely that the oxidation of **19** gave the two isomers **20** and **21**. This result ascertained that a one-step conversion of **18** to **22** and **4** is feasible.

Selective methylation of the phenolic groups of **17** was achieved following the HSAB principal. Thus, methylation of **17** in basic solution by dimethyl sulfate, whose conjugate anion and the phenolic anion were hard bases, gave exclusively the desired product **18**. Oxidation of **18** by molecular oxygen as before gave the *trans*-diol **22**. This convenient bishydroxlation process, reported independently by Swenton and co-workers (18*a*, *b*) and Wong *et al.* (18*c*), provided an easy route to the fully functionalized D-ring of the hetero- and noranthracyclinones. The monohydroxy compound **14** could be isolated as the major product if the reaction was quenched within 0.5 h by dilute acid.

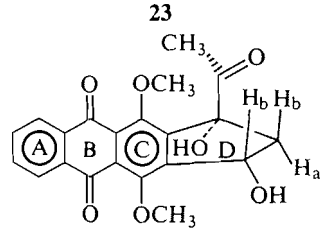
The *trans*-diol **22** exhibits none of the general properties of daunomycinone and heteroanthracyclinone analogues, which gave a mixture of *cis*- and *trans*-diols under similar oxidation conditions, the *trans* isomers isomerizing to the *cis* isomers upon heating in trifluoroacetic acid; furthermore, the *trans* isomers exist in an equilibrium involving the C7-OH and the C9-acetyl groups (11–13) to form hemiacetals. The *trans*-diol **22** was recovered completely after being heated in trifluoroacetic acid for 72 h. Attempts to crystallize it also failed. The corresponding *trans*-diols in the heteroanthracyclinone and anthracyclinone series are also adverse to crystallization. The ^{1}H nmr spectrum of **22** (Fig. 1) shows no sign of an equilibrium between **22** and the hemiacetal **23**. It was thus easily mistaken for the *cis* isomer **24**. The epimerization to **24** was successfully carried out when **22** was heated in an acetone



22 R = CH_3
25 R = H



23



24

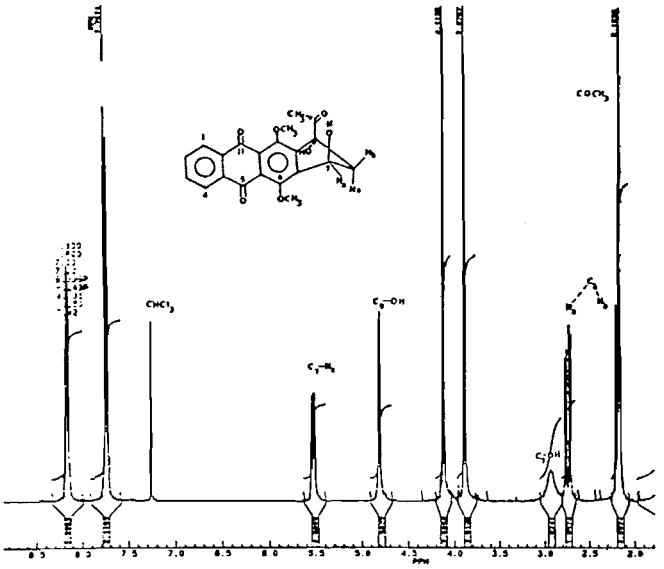


FIG. 1. The ^{1}H nmr spectrum of **22**.

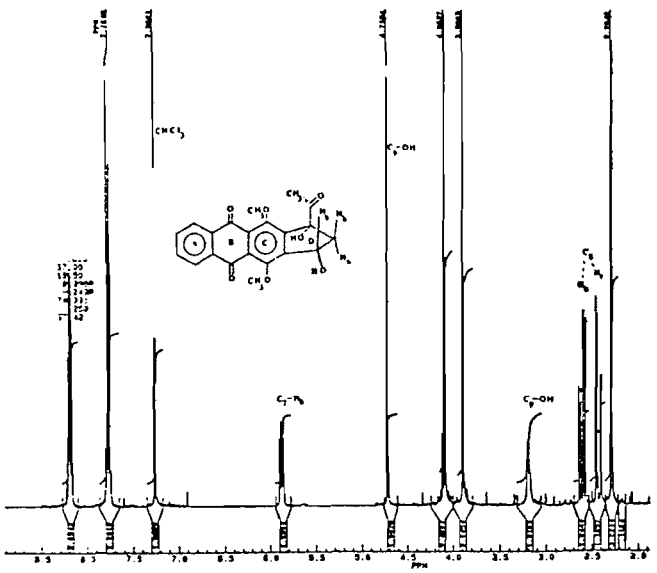


FIG. 2. The ^{1}H nmr spectrum of **24**.

