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SYNTHESIS OF rac- AND ent-FRIDAMYCIN E

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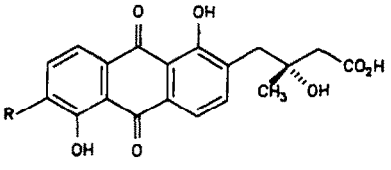
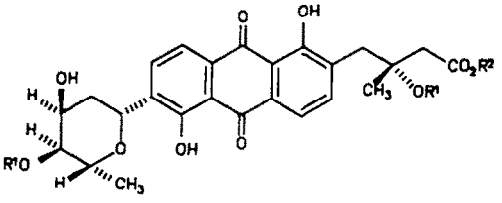
Abstract: Racemic fridamycin E (rac-1) was synthesized in two ways: 1. Addition of lithium tert-butyl acetate to ketone 15 followed by ether and ester cleavage to rac-1; 2. Grignard reaction of allylmagnesium bromide with 15 to rac-18 and subsequent ozonolysis, oxidation, methylation, ester and ether cleavage. The enantiomer ent-18 was obtained by Marschalk reaction of 7 with the chiral building block 20 derived from (S)-lactic acid. A similar reaction sequence converted ent-18 to ent-1 thus proving natural fridamycin E to be of (R)-configuration.

Fridamycin E (1) was isolated by Zähner and Lasar[1] from mutants of Streptomyces parvulus (strain Tü 1989); the structure elucidation were done by Zeeck and Kricke[2]. Compound 1 belongs to a group of closely related anthraquinone antibiotics, further components of the mycelium of the producing strain are the fridamycins A (2), B (3) and D (4)[2]. This class of C-glycosides resembles vinenomycin B_2 (5) isolated by Omura et al.[3] from Streptomyces matensis. Thus, fridamycin E (1) can be regarded as the aglycone of the more complex C-glycosides 2 - 6. Interestingly, 1 has the highest activity against gram positve batceria. However, little is yet known about the possible antitumor activity of these compounds.

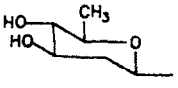


fridamycin		R =
1	E	H
2	A	sugar I
3	B	sugar II
4	D	sugar III

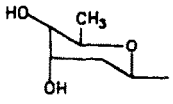


vineomycin B_2 — 5: R^1 = sugar IV

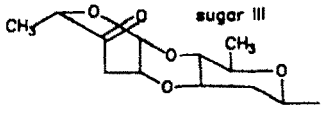
vineomycin B_2 methyl ester — 6: R^1 = H, R^2 = Me



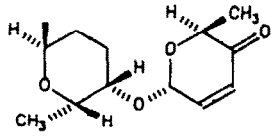
sugar I



sugar II



sugar III



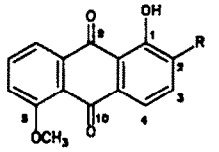
sugar IV

The only synthesis of the related vineomycin B_2 aglycone methyl ester, derived from 5 by methanolysis, was published by Danishefsky et al.[4]. In Danishefsky's synthesis the pyranoside ring was constructed in an asymmetric hetero Diels-Alder reaction of a siloxydiene with an anthraqtinone aldehyde in the presence of $Eu(fod)_3$[5]. The chiral centre of the side chain was created in the reaction of the corresponding ketone with the bromomagnesium salt of 1-menthyl acetate in moderate yield and selectivity[4].

In the present paper we describe an easy access to racemic fridamycin E (1) as well as the enantiomer ent-(1) of the natural product via incorporation of a chiral building block derived from (S)-lactic acid.

An important intermediate for the synthesis of racemic fridamycin E (1) was the ketone 15 and two methods of obtaining this material from commercially available 1,5-dihydroxy-9,10-anthraquinone (anthrarufin) were investigated. A prerequisite for monoalkylation was the selective blocking of one of the phenolic hydroxy groups. The monomethyl ether 7 was obtained

by BF_3-treatment of the corresponding anthrarufin dimethyl ether according to a literature procedure.[6] A straightforward way to alkylate hydroxylated anthraquinones is through the reaction of the corresponding hydroanthraquinones with aldehydes in aqueous alkali (Marschalk reaction).[7,8] Extensive use has been made of this reaction in anthracyclinone syntheses starting from 1,4-dihydroxy-9,10-anthraquinones.[9] However, in contrast to the enhanced reactivity of 1,4-dihydroxy-anthrahydroquinones the less reactive monophenol **7** could not be reacted with nonenolizable aliphatic aldehydes. In order to study the scope and limitation of the Marschalk reaction of monohydroxy-anthrahydroquinones a number of different aldehydes were reacted with the hydroquinone of **7** under various reaction conditions. The result of these experiments are shown in Table 1 and demonstrate that steric hindrance does play an important but not decisive role. For instance, pivalic aldehyde barely reacts at room temperature but steric congestion is overcome at elevated temperatures. In contrast, enolizable aldehydes such as acetic or propionic aldehyde do not react at all most likely due to aldol side reactions prior to Marschalk reaction.



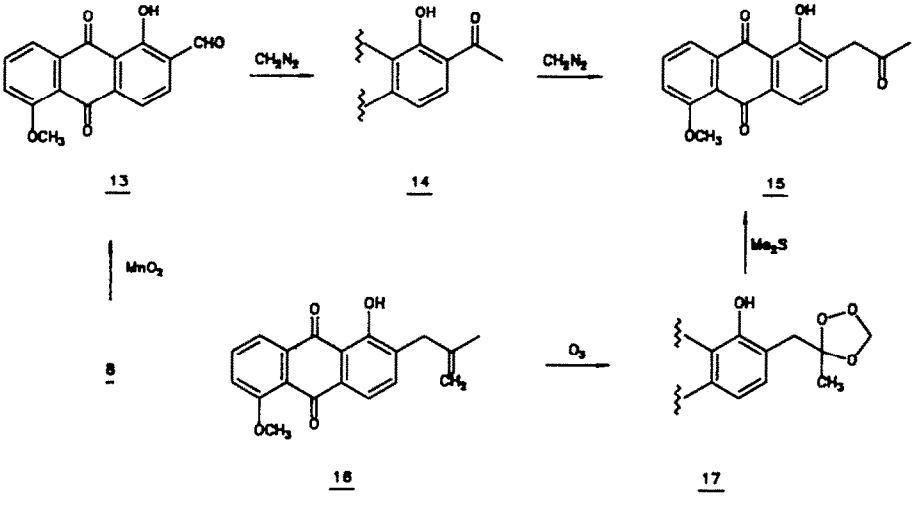
	7	8	9	10	11	12
R	H	CH_2OH	Me	CH(OH)Ph	CH_2Ph	CH_2CMe_3

