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SYNTHESIS OF 4-DEOXYRHODOMYCINONES WITH INCORPORATION OF (S)-LACTIC ACID[1)]

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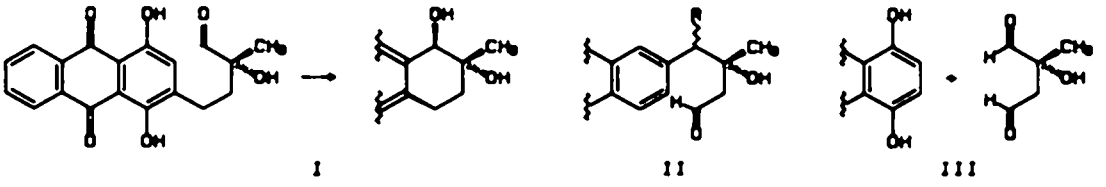
Abstract: The aldehydes 4 ,8a/8b and the acetals 5a/5b are prepared from the (S)-lactic acid derivative 3. Marschalk reaction with leucoquinizarine (10) affords rhodomycinones with one, two or three hydroxy groups in ring A. The 7,9-cis-diol 21(6-demethoxy-feudomycinone C) is the major cyclization product of the acetonides 20a/20b.

Anthracyclinones exhibit their biological activity, as do most other chiral drugs, only in form of one enantiomer of definite absolute configuration[2)]. Enantiomerically pure glycosides (anthracyclines) can be prepared from the glycosidation of racemic aglycones (anthracyclinones). In this reaction diastereomeric products are formed which can be separated chromatographically. In attempts to avoid the separation step, considerable efforts have been made to synthesize enantiomerically pure anthracyclinones,especially in the daunomycinone series[4,5)]. Several enantiomerically pure 1-deoxyrhodomycinones have been synthesized with incorporation of chiral building blocks derived from sugars, yielding products with additional hydroxy groups either at C-9[6)] or in the side chain[7)] (for IUPAC numbering see 18).

We now report the results of a program directed towards the incorporation of (S)-lactic acid to afford 4-deoxyrhodomycionones containing a methyl side chain. In a previous paper[8)] we have outlined our strategy using the Marschalk reaction[9)] in the cyclization of α-hydroxy aldehydes of type I to yield racemic rhodomycinones. Retrosynthetic analysis reveals that in addition to type I, two other modes of cyclization II and III (scheme 1) are possible. Since the addition is a stepwise process mode III will enter into either I or II but it seemed interesting to include this convergent approach, in order to see which is the best way to control stereochemistry.

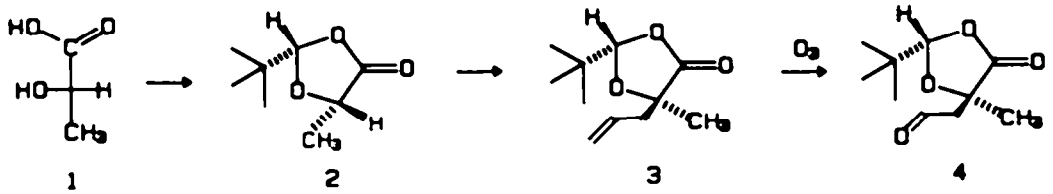


I II III

Scheme 1

Synthesis of the enantiomerically pure hydroxy aldehydes

The common feature of all three modes is the construction of aldehydes with a quaternary chiral center. These structural requirements are rarely found in small natural products that are useful as chiral building blocks with exception perhaps of the quite expensive citramalic acid[10]. Consequently, the chiral quaternary center has to be newly constructed. However, all direct methods of maintaining the chirality of lactic acid will fail due to enolization during the alkylation. In order to overcome this problem Seebach et al.[11] have worked out a procedure to preserve the chiral information of α-hydroxy acids by acetalization with pivalaldehyde. For instance, (S)-lactic acid 1 affords the cis-adduct 2 as the major product. The principle of this methodology is shown in scheme 2.



1 2 3 4

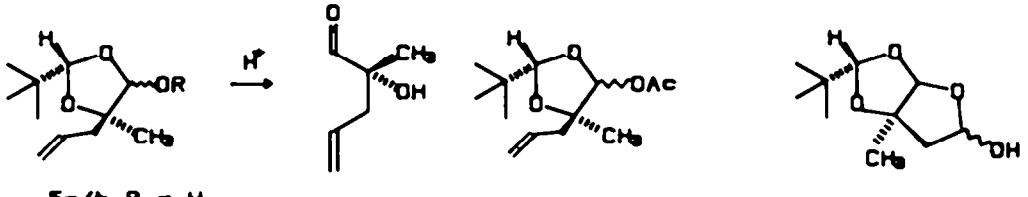
Scheme 2

It is important that the adduct 2 can easily be purified by crystallization to yield the pure diastereomer (45% after two crystallizations). The attack of the electrophile (in our case allyl bromide) occurs predominantly from the Re side to afford the alkylation product 3 with 98% ds in about 70 % chemical yield[11].

The future aldehyde functions are already present in molecule 3. Thus, the aldehyde 4 was easily obtained by ozonolysis of 3 using dimethyl sulfide as reducing agent. The ß-hydroxy aldehyde 4 is not very stable and was immediately used for the following Marschalk reactions (see below). However, ^{1}H-NMR and IR spectra as well as the subsequent chemical transformations fully confirm the structure of 4.