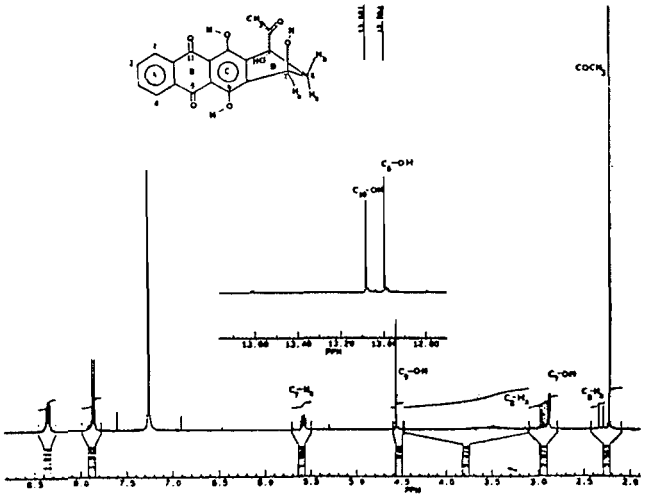


FIG. 3. The ^{1}H nmr spectrum of **25**.

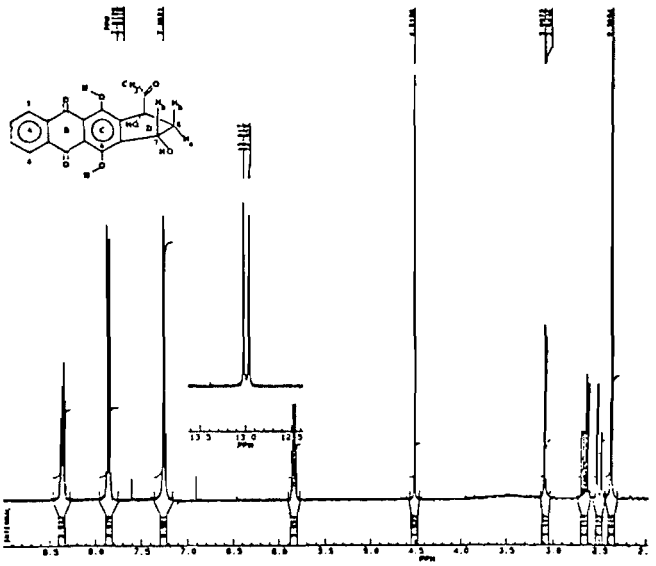


FIG. 4. The ^{1}H nmr spectrum of **4**.

solution of 2,2-dimethoxypropane and trifluoroacetic acid. The ^{1}H nmr spectra of **22** (Fig. 1) and **24** (Fig. 2) detail the structural features of these two isomers. Comparison of these two spectra reveals that the major differences are the chemical shifts and coupling constants of the C7-H_a, C7-H_b, and C8-H_a, H_b. For the *trans*-diol **22**, the free rotation of both C7-OH and C9-$COCH_3$ groups is impeded by the hydrogen bonding between these two groups, freezing the D-ring conformation to the extent that the acetyl methyl group experiences the diamagnetic anisotropic effect of the C-ring and thus appears at δ 2.163 ppm instead of δ 2.285 ppm for that of the *cis*-diol **24**. This conformation of the D-ring also places the C8-H_b of **22** at the fringe of the diamagnetic shielding zone of the acetyl carbonyl function, shifting it to a higher field of δ 2.174 ppm as compared to the C8-H_b of **24** at δ 2.428 ppm. The **22** value J_{7a8b} = 1.7 Hz versus the **24** J_{7b8a} = 5.1 Hz also reflects that the H8b—C8—H7a dihedral angle of **22** is close to 90° instead of 120° for the H7b—C7—C8—H8a dihedral angle of **24**. The H7b of **22** at δ 5.517 ppm, appearing as a broad doublet instead of an eight-line pattern of the X part of a ABMX spin system, is due to the small coupling of $J_{7a,8b}$ = 1.7 Hz and the spin–spin interaction with the fast exchanging C7-OH proton. Also in agreement with the structure is the H7b of **24** at δ 5.875 ppm appearing as a doublet of a doublet with J_{7b8b} = 7.2 Hz and J_{7b8a} = 5.1 Hz.

