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A REGIOSELECTIVE SYNTHESIS OF DAUNOMYCINONE AND RELATED ANTHRACYCLINONES

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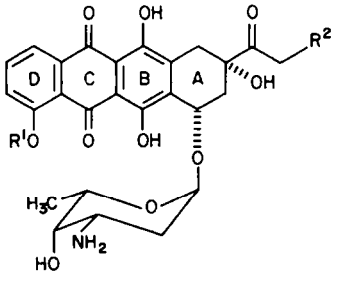
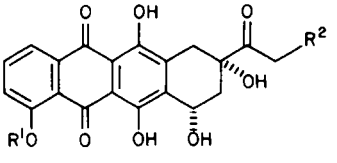
Abstract—The phthalic anhydrides **4a** and **4b** are attacked by the Grignard reagents **15** and **33** in tetrahydrofuran/tetramethylethylene diamine almost exclusively at the carbonyl group, which is situated in the meta position of the methoxy substituent(s). This highly regioselective reaction (minimum : 95 : 5) is used as the key step in a short synthesis of daunomycinone (**2a**), 2-methoxy-7-deoxycarminomycinone (**22b**), γ-rhodomycinone (**8**), and 10-deoxy-γ-rhodomycinone (**9**). The products of the addition of **15** to **4a** and **4b**, the pseudoacids **16** are converted via the olefins **17** and the epoxides **18** into the ketones **19**, which lead by application of known reactions to the anthracyclinones **2a**, **22a**, and **9**. The product, formed by addition of **33** to **4a**, is converted to γ-rhodomycinone (**8**) via the quinone **27**. The precursors of the Grignard reagents **15** and **33**, the bromides **14** and **32**, can be prepared easily and in large scale from the carboxylic acid **10**, which is readily available from the cheap chemicals hydroquinone and succinic anhydride.

The anthracycline antibiotics daunomycin (daunorubicin) (**1a**), adriamycin (doxorubicin) (**1b**), and carminomycin (**1c**) have proven their value as effective chemotherapeutics against several types of human cancer.[1] The total synthesis of these glycosides and related derivatives was felt to be an interesting challenge by many organic chemists, most of them directing their efforts to the synthesis of the corresponding aglycones, the so-called anthracyclinones† daunomycinone (**2a**), adriamycinone (**2b**), and carminomycinone (**2c**).[3] The very early efforts in this field resulted in a non-regioselective preparation, which means that a 1 : 1 mixture of daunomycinone (**2a**) and iso-daunomycinone (**3**) is formed.[4] It turned out, that regioselectivity is a key to any effective synthesis of the aglycones **2a–c**. In order to attain this goal, several synthetic strategies have been applied, the most important being (a) Friedel–Crafts and Fries type reactions,[5] (b) Marschalk reaction,[6] (c) Diels–Alder reaction,[7] and (d) application of metalorganic intermediates.[8] We found, that the anhydrides **4a** and **4b** are attacked by aryl Grignard reagents in a highly selective manner (typical ratio 97 : 3) at the carbonyl group in meta position to the methoxy substituent(s).‡ As the adducts formed in that way can be converted into anthraquinones **5** by intramolecular Friedel–Crafts acylation, an easy way to several naturally occurring anthraquinones[9] like islandicin (**6a**), catenarin (**6b**), erythroglaucin (**6c**), and digitopurpone (**7**) is opened.[10a–c] In this paper the application of this method to the regioselective synthesis of daunomycinone (**2a**) and of the related anthracyclinones 2-methoxy-7-deoxycarminomycinone (**22b**), γ-rhodomycinone (**8**), and 10-deoxy-γ-rhodomycinone (**9**) is described.[10e]

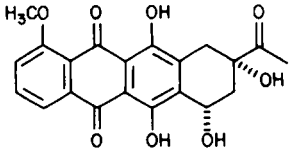


1a–c

a $R^1 = CH_3$, $R^2 = H$
b $R^1 = CH_3$, $R^2 = OH$
c $R^1 = R^2 = H$



2a–c



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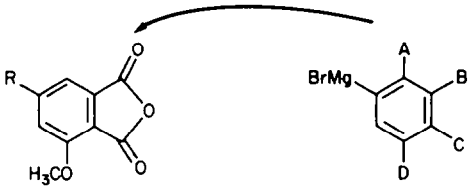
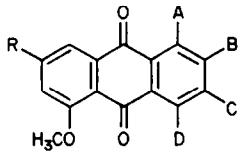
† The terms "anthracyclines" and "anthracyclinones" were created by Brockmann, see ref. 2.

‡ The regioselectivity strongly depends on the solvent system: tetrahydrofuran/tetramethylethylene diamine is the medium of choice to obtain almost exclusively the meta adduct, whereas **4a** is attacked by Grignard compounds predominantly, but with lower selectivity at the ortho carbonyl group, when diethylether is used; see ref. 10*d*.



4a R = H
4b R = OCH_3



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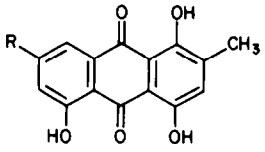
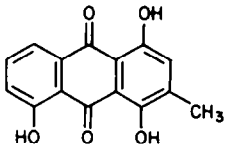


6a R = H
6b R = OH
6c R = OCH_3



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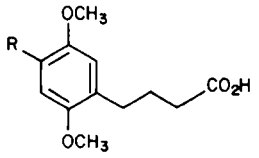
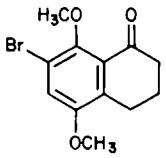


10 R = H
11 R = Br



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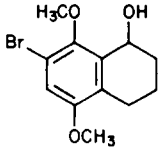

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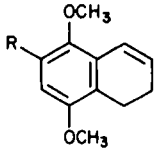


14 R = Br
15 R = MgBr

Daunomycinone (**2a**)

The key step in the synthesis of daunomycinone (**2a**) outlined in Scheme 1 is the regioselective reaction of 3-methoxyphthalic anhydride (**4a**) with the Grignard reagent **15**, prepared from the bromide **14** which proved to be a suitable precursor of the AB-part of the target molecule **2a**.