The next step was to find the best conditions for selective reduction of the ester group, which is also part of an acetal function. Alanat reduction was shown to afford the corresponding diols[11]. After experimentation with a number of diborane derived reagents[12], diisobutyl aluminum hydride (DIBAH) was tried, which is known to convert lactones to lactols[13]. The crucial question was the stability of the resulting lactol. The hemiacetal 5 could possibly open to give pivaldehyde and the

unstable α-hydroxy aldehyde 7 on workup. Fortunately, the hemiacetal proved to be sufficiently stable at low temperature under the conditions of mild acid hydrolysis of the aluminum complex, allowing for an excellent yield (90 %) of the anomeric mixture 5a/5b. The existence of an approximate 1 : 1 mixture of anomers was clearly seen from the doubling of many signals in the ^{1}H-NMR spectrum. In order to obtain a 1,4-dialdehyde precursor (see III), the ozonolysis of the double bond in 5a/5b was next investigated. However, this way was abandoned since the ^{1}H NMR spectrum of the product indicated the existence of a bicyclic acetal structure 9. The sequential liberation of the aldehyde functions during the anticipated Marschalk reaction presented too many uncertainties. Therefore, it was decided to protect the hemiacetal first by acetylation to 6a/6b. Again, ^{1}H-NMR showed the presence of two isomers (ratio approximately 1 : 1) of the mixture. The following ozonolysis of 6a/6b was monitored by NMR, confirming the almost quantitative conversion to the aldehydes 8a/8b which could be used for the Marschalk reactions without further purification.



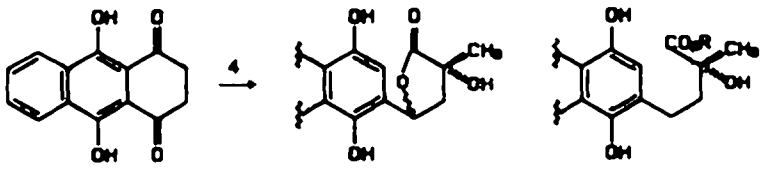
5a/b R = H
6a/b R = Ac

7 8a/b 9

Scheme 3

Marschalk Reaction with Dihydroquinizarine

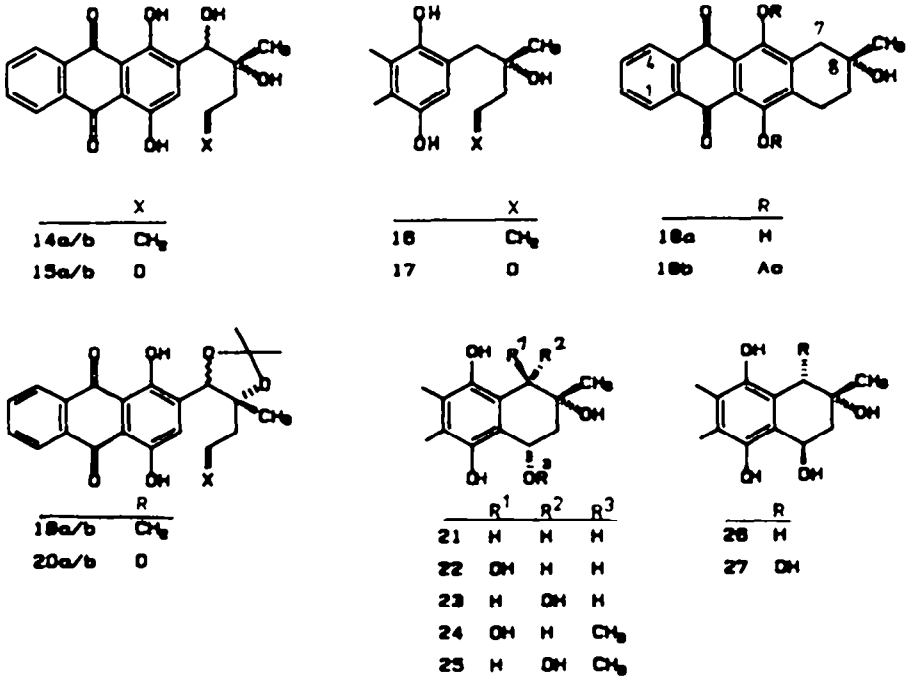
A number of highly functionalized chiral aldehydes (or equivalents) of 98% ee[11] were now available for study of the different modes of the Marschalk reaction outlined in Scheme 1. In order to optimize the incorporation of the more precious chiral buildng blocks, a two- to threefold excess of leucoquinizarine (10) was used to trap the aldehydes. Under the conditions originally used by Marschalk (boiling aqueous alkali) the benzylic hydroxy groups primarily formed during the addition undergo elimination[9]. However, the hydroxy groups can be preserved if the reacton is conducted at much lower temperatures (usually 5 - 10°)[14,15]. In agreement with this finding, a mixture of the epimeric lactones 11/12 and the carboxylc acid 13a were formed in 46 % and 9 % yield respectively. The ratio of the diastereomeric mixture 11/12 of about 1 :1.13 (^{1}H NMR) showed the low asymmetric 1,3-indction of this open chained kind of aldol reaction. This mixture could then be reduced with dithionite to form the pure acid 13a. Alternatively, the reaction can be run at higher temperatures to form the acid 13a directly, which was characterized as the ester 13b. Reduction of the acid 13a or the ester 13b should lead to the α-hydroxy aldehyde shown in I and then enter the pathway described in detail on racemic material[8,16]. This reaction has at this time not yet been investigated.



10 11/12 13a R = H
13b R = CH_3

Scheme 4

The hemiacetals 5a/5b which are protected forms of the α-hydroxy aldehyde 7, were used to investigate pathway II. The aldehyde 7 was obtained by treatment of 5a/5b with dilute hydrochloric acid. It has a tertiary neighbouring center and is sterically more hindered than the β-branched aldehyde 4. However, α-branched aldehydes were successfully reacted with 10 under the conditions of Lewis[7,17] (boiling isopropanol). The α-hydroxy group considerably enhances the carbonyl activity of 7. In fact, the reaction proceeded smoothly even at room temperature within 6 h. The mixture of the diastereomeric diols 14a/14b was the main product (58 %) and the less polar monoalcohol 16 was isolated in only 6 % yield. The mixture of isomers 14a/14b could not be separated chromatographically but gave the pure carbinol 16 almost quantitatively upon reduction with dithionite. The isomeric ratio of about 2:1 established by ^{1}H-NMR was slightly superior to that observed in the 1,3-induction in the reaction of the β-hydroxy aldehyde 4 to afford 11/12. Reaction of the diols 14a/14b with acetone afforded the isopropylidene ethers 19a/19b in good yield, without affecting the original ratio of isomers.