The demethylation of **22** and **24** to **25** and **4** by aluminum chloride was very easily achieved. Having observed the averseness of **22** to epimerize to **24**, it is surprising to note that **22** gave exclusively **25** and **24** gave exclusively **4**. No epimerization of **4** to **25** or vice versa was observed. The ^{1}H nmr spectra of **25** (Fig. 3) and **4** (Fig. 4) reveal explicitly the structural features of both **25** and **4** and are compatible with those of **22** (Fig. 1) and **24** (Fig. 2). Coupling of **4** to several amino sugars and their cytotoxic activities will be reported separately, together with the biological data of heteroanthracyclines.

Experimental

The ^{1}H nmr spectra were recorded on Bruker WH-90 or Bruker AM-300 spectrometers. Chemical shift is quoted in δ ppm downfield

from TMS using $CDCl_3$ as solvent, unless otherwise specified. The ir spectra were recorded on a Perkin–Elmer 710 Infracord or a Nicolet MX-1 FT spectrometer using CH_2Cl_2 as solvent, and transmittance is quoted in wave numbers (cm^{-1}). Mass spectra were recorded on a Finnigan 1015 spectrometer and high resolution mass spectra were recorded on a V.G. 7070 E HF spectrometer. Melting points were determined on a Fisher–Johns apparatus and are uncorrected.

Preparation of 4,7-dimethoxy-1-ethynyl-1-indanol (7)

To a 3-necked flask (2 L), equipped with a pressure equalized dropping funnel, condenser with drying tube, and a gas dispersion tube, and containing anhydrous tetrahydrufuran (750 mL) saturated with anhydrous acetylene, was added ethyl magnesium bromide in tetrahydrofuran solution (200 mL, 2 *M* solution) dropwise through the dropping funnel at room temperature. Acetylene was introduced continuously. The addition of the ethyl magnesium bromide – tetrahydrofuran solution was controlled at the rate of about 2 mL/min. The solution was then stirred for an additional 20 min and 4,7-dimethoxy-1-indanone (**8**) (30 g) (19) was added. Acetylene was introduced continuously for an additional 0.5 h. The solution was stirred for 2 h at room temperature under anhydrous conditions, poured into ice-cooled saturated ammonium chloride solution (100 mL) to decompose the excess ethynyl magnesium bromide, and then extracted by methylene chloride (3 × 700 mL), washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness to give the crude product (**7**) (26 g), a portion (1 g) of which was purified by fast chromatography over silica and recrystallized from ether–hexane; mp 77–79°C; ir: 3560 (OH), 3300 (C≡C—H), 1610 (aromatic); ^{1}H nmr: 2.38 (q, 1H, C2-H), 2.60 (s, 1H, —C≡C—H), 2.70 (dq, 1H, C2-H), 2.86 (q, 1H, C3-H), 2.97 (dq, 1H, C3-H), 3.74 (s, 1H, —OH), 3.79 (s, 3H, —OCH_3), 3.88 (s, 3H, —OCH_3), 6.72 (s, 2H, aromatic); ms: 218 (M^+), 203 ($M^+ - CH_3$), 201 ($M^+ - OH$), 185 ($M^+ - H_2O - CH_3$).