Table 1: Marschalk Reaction of aldehydes with **7**

R-CHO R-	Reaction conditions [°C], [h]	R'-CH(OH)-R [%]	R'-CH_2-R [%]
H	20, 6	51	10
H	90, 2	12	67
CH_3	20-90, 24	-	-
CH_3CH_2	20-90, 24	-	-
Ph	20, 3	43	14
Ph	90, 2	-	60
Me_3C	90, 6	3	mixture

As a result of these experiments we decided to attach the side chain in a stepwise manner. It was known from the work of Eistert [10] that diazomethane reacts with aldehydes and ketones with insertion of methylene groups. We also knew from previous experiments that diazomethane reacted only very slowly with the chelated phenolic groups. In fact, a 45% yield of the desired propylketone **15** in addition to 19% of the intermediate acetyl compound **14** was isolated in the reaction of the aldehyde **13** with diazomethane in dichloromethane. The starting material **13** was obtained from the hydroxymethyl-anthraquinone **8** by MnO_2 oxidation.

In a second approach to **15** we made use of the unusual mild conditions of the Claisen rearrangement of hydroanthraquinone allyl ethers. This method has been introduced by Rutledge et al.[11] into anthraquinone chemistry and the requisite rearrangement product **16** was known from the work of Baldwin and Rajecka.[12] The olefin **16** was treated with ozone to cleave the double bond and a remarkably stable ozonide **17** could be isolated and fully characterized. Usual reductive workup after ozonolysis provided the ketone **15** in 79 % overall yield from **7**.

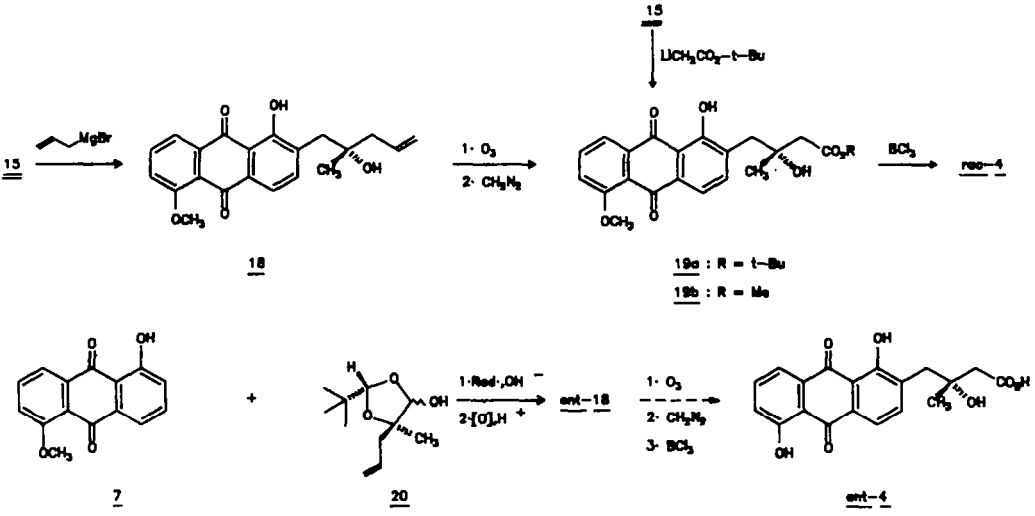


The reaction of the ketone **15** with C_2-nucleophiles was studied next. The work of Danishefsky et al.[4] had shown that the presence of the free phenolic hydroxy group is necessary for the reaction of similar ketones with organometallic reagents. Side reactions occurred with protected derivatives. Addition to the quinone carbonyls and simple enolization of the ketone due to the acidic benzylic protons also took place. In our first experiments poor results were obtained from the reaction of **15** with the lithium enolate from tert-butyl acetate using lithium diisopropylamide (LDA) as a base. However, employing lithium cyclohexylisopropyl amide (LiICA)[13] and a fourfold excess of the reagent we were able to isolate 67% of the adduct **18a** in addition to 17% of starting material after 24 h at room temperature. In an attempt for enantioselective synthesis, the reaction of menthyl acetate with **15** under the above described conditions gave a 2 : 1 mixture of diastereomeric products as inferred from the ^{1}H-NMR spectrum of the crude reaction mixture. Since the asymmetric induction was very low this approach to enantiomerically pure fridamycin E (**1**) as well as the addition of chiral sulfoxides[14] to **15** was abandoned.

Another means of attaching a C_2-fragment which we investigated was the reaction of ketone **15** with allylmagnesium bromide followed by ozonolysis of the double bond and oxidative workup. The expected product rac-**18** was isolated in 44% yield from the Grignard reaction and was very valuable for comparison with an optically active sample (see below). Further conversion to the fridamycin derivative rac-**19b** was effected by ozonolysis of rac-**18** followed by oxidation of the intermediate ozonide with hydrogen peroxide and methylation of the resulting carboxylic acid with diazomethane (37% overall).

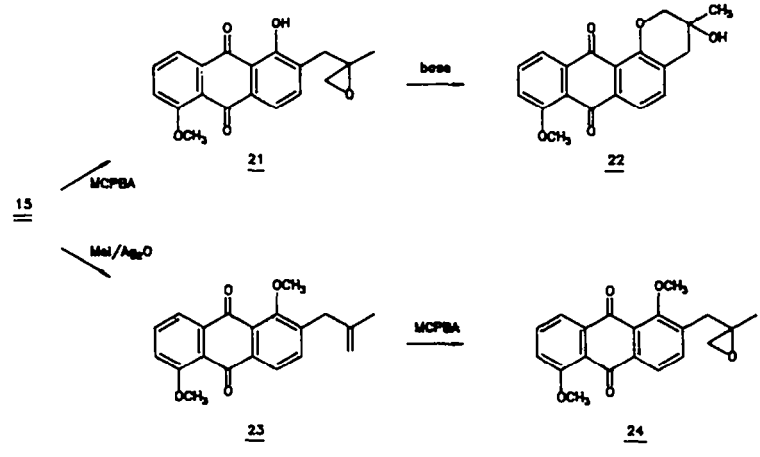
The similarity of the spectral data of rac-**19b** with the previously prepared tert-butyl ester rac-**19a** was used to confirm the structure of rac-**19b**. Treatment of both esters with boron trichloride at -78° cleaved the methyl ethers as well as the ester groups to afford racemic fridamycin E (rac-**1**) identical in all respect except chiroptical properties with a sample of natural fridamycin kindly provided by Prof. Zoeck.