	X
14a/b	CH_3
15a/b	O

	X
16	CH_3
17	O

	R
18a	H
18b	Ac

	R
19a/b	CH_3
20a/b	O

	R^1	R^2	R^3
21	H	H	H
22	OH	H	H
23	H	OH	H
24	OH	H	CH_3
25	H	OH	CH_3

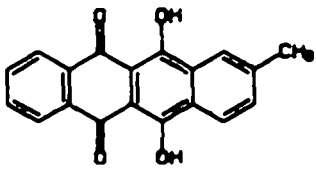
	R
26	H
27	OH

Scheme 5

All olefinic compounds were subjected to ozonolysis, affording the corresponding aldehydes **15a/15b**, **17**, and **20a/20b**. The reductive cleavage of the hydroperoxy ethers, formed by ozonolysis in methanolic solution[18] with dimethyl sulfide proceeded rather slowly (up to 12 h). It was found later that the corresponding aldehydes could be formed more rapidly upon treatment with a neutral solution of dithionite in methanolic THF. We first studied the cyclization of the most simple aldehyde **17** in aqueous methanolic solution. A rapid and almost quantitative conversion to cyclic products was observed within 15 minutes at 0°. The main product was the trans-diol **26**, which had a typical signal for 10e-H ($J_{10e,7a}$ = 5 Hz) in the ^{1}H-NMR spectrum. Depending on the reaction conditions (temperature, time, excess of dithionite), various amounts of the cis-diols **21** and the tertiary alcohol **18a** were also formed (**26** : **21** = 4 : 1). In some cases small amounts of dark red dimerization products of **18a** coupled at C-10 were isolated as mixtures of diastereoisomers. Both the cis- and the trans-diols were easily dehydrated upon heating above 50° to yield the naphthacenequinon **28**. The benzylic hydroxy group of **21** and **26** could be removed reductively to give the mono-alcohol **18a**. The stereochemical outcome of the cyclization was inverted employing phase transfer conditions[8], thereby affording predominantly the cis-diol **21** (**21** : **26** = 1.5 : 1).

A more complex mixture was obtained from the diastereomeric alcohols **15a/15b** whose cyclization yielded six products. The ^{1}H-NMR data of all possible isomers were known from the similar feudomycinone series[8]. In addition many cyclization compounds in racemic form were available for comparison from previous work[16,19]. The most polar fraction (20 %) contained a mixture of the triols **22** and **27**. The structure of **22** corresponds to that of the most current natural configuration and can be named 1-deoxy-β_1-rhodomycinone. The configuration of **27** as well as that of a third triol **23** isolated in pure form was elucidated by comparison with the feudomycinones having an additional methoxy group at C-1[8,20]. The 7,8-cis-diol **21** isolated in 5 % had been previously prepared via cyclization of **17**. The two least polar cyclization products **24** (9 %) and **25** (11 %) were identified as the corresponding C-7-methyl ethers of the triols **22** and **23**. The formation of these side products is of mechanistic interest. On the basis of previous observations of quinone methides[21,22] we propose the addition of methanol to the ortho-quinone methide **IV**. This would also explain why no 8,10-trans-methyl ethers were isolated; since the addition of nucleophiles is cis-directed by the neighbouring axial hydroxy group as shown in **IV**[5].

In conclusion, stereochemical control in the cyclization of both the β-hydroxy aldehydes **15a/15b**, and **17** is difficult to obtain, and a variety of stereoisomers are produced.



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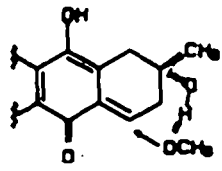
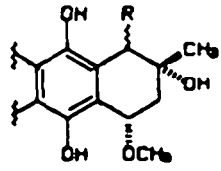


IV



24/25

Scheme 6

Fortunately, the cyclization of the acetonides 20a/20b obtained from 19a/19b gave a less complicated picture. The main product (51 %) was the cis-diol 21 (ent-1-demethoxyfeudomycinone C). Evidently, the protection of 9-OH leads to a reversal of the normal stereochemistry of the Marschalk reaction. This is in agreement with observations of Monneret et al.[7]. The preferential elimination of the C-7 substituent can be understood, since the alkoxy group is a better leaving group in basic solution thanthenewly formed hydroxy group at C-10.

Finlly, we have looked at the convergent approach to anthracyclinones in the reaction of leucoquinizarine with the aldehydes 8a/8b, which are protected forms of the 1,4-dialdehyde of type III. The reaction was monitored by TLC and a number of polar intermediates were detected, which might correspond to open chained, as well as cyclic forms 21 - 27. All polar products were however smoothly converted to the monoalcohol 18a (45 %) on prolonged reaction times. Thus, in spite of the convergency, it is difficult to obtain rhodomycinones with benzylic hydroxy groups and definite configuration via reactions of dialdehydes with hydroanthraquinones.

In agreement with the literature[11], our NMR measurements indicated the starting material 3 to be at least 98 % diastereomerically pure. All subsequent transformations (ozonolysis, DIBAH reduction, and Marschalk reaction) proceed under very mild conditions which should not affect the not enolizable chiral center. Accordingly, the optical rotation of the cis-diol 21 ($[\alpha]_D^{20}$ = + 125.4 °) and the trans-diol 26 ($[\alpha]_D^{20}$ = - 131.5 °) were in the same order of magnitude as synthetic[7] as well as natural analogues[20].