Preparation of 4,7-dimethoxy-1-acetoxy-1-acetylidane (6)

The crude indanol (**7**) from the previous preparation was dissolved in ethyl acetate (1.5 L) to which was added mercuric acetate (99.5 g) and the mixture was stirred for a period of 24 h at room temperature. Hydrogen sulfide was introduced into the solution until the formation of black precipitate ceased. The precipitate was removed by filtration and the solution was evaporated to dryness under reduced pressure giving the crude crystalline product (**6**) (52 g), which was further purified by recrystallization from methylene chloride – petroleum ether; mp 98–100°C; ir: 1730 (—O—$COCH_3$), 1715 (—$COCH_3$), 1605 (aromatic); ^{1}H nmr: 2.13 (s, 3H, —O—$COCH_3$), 2.25 (s, 3H, —$COCH_3$), 2.30–2.80 (m, 1H, C2-H), 2.85–3.20 (m, 3H, C2-H and C3-H), 3.78 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 6.72 (q, 2H, aromatic); ms: 278 (M^+), 235 ($M - COCH_3$), 192 ($M - 2 \times COCH_3$). *Exact Mass* (high resolution ms) calcd. for $C_{15}H_{18}O_5$: 278.1154; found: 278.1158. *Anal.* calcd.: C 64.72, H 6.52; found: C 64.8, H 6.57.

Preparation of 4,7-dimethoxy-1-acetylindane (16)

An *o*-xylene solution (250 mL) of iron pentacarbonyl (40 mL), tri-*n*-butyltin hydride (2 mL), and **6** (4.6 g) was heated in a 130°C oil bath under N_2 for 72 h. The solution was allowed to cool to room temperature and cupric chloride in acetone solution was added slowly until fizzing or carbon monoxide evolution ceased. The mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with aqueous cupric chloride solution, dried, and evaporated to dryness, giving the crude product (**16**) (3.2 g), which was readily purified by column chromatography over silica and recrystallization from ether – petroleum ether; mp 56–58°C; ir: 1705 ($COCH_3$), 1610 (aromatic); ms: 220 (M^+), 177 ($M - COCH_3$); ^{1}H nmr: 2.144 (s, 3H, $COCH_3$), 2.223 (m, 1H, C2-H), 2.338 (m, 1H, C2-H), 2.78 and 3.03 (2 sym. m, 2H, C3-H3), 3.754 (s, 3H, OCH_3), 3.787 (s, 3H, OCH_3), 4.122 (dd, 1H, C1-H, J = 9 Hz, J = 5.4 Hz), 6.659 (1, 2H, aromatic, J = 9 Hz).

Preparation of 17

Pulverized phthalic anhydride (2.3 g), 4,7-dimethoxy-1-acetylindane (**16**) (2.2 g), NaCl (4 g), and pulverized freshly sublimed aluminum chloride (22 g) was mixed mechanically and heated in a 180°C oil bath for 10 min. The dark red syrupy mixture was allowed to cool, taken up in saturated oxalic acid solution, and stirred overnight at room temperature. The solution with red solid suspension was extracted exhaustively with chloroform and the chloroform extract was washed with saturated oxalic acid solution and water, dried, and evaporated to dryness. The red solid residue (2.7 g) was recrystallized from chloroform–ether; mp 188–192°C; ir: 3500–2700 (chelated OH), 1720 ($COCH_3$), 1625 (chelated quinone), 1595 (aromatic); ^{1}H nmr: 2.37 (s, 3H, $COCH_3$), 2.44 (m, 2H, C8-H2), 3.16 (m, 2H, C7-H2), 4.36 (dd, 1H, C9-H, J = 9 Hz, J = 5 Hz), 7.82 (m, 2H, C2-H, C3-H), 8.33 (m, 2H. C1-H, C4-H), 1304 (s, 1H, chelated OH), 13.15 (s, 1H, chelated OH); ms: 322 (M^+, 40%), 279 ($M - COCH_3$, 100%). *Exact Mass* (high resolution ms) calcd. for $C_{19}H_{14}O_5$: 322.0842; found: 322.0844. *Anal.* calcd.: C 70.78, H 4.38; found: C 70.81, H 4.42.