We next turned our attention to the synthesis of an enantiomerically pure sample of **1**. Our basic approach was to attach a chiral C_4 building block in a convergent manner making use of the Marschalk reaction. Possible building blocks for this reaction were previously prepared by our group from (S)-lactic acid and were successfully applied in the synthesis of anthracyclinones.[15] The lactol **20** was obtained in good yield by DIBAH reduction of the corresponding lactone acetal synthezised according to the method of Seebach et al.[16] from (S)-lactic acid. Due to the reduced reactivity (see Table 1) of the monophenol **7** compared with quinizarine its reaction with **20** was very slow and partial decomposition of the product to the ketone **15** occurred. However, a pure sample of the optically active ent-**18** ($[\alpha]_D$ = 24°) could be isolated from the reaction mixture by thin layer chromatography. This material was identical in all anisotropic properties with the racemic material prepared earlier. Similar chemical transformations (ozonolysis, oxidative workup and CH_2N_2 treatment) gave the ester ent-**19b**, which then was cleaved to the antipode of Fridamycin E ent-**1**. In fact, no loss of chiral information had occurred during the synthetic sequence. This was shown by the identical melting point of 168° and by an optical rotation approximately opposite (-11.0°) to the value observed for the natural product (+9.67°).[2]

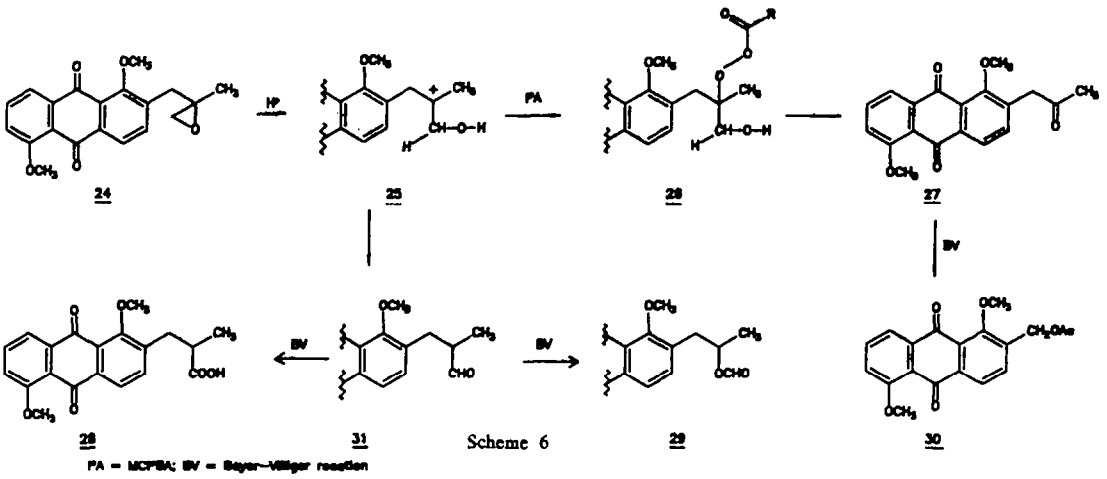


Finally a third approach to fridamycin E (**1**) based on the addition of nucleophilic acyl anion equivalents to the epoxide **21** was investigated. This synthetic scheme is potentially also applicable to the "angucycline"[17] class of quinone antibiotics. A total synthesis of **1** has not yet been completed in this manner, but some interesting observations during the epoxidation step shall be recorded here.

The olefin **16** was treated in preliminary experiments with meta-chloroperbenzoic acid (MPBCA) to yield the phenolic epoxide **21**. This compound proved to be very unstable and easily underwent cyclization by intramolecular nucleophilic attack of the phenolic group to the oxirane ring to afford the anthrapyran ring system **22**. Obviously the phenolic group had to be protected prior to any interaction with nucleophiles. Methylation of **21** with methyl iodide and silver oxide gave the dimethyl ether **24** in only moderate yield (38 %).



A better way to obtain **24** seemed to be the epoxidation of the corresponding dimethyl ether **23**. However, four new products **27** - **30** were isolated instead of the epoxide **24** in the reaction of **23** with excess MCPBA. Especially unexpected was the formation of ketone **27** as the result of a formal oxidative C=C-cleavage. An explanation of the possible mechanistic reaction pathway is shown in Scheme 6. In the first event the epoxide **24** is protolytically opened to the relatively stable tertiary cation **25** in presence of meta-chlorobenzoic acid liberated during the reaction. This cation **25** can rearrange to the intermediate aldehyde **31** which then undergoes normal Bayer-Villiger rearrangement in presence of MCPBA to yield **29**. However, and this is rather unusual and perhaps due to the relative stability of the cation **25**, addition of the nucleophilic MCPBA to **25** could lead to a perester intermediate **26** which then decomposes to the ketone **27**.



Scheme 6

EXPERIMENTAL

For general remarks and instrumentaion see ref.[18]. Elemental analyses were performed at the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig. The optical rotations were measured with a Perkin Elmer Model 241 polarimeter.

1-Hydroxy-2-hydroxymethyl-5-methoxy-9,10-anthraquinone (**8**). A soln of 5.00 g (19.6 mmol) of phenol[6] **7** in 300 ml of methanol and 400 ml of 1 N NaOH was reduced by addition of a soln 5.3 g of sodium dithionite in 100 ml of water (N_2). 28.3 g (0.35 mol) of 37% aqueous formaldehyde was added and the reaction monitored by TLC. After 3 h at 20° the solution was poured into 500 ml of water containing 2 ml of 30% hydrogen peroxide. The soln was acidified (1 N HCl) and extracted with CH_2Cl_2. Less polar products and starting material were removed by filtration (CH_2Cl_2) through a short column of silica gel. Elution with CH_2Cl_2/5% MeOH and crystallization from ether afforded 2.54 g (51%) of **8**, m.p. 200°C. IR: 3260 cm^{-1} (OH), 1670 (quinone), 1636 (quinone), 1589 (Ar); UV: 225 nm (4.57), 253 (4.34), 274 (sh, 4.05), 409 (3.96); ^{1}H-NMR (300 MHz) δ 4.05 (s, 3 H, 5 -OCH_3), 4.83 (d, J = 6 Hz, 2 H, 1'-H), 7.37 (dd, J = 8.0 Hz, 1.0 Hz, 1 H, 6-H), 7.7 - 7.82 (m, 3 H, 3,4,7-H), 8.0 (dd, J = 8.0 Hz, 1.0 Hz, 1 H , 8-H), 12.87 (s, 1 H , 1-OH); mass spectrum (150°) 284 (M^+, 100%), 267 (37), 237 (53). Found: C, 67.15; H, 4.35. Calc for $C_{16}H_{12}O_5$: C, 67.15; H, 4.35%.