In addition we have checked the enantiomeric excess by ^{1}H-NMR measurements using chiral shift reagents. For this purpose the phenolic groups of the anthraquinoic moiety of 18a had tobe converted to the acetate 18b to avoid precipitation of chelated complexes with the shift reagent. The racemic material rac-18b[16] did indeed show a splitting of the acethyl group. No such effect was seen in the 400 MHz ^{1}H-NMR spectra of 18b confirming the enantiomeric excess to be at least 97%.

The various masked 1,4-dialdehydes (e.g. 4, 5a/5b, 8a/8b) can generally be employed as chiral building blocks in the total synthesis of natural products containing quarternary centers. Investigations of this kind are on the way in our laboratories.

Acknowledgement: We thank the Deutsche Forschungsgemeinschaft for support of this work.

Experimental

For general remarks see ref.[8]. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter. The diastereomeric composition (%ds) was determined by ^{1}H-NMR and enantiomeric excess (%ee) by addition of a chiral shift reagent (Eufod).

(2S,5R)-2-(t-Butyl)-5-methyl-4-oxo-1,3-dioxolan-5-yl acetaldehyde (4): A solution of 2.00 g (10 mmol) of the olefin 3[11] in 100 ml of methanol was treated with 2 mg of sudan 3[*] cooled to -78°. A rapid current of ozone was bubbled through the solution until the colour of the indicator disappeared (about 20 min). Excess O_3 was removed by a stream of nitrogen and 5 ml of dimethyl sulfide was added. After 12 h the solvent was removed at reduced pressure to afford 2.00 g of a colourless oil of 4 contaminated with 5 % of DMSO (95 % yield). An analytical pure sample was obtained by Kugelrohr distillation, b.p. 110°, 0.1 mm Hg. $[\alpha]_D^{20}$ = -23.2° (c = 4.6; $CHCl_3$). IR (film): 1801 (lactone), 1732 cm^{-1} (aldehyde). ^{1}H-NMR (400 MHz): δ 0.97 (s; 9 H, CMe_3), 1.51 (s; 3 H, CH_3), 3.00 (s; 2 H, CH_2) 5.33 (s; 1 H, 2-H), 9.73 (s; 1 H, CHO). MS m/e: 200 (2 %), 185 (16), 143 (64, $M^+ - C_4H_9$), 128 (9), 115 (11), 97 (72), 87 (4), 78 (63), 70 (55), 63 (70), 57 (78), 43 (100). (Found: C, 59.79; H, 8.23. Calc.for $C_{10}H_{16}O_4$: C, 59.98; H 8.05 %).

(2S,4R,5R)- and (2R,4S,5R)-5-Allyl-2-(t-butyl)-5-methyl-1,3-dioxolan-4-ol (5a/5b): A solution of 4.00 g (20 mmol) in 100 ml of dry THF was treated at -78° under N_2 with 20 ml of a 1.2 molar solution of DIBAH in toluene. The solution was stirred at -78° for 3 h and then hydrolyzed by dropwise additon of 6 ml of 1 N sulfuric acid at -30°. After stirring for 1 h at this temperature, 20 g of sodium sulfate was added and the solution was filtered (twice if necessary). The solution was evaporated at reduced pressure, the residue redissolved in dichloromethane, filtered and evaporated to dryness to afford 3.60 g (90 %) of the diastereomeric mixture 5a/5b which solidified on storage at -20°. $[\alpha]_D^{20}$ = 23.8° (c = 2.4, $CHCl_3$). IR (film): 3430 (OH, broad), 3070 (CH), 2970, 2860 (CH), 1635 (C=C), 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.91 and 0.93 (each s; each 9 H, CMe_3) 1.29 and 1.31 (each s, each 3 H, CH_3), 2.17 - 2.55 (m; 6 H, 2 CH_2 and 2 OH), 4.73 and 4.93 (each s; each 1 H, 4-H), 5.07 - 5.16 (m; 4 H, 2 $=CH_2$), 5.14 and 5.16 (each s; each 1 H, 2-H), 5.72 - 5.97 (m; 2 H, 2 -CH=).

(2S,4R,5R)-and (2S,4S,5R)-4-Acetoxy-5-allyl-2-(t-butyl)-5-methyl-1,3-dioxolan (6a/6b): 1.00 g (5 mmol) of 5a/5b was dissolved in a mixture of 3 ml of acetanhydride and 2 ml of pyridine and stirred for 1 day at 20°. The volatile substances were removed by repeated distillation at reduced pressure with addition of toluene to afford 1.16 g (96 %) of a mixture of the acetates 6a/6b as an oil. An analytical sample was obtained by Kugelrohr distillation (130°, 0.1 mm Hg). IR (film): 1750 cm^{-1} (acetate). $[\alpha]_D^{20}$ = +10.5 (c = 0.35, $CHCl_3$). ^{1}H-NMR (400 MHz): δ 0.88 and 0.89 (each s; each 9 H, CMe_3), 1.23 and 1.24 (each s; each 3 H, 2 CH_3), 2.05 and 2.09 (each s; each 3 H, $COCH_3$), 2.26 (m; 2 H, CH_2), 2.40 and 2.50 (each dd, J = 13.5, J = 6.5 Hz; each 1 H, CH_2), 4.81 and 4.87 (each s; each 1 H, 2-H), 5.04 - 5.15 (m; 4 H, $=CH_2$), 5.70 and 5.81 (m; 2 H, 2-H), 5.97 and 6.00 (each s; each 1 H, 4-H). MS m/e: 242 (0.4 %, M^+), 241 (1.7, M^+ -1), 224 (9, $M^+ - H_2O$), 201 (26), 185 (100), 169 (18), 143 (60), 129 (58), 117 (53), 97 (74), 87 (63), 69 (70), 57 (65), 43 (82).