Preparation of 18 and 19

An acetone solution (100 mL) of dimethyl sulfate (5 mL), potassium carbonate (15 g), and **17** (1 g) was heated under reflux for 24 h. The acetone solution was cooled, filtered, and concentrated. The residue was taken up in methylene chloride, filtered, and evaporated to dryness under reduced pressure. The residue crystallized on standing and was recrystallized from methylene chloride – ether (910 mg); mp 135–137°C; ir: 1715 ($COCH_3$), 1675 (quinone), 1600–1585 (aromatic); ^{1}H nmr: 2.99 (s, 3H, $COCH_3$), 2.30 (m, 1H, C8-H), 2.43 (m, 1H, C8-H), 3.11 (m, 1H, C7-H), 3.25 (m, 1H, C7-H), 3.856 (s, 3H, OCH_3), 3.935 (s, 3H, OCH_3), 4.343 (dd, 1H, C9-H, J = 9.1 Hz, J = 5.7 Hz), 7.75 (m, 2H, C2-H, C3-H), 8.37 (m, 2H, C1-H, C4-H); ms: 350 (M^+, 90%), 307 ($M - COCH_3$, 100%). *Anal.* calcd. for $C_{21}H_{18}O_5$: C 72.0, H 5.14; found: C 72.1, H 5.1.

When dimethylsulfate was replaced by methyl iodide, **19** was isolated as the only product, mp 104–106°C; ir: 1710 ($COCH_3$), 1675 (quinone), 1600–1580 (aromatic); ^{1}H nmr: 1.55 (s, 3H, C9—CH_3), 2.01 (m, 1H, C8-H), 2.44 (m, 1H, C8-H), 3.18 (m, 2H, C7-H2), 3.86 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.75 (m, 2H, C2-H, C3-H), 8.19 (m, 2H, C1-H, C4-H); ms: 364 (M^+, 10%), 321 ($M - COCH_3$, 100%).

Preparation of 6,10-di-O-methyl-4-demethoxy-7-epi-10-nordaunomycinone (22) and 6,10-di-O-methyl-4-demethoxy-7-deoxy-10-nordaunomycinone (23)

To a solution of dry *N,N*-dimethylformamide (50 mL), *tert*-butyl alcohol (10 mL), and potassium *tert*-butoxide (2.2 g) was added **18** (700 mg). The solution was then cooled in a −30°C bath and dry O_2 was introduced for a period of 4 h. Trimethylphosphite (1 mL) was added, the solution was adjusted to pH 8–9 by dilute hydrochloric acid, stirred for 2 h, diluted with water, and extracted exhaustively with chloroform. The residue, obtained after routine work-up of the chloroform solution, was subjected to column chromatography on silica. Elution of the column by chloroform gave **23** (170 mg), recrystallized from methylene chloride – ether; mp 182–184°C; ir: 3450 (C9-OH), 1715 ($COCH_3$), 1675 (quinone), 1595, 1580 (aromatic); ^{1}H nmr: 2.21 (s, 3H, $COCH_3$), 2.22 (ddd, 1H, C8-H_b, J_{8b8a} = 14 Hz, J_{8b7b} = 8.2 Hz, J_{8b7a} = 3 Hz), 2.49 (ddd, 1H, C8-H_a, J_{8a8b} = 14 Hz, J_{8a7a} = 8.4 Hz, J_{8a7b} = 8.0 Hz), 3.23 (ddd, 1H, C7-H_a, J_{7a7b} = 17.5 Hz, J_{7a8a} = 8.5 Hz, J_{7a8b} = 3 Hz), 3.44 (ddd, 1H, C7-H_b, J_{7b7a} = 17.5 Hz, J_{7b8b} = 8.2 Hz, J_{7b8a} = 8.1 Hz), 3.88 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.75 (s, 1H, OH), 7.72–7.78 (m, 2H, C2-H, C3-H), 8.17–8.23 (m, 2H, C1-H, C4-H); ms: 366 (M^+, 1%), 323 ($M - COCH_3$, 100%). In a separate batch where **18** (70 mg) was oxidized under similar conditions for 0.5 h, only **23** (62 mg) was isolated. Further elution of the column by chloroform–acetone (10%) gave the product **22** (280 mg), which defied all attempts to induce crystallization; ir: 3550, (C7-OH), 3440 (C9-OH), 1715 ($COCH_3$), 1670 (quinone), 1600–1580 (aromatic); ^{1}H nmr: 2.163 (s, 3H, $COCH_3$), 2.173 (dd, 1H, C8-H_b, J_{8b8a} = 14.5 Hz, J_{8b7a} = 1.7 Hz), 2.730 (dd, 1H, C8-H_a, J_{8a8b} = 14.5 Hz, J_{8a7a} = 6.5 Hz), 2.920 (s, 1H, C7-OH), 3.877 (s, 3H, OCH_3), 4.113 (s, 3H, OCH_3), 4.80 (s, 1H, C9-OH), 5.517 (bd, 1H, C7-H, $J_{7,8a}$ = 5.9 Hz); ms: 382 (M^+, 1%), 339 ($M - COCH_3$, 100%).