2-Formyl-1-hydroxy-5-methoxy-9,10-anthraquinone (**13**). A soln of 1.00 g (3.5 mmol) of **8** in 200 ml of dry CH_2Cl_2 was stirred at 20° with 10.00 g (116 mmol) of activated MnO_2. The mixture was filtered after 2 h and carefully washed with acetone. The solvent was removed i. vac. and the residue crystallized from ether to afford 0.89 g (89%) of **13**, m.p. 215°. IR 1695 (CH=O), 1665 (quinone), 1635 (quinone) 1583 (Ar); UV 224 nm (4.50), 235 (sh, 4.36), 243 (sh, 4.34), 410 (3.98); - ^{1}H-NMR (300 MHz) δ 4.08 (s, 3 H, 5-OCH_3), 7.41 (dd, J = 8.0 Hz, 1.0 Hz, 1 H, 6-H), 7.78 (t, J = 8.0 Hz, 1 H, 7-H), 7.85 (d, J = 8.0 Hz, 1 H, 4-H), 8.01 (dd, J = 8.0 Hz, 1.0 Hz, 1 H, 8-H), 8.21 (d, J = 8.0 Hz, 1 H, 3-H), 10.60 (s, 1 H , CHO), 13.12 (s, 1 H, 1-OH); mass spectrum (120°) 282 (M^+, 50%), 268 (M^+ - 14, 13), 254 (M^+ - CO, 100). Found: C, 68.03; H, 3.58. Calc for $C_{16}H_{10}O_5$: C, 68.09; H, 3.57%.

General procedure for the reaction of various aldehydes with **7**. A soln of 1.00 g (4 mmol) of **7** in 100 ml of THF and 50 ml of MeOH was treated with 3 mmol 1 N NaOH and 25 mmol of sodium dithionite (change of colour from red to yellow). A sol of 40 mmol of the corresponding aldehyde in 20 ml of THF was then added and the reaction monitored by TLC. Reaction tem peratures and times are given in Table 1. Reoxidation was effected by bubbling air through the solution after consumption of the starting material. Workup proceeded as described for **8** and the products were isolated by column chromatography

1-Hydroxy-5-methoxy-2-methyl-9,10-anthrachinon (**9**). Starting material: 200 mg; yield 141 mg of **9** (67%); m.p. 183° (ref.[19] 185° -186°). ^{1}H-NMR (300 MHz) δ 2.33 (s, 3 H, 2-CH_3), 4.02 (s, 3 H, OCH_3), 7.38 (dd, J = 8 Hz, 1 Hz, 1 H, 6-H), 7.75-7.83 (m, 3 H, 3,4,7-H), 7.95 (dd, J = 8 Hz, 1 Hz, 1 H, 8-H), 12.70 (s, 1 H, OH).

1-Hydroxy-2-hydroxybenzyl-5-methoxy-9,10-anthraquinone (**10**). Conditions A: 200 mg (0.8 mmol) of **7**, 840 mg (4.8 mmol) of $Na_2S_2O_4$, 848 mg (0.8 ml/8 mmol) of PhCHO; 3 h at 20°. Yield: 122 mg (43%) of **10**; 37 mg (19 %) of **11**. m.p. 138°C. IR 3460 cm^{-1} (OH), 1655 (quinone), 1630 (quinone), 1583 (Ar); UV 227 nm (4.53), 255 (4.39), 272 (sh, 4.15), 414 (3.96); ^{1}H-NMR (300 MHz) δ 4.05 (s, 3 H, OCH_3), 6.21 (s, 1 H, 1'-H), 7.17 - 8.13 (m, 10 H, Ar), 12.93 (s, 1 H, OH); mass spectrum (160°) 360 (M^+, 100%), 341 (82), 325 (23), 313 (20), 206 (8), 283 (25), 267 (25), 255 (61), 77 (53). Found: C, 73.53; H, 4.21. Calc for $C_{22}H_{16}O_5$: C, 73.33; H, 4.47%.

2-Benzyl-1-hydroxy-5-methoxy-9,10-anthraquinone (**11**). Conditions B: Same as A but reaction maintained for 2 h at 90°. Yield: 152 mg (60%). m.p. 155°C. IR 1660 cm^{-1} (quinone), 1628 (quinone), 1580 (Ar); UV 212 nm (sh, 4.42), 226 (4.49), 254 (4.32), 272 (sh, 4.13), 412 (3.82); ^{1}H-NMR (300 MHz) δ 4.05 (s, 3 H, OCH_3), 4.15 (s, 2 H, 1'-H), 7.20-7.95 (m, 10 H, Ar-H), 12.83 (s, 1 H, OH); mass spectrum (110°) 344 (M^+, 64%), 330 (40), 253 (100), 239 (54), 225 (10), 77 (15). Found: C, 76.69; H, 5.05. Calc for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68%.

1-Hydroxy-2-(2,2-dimethyl-2-hydroxypropyl)-5-methoxy-9,10-anthraquinone (**12**). Conditions B. 200 mg (0.8 mmol) of **7**, 840 mg (4.8 mmol) of $Na_2S_2O_4$, and 688 mg (8 mmol) of pivalaldehyde; reaction for 6 h at 90°. Yield 8 mg (3%); m.p. 110°. IR 3450 cm^{-1} (OH), 1670 (quinone), 1620 (quinone), 1585 (Ar); UV 220 nm (4.33), 224 (4.34), 253 (4.14), 410 (3.63), 416 (3.63); ^{1}H-NMR (300 MHz): δ 0.99 (s, 9 H, t-butyl), 4.06 (s, 3 H, OCH_3), 4.94 (s, 1 H, 1'-H), 7.25 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 6-H), 7.72 (t, J = 8.5 Hz, 1 H, 7-H), 7.77 (s, 2 H, 3-H, 4-H), 7.96 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 8-H), 13.11 (s, 1 H, OH). Found: C, 70.00; H, 5.88. Calc for $C_{20}H_{20}O_5$: C, 70.37; H, 5.92%.