(2S,4R,5S)- and (2S,4S,5S)-4-Acetoxy-2-(t-butyl)-5-methyl-1,3-dioxolan-5-yl-acetldehyde (8a/8b): A solution of 1 g of 6a/6b was subjected to ozonolysis as described for 4 to afford 0.95 g (95 %) of 8a/8b. An analytical sample was obtained by Kugelrohr distillation (140°, 0.1 mm Hg), $[\alpha]_D^{20}$ = -2.1° (c = 6.1, $CHCl_3$). IR (film): 1750 (acetate), 1730 cm^{-1} (aldehyde). ^{1}H-NMR (60 MHz): δ 0.95 (s; 9 H, CMe_3), 1.41 and 1.45 (each s; each 3 H, CH_3), 2.03 and 2.10 (each s; each1 H, 4-H), $COCH_3$), 2.75 (m; 4 H, CH_2), 4.88 and 4.93 (each s; each 1 H, 4-H), 6.06 and 6.15 (each s, each 1 H, 2-H), 9.80 (m; CHO). (Found: C, 58.11; H, 8.31. Calc.for $C_{12}H_{20}O_5$: C,58.90; H, 8.25%)

Methyl (2R)-4-(9,10-Dihydro-1,4-dihydroxy-9,10-dioxoanthracen-2-yl)-2-hydroxy-2-methyl butanoate (13b): A solution of 1.80 g (7.5 mmol) of 10 in 50 ml of THF/methanol (1 : 1) was treated with 0.50 g (2.5 mmol) of 4 and 10 ml of 1 N NaOH. The mixture was stirred under N_2 for 1 h at 5°, followed by 2h at 20°, and was then reoxidized by rapidly bubbling air through the solution. The mixture was acidified with diluted HCl, repeatedly extracted with CH_2Cl_2 (200 ml), treated with 20 ml of a 0.5 M etheral solution of diazomethane, and evaporated to dryness. The residue was separated by chromatography on silica gel. Elution with CH_2Cl_2 removed excess quinizarine. The ester 13b (86 mg, 9 %) was then eluted with CH_2Cl_2/5 % ether. An improved yield (53 %) of the ester 13b was obtained by refluxing the reaction mixture for 1 h followed by similar workup. m. p. 90°. $[\alpha]_D^{20}$ = -55.4° (c = 0.3 $CHCl_3$/4 % MeOH). UV: 210 (4.12), 233 (4.32), 250 (4.59), 255 (4.53), 285 (4.00), 310 (3.47), 458 (3.94), 475 (3.97), 483 (3.99), 497 nm (3.88). ^{1}H-NMR 400 MHz): 1.48 (s; 3 H, CH_3), 2.02 and 2.15 (each ddd, J = 13.5, J = 11 , J = 5 Hz; each 1 H, CH_2), 2.64 and 2.90 (each ddd, J = 13.5, J = 11, J = 5 Hz; each 1 H, CH_2), 3.80

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*) 1-[(phenylazo)-phenyl]azo-2-naphthol

(s; 3 H, CO_2CH_3), 7.16 (s; 1 H, 3-H), 7.82 (m; 2 H, 6-, 7-H), 8.34 (m; 2 H, 5-, 8-H), 12.93 and 13.38 (each s; each 1 H; 2 OH). MS (150°) m/e: 370 (35 %, M^+), 352 (11, $M^+ - H_2O$), 320 (8), 311 (8), 293 (92), 277 (6), 267 (100), 253 (24), 239 (7), 225 (28). Found: C, 64.68; H, 4.88. Calc. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90 %).

(3R,5R)- and (3R,5S)-5-(9,10-Dihydro-1,4-dihydroxy-9,10-dioxoanthracen-2-yl)-3-hydroxy-3-methyl-tetrahydro-2-furanone (11/12): From the polar fraction of the chromatography (see 13b), 407 mg (46 %) of a 1 : 1.2 mixture of the isomers 11/12 was isolated; m. p. 225°. UV: 211 (4.15), 299 (4.34), 250 (4.55), 255 (4.49), 284 (3.99), 310 (3.43), 468 (3.94), 480 (3.95), 509 (3.74), 566 nm (3.07). IR (KBr): 3440 (OH, broad), 1792, 1785, 1768 (C=O), 1628 cm^{-1} (quinone). ^{1}H-NMR (400 MHz; major isomer): δ 1.54 (s; 3 H, CH_3), 2.29 (s; 1 H, OH), 2.32 (dd, J = 13.2, J = 6.5 Hz; 1 H, 4-H), 2.99 (dd, J = 13.2, J = 6.5, J = 1 Hz; 1 H, 4-H), 5.71 (ddd, J = 9.5, J = 6.5, J = 1 Hz; 1 H, CH), 7.20 (s; 1 H, 3-H), 7.86 (m; 2 H, 6-, 7-H), 8.37 (m; 2 H, 5-, 8-H), 12.84 and 13.31 (each s, each 1 H, 2 OH). ^{1}H-NMR (minor isomer): δ 1.65 (s; 3 H, CH_3), 2.12 (dd, J = 14, J = 8 Hz; 1 H, 4-H), 2.53 (s; 1 H,), 3.08 (dd, J = 14, J = 7 Hz; 1 H, 3-H), 5.93 (ddd, J = 8, J = 7, J = 1 Hz; 1 H, 5-H), 7.45 (s; 1 H, 3-H), 7.86 (m; 2 H, 6-, 7-H), 8.37 (m; 2 H, 5-, 8-H), 12.83 and 13.27 (each s; each 1 H, 2 OH). MS (200°) m/e: 354 (41 %, M^+), 310 (4), 292 (15), 267 (46), 240 (12). (Found: C, 64.04; H, 3.83. Calc. for $C_{19}H_{14}O_7$: C, 64.41, H, 3.98 %).