The preparation of the intermediate starts with the carboxylic acid **10**, which is easily available in two steps in a 100 g scale from the cheap chemicals hydroquinone dimethyl ether and succinic anhydride.[11] Treatment of **10** with one equivalent of bromine affords the product **11** in quantitative yield; obviously the bromine substitutes specifically in para position to the alkyl side chain of the aromatic ring. In a simple three step sequence, which involves Friedel–Crafts cyclization to the α-tetralone **12**, reduction with sodium borohydride to the alcohol **13** and acid catalyzed elimination of water, the olefin **14** is obtained in 76% overall yield from **11**. In the following key step, the bromide **14** (Scheme 1) is converted in the conventional manner into the Grignard reagent **15**, which is allowed to react *in situ* with 3-methoxyphthalic anhydride **4a** in tetrahydrofuran/tetramethylethylene diamine, giving in 65% yield the pseudoacid **16a**, which can be purified by recrystallization from methanol. Very conveniently, however, the crude adduct **16a** is dissolved in anhydrous hydrogen fluoride to afford in 89% yield the anthraquinone **17a**. Application of a simple method for a 1,2 carbonyl transposition, developed in our laboratory,[12] leads to the ketone **19a**. For this purpose, the olefin **17a** is oxidized with meta-chloroperbenzoic acid in the two phase system methylene chloride/phosphate-buffered water to the epoxide **18a**, identified by the ^{1}H-NMR-spectrum. When **18a** is heated in toluene containing catalytic amounts of *p*-toluenesulfonic acid, the ketone **19a** can be isolated in 65% yield after purification by column chromatography. Demethylation with aluminum chloride affords the anthraquinone **20a**.

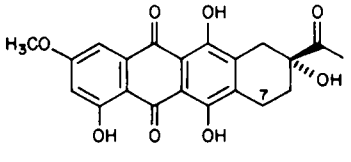
The introduction of the acetyl side chain is effected by the application of a procedure previously used by Kende[7b] and Krohn[7d] in anthracyclinone syntheses: reaction of **20a** with acetylene magnesium bromide, which gives the carbinol **21a**, followed by treatment with mercuric oxide in acidic solution leads to the α-hydroxyketone **22a**.

In order to prove the structure of this product, a sample of natural daunomycine (**1a**) was hydrogenated[13] to **23**. When this carbinol was submitted to demethylation with aluminum chloride, 7-deoxycarminomycinone was obtained, identical with our synthetic product **22a** according to ^{1}H-NMR-, UV-, and IR-spectra and m.p.

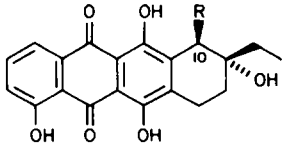
The conversion of 7-deoxycarminomycinone (**22a**) into daunomycinone (**2a**) by selective methylation,[14] followed by bromination at C atom 7, and hydrolysis[7b] is known. On the other hand, the dioxolan **24**, which is easily available by protection of the ketone **19a** has been transformed into **2a**.[15] Thus, the regioselective synthesis of the intermediates **19a** and **22a** opens an easy way to daunomycinone (**2a**).

2-Methoxy-7-deoxycarminomycinone (**22b**)

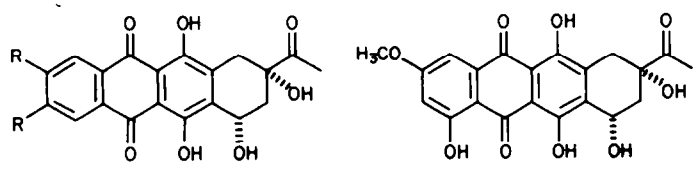
A large number of synthetic and semisynthetic derivatives of **1a–c** have been prepared in order to