Ozonide (**17**). Sudan III (1-[(phenylazo)-phenyl]azo-2-naphthol) (10 mg) was added to a soln of 1.00 g (3.2 mmol) of **16** in 250 ml of CH_2Cl_2. Ozone was bubbled into the cooled soln (-78°) until the colour changed from red to yellow. Excess O_3 was removed by flushing the soln with N_2. The solvent was removed i. vac. at 20° and the residue crystallized from ether to afford 0.98 g (87%) of ozonide **17** as yellow needles; m. p. 90°. IR 1665 cm^{-1} (quinone), 1620 (quinone), 1583 (Ar); UV 226 nm (4.58), 2.54 (4.38), 280 (sh, 4.04), 413 (4.01); 1H-NMR (300 MHz) δ 1.49 (s, 3 H, 3'-CH_3), 3.19/3.28 (AB, J = 14 Hz, 2 H, 1'-CH_2), 4.06 (s, 3 H, 5-OCH_3), 5.09 (AB, J = 14 Hz, 2 H, 4'-CH_2), 7.38 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 6-H), 7.76 (m, 3 H, 3,4,7-H), 8.0 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 8-H), 12.93 (s, 1 H, 1-OH); ^{13}C-NMR (100 MHz) δ 21.90 (C-3'), 36.08 (C-1'), 56.60 (5-OCH_3), 94.03 (C-4'), 109.30 (C-2'), 115.20 (C-13), 118.50 (C-6), 118.74 (C-7), 121.57 (C-11),

130.34 (C-12), 133.90 (C-2), 135.01 (C-4), 135.44 (C-14), 139.50 (C-3), 160.53 (C-1), 188.8 (C-9/C-10); mass spectrum (110°) 269 (100%), 253 (93), 239 (21), 225 (14), 209 (8). Found: C, 64.00; H, 4.51. Calc for $C_{19}H_{16}O$: C, 64.04; H, 4.53%.

1-Hydroxy-5-methoxy-2-(2-oxopropyl)-9,10-anthraquinone (**15**). a) Via reduction of ozonide **17**. Ozonolysis was performed as described for **17** with the same amount (1.00 g) of starting material **16**. 15 ml (0.2 mol) of dimethylsulfide was added and the solution was stirred an additional 12 h at 20°. The solvent was removed i vac and the residue filtered through a short column of silica gel (CH_2Cl_2) to afford 840 mg (96%) of **15** as yellow plates (ether/petrol ether), m.p. 182 - 183° (ref [2] 183°). IR 1717 cm^{-1} (C=O), 1668 (quinone), 1635 (quinone), 1585 (Ar); UV 225 nm (4.40), 254 (4.20), 278 (sh, 3.86), 412 (3.80); ^{1}H-NMR (400 MHz) δ 2.30 (s, 3 H, 3'-CH_3), 3.84 (s, 2 H, 1'-CH_2), 4.05 (s, 3 H, 5-OCH_3), 7.35 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 6-H), 7.49 (d, J = 8.5 Hz, 1 H, 3-H), 7.71 (d, J = 8.5 Hz, 1 H, 4-H), 7.74 (t, J = 8.5 Hz, 1 H, 7-H), 7.95 (dd, J = 8.5 Hz, 1.0 Hz, 1 H, 8-H), 12.75 (s, 1 H, 1-OH); ^{13}C-NMR (100 MHz) δ 29.85 (C-3'), 44.32 (C-1'), 56.54 (5-OCH_3), 115.25 (C-13), 118.67 (C-6), 119.01 (C-7), 119.44 (C-8), 121.47 (C-11), 129.51 (C-12), 134.01 (C-2), 134.98 (C-4), 135.25 (C-14), 138.18 (C-3), 159.88 (C-5), 160.51 (C-1), 181.32 (C-10), 188.70 (C-9), 204.68 (C-2'); mass spectrum (110°) 310 (M^+; 71%), 295 (28), 282 (26), 268 (M^+ - C_2H_2O; 100), 253 (85). Found: C, 69.82; H, 4.45. Calc for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55%.

b) Via reaction of **13** with diazomethane. A soln of 500 mg (1.8 mmol) of **13** in 50 ml of CH_2Cl_2 was treated with 10 ml of a solution (0.1 molar) of diazomethane in ether. The solvent was removed i. vac. and the residue separated by column chromatography on silica gel (CH_2Cl_2) to afford 250 mg (45%) of **15** from the polar fraction.

1-Hydroxy-5-methoxy-2-acetyl- 9,10-anthraquinone (**14**). From the less polar fraction of the chromatography 102 mg (19%) of (**14**) was isolated; m. p. 210°. IR 1670 cm^{-1} (C=O, quinone), 1630 (quinone), 1587 (Ar); UV 234 nm (4.39), 282 (sh, 3.88), 409 (3.83), ^{1}H-NMR δ 2.77 (s, 3 H, 2'- CH_3), 4.08 (s, 3 H, 5-OCH_3), 7.41 (dd, J = 8.0 Hz, 1.0 Hz, 1 H, 6-H), 7.78 (t, J = 8.0 Hz, 1 H, 7-H), 7.81 (d, J = 8.0 Hz, 1 H, 4-H), 8.02 (dd, J = 8.0 Hz, 1.0 Hz, 1 H, 8-H), 8.19 (d, J = 8.0 Hz, 1 H, 3-H), 13.52 (s, 1 H, 1-OH); mass spectrum (140°) 296(M^+, 100%), 281 (M^+ - 15, 84), 263 (11), 254 (33), 236 (11), 225 (22). Found: C, 68.65; H, 4.15. Calc for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08%.