(2'R)-1,4-Dihydroxy-2-(2-hydroxy-2-methyl-4-pentenyl)-9,10-anthraquinone (16): A solution of 0.50 g (2.5 mmol) of 5a/5b in 10 ml of methanol and 5 ml of 1 N HCl was stirred for 30 min. The volume of the solution was reduced by one half the volume to remove the pivalaldehyde. 10 ml of THF, 10 ml of 1 N NaOH and 1.81 g (7.5 mmol) of 10 were then added under N_2 and the solution was stirred for 6 h at 20° followed by heating to 50° for 1 h. Workup proceeded as described for 13b. The crude product was filtered through a short column of silica gel (CH_2Cl_2) to remove the excess of quinizarine. Elution with CH_2Cl_2/5 % ether afforded 0.47 g (56 %) of 16 : m. p. 124°. $[\alpha]_D^{20}$ = -21.5 (c = 0.3, $CHCl_3$). UV: 210 (4.14), 228 (4.27), 235 (4.32), 250 (4.59), 255 (4.55), 288 (3.97), 312 (3.51), 457 (3.92), 475 (3.96), 485 (4.00), 498 (3.90), 519 (3.81), 563 nm (2.91). IR (KBr): 3500 (OH), 1620 (quinone), 1590 cm^{-1} (aromate). ^{1}H-NMR (400 MHz): δ 1.22 (s, 3 H, CH_3), 2.35 (d, J = 7.4 Hz; 2 H, CH_2), 2.46 (s; 1 H, 2-OH), 2.89 and 3.03 (each d, J = 13.5 Hz; each 1 H, CH_2), 5.14 - 5.30 (m; 2 H, $=CH_2$), 5.91 - 6.02 (m; 1 H, =CH-), 7.26 (s; 1 H, 3-H), 7.83 (m; 2 H, 6- and 7-H), 8.34 (m; 2 H, 5- and 8-H), 12.89 and 13.65 (each s; each 1 H, 2 OH). MS (110°) m/e: 338 (2 %, M^+), 320 (7, $M^+ - H_2O$), 302 (3), 297 (13), 287 (3), 279 (11), 254 (100), 239 (2), 225 (3). (Found: C, 70.90; H, 5.32. Calc. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36 %)

(1'R,2'R)- and (1'S,2'R)-1,4-Dihydroxy-2-(1,2-dihydro-2-methyl-4-pentenyl)-9,10-anthraquinone (14a/14b): 1.81 g of leucoquinizarine (10) and 0.50 g of 5a/5b were reacted as described for 16a (6 h at 20°, no heating) to afford 0.51 (58 %) of a 1 : 2 mixture of the diastereoisomers 14a/14b; m. p. 158°. $[\alpha]_D^{20}$ = + 82.2° (c = 0.4, $CHCl_3$). UV: 210 (4.16), 230 (4.29), 236 (4.32), 250 (4.60), 255 (4.55), 288 (3.97), 312 (3.52), 460 (3.96), 476 (3.98), 485 (4.01), 498 (3.92), 512 (3.82), 564 nm (2.01). IR (KBr): 3413 (OH), 1624 (quinone), 1588 cm^{-1}. ^{1}H-NMR (400 MHz, major isomer): δ 1.28 (s; 3 H, CH_3), 2.24 and 2.40 (each dd, J = 14, J = 7 Hz, each 1 H, CH_2), 2.44 (s; 1 H, OH), 2.88 (d, J = 5.2 Hz; 1 H, OH), 5.14 (d, J = 5.2 Hz; 1 H, -CH=), 5.15 - 5.30 (m; 2 H, $=CH_2$), 5.88 - 6.05 (m; 1 H -CH=), 7.55 (s; 1H, 3-H), 7.85 (m; 2H, 6-,7-H), 8.36 (m; 2 H, 5-,8-H), 12.84 and 13.70 (each s; each 1H, 2 OH). Minor isomer: δ 1.10 (s; 3 H, CH_3), 2.33 (s; 1 H, OH), 2.38 and 2.54 (each dd, J = 14, J = 7 Hz; each 1 H, CH_2), 3.01 (d, J = 5.5 Hz; 1 H, OH), 5.12 (d, J = 5.5 Hz; 1 H, -CH-), 5.15 - 5.30 (m; 2 H, $=CH_2$), 5.88 - 6.05 (m; 1 H, -CH=), 7.25 (s; 1 H, 3-H), 7.85 (m; 2 H, 6-, 7-H), 8.36 (m; 2 H, 5-, 8-H), 12.84 and 13.64 (each s; each 1 H, 2-H). MS (20°) m/e: 354 (0.1 %, M^+), 313 (4) 295 (15, 313 - H_2O), 270 (100), 252 (17), 241 (27), 224 (19). (Found: C, 67.70; H, 5.10. Calc. for $C_{20}H_{16}O_6$: C, 67,79; H, 5.12 %)