22b



8 R = OH
9 R = H

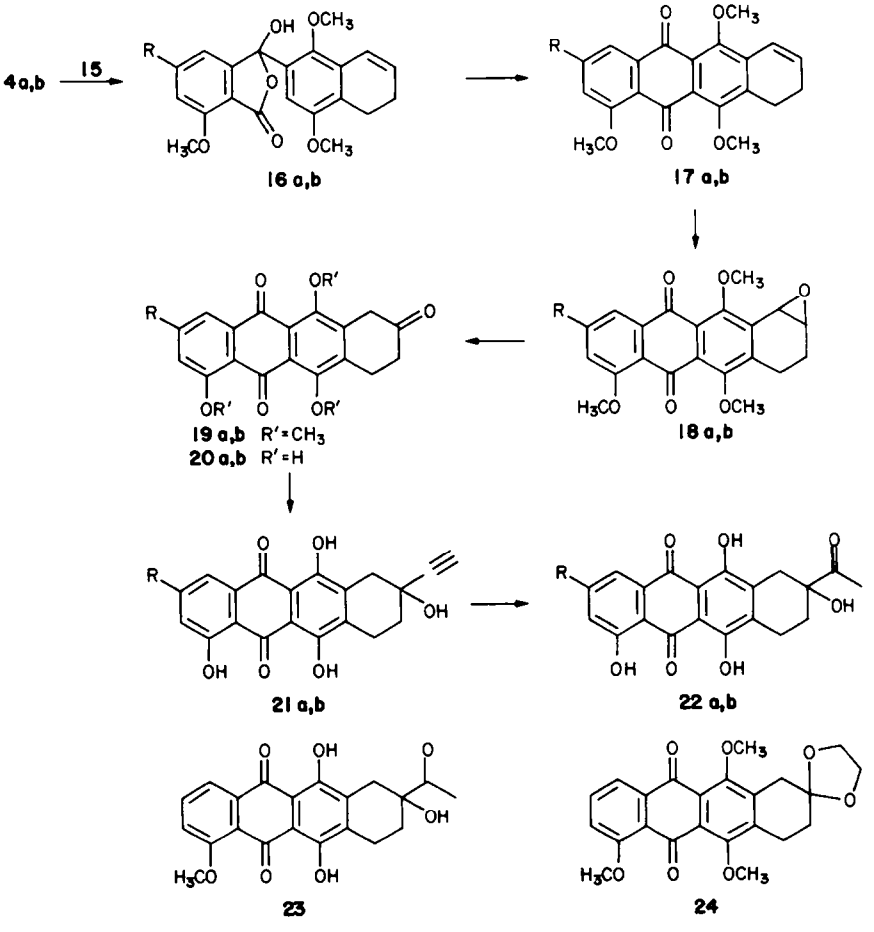


25a R = H
25b R = Cl
25c R = CH_3

26

obtain compounds, which are less toxic than the natural products.[16] However, only a few synthetic anthracyclines, modified in the aromatic D-ring, were tested with respect to their antitumor activity. They have a symmetrical substitution pattern, for example 4-deoxydaunomycinone (**25a**) or the dichloro- and the dimethyl derivative (**25b** and **25c**).[17]

Using the regioselective Grignard addition, we have been able to open a way to 2-methoxycarminomycinone (**26**), a synthetic aglycone, unsymmetrically substituted in the D-ring. Starting with 3,5-dimethoxyphthalic anhydride **4b**,[18] the synthesis of **22b** (Scheme 1; series b) is analogous to that described above for 7-deoxycarminomycinone (**22a**) (Scheme 1, series a). As aryl Grignard reagents were found to attack the anhydride **4b** exclusively at the carbonyl group which is located in the position meta to the methoxy substituents,[10b,c] it is obvious that the product formed in the reaction of **4b** with the aryl magnesium bromide **15** has the structure **16b**. The crude pseudoacid **16b**, isolated in 48% yield, is converted into the tetramethyl ether **19b** via the intermediates **17b** and **18b**. Demethylation to the trihydroxyanthracyclinone **20b** is easily effected with aluminum chloride in methylene chloride. This selective cleavage of the methyl ethers in positions peri to the carbonyl is well known and was applied by us earlier in a synthesis of erythroglaucin (**6c**).[10b,c] By the two step procedure described above in



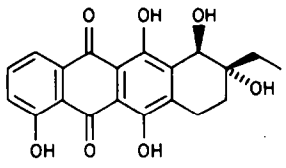
4a,b —15→ **16 a,b** → **17 a,b** → **18 a,b** → **19 a,b** R′ = CH_3 / **20 a,b** R′ = H → **21 a,b** → **22 a,b**

23

24

SERIES a: R = H
SERIES b R = OCH_3

Scheme 1. Regioselective synthesis of 7-deoxycarminomycinone (**22a**) and 2-methoxy-7-deoxycarminomycinone (**22b**).



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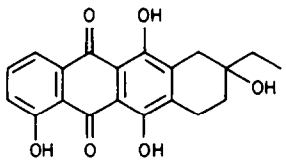

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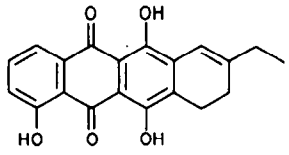
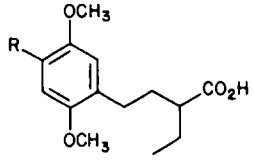
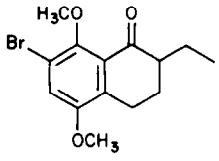


27



28 R = H
29 R = Br



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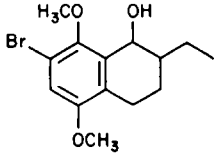

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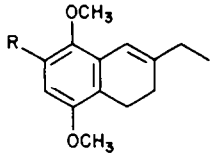
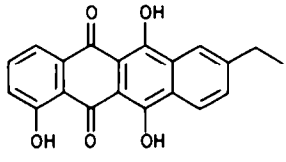


32 R = Br
33 R = MgBr



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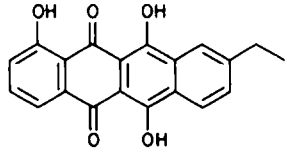

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the series a, 2-methoxy-7-deoxycarminomycinone **22b** is prepared from **20b** via the alkyne **21b**. The hydroxy ketone **22b** is separated from unchanged β-tetralone **20b** by column chromatography and finally isolated in 78% yield relative to consumed **20b**. The hydroxylation at C 7 to give **26** should be possible by the application of the method developed by Kende[7b] in the synthesis of daunomycinone.

γ-Rhodomycinone (**8**) *and* 10-*deoxy-γ-rhodomycinone* (**9**)

In a very elegant way, Brockmann *et al.* have elucidated the structures of many anthracyclinones, which had been isolated from cultures of streptomycetes. γ-Rhodomycinone (**8**) and 10-deoxy-γ-rhodomycinone (**9**) are two representatives of this large family of compounds.[2,19] When we started our work, only a non-regioselective way to **8** and **9** via the olefin **27** was known.[7c]

In the key step of our regioselective synthesis, the Grignard reagent **33** is coupled in the desired regioselective manner with the phthalic anhydride **4a**. Again, the carboxylic acid **10** was chosen as starting material. The attachment of the ethyl side chain is easily accomplished by using Cregers[20] method of double deprotonated carboxylic acids. When the dilithium reagent, prepared from **10**, was quenched with ethyl bromide, the branched **28** was obtained in 94% yield. In analogy to the synthesis of daunomycinone (**2a**), the olefin **32** is prepared in 54% total yield via **29**, **30**,† and **31**. The reaction of the Girgnard compound **33**, produced *in situ* from the bromide **32**, with the anhydride **4a** in tetrahydrofuran/tetramethylethylene diamine, followed by treatment of the crude adduct with anhydrous hydrogen fluoride and demethylation with aluminum chloride lead to the tetracyclic olefin **27** in 45% yield. The spectroscopic data and the melting