(R)-1-Hydroxy-2-(2-hydroxy-2-methyl-4-pentenyl)-9,10- anthraquinone (**18**). According to the general procedure for the Marschalk reaction 100 (0.4 mmol) of **7**, 420 mg (2.4 mmol) of $Na_2S_2O_4$ and 800 mg (4 mmol) of lactol **20**[15] at 90° for 24 h to afford 12 mg (10%) of ent-**18** m.p. 72°, $[\alpha]_D$ = -24° (c 0.2, chloroform); IR 3450 cm^{-1} (OH), 1660 (quinone), 1628 (quinone), 1580 (Ar); UV 225 nm (4.39), 254 (4.23), 282 (sh, 3.93), 416 (3.85); ^{1}H-NMR (300 MHz) δ 1.20 (s, 3 H, -CH_3), 2.33 (d, J = 7.4 Hz, 2 H, 3'-H), 2.46 (s, 1 H, OH), 2.90/3.03 (AB, J = 13.6 Hz, 2 H, 1'-H), 4.06 (s, 3 H, OCH_3), 5.18 (dt, J = 16 Hz, 2 H, 5'-H), 5.97 (mc, J = 16 Hz, 2.2 Hz, 7.4 Hz, 13 Hz, 4'-H), 7.37 (dd, J = 8.5 Hz, 1 Hz, 1 H, 6-H), 7.59 (d, J = 8.5 Hz, 1 H, 3-H), 7.73 (t, J = 8.5 Hz, 1 H, 7-H), 7.76 (d, J = 8.5 Hz, 1 H, 4-H), 7.99 (dd, J = 8.5 Hz, 1 Hz, 1 H, 8-H), 13.10 (s, 1 H, OH). Found: C, 71.33; H, 5.68. Calc for $C_{21}H_{20}O_5$: C, 71.58; H, 5.73%.

rac-1-Hydroxy-2-(2-hydroxy-2-methyl-4-pentenyl)-9,10-anthraquinone (rac-**18**). A soln of allylmagnesium bromide, prepared from 1.0 ml (11.4 mmol) of allylbromide and 280 mg (11.6 mmol) of magnesium in 30 ml of dry ether was added to a soln of 200 mg (0.66 mmol) of **15** in 20 ml of dry THF. The mixture was quenched with 30 ml of a saturated soln of ammonium - chloride after 2 h. Usual workup and chromatography on silica gel afforded 50 mg (44%) of rac-**18** as an oil; for data see **18**.

tert-Butyl 2-(9,10-Dihydro-1-hydroxy-5-methoxy-9,10-dioxo-2-anthryl)-3-hydroxy-3-methyl butanoate (rac-**19a**). A soln of lithium isopropylcyclohexyl amide was prepared from 1.53 ml of isopropylcyclohexyl amine and 4 ml of BuLi (1.6 molar) at 0°. The ester enolate of tert-butyl acetate was prepared by treatment of 330 mg (2.84 mmol) of the acetate in 30 ml of dry THF for 0.5 h at -78° with LiICA. A soln of 200 mg (0.65 mmol) of ketone **15** in 20 ml of THF was added and the soln stirred for 24 h. The reaction mixture was diluted with 200 ml of CH_2Cl_2 and acidified with a saturated aqueous soln of ammonium chloride. Usual workup and TLC separation afforded 180 mg (65%) of rac-**19a**; m.p. 80°. IR 3450 cm^{-1} (OH), 1735 (CO), 1670 (quinone), 1635 (quinone), 1590 (Ar); UV 226 nm (4.54), 254 (4.35), 280 (sh, 3.97), 416 (3.97); ^{1}H-NMR (400 MHz) δ 1.28 (s, 3H, 2'-CH_3), 1.48 (s, 9 H, C(CH_3)$_3$), 2.46 (s, 2 H, 3'-H), 2.94/3.02 (AB, J = 13.4 Hz, 2 H, 1'-H), 4.05 (s, 3 H, 5-OCH_3), 4.14 (broad s, 2'-OH), 7.37 (dd, J = 8.0 Hz, J = 1.5 Hz, 1 H, 6-H), 7.69 (t, J = 8.0 Hz, 1 H, 7-H), 7.73 (d, J = 8.0 Hz, 1 H, 3- or 4-H), 7.74 (d, J = 8.0 Hz, 1 H, 3- or 4-H), 7.98 (dd, J = 8.0 Hz, J = 1.3 Hz, 1 H, 8-H), 12.95 (s, 1 H, 1-OH); mass spectrum (110°) 353 (10%), 269 (22), 268 (100), 253 (28). Found: C, 66.83; H, 6.24. Calc for $C_{24}H_{26}O_7$: C, 67.60; H, 6.15%.

Methyl 4-(9,10-dihydro-1-hydroxy-5-methoxy-9,10-dioxo-2-anthryl)-3-hydroxy-3-methyl-butanoate (rac-**19b**) (5-O-methyl-fridamycin E methyl ester). A soln of 50 mg (1.4 mmol) of rac-**18** in 30 ml of dry acetone was treated with O_3 at -78° as described for **15**. After completion of the ozonolysis 1 ml of a 10% soln of hydrogen peroxide was added at -78°. The mixture was slowly warmed to room temperature. After usual workup a soln of the product in CH_2Cl_2 was treated with 5 ml of a 0.1 molar soln of diazomethane in ether for 5 min. The solvent was removed i. vac. and the residue was purified by TLC to afford 20 mg (37%) of rac-**19b** m.p. 130°. IR 3510 cm^{-1} (OH), 1720 (C=O), 1670 (quinone), 1630 (quinone), 1587 (Ar); UV 227 nm (4.58), 255 (4.37), 283 (3.99), 416 (4.00); ^{1}H-NMR (300 MHz) δ 1.31 (s, 3 H, 2'-CH_3), 2.57 (s, 2 H, 3'-H), 3.01/3.05 (AB, J = 13.4 Hz, 2 H, 1'-H), 3.72 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 7.37 (dd, J = 8.3 Hz, 1.0 Hz, 1 H, 6-H), 7.66 (d, J = 8.3 Hz, 1 H, 3-H), 7.72 (t, J = 8.3 Hz, 1 H, 7-H), 7.76 (d, J = 8.3 Hz, 1 H, 4-H), 7.98 (dd, J = 8.3 Hz, 1.0 Hz, 1 H, 8-H), 13.0 (s, 1 H, OH); mass spectrum (100°) 268 (100), 253 (54), 239 (6), 225 (8), 117 (14). Found: C, 65.64; H, 4.96. Calc for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24%.