(4R, 5R)- and (4S,5R)-5-Allyl-4-(9,10-dihydro-2,4-dihydroxy-9,10-dioxo-2-anthracenyl)-2,2,5-trimethyl-1,3-dioxolane (19a/19b): 3 g of dry $CuSO_4$ was added to a solution of 0.708 g (2 mmol) of 14a/14b and 100 mg of p-toluenesulfonic acid in 50 ml of dry acetone. The mixture was stirred under reflux for 2 h, filtered and evaporated to dryness at reduced pressure. The residue was dissolved in 100 ml of ether, shaken with a dilute solution of $NaHCO_3$, dried (Na_2SO_4) and evaporated at reduced pressure. Filtration over a short column of silica gel afforded 0.670 mg (85 %) of the mixture of epimers 19a/19b ; m. p. 126°. $[\alpha]_D^{20}$ +146.3° (c = 0.5, $CHCl_3$). UV see 14a/14b. IR (KBr): 3450 (OH), 1630 (quinone), 1594 cm^{-1}. ^{1}H-NMR (400 MHz; minor isomer): δ 0.91 (s; 3 H, CH_3), 1.48 and 1.60 (each s; each 3 H, CH_3), 2.60 and 2.68 (each dd, J = 14, J = 7 Hz; each 1 H, CH_2), 5.16 - 5.24 (m; 2H, $=CH_2$), 5.42 (d, J = 1 Hz; 1 H, 4-H), 6.01 - 6.11 (m; 1 H, -CH=), 7.68 (s; 1 H, 3-H), 7.85 (m; 2 H, 6-, 7-H), 8.37 (m; 2 H, 5-, 8-H), 12.88 and 13.47 (each s; each 1 H, 2 OH). Major isomer: δ 1.51 (s; 3 H, CH_3), 1.56 and 1.61 (each s; each 3 H, 2 CH_3), 1.56 and 2.23 (dd, J = 14, J = 6 Hz; 1 H, CH_2), 4.87 (ddd, J = 17, J = 3, J = 1 Hz; 1 H, $=CH_2$), 5.00 (dt, J = 10, J = 1 Hz; 1 H, $=CH_2$), 5.41 (d, J = 1 Hz; 1 H, 4-H), 5.69 - 5.79 (m; 1 H, -CH=), 7.68 (s; 1 H, 3-H), 7.85 (m; 2 H, 6-, 7-H), 8.37

(m; 2 H, 5-, 8-H), 12.88 and 13.45 (each s, each 1 H, 2 OH). MS(120 °) m/e: 394 (1 %, M^+), 379 (4, $M^+ - CH_3$), 353 (6), 337 81), 319 (13), 310 (100), 295 (93), 267 (52), 240 (71). (Found: C, 70.17; H, 5.98. Calc. for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62 %)

Cyclization of the β-hydroxy aldehyde 17 (procedure A): The ozonolysis of 400 mg (1.2 mmol) of 14a/14b was performed as described for 4 (CH_2Cl_2 solution, TLC control). The resulting aldehyde 17 was dissolved in 50 ml of THF/methanol (1 : 1) and cooled to -10 °. A solution of sodium dithionite (about 1.2 mmol) was added under nitrogen (colour change from red to brown) followed by 2 ml of 1 N NaOH. The reaction was monitored by TLC and the cyclization was terminated after about 15 - 20 min. The products were reoxidized with air and separated by TLC (polar fraction 26, 1 mm silica gel, CH_2Cl_2/2 - 4 % CH_3OH).

Procedure B: The aldehyde 17 was dissolved in CH_2Cl_2 and treated at 0° under N_2 with 2 equivalents of aqueous sodium dithionite and 0.5 ml of Triton B (40 % in methanol) with vigorous stirring. The solution was shaken with air for reoxidation and then twice with cold diluted HCl to remove excess Triton B. The products were separated by TLC on silica gel.

(7S,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (21): Procedure A: 33 mg (26 %); procedure B: 69 mg (17 %). m. p. 185 °[16]. $[\alpha]_D^{20}$ = +125.4 (c = 0.15 $CHCl_3$/5 % CH_3OH). For spectroscopic data see ref.[16].

(7R,9S)-7,8,9,10-Tetrahydro-6,7,9,11-tetrahydroxy-9-methyl-5,12-naphthacenedione (26): Procedure A: 106 mg (26 %); procedure B: 69 mg (17 %). m. p. 194 °. $[\alpha]_D^{20}$ = -131.5° (c = 0.04, $CHCl_3$/5 % CH_3OH). UV see 21. IR (KBr): 3510, 3440 (OH), 1625 (quinone), 1590 cm^{-1} (aromate). ^{1}H-NMR (400 MHz): δ 1.50 (s, 3 H, CH_3), 1.87 (dd, J = 13.5, J = 9 Hz; 1 H, 8a-H), 2.40 (dd, J = 13.5, J = 7, J = 2.2 Hz; 1 H, 8e-H), 2.79 (d, J = 19 Hz; 1 H, 10a-H), 3.01 (dd, J = 19, J = 2.2 Hz; 1 H, 10e-H), 5.34 (t, J = 9, J = 7 Hz, 1 H, 7a-H), 7.83 (m; 2 H, 2-, 3-H), 8.33 (m; 2 H, 1-, 4-H), 13.33 and 13.91 (each s; each 1 H, 2 OH). MS (160 °) m/e: 340 (3 %, M^+), 322 (12, $M^+ - H_2O$), 304 (26, $M^+ - 2\,H_2O$) 280 (24), 267 (13), 254 (19), 239 (20), 57 (100).

(8R)-7,8,9,10-Tetrahydro-6,8,11-trihydroxy-8-methyl-5,12-naphthacenedione (18a): A solution of 1.00 g (4.13 mmol) of 6a/6b was subjected to ozonolysis as described for 4 to afford 8a/8b. The solution was evaporated at reduced pressure to remove the formaldehyde formed, redissolved in 10 ml of methanol and treated with 1.94 g (8 mmol) of 10 (see 16a, 2 h at 20 ° and 1 h at 50 °). After usual oxidative workup and chromatography on silica gel (first CH_2Cl_2, then CH_2Cl_2/10 % ether) 335 mg (32 %) of 18a crystallized from ether; m. p. 237 -239 °. The product was identical in chromatographic behaviour and spectral data with the racemic material[16].

(8R)-6,11-Diacetoxy-7,8,9,10-tetrahydro-8-hydroxy-8-methyl-5,12-naphthacenedione (18b). 50 mg of racemic 18a[16] was acetylated with 1 ml of pyridine and 1 ml of acetanhydride (20°, 12 h). The product was purified by TLC to afford 51 mg (81 %) of racemic 18b; m. p. 225°. ^{1}H-NMR (400 MHz): δ 1.40 (s;3 H, CH_3), 1.76 and 1.95 (each m; 2 H, CH_2), 2.52 (s; 6 H, 2 $COCH_3$), 2.6 - 3.0 (m; 4 H, 2 CH_2), 7.74 (m; 2 H, 1-,4-H), 8.16 (m; 2 H, 2-, 3-H). (Splitting of the signals for the two acetate groups on addition of 1 equivalent of eufod(2.55, 2.54, 2.53 and 2.52).MS (200°) m/e: 408 (0.3 %; M^+), 366 (9, $M^+ - COCH_2$), 324 (100, $M^+ - 2\,COCH_2$), 306 (63), 291 (26), 281 (19), 266 (29).