† Recently, the ketone **30**, prepared according to this procedure,[10a] was used in a synthesis of α-citromycinone: see ref. 21.

point of the product thus obtained are in accordance with the corresponding values given in the literature.[7c,22] Furthermore, the structure of the olefin **27** and by the way the correct regioselectivity in the addition of **33** to **4a** was proven by the following correlation: heating the quinone **27** with Pd—C leads to aromatization of the A-ring. Brockmann and Zunker have prepared by an unambiguous synthesis the naphthacene quinones **34** and **35**, which show significant differences in the finger print region of the IR-spectra.[22] When the spectrum of the product, obtained by aromatization of **27**, is compared with the spectra given by Brockmann and Zunker, it becomes evident, that the structure **34** has to be assigned to our product. Thus the correct regiochemistry is proven.

The isomeric purity of the trihydroxyanthraquinones described in this work was established by the ^{1}H-NMR spectra. As we[10] and others[23] could demonstrate, the presence of regioisomeric byproducts is easily noticed based on the signals of the chelated OH protons. This method allowed us to conclude that the amount of the undesired regioisomers formed in the Grignard additions, is in all cases less than 5%. Treatment of **27** with *o*-sulfoperbenzoic acid leads to (±)-γ-rhodomycinone (**8**).[7c]

(±)-10-Deoxy-γ-rhodomycinone **9** is prepared by catalytic hydrogenation of the alkyne **21a**, mentioned above as an intermediate in the synthesis of daunomycinone (**2a**).

EXPERIMENTAL

M.ps were determined using a Büchi m.p. apparatus and are uncorrected. ^{1}H-NMR-spectra were recorded using Bruker WH 90 and WH 250 spectrometers; the chemical shifts (δ) are expressed in ppm downfield from TMS. Mass spectra were taken with a Varian MAT CH-5. IR-spectra were recorded on Perkin–Elmer 221, Beckman Acculab 8, and Beckman IR 8 spectrometers. UV-spectra were measured with a Cary 14 apparatus. Sila-gel (Merck; 0.2–0.5 mm) was used for column chromatography; silica gel GF_{254} (Merck) and "DC Fertigplatten Sil G 200" (Merck) for TLC. Tetrahydrofuran (THF) was refluxed over KOH, distilled, then redistilled over $LiAlH_4$ under an N_2 atm. Tetramethylethylene diamine (TMEDA) is refluxed over CaH_2 and distilled under an N_2 atm. See ref. 10c for experimental details concerning the preparation and the reactions of the Grignard compounds.

2 - Ethyl - 4 - (2',5' - dimethoxyphenyl)butyric acid (**28**). To a mixture of 5.7 ml (40 mmol) diisopropylamine in 40 ml THF, which is stirred at −20° under N_2, 25 ml of a 1.6 M soln of n-BuLi in hexane is added. After stirring for 20 min, a soln of 4.48 g (20 mmol) **10** in 10 ml THF is injected with a syringe. The soln is allowed to warm up to room temp, stirred for 90 min, cooled to 0°, treated first with 5 ml hexamethylphosphoric acid triamide (HMPA) and then with 1.5 ml (20 mmol) EtBr. After stirring overnight, the mixture is poured into 300 ml 2% HCl, and extracted five times with a total amount of 500 ml $CHCl_3$. The combined organic layers are washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to give an oil, which is purified by column chromatography (silica gel; $CHCl_3$/EtOAc, 1:1) in order to remove the HMPA. Collection of the yellow eluate, evaporation of the solvent and distillation of the residue under reduced pressure affords 4.75 g (94%) **28** as a colorless oil; b.p. 140° bath temp (0.5 mm); ref. 24 175° (14 mm). IR (neat 3500–2300, 2950, 2830, 1700, 1588, 1498, 1460, 1278, 1220, 1175, 1155, 1120, 1045, 1020, 905, 870, 795, 725, 705. ^{1}H-NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7 Hz, CH_2—$C\underline{H}_3$), 1.44–2.47 (5H, m, 2-H, 3-H and $C\underline{H}_2$—CH_3), 2.64 (2H, t, J = 7 Hz, 4-H), 3.77 (6H, s, OCH_3), 6.74 (3H, s, aromatic H), 11.0 (1H, broad s, OH).

4 - (4' - Bromo - 2',5' - dimethoxyphenyl)butyric acid (**11**). Within 30 min, a mixture of 10.7 g (67.0 mmol) Br_2 and 120 ml AcOH is added drop by drop to a stirred soln of 15.0 g (66.9 mmol) **10** in 200 ml AcOH at room temp. After stirring overnight, the solvent is removed under reduced pressure to give an oily residue, which solidified after several hr. The yield of crystalline **11** is 20.4 g (100%). An analytically pure sample is obtained by recrystallization from aqueous MeOH; m.p. 102–103°. IR(KBr) 3600–2400, 3000, 2940, 2845, 1705, 1500, 1462, 1435, 1412, 1378, 1352, 1310, 1295, 1210, 1138, 1052, 930, 870, 860, 819, 807, 751, 720, 680 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 1.94 (2H, m, 3-H), 2.37 and 2.63 (2H each, t, J = 7 Hz, 2-H and 4-H), 3.76 and 3.84 (3H each, s, OCH_3), 6.73 (1H, s, 6'-H), 7.02 (1H, s, 3'-H), 9.78 (1H, broad s, OH). MS (70 eV) *m/e* 304/302 (100% M^+), 231/229 (81%), M—$CH_2CH_2CO_2H$). (Found: C, 47.21; H, 4.99. Calc for $C_{12}H_{15}BrO_4$ (303.2): C, 47.53; H, 4.99).