(S)-Fridamycin E (ent)-(**1**). A soln of 20 mg (0.05 mmol) of ent-**19b** in 5 ml of CH_2Cl_2 was treated at -78° with 0.3 ml (0.3 mmol) of boron trichloride for 30 min. The mixture was poured into a dil. soln of sodium hydrogen carbonate, acidified with HCl, extracted with CH_2Cl_2 and dried over Na_2SO_4. Crystallization of the residue afforded 15 mg (81%) of ent-**19b**, m.p. 168°, $[\alpha]_D$ = -11° (c 1,dioxane); IR 1705 cm^{-1} (COOH), 1627 (quinone), 1590 (Ar); UV 228 nm (4.50), 256 (4.4), 280 (3.88), 290 (3.9), 431 (3.98); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.18 (s, 3 H, 2'-CH_3), 2.39 (s, 2 H, 3'-CH_2), 2.89/3.08 (AB, J = 13 Hz, 2 H, 1'-H), 7.4 - 7.87 (m, 5 H, Ar-H); mass spectrum (128°) 255 (17%), 254 (100), 253 (8), 237 (4), 225 (6), 197 (5), 103 (6). Found: C, 64.07; H, 4.53. Calc for $C_{19}H_{16}O_7$: C; 64.04; H, 4.53%.

rac-Fridamycin E (rac-**1**). A soln of 100 mg of rac-**19b** was treated with a soln of 1.5 ml of 1 N BCl_3 as described above to afford 80 mg (87%) of rac-**1**.

1,5-Dimethoxy-2-(2-methyl-2-propenyl)-9,10-anthraquinone (**23**). A soln of 2.00 g (6.5 mmol) of **15** in 300 ml of dry CH_2Cl_2 was stirred for 18 h with 15 g (65 mmol) of silver(I)oxide and 9.2 g (4.05 ml, 65 mmol) of methyl iodide. The mixture was filtered, washed with CH_2Cl_2 and the solvent was removed i. vac. to afford 1.89 g (96%) of **23**, m.p. 93°. IR 1660 cm^{-1} (quinone), 1595 / 1585 (Ar); UV 220 nm (4.46), 258 (4.54), 387 (3.88); ^{1}H-NMR (400 MHz) δ 1.73 (s, 3 H, 2'-CH_3), 3.46 (s, 2 H, 1'-H), 3.88 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.65 (broad s, 1 H, 3'-H), 4.94 (broad s, 1 H, 3'-H), 7.29 (dd, J = 8.5 Hz, 1.3 Hz, 1 H, 6-H), 7.59 (d, J = 8.5 Hz, 1 H, 3-H), 7.71 (t, J = 8.5Hz, 1 H, 7-H), 7.90 (dd, J = 8.5 Hz, 1.3 Hz, 1 H, 8-H), 8.03 (d, J = 8.5 Hz, 1 H, 4-H); mass spectrum (130°) 322 (M^+, 60%), 307 (M^+-15, 100), 291 (96), 277 (20), 267 (22). Found: C, 74.47; H, 5.60. Calc for $C_{20}H_{18}O_4$: C, 74.51; H, 5.63%.

2-(9,10-Dihydro-1-hydroxy-5-methoxy-9,10-dioxo-2-anthrylmethyl)-2-methyl-oxirane (**21**). meta-Chlorobenzoic acid (2.8 g (1 mmol) was added to a soln of 2.00 g (6.5 mmol) of **16** in 400 ml of dry CH_2Cl_2 and the soln was stirred for 3 h. The mixture was shaken with a diluted soln of Na_2HCO_3 and after usual workup filtered rapidly through a short column of silica gel to afford 1.80 g (86%) of **21** (yellow plates), m.p. 185°. IR 1672 cm^{-1} (C=O), 1630 (quinone), 1590 (Ar); UV 226 nm (4.57), 254 (4.86), 281 (sh, 3.99), 400 (3.96), 413 (3.98), 430 (sh, 3.88); ^{1}H-NMR (400 MHz) δ 1.36 (s, 3 H, 2'-CH_3), 2.63 (AB, J = 4.8 Hz, 1 H, 3'-H), 2.69 (AB, J = 4.8 Hz, 1 H, 3'-H), 3.05 (AB, J = 14 Hz, 2 H, 1'-H), 4.05 (s, 3 H, OCH_3), 7.36 (dd, J = 8.5 Hz, 1 Hz, 1 H, 6-H), 7.61 (d, J = 8.5 Hz, 1 H, 3-H), 7.74 (t, J = 8.5 Hz, 1 H, 7-H), 7.75 (d, J = 8.5 Hz, 1 H, 4-H), 7.98 (dd, J = 8.5 Hz, 1 Hz, 1 H, 8-H), 12.87 (s, 1 H, OH); mass spectrum (85°C) 325 (M^+ + 1, 19%), 3 (M^+, 82), 295 (18), 294 (52), 293 (100), 279 (29). Found: C, 70.26; H, 4.87. Calc for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97%.

2,3,4,7,12-Pentahydro-3-hydroxy-8-methoxy-3-methyl-anthraceno-[1,2b]pyran-7,12-dione (**22**). A soln of 1.00 g (3.1 mmol) of epoxide **21** in 200 ml of THF was treated with 4 ml of 1 N NaOH soln at room temp. The mixture was acidified with HCl, extracted with CH_2Cl_2 and the solvent evaporated i. vac. Crystallization from ether afforded 0.96 g (96%) of **22** m.p. 230°. IR 3490 cm^{-1} (OH), 1670/1650 (quinone); UV 226 nm (4.42), 254 (4.17), 272 (sh, 3.94), 4.05 (3.79); ^{1}H-NMR (400 MHz) δ 1.56 (s, 3 H, 3-CH_3), 2.96 (d, J = 16.5 Hz, 1 H, 4_{ax}-H), 3.38 (d, J = 16.5 Hz, 1 H, 4_e-H), 3.70 (d, J = 13.5 Hz, 1 H, 2_{ax}-H), 3.90 (d, J = 13.5 Hz, 1 H, 2_e-H), 4.03 (s, 3 H, OCH_3), 7.27 (dd, J = 8.5 Hz, 1.0 Hz, 1H, 8-H), 7.49 (d, J = 8.5 Hz, 1 H. 5-H), 7.66 (t, J = 8.5 Hz, 1 H, 9-H), 7.80 (d, J = 8.5 Hz, 1 H, 6-H), 7.82 (dd, J = 8.5 Hz, 1 Hz, 1 H, 10-H); mass spectrum (235°) 324 (M^+, 50%), 306 (9), 293 (100), 278 (15). Found: C, 70.50; H, 4.80. Calc for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97%.