Preparation of 6,11-di-O-methyl-4-demethoxy-10-nordaunomycinone (24)

An acetone solution (20 mL) of 2,2-dimethoxypropane (5 mL), trifluoroacetic acid (1/3 mL), and **22** (80 mg) was heated under reflux in a dry nitrogen atmosphere. The solution was concentrated under reduced pressure, diluted with CH_2Cl_2 (100 mL), and washed with water and sodium bicarbonate solution, then dried and evaporated to dryness. The residue, after separation by tlc on silica, afforded starting material **22** (12 mg) and the product **24** (42 mg), which was recrystallized from CH_2Cl_2–ether; mp 148–151°C; ir: 3560 (C7-OH), 3450 (C9-OH), 1715 ($COCH_3$), 1670 (quinone), 1600, 1580 (aromatic); ^{1}H nmr: 2.285 (s, 3H, $COCH_3$), 2.428 (dd, ^{1}H, C8-H_a, J = 14.4 Hz, J_{8a7b} = 5.1 Hz), 2.602 (dd, 1H, C8-H_b, J_{8b8a} = 14.4 Hz, J_{8b7b} = 7.2 Hz), 3.187 (s, H, C-OH), 3.889 (s, 3H, OCH_3), 4.093 (s, 3H, OCH_3) 4.718 (s, 1H, C9-OH), 5.874 (dd, 1H, C7-H_b, J_{7b8b} = 7.2 Hz, J_{7b8a} = 5.1 Hz), 7.785 (m, 2H, C2-H, C3-H), 8.178 (m, 2H, C1-H, C4-H).

Demethylation of 22 and 24

The *trans*-diol **22** (90 mg) was allowed to react with $AlCl_3$ (500 mg) in anhydrous chloroform solution (20 mL) for a period of 3 h at room temperature. Saturated oxalic acid solution (15 mL) was added and the solution was stirred for $1\frac{3}{4}$ h at room temperature. The aqueous phase was separated and extracted by chloroform, and the combined chloroform solutions, dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure, gave a red solid residue (50 mg), which was purified by precipitation from methylene chloride – ether; mp 225–228°C; ir: 3560 (C7-OH), 3450 (C9-OH), 3600–2600 (chelated phenols), 1720 ($COCH_3$), 1630 (chelated quinone), 1590 (aromatic); ^{1}H nmr: 2.222 (s, 3H, $COCH_3$), 2.307 (dd, 1H, C8-H_b, J_{8b8a} = 14.7 Hz, J_{8b7a} = 3.9 Hz), 2.881 (d, 1H, C7-OH, $J_{OH,7a}$ = 4.6 Hz), 2.943 (dd, 1H, C8-H_a, J_{8a8b} = 14 ***Hz,*** J_{8a7a} = 7.3 Hz), 4.561 (s, 1H, C9-OH), 5.583 (ddd, 1H, $J_{OH,7a}$ = 4.5 Hz, J_{7a8b} = 4.0 Hz, J_{7a8a} = 7.3 Hz), 7.849–7.878 (m, 2H, C2-H, C3-H), 8.235–8.370 (m, 2H, C1-H, C4-H), 12.994 (s, 1H, C6-OH), 13.081 (s, 1H, C10-OH); ms: 354 (M^+, 1%), 311 (M − $COCH_3$, 100%), 293 (M − $COCH_3$ − H_2O, 70%).