2 - Ethyl - 4(4' - bromo - 2',5' - dimethoxyphenyl)butyric acid (**29**) is prepared in the analogous way, starting with 4.75 g (18.8 mmol) **28** and 3.20 g (20 mmol) Br_2. The yield of **19** is 5.48 g (88%); m.p. 82–83°. IR(KBr) 3600–2300, 2920, 1700, 1490, 1450, 1432, 1382, 1330, 1300, 1250, 1210, 1165, 1040, 935, 865, 775 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 0.96 (3H, t, J = 7 Hz, CH_2—$C\underline{H}_3$), 1.47–2.44 (5H, m, 2-H, 3-H, and $C\underline{H}_2$—CH_3), 2.62 (2H, t, J = 7 Hz, 4-H), 3.77 and 3.84 (3H each, s, OCH_3), 6.76 (1H, s, 6'-H), 7.02 (1H, s, 3'-H), 11.1 (1H, broad s, OH). Found: C, 50.90; H, 5.89. Calc for $C_{14}H_{19}BrO_4$ (331.2): C, 50.77; H, 5.78).

7-Bromo-5,8-dimethoxy-1-tetralone (**12**). In a 1 l 3-necked flask, equipped with an overhead stirrer, a drying tube and a glass stopper, 700 g of 85% polyphosphoric acid is heated to 75° (oil bath temp). Under vigorous stirring, 27.5 g (90.7 mmol) **11** is added in small portions over a period of 10 min. The yellow soln is stirred for 40 min at the same temp, then allowed to cool off and poured into 1 kg ice. The mixture is allowed to stand 2 hr under occasional shaking and extracted five times with a total amount of 800 ml $CHCl_3$. The combined organic layers are washed with water, 10% K_2CO_3-soln, and again with water, and dried over Na_2SO_4. The solvent is evaporated, and the solid residue is recrystallized from EtOH to give 22.1 g (86%) **12**; m.p. 78–79°. IR(KBr) 3000, 2940, 2870, 2840, 1680, 1565, 1468, 1440, 1425, 1388, 1320, 1300, 1270, 1220, 1175, 1145, 1065, 1028, 968, 920, 898, 855, 770 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 1.95–2.22 (2H, m, 3-H), 2.53–2.91 (4H, m, 2-H and 4-H), 3.83 (6H, s, OCH_3), 7.20 (1H, s, 6-H). (Found: C, 50.57; H, 4.71. Calc for $C_{12}H_{13}BrO_3$ (285.1): C, 50.55; H, 4.59).

2 - Bromo - 5,6 - dihydro - 1,4 - dimethoxynaphthalene (**14**). A soln of 2.50 g (8.77 mmol) **12** in 100 ml EtOH is added drop by drop to a magnetically stirred suspension of 2.50 g (66 mmol) $NaBH_4$ in 50 ml EtOH at room temp. The mixture is stirred overnight, treated with 2% HCl until the ppt dissolves, and concentrated under reduced pressure to about half of the original volume. After addition to 500 ml water, the soln is extracted five times with a total amount of 400 ml $CHCl_3$. The combined organic extracts are washed twice with water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure leaves 2.7 g crude, oily **13**. [IR (neat) 3430 cm^{-1}], which is dissolved in 100 ml benzene and heated for 90 min with catalytic amounts of *p*-toluenesulfonic acid on a water separator. When the mixture has cooled off, 100 ml diethylether are added. The soln is washed with water and dried over Na_2SO_4. Evaporation of the solvent, followed by distillation of the residue under reduced pressure gives 2.10 g (89%) **14** as a colorless oil, which solidifies when kept in the refrigerator; b.p. 105° (0.005 mm). IR (neat) 3040, 2985, 2930, 2875, 2820, 1560, 1455, 1425, 1410, 1372, 1335, 1293, 1228, 1180, 1090, 1062, 1020, 1010, 980, 955, 822, 790, 765, 725, 700 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.58–2.84 (2H, m, 5-H), 3.75 and 3.78 (3H each, s, OCH_3), ABX_2-signal (4H, δ_A 6.72, δ_B 6.11, δ_X 2.25, J_{AB} = 10 Hz, J_{AX} = 1.5 Hz, J_{BX} = 4.5 Hz, 8-H, 7-H, and 6-H), 6.91 (1H, s, 3-H). (Found: C, 52.75; H, 4.84. Calc for $C_{12}H_{13}BrO_2$ (269.1): C, 53.56; H, 4.87).

2 - Bromo - 7 - ethyl - 5,6 - dihydro - 1,4 - dimethoxynaphthalene (**32**). According to the procedure given for the preparation of **12**, 4.60 g (13.9 mmol) **29** is converted into 3.7 g

30, which is used for the following steps without purification. IR (neat) 3000, 2930, 2870, 2830, 1685, 1565, 1490, 1460, 1415, 1380, 1330, 1290, 1258, 1235, 1210, 1175, 1048, 965, 895, 845, 750 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 0.97 (3H, t, J = 7 Hz, CH_2—C$\underline{H_3}$), 1.25–3.05 (7H, m, other aliphatic H), 3.88 (6H, s, OCH_3), 7.22 (1H, s, aromatic H). In analogy to the preparation of **14**, the crude **30** (3.7 g) is converted into 2.85 g crude **31** [IR (neat) 3450 cm^{-1}], which affords 2.23 g (54%, relative to **29**) **32**; b.p. 140° bath temp. (0.002 mm). IR (neat) 2960, 2930, 2870, 2830, 1640, 1575, 1460, 1430, 1405, 1377, 1335, 1300, 1230, 1170, 1100, 1070, 1040, 1025, 985, 960, 870, 820, 770, 705 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 1.13 (3H, t, J = 7 Hz, CH_2—C$\underline{H_3}$), 2.24 (4H, m, 6-H and C$\underline{H_2}$—CH_3), 2.73 (2H, m, 5-H), 3.75 and 3.78 (3H each, s, OCH_3), 6.46 (1H, broad s, 8-H), 6.87 (1H, s, 3-H). (Found: C, 56.05; H, 5.64. Calc for $C_{14}H_{17}BrO_2$ (297.2): C, 56.75; H, 5.77).