2-(9,10-Dihydro-1,5-dimethoxy-9,10-dioxo-2-anthrylmethyl)-2-methyl-oxirane (**24**). A soln of 1.00 g (3.1 mmol) of **23** in 100 ml of CH_2Cl_2 was treated with 0.90 g (3.1 mmol) MCPBA as described for **21**. The soln was stirred for 1h at 20° and 3 h at -20° and the meta-chlorobenzoic acid was filtered off. The volume of the solvent was reduced at 0° to 10 ml and the procedure was repeated. Crystallization from ether afforded 700 mg (67%) of **24**, m.p. 130°. IR 1675 cm^{-1} (quinone), 1570/1588 (Ar); UV 226 nm (4.56), 254 (4.32), 270 (sh, 4.11), 409 (3.93); ^{1}H-NMR (400 MHz) δ 1.34 (s, 3 H, 2'-CH_3), 2.64 (AB, J = 6 Hz, 2 H, 3'-H), 3.03/3.10 (AB, J = 14.2 Hz, 2 H, 1'-H), 3.87 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.30 (dd, J =8.5 Hz, 1 Hz, 1 H, 6-H), 7.70 (d, J = 8.5 Hz, 1 H, 3-H), 7.72 (t, J = 8.5 Hz, 1 H, 7-H), 7.91 (dd, J = 8.5 Hz, 1 Hz, 1 H, 8-H), 8.04 (d, J = 8.5 Hz, 1 H, 4-H); mass spectrum (160°) 338 (M^+-1, 22%), 323 (16), 308 (100), 293 (92), 251 (77). Found: C, 70.21; H, 5.49. Calc for $C_{20}H_{19}O_5$: C, 70.78; H, 5.64%.

Rearrangement of (**24**). A soln of 1.00 g (3.1 mmol) in 100 ml of CH_2Cl_2 was treated with 1.85 g (6.3 mmol) of MCPBA (95 without cooling. The products were isolated by preparative TLC (silica gel, CH_2Cl_2/5 % ether) after 3 h of reaction time at 20°. The fractions were eluated with decreasing polarity.

Fraction 1; 2-(9,10-Dihydro-1,5-dimethoxy-9,10-dioxo-2-anthrylmethyl)-2-methyl-propionic acid (**28**). Yield: 428 mg (39 %), m.p. 148°. IR 1705 cm^{-1} (C=O), 1670 (quinone), 1585/1570 (Ar); UV 226 nm (4.54), 254 (4.33), 278 (sh, 4.00), 414 (3.91); ^{1}H-NMR (300 MHz) δ 1.21 (d, J = 6.9 Hz, 3 H, CH_3), 2.86 (m, 1 H, 2-H), 2.93 (q, J = 7.4 Hz, 1 H, 3-H), 3.14 (q, J = 7.4 Hz, 1 H. 3-H), 3.93 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 7.29 (dd, J = 8.4 Hz, 1 Hz, 1 H, 6'-H), 7.59 (d, J = 8.4 Hz, 1 H, 3'-H), 7.70 (t, J = 8.4 Hz, 1 H, 7'-H), 7.89 (dd, J = 8.4 Hz, 1 Hz, 1 H, 8-H), 8.01 (d, J = 8.4 Hz, 1 H, 4'-H). Found: C, 67.11; H, 5.08. Calc. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.

Fraction 2: 1-(9,10-Dihydro-1,5-dimethoxy-9,10-dioxo-anthryl)-2-oxyformylpropane (**29**). Yield: 18 mg (2%), m.p. 161°. IR 1670 (quinone), 1580/1570 (Ar); ^{1}H-NMR (300 MHz) δ 1.33 (d, J = 6.3 Hz, 3 H, CH_3), 3.04 (AB, J = 6.5 Hz, 2 H, 1-H), 3. (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 5.34 (mc, 1 H, 2-H), 7.29 (dd, J = 8.5 Hz, 1 Hz, 1 H, 6'-H), 7.60 (d, J = 8.5 Hz, 1 H, 3'-H), 7.73 (t, J = 8.5 Hz, 1 H, 7'-H), 7.90 (dd, J = 8.5 Hz, 1 Hz, 1 H, 8'-H), 7.97 (s, 1 H, formate-H), 8.05 (d, J = 8.5 Hz, 1 H, 4-H). Found: C, 66.87; H, 5.08. Calc for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.

Fraction 3: 1,5-Dimethoxy-2-(2-oxopropyl)-9,10-anthra- quinone (**27**). Yield: 48 mg (5%), m.p. 108°. IR 1720 cm^{-1} (C=O), 1678 (quinone); UV 221 nm (4.43), 258 (4.62), 373 (3.86), 390 (3.96), 397 (3.86), 420 (3.52); ^{1}H-NMR (400 MHz) δ 2.27 (s, 3 H, 3'-CH_3), 3.87 (s, 2 H, 1'-H), 3.88 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.31 (dd, J = 8.5 Hz, 1 Hz, 1 H, 6-H), 7.55 (d, J = 8.5 Hz, 1 H, 3-H), 7.72 (t, J = 8.5 Hz, 1 H, 7-H), 7.90 (dd, J = 8.5 Hz, 1 Hz, 1 H, 8-H), 8.02 (d, J = 8.5 Hz, 1 H, 4-H); MS (100 °) 325 (M^+ + 1, 4%), 324 (M^+, 18), 294 (18), 292 (56), 282 (44), 267 (100). Found: C, 70.00; H, 5.02. Calc for $C_{19}H_{16}O_7$: C, 70.36; H, 4.97%.

Fraction 4: 2-Acetoxymethyl-1,5-dimethoxy-9,10-anthraquinone (**30**). Yield: 88 mg (8%), m.p. 138°; IR 1750 cm^{-1} (ester C=O), 1670 (quinone), 1590/1575 (Ar); UV 225 nm (4.42), 257 (4.20), 270 (sh, 3.94), 392 (3.67); ^{1}H-NMR (300 MHz) δ 2.16 (s, 3 H, $OCOCH_3$), 3.98 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 5.30 (s, 2 H, 1'-H), 7.31 (dd, J = 7.5 Hz, 1.0 Hz,1 H, 6-H), 7.72 (t, J = 7.5 Hz, 1 H, 7-H), 7.77 (d, J = 8.0 Hz, 1 H, 3-H), 7.99 (dd, J = 7.5 Hz, 1 Hz, 1 H, 8-H), 8.10 (d, J = 8.0 Hz, 1 H, 4-H). Found: C, 66.68; H, 4.74. Calc for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74%.

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