Demethylation of **24** to 4-demethoxy-10-nordaunomycinone (**4**) was carried out under identical condition with similar yield, and the crude product showed in tlc that **4** was the only demethylated product; mp 230–232°C; ir: 3560 (weak) (OH), 3430 (OH), 3560–2700 (chelated OH), 1715 ($COCH_3$), 1630 (chelated quinone), 1590 (aromatic); ^{1}H nmr (Fig. 4): 2.369 (s, 3H, $COCH_3$), 2.50 (dd, 1H, C8-H_a, J_{8a8b} = 10.75 Hz, J_{8a7b} = 3.96 Hz), 2.659 (dd, 1H, C8-H_b, J_{8b8a} = 10.74 Hz, J_{8a7b} = 7.4 Hz), 3.091 (d, 1H, C7-OH, $J_{OH,7b}$ = 3.8 Hz), 4.5 (s, 1H, C9-OH), 5.839 (ddd, 1H, C7-H_b, $J_{OH,7b}$ = 3.8 Hz, J_{7b8b} = 7.3 Hz, J_{7b8a} = 4.0 Hz), 7.842 (m, 2H, C2-H, C3-H), 7.872 (m, 2H, C1-H, C4-H), 12.956 (s, 1H, C6-OH), 13.017 (s, 1H, C10-OH).

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1. (*a*) H. Brockman. Fortschr. Chem. Org. Naturst. **21**, 121 (1963); (*b*) L. Ettinger, E. Gaumann, R. Hutter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, P. Reusser, and H. Zahner. Chem. Ber. **92**, 1867 (1959).
2. EORTC International Symposium. Adriamycin Review, Brussels. May, 1974. European Press Medikon. Ghent, Belgium. 1975.
3. F. Arcamone. Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol. 17. Academic Press, New York, 1981.
4. E. Hodgson, J. R. Bend, and R. M. Philpot. Rev. Biochem. Toxicol. **5**, 48 (1983).
5. F. Arcamone. Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol. 17. Academic Press, New York, 1981. Chap. 7. p. 261.
6. G. Cassinelli, F. DiMatteo, A. DiMarco, A. M. Casazza, C. Soranzo, and G. Pratesi. J. Antibiot. **33**, 1468 (1980).
7. F. Arcamone. Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol. 17. Academic Press, New York, 1981. Chap. 6. p. 209.
8. F. Arcamone. Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol. 17. Academic Press, New York, 1981. Chap. 6. p. 196.
9. E. M. Acton, G. L. Tong, C. W. Mosher, and R. L. Wolgemuth. J. Med. Chem. **27**, 638 (1984).
10. H. S. El Khadem. Anthracycline antibiotics. Academic Press, New York. 1982.
11. (*a*) C. M. Wong, W. Haque, H. Y. Lam, K. Marat, E. Bock, and A. Q. Mi. Can. J. Chem. **61**, 1788 (1983); (*b*) L. W. Lown and S. M. Sondhi. J. Org. Chem. **50**, 1413 (1985).
12. C. M. Wong, A. Q. Mi, J. Ren, W. Haque, H. Y. Lam, and K. Marat. Can. J. Chem. **62**, 1600 (1984).
13. C. M. Wong, A. Q. Mi, J. Ren, W. Haque, and K. Marat. Tetrahedron, **40**, 4789 (1984).
14. C. M. Wong. Cancer Chemotherapy Symposium, 69th Canadian Chemical Conference, Saskatoon. June, 1986.
15. F. Arcamone. Doxorubicin anticancer antibiotics. Medicinal Chemistry. Vol. 17. Academic Press, New York, 1981. Chap. 8.
16. (*a*) G. A. Flynn, M. J. Vaal, K. T. Stewart, D. L. Wenstrup, D. W. Beight, and E. H. Bohme. J. Org. Chem. **49**, 2252 (1984); (*b*) I. K. Khanna and L. A. Mitscher. Tetrahedron Lett. **26**, 691 (1985).
17. C. M. Wong, D. Popien, R. Schwenk, and J. TeRaa. Can. J. Chem. **49**, 2717 (1971).
18. (*a*) C. E. Coburn, D. K. Anderson, and J. S. Swenton. J. Chem. Soc. Chem. Commun. 987 (1982); (*b*) J. Org. Chem. **48**, 1455 (1983); (*c*) C. M. Wong, A. Q. Mi, H. Y. Lam, and K. Marat. Synth. Commun. **13**, 15 (1983).
19. R. T. Arnold and H. E. Zaugg. J. Am. Chem. Soc. **63**, 1317 (1941).