3 - (*5',6' - Dihydro - 1',4' - dimethoxynaphthyl - 2'*) - 3 - *hydroxy* - 7 - *methoxy* - 1 (3H) *isobenzofuranone* (**16a**). To 20 ml THF, which is heated to boiling along with 300 mg (12.4 mmol) Mg turnings under a N_2 atm, are added 2 ml of a soln of 2.69 g (10.0 mmol) **14** in 10 ml THF, then 3 drops of 1,2-dibromoethane and finally the remaining soln of **14**. During this addition the boiling continues without external heating. Then, the mixture is refluxed for 15 min, cooled to room temp, treated with 4 ml TMEDA and the resulting soln finally added within 5 min at −78° to a stirred suspension of 1.78 g (10 mmol) **4a** in 200 ml THF. After stirring overnight at −78° 10 ml 10% HCl is added and the solvent is removed in a rotary evaporator. The residue is taken up in 100 ml ether and 200 ml 7% KOH aq. After separation of the aqueous phase and repeated extraction of the etheral phase with 200 ml 7% KOH aq the combined KOH phases are poured into a mixture of 500 g ice and 100 g conc HCl. Five extractions with a total amount of 500 ml $CHCl_3$, washing the combined $CHCl_3$ phases with water, drying over Na_2SO_4, and removal of the solvent under reduced pressure affords 2.40 g (65%) solid **16a**, which is used for the further steps without purification. A small amount was recrystallized from MeOH to give **16a** with m.p. 182–183°. IR(KBr) 3440, 2930, 2820, 1750, 1605, 1485, 1465, 1390, 1345, 1280, 1225, 1188, 1170, 1150, 1100, 1085, 1050, 1022, 1005, 980, 925, 860, 810, 745 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.76 (2H, m, 5'-H), 3.59, 3.88, and 4.02 (3H each, s, OCH_3), 6.32 (1H, s, 3'-H), ABX_2 signal (4H, δ_A 6.69, δ_B 6.17, δ_X 2.29, J_{AB} = 10 Hz, J_{AX} = 1.5 Hz, J_{BX} = 4.5 Hz, 8'-H, 7'-H, and 6'-H), 7.07 and 7.10 (1H each, d, J = 8 Hz, 4-H and 6-H), 7.66 (1H, t, J = 8 Hz, 5-H), 7.21 (1H, broad s, OH). (Found: C, 68.53; H, 5.37. Calc for $C_{21}H_{20}O_6$ (368.4): C, 68.46; H, 5.47).

3 - (*5',6' - Dihydro - 1',4' - dimethoxynaphthyl - 2'*) - 5,7 - *dimethoxy* - 3 - *hydroxy* - 1 (3H) *isobenzofuranone* (**16b**) is obtained in an analogous procedure starting with **14** and **4b** in 48% (3.98 g) [IR(KBr) 1750] and used without purification.

9,10 - *Dihydro* - 1,6,11 - *trimethoxy* - 5,12 - *naphthacenequinone* (**17a**). In a polyethylene bottle 1.00 g (2.71 mmol) crude **16a** is dissolved in 20 ml ice-cold HF and kept for 2 hr at 0°. The mixture is poured carefully into a 1 l polyethylene beaker, filled to the middle with ice, and extracted five times with a total amount of 400 ml $CHCl_3$. The combined organic extracts are washed with 10% K_2CO_3 aq soln and with water and dried over Na_2SO_4. The crude product, obtained after the evaporation of the solvent, is filtered through a column filled with 100 g silica gel, and eluted with EtOAc to afford 850 mg (89%) **17a** m.p. 163–164°. ^{1}H-NMR($CDCl_3$) δ 2.96 (2H, m, 10-H). 3.91, 3.94 and 4.00 (3H each, s, OCH_3), ABX_2 signal (4H, δ_A 6.90, δ_B 6.31, δ_X 2.33, J_{AB} = 10 Hz, J_{AX} = 1.5 Hz, J_{BX} = 4.5 Hz, 7-H, 8-H, and 9-H), 7.24 (1H, dd, $J_{2,3}$ = 8 Hz, $J_{2,4}$ = 1.5 Hz, 2-H), 7.62 (1H, t, J = 8 Hz, 3-H), 7.78 (1H, dd, $J_{3,4}$ = 8 Hz, $J_{2,4}$ = 1.5 Hz, 4-H).

9,10 - *Dihydro* - 1,3,6,11 - *tetramethoxy* - 5,12 - *naphthacenequinone* (**17b**) is obtained from **16b** in the analogous way in 63% yield; m.p. 182–183°. IR(KBr) 2930, 1670, 1600, 1570, 1455, 1325, 1280, 1240, 1200, 1160, 1100, 1040, 980, 970, 845, 770 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.91 (2H, m, 10-H), 3.88, 3.90, 3.92, 3.94 (3H each, s, OCH_3), ABX_2 signal (4H, δ_A 6.87, δ_B 6.28, δ_X 2.33, J_{AB} = 10 Hz, J_{AX} = 1.5 Hz, J_{BX} = 4.5 Hz, 7-H, 8-H, and 9-H), 6.69 1H, d, J = 2 Hz, 2-H7, 7.22 (1H, d, J = 2 Hz, 4-H). (Found: C, 69.32; H, 5.32. Calc for $C_{22}H_{20}O_6$ (380.4): C, 69.46; H, 5.30).