Cyclization of 14a/14b: 100 mg (0.28 mmol) of the mixture 14a/14b was subjected to ozonolysis and subsequent Marschalk reaction as described for 17. The following products of decreasing polarity were isolated: 1. 20 mg (20 %) of a 1 : 1 mixture of 22 and 27 (^{1}H-NMR for 22 see ref.[16c]); 2. 21 mg (21 % of 23; 3. 11 mg (11 % of 25; 4. 5 mg (5 %) of 28; and 5. 9 mg (9 %) of 24.

(7R,8R,10R)-7,8,9,10-Tetrahydro-6,7,8,10,11-pentahydroxy-8-methyl-5,12-naphthacenedione (27): ^{1}H-NMR (400 MHz): δ 1.47 (s; 3 H, CH_3), 1.82 (ddd, J = 14, J = 7.5, J = 2 Hz; 1 H, 9a-H), 2.53 (dd, J = 14, J = 6.3 Hz; 1 H, 9e-H), 2.74 (d, J = 1.8; 1 H, 10-OH), 3.95 (d; J = 2 Hz; 1 H, 8-OH), 4.23 (d, J = 1.5 Hz; 1 H, 7-OH), 4.84 (d, J = 1.5 Hz, 1 H, 7a-H), 5.33 (dt, J = 7.5, J = 6.3, J = 1.8 Hz; 1 H, 10-H), 7,86 (m; 2 H, 2-, 3-H), 8.36 (m; 2 H, 1-, 4-H), 13.73 and 13.84 (each s; each 1 H, 2 OH).

(7S,8R,10S)-7,8,9,10-Tetrahydro-6,7,8,10,11-pentahydroxy-8-methyl-5,12-naphthacenedione (23): ^{1}H-NMR (400 MHz): δ 1.46 (s; 3 H, CH_3), 1.94 (dd, J = 15, J = 5 Hz; 1 H, 9a-H), 2.47 (dd, J = 15, J = 3 Hz; 1 H, 9e-H), 4.79 (s; 1 H, 7a-H), 5.09 (t, J = 5, J = 3 Hz; 1 H, 10e-H), 7.86 (m; 2 H, 2-, 3-H), 8.37 (m; 2 H, 1-, 4-H), 13.49 and 13.99 (each s; each 1 H, 2 OH).

(7S,8R,10S)-7,8,9,10-Tetrahydro-6,7,8,11-tetrahydroxy-10-methoxy-8-methyl-5,12-naphthacenedione (25): m. p. 194 °. UV: 209 (4.07), 234 (4.21), 251 (4.44), 255 (4.40), 284 (3.90), 462 (3.76), 473 (3.78), 485 (3.81), 519 (3.61), 565 nm (2.56): IR (KBr): 3440 (OH), 1630 (quinone), 1590 cm^{-1} (aromate). ^{1}H-NMR (400MHz): δ 1.50 (s; 3 H, CH_3), 1.85 (dd, J = 15 Hz; J = 4 Hz; 1 H, 9a-H), 2.54 (dd, J = 15, J = 3

Hz; 1 H, 9e-H), 3.62 (s; 3 H, OCH_3), 4.09 (d, J = 7 Hz; 1 H, 7-OH), 4.58 (s; 1 H, 8-OH), 4.76 (d, J = 7 Hz; 1 H, 7a-H), 4.83 (t, J = 4, J = 3 Hz; 1 H, 10e-H), 7.86 (m; 2 H, 2-, 3-H), 8.38 (m; 2 H, 1-, 4-H), 13.50 and 13.75 (each s, each 1 H, 2 OH). MS (180°) m/e: 338 (28 %, $M^+ - CH_3OH$), 320 (44, 338 - H_2O), 304 (100), 295 (20), 280 (30), 267 (12), 254 (28).

(7R,8R,10S)-7,8,9,10-Tetrahydro-6,7,8,11-tetrahydroxy-10-methoxy-8-methyl-5,12-naphthacenedione (24): m. p. 195°. UV: see 25. IR (KBr): 3480 (OH), 1625 (quinone), 1590 cm^{-1} (aromate). ^{1}H-NMR (400 MHz): δ 1.50 (s; 3 H, CH_3), 2.06 (dd, J = 15, J = 4 Hz; 1 H, 9a-H), 2.26 (dd, J = 15, J = 2 Hz; 1 H, 9e-H), 2.74 (d, J = 4 Hz; 1 H, 7-OH), 3.65 (s; 3 H, OCH_3), 4.55 (s; 1 H, 8-OH), 4.80 (dd, J = 4, J = 2 Hz; 1 H, 10e-H), 4.87 (d, J = 4 Hz, 1 H, 7e-H), 7.85 (m; 2 H, 2-, 3-H), 8.37 (m; 2 H, 1-, 4-H), 13.48 and 13.49 (each s; each 1 H, 2 OH). MS (170°) m/e: 338 (56 %, $M^+ - CH_3OH$), 320 (94), 312 (76), 304 (100), 295 (46), 280 (46), 267 (23).

Cyclization of 20a/20b: 394 mg (1 mmol) of 19a/19b was subjected to ozonolysis as described for 4 (CH_2Cl_2 solution, 15 min) and subsequently cyclized as described for 17. After filtration through a short column of silica gel 201 mg (51 %) of the cis-diol 21 was isolated.

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