3,4 - *Dihydro* - 5,7,12 - *trimethoxy* - 2,6,11(1H) - *naphthacenetrione* (**19a**). An ice-cold mixture of 1.2 g (3.42 mmol) **16a**, 100 ml CH_2Cl_2, and 100 ml pH 7 buffer soln (potassium dihydrogen phosphate/disodium hydrogen phosphate; Riedel de Haen) is treated with a soln of 900 mg (5.22 mmol) *m*-chloroperbenzoic acid in 50 ml CH_2Cl_2 and stirred overnight at 0°. After separation of the aqueous layer the organic phase is washed with conc $NaHCO_3$ aq, with 3% $NaHSO_3$ aq, and finally with water. Drying with Na_2SO_4, evaporation of the solvent *in vacuo* affords 1.3 g crude epoxide **17a**, [^{1}H-NMR($CDCl_3$) δ 4.42 (1H, d, J = 4 Hz)], which is dissolved in 400 ml dry toluene and refluxed with 50 mg *p*-toluenesulfonic acid for 60 min. Washing with conc $NaHCO_3$ aq and with water, drying over Na_2SO_4 and evaporation of the solvent under reduced pressure afford 1.35 g crude **19a** (R_f = 0.60) which contains—according to TLC (silica gel, EtOAc)—an impurity (R_f = 0.78), obviously formed by aromatization. By column chromatography (silica gel, EtOAc) 816 mg (65%) **19a** are obtained; m.p. 196–197° (from EtOAc). IR(KBr) 2975, 2940, 2840, 1715, 1675, 1590, 1555, 1455, 1420, 1405, 1330, 1270, 1253, 1210, 1080, 1030, 998, 950, 858, 800, 770, 725, 740, 715, 675 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.57 (2H, m, 3-H), 3.27 (2H, m, 4-H), 3.71 (2H, s, 1-H), 3.91, 3.98, and 4.02 (3H each), 7.27 (1H, dd, $J_{8,9}$ = 8 Hz, $J_{8,10}$ = 1.8 Hz, 8-H), 7.64 (1H, t, J = 8 Hz, 9-H), 7.78 (1H, dd, $J_{9,10}$ = 8 Hz, $J_{8,10}$ = 1.8 Hz, 10-H). (Found: C, 68.90; H, 5.05. Calc for $C_{21}H_{18}O_6$ (366.4): C, 68.83; H, 4.95).

3,4 - *Dihydro* - 5,7,9,12 - *tetramethoxy* - 2,6,11(1H) - *naphthacenetrione* (**19b**) is obtained in the analogous way starting from **17b** via the epoxide **18b** [^{1}H-NMR($CDCl_3$) δ 4.33 (1H, d, J = 4 Hz)] in 53% yield; m.p. 209–210° from EtOAc). IR(KBr) 2950, 1715, 1675, 1600, 1570, 1460, 1405, 1325, 1278, 1240, 1205, 1160, 1088, 1035, 1008, 960, 940, 875, 855, 770 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.58 (2H, m, 3-H), 3.25 (2H, m, 4-H), 3.70 (2H, s, 1-H), 3.92, 3.95, 3.96, 3.98 (3H each, s, OCH_3), 6.75 (1H, d, J = 2 Hz, 8-H), 7.26 (1H, d, J = 2 Hz, 10-H). (Found: C, 66.74; H, 4.98. Calc for $C_{22}H_{20}O_7$ (396.4): C, 66.66; H, 5.09).

3,4 - *Dihydro* - 5,7,12 - *trihydroxy* - 2,6,11(1H) - *naphthacenetrione* (**20a**). A mixture of 253 mg (0.69 mmol) **19a**, 30 ml CH_2Cl_2, and 1.5 g (11.2 mmol) $AlCl_3$ is stirred for 2 hr at room temp and then poured into 300 ml H_2O. Conc HCl (30 ml) is added and the mixture is heated to boiling in an open beaker for 1.5 hr. When the red ppt thus formed is collected and dried *in vacuo*, 180 mg (80%) **20a** are obtained; m.p. 261–264° (ref.[7c] 263–266°). IR(KBr) 3420 (broad), 2940, 1720, 1600, 1455, 1410, 1265, 1195, 1165, 1030, 1010, 935, 780, 740 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.65 (2H, t, J = 7 Hz, 3-H), 3.25 (2H, t, J = 7 Hz, 4-H), 3.65 (2H, s, 1-H), 7.25 (1H, dd, $J_{8,9}$ = 8 Hz, $J_{8,10}$ = 1.5 Hz, 8-H), 7.63 (1H, t, J = 8 Hz, 9-H), 7.79 (1H, dd, $J_{9,10}$ = 8 Hz, $J_{8,10}$ = 1.5 Hz; 10-H), 12.20, 12.80, and 13.47 (1H each, s, OH).

3,4 - *Dihydro* - 5,7,9,12 - *trihydroxy* - 2,6,11(1H) - *naphthacenetrione* (**20b**) is obtained from **19b** (350 mg) in 84% yield (260 mg); m.p. 215–127°. IR(KBr) 1725, 1600 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.63 (2H, t, J = 7 Hz, 3-H), 3.22 (2H, t, J = 7 Hz, 4-H), 3.62 (2H, s, 1-H), 3.93 (3H, s, OCH_3), 6.66 (1H, d, J = 2 Hz, 8-H), 7.35 (1H, d, J = 2 Hz, 10-H), 12.30, 12.76, and 13.26 (1H each, s, OH). (Found: C, 63.64; H, 3.98. Calc for $C_{19}H_{14}O_7$ (354.3): C, 64.41; H, 3.98).

9 - *Acetyl* - 7,8,9,10 - *tetrahydro* - 4,6,9,11 - *tetrahydroxy* - 5,12 - *naphthacenequinone* [(±) - 7 - *deoxycarminomycinone*] (**22a**). A soln of EtMgBr in 15 ml THF, which was prepared from 1.70 g (15 mmol) EtBr and 350 mg (14.4 mmol) Mg turnings, is added within 5 min at 0° to a sat soln of acetylene in THF. During the addition acetylene is passed into the mixture. After addition of 120 mg (0.37 mmol) **20a**, dissolved in 10 ml THF, and stirring for 30 min at 0° the deep purple soln is poured into a mixture of conc HCl and ice. Seven extractions each with 100 ml $CHCl_3$, washing of the combined organic layers with water, drying over Na_2SO_4 and evaporation of the solvent on a rotary evaporator affords 142 mg crude **21a**, which is dissolved in 50 ml acetone and refluxed with 1.00 g HgO and 20 ml 7% HCl for 40 min. The mixture is poured into

500 ml H_2O and extracted seven times with a total amount of 500 ml $CHCl_3$. The combined extracts are washed three times with water and dried over Na_2SO_4. The crude product (140 mg), obtained after evaporation of the solvent, contains according to the (silica gel; $CHCl_3$/EtOAc 1 : 1) unreacted **20a** ($R_f = 0.65$) and the product **22a** ($R_f = 0.52$). Column chromatography affords 72 mg (53%) (±)-**22a**; m.p. 258–260° (ref.[25] 261–262° for (−)-**22a**. ^{1}H-NMR($CDCl_3$) δ 2.00 (2H, m, 8-H), 2.38 (3H, s, $COC\underline{H}_3$), 2.98 (4H, m, 7-H and 10-H), 3.78 (1H, s, OH at C-9), 7.28 (1H, dd, $J_{2,3} = 8$ Hz, $J_{1,3} = 1.5$ Hz; 3-H), 7.68 (1H, t, J = 8 Hz, 2-H), 7.85 (1H, dd, $J_{1,2} = 8$ Hz, $J_{1,3} = 1.5$ Hz, 1-H), 12.22, 12.75, and 13.53 (1H, each, s, chelated OH).

An identical product is obtained by $AlCl_3$-demethylation of **2a**, prepared by hydrogenation of **1a**.[13]

9 - *Acetyl* - 2 - *methoxy* - 7,8,9,10 - *tetrahydro* - 4,6,9,11 - *tetrahydroxy* - 5,12 - *naphthacenequinone* [(±) - 2 - *methoxy* - 7 - *deoxycarminomycinone*] (**22b**) is prepared in the analogous manner from **20b**. The yield of **22b** is 42% (78% in relation to consumed **20b**); m.p. 195–196° IR(KBr) 1710, 1605 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.03 (2H, m, 8H), 2.36 (3H, s, $COC\underline{H}_3$), 3.0 (4H, m, 7-H and 10-H), 3.92 (3H, s, OCH_3), 6.63 (1H, d, J = 2 Hz, 3-H), 7.30 (1H, d, J = 2 Hz, 1-H), 12.32, 12.70, and 13.32 (1H each, s, chelated OH). (Found: C, 63.14; H, 4.65. Calc for $C_{21}H_{18}O_8$ (398.4): C, 63.31; H, 4.55).

8 - *Ethyl* - 9,10 - *dihydro* - 1,6,11 - *trihydroxy* - 5,12 - *naphthacenequinone* (**27**). According to the procedure described above for the preparation of **16a** the bromide **14** is converted into the Grignard reagent **15** and allowed to react with **4a** to give a crude adduct in 73% yield, which is treated with anhydrous HF and finally demethylated with $AlCl_3$ in analogy to the transformations **16a** to **17a** and **19a** to **20a**. In this manner **27** is isolated in 61% yield after recrystallization from AcOH; m.p. 183–185° (ref.[26] 187°; ref.[7c] 180–183°). According to IR-, UV- and mass spectra, the material is identical with that described in ref.[26] ^{1}H-NMR($CDCl_3$) δ 1.18 (3H, t, J = 7 Hz, $CH_2—C\underline{H}_3$), 2.33 (4H, m, 9-H and $C\underline{H}_2—CH_3$), 2.93 (2H, m, 10-H), 6.33 (1H, s, 7-H), 7.25 (1H, dd, $J_{2,3} = 8$ Hz, $J_{2,3} = 1.5$ Hz, 2-H), 7.63 (1H, t, J = 7 Hz, 3-H), 7.84 (1H, dd, $J_{3,4} = 8$ Hz, $J_{2,4} = 1.5$ Hz, 4-H), 12.25, 12.78 and 13.63 (1H each, s, OH).

8 - *Ethyl* - 1,6,11 - *trihydroxy* - 5,12 - *naphthacenequinone* (**34**). In a sublimation apparatus, 10 mg (0.03 mmol) **27** and 10 mg Pd—C are heated to 220° at 0.005 mm. The volatile material is purified by TLC (silica gel; $CHCl_3$; $R_f = 0.3$) and again by sublimation. Thus 6 mg (60%) **34** is isolated; m.p. 198° (ref.[22] 206°). The material is identical with that described in ref.[22] according to IR- and UV-spectra. ^{1}H-NMR($CDCl_3$) δ 1.39 (3H, t, J = 7 Hz, $CH_2—C\underline{H}_3$), 2.86 (2H, t, J = 7 Hz), 7.17–8.33 (6H, m, aromatic-H), 12.39, 14.22, and 15.36 (1H each, s, OH).

(±)-*γ-Rhodomycinone* (**8**) is prepared according to the method described by Kende[7c] from **27**. The yield of **8** is 57%; the product is identical with the natural material according to UV-, IR- and mass spectra.[27] ^{1}H-NMR([D_6]dmso) δ 12.03, 12.66, and 13.68 (s, chelated OH).

(±)-10-*Deoxy-γ-rhodomycinone* (**9**). A mixture of 20 mg (0.057 mmol) **21a**, 15 mg Pd—C, and 20 ml MeOH are hydrogenated at room temp for 2 hr. After separation of the catalyst, 20 ml of a 2N NaOH soln is added and a stream of air is passed through the mixture. Acidification and the usual work-up gives 20 mg crude **9**, which is purified by TLC; m.p. 201–203° (ref.[7c] 203–204°). The yield is 11 mg (55%).

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