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A CONVENIENT SYNTHESIS OF NATURALLY OCCURRING QUINIZARINS

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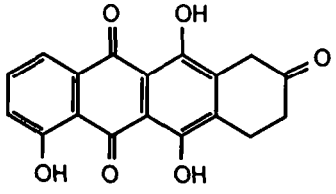
Summary - A general and regiospecific method for the preparation of quinizarins involves the cycloaddition of electron-rich dienes. Advantageous syntheses of several natural products, 2-methylquinizarin, islandicin, digitopurpone, erythroglaucin, 5-O-methylislandicin and 8-O-methyldigitopurpone illustrate this procedure. A structure attributed to ventinone B is incorrect and 1,4,8-trihydroxy-6-methylanthraquinone is different from a natural substance so described.

The synthesis of 1,4-dihydroxylated anthraquinones, known as quinizarins, has aroused considerable interest since such products are widely distributed in nature and resemble some anthracyclinones. In general, their use as intermediates or models for the elaboration of antitumour antibiotics revolves around solutions to the regiochemical problems. As a result, numerous increasingly effective approaches have been suggested for the synthesis of helminthosporin[1-4] (22), 2-methylquinizarin[5-7] (14), islandicin[8-15] (15), digitopurpone[9,11-16] (16), erythroglaucin[14,17,18] (17) or their partially methylated derivatives[11,12,19-21] 18 and 19.

Most natural naphthazarins and quinizarins carry a methyl group on the 1,4-dihydroxylated ring and although higher homologues are seldom isolated, a few ethyl- or propyl-substituted systems have nevertheless been encountered. The methodology involving the regiospecific cycloaddition of electron-rich dienes to halogenated quinones[5] seemed particularly appropriate in this area, since it could readily be adapted to the realization of all the foregoing substitution patterns as well as of those of more complex anthracyclinones via important intermediates such as 1.



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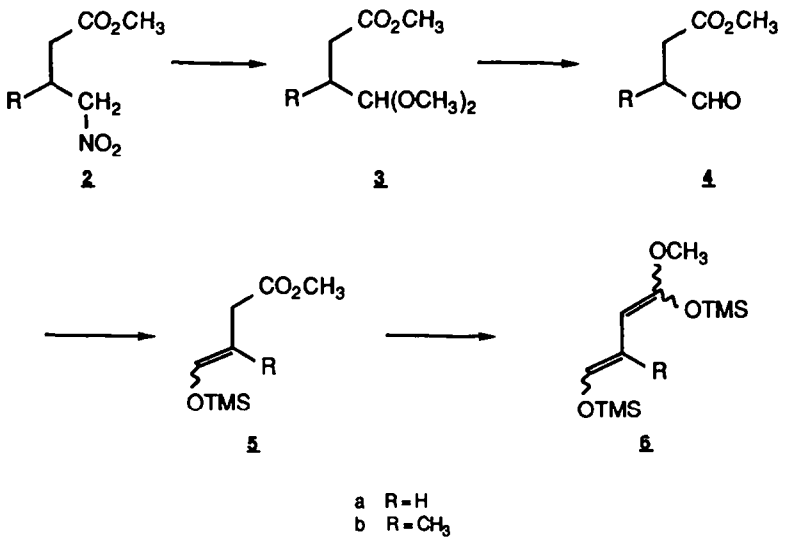
Numerous methods are available for the preparation of the required substrates, the 4-oxobutanoates 4a,b; among these, a modification[22] of the enamine method proceeded satisfactorily in the case of 4-oxo-3-propylbutanoates but could not be induced to give more than a very low yield (~5%) of the 3-methyl analogue 4b. In a preliminary communication[23], enolization of a 3-(methoxymethyl)crotonate had also been shown to be inconvenient. Eventually, a modified Nef reaction[24] was selected in which the alcoholysis of a 4-nitrobutanoate (2a,b) (as the sodium salt) produced the acetal (3a,b) and an efficient hydrolysis[25] of the latter afforded aldehyde 4a,b. The process occurs in overall high yield (76-77%) with the required flexibility and ease of operation.

The p-toluenesulfonic acid-catalyzed pyrolysis of acetal 3b produced some elimination but did not give the enol methyl ether cleanly. On the other hand, enolization of aldehyde 4b in the presence of chlorotrimethylsilane using the triethylamine-zinc chloride complex[26] provided a 90% yield of the β,γ-unsaturated ester 5b as a 5:4 mixture of the Z- and E-isomers (aldehyde 4a gave a

78% yield of the corresponding products in a 2.9: 1.0 ratio). A combination consisting largely of the E-isomer could also be obtained by the use of trimethylsilyl triflate in triethylamine[27] but the yield did not exceed 56%. Analogous compounds have also recently been prepared by an iodotrimethylsilane - induced rearrangement of 2-siloxycyclopropanecarboxylates[28].

A second enolization, using the Corey and Gross procedure[29], was carried out on the foregoing esters 5a,b and gave slightly better yields of a purer product (85-90%) than with the method used previously[4]. Under these two sets of conditions, the proportions of stereoisomers can be quite different but it has been shown in another case that the distribution of isomers has little effect on subsequent cycloadditions. Thus, ester 5a gave a mixture of three isomers (a fourth is barely perceptible) of Z,Z-, E,Z- and Z,E-configuration in a 2.9: 0.9: 1.0 ratio and the method seems to favor the Z-arrangement at the 1,2-position. On the other hand, a similar enolsilylation of ester 5b affords only two detectable isomers, the Z,Z- and Z,E- forms. Overall yields of dienes 6a and 6b from 4-nitrobutanoates, for the four steps, thus reach 50 and 63% respectively (SCHEME I).



SCHEME I

Dienes 6a and b react readily with dichlorobenzoquinones at room temperature but only traces of the expected naphthoquinones can be detected. The main products cannot be isolated without decomposition but probably result from addition to a carbonyl group as it has earlier been established with the use of 4-methoxyvinylketene acetals[30]. Attempts to isolate the adducts by chromatography yielded only the hydroquinone corresponding to the starting material and illustrate a typical behavior of such products, reminiscent of a dienone-phenol rearrangement. Naphthazarins therefore cannot at present be prepared by this approach.

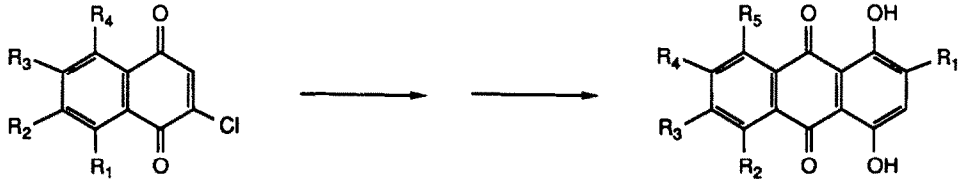
The effectiveness of diene 6b in the synthesis of naturally occurring anthraquinones, i.e. quinizarins was first examined using a simple substrate, 2-chloronaphthoquinone (7). The reaction was sluggish even at 80 °C and required more than five days to reach completion. Under these conditions the diene decomposes slowly and supplemental quantities of the reagent had to be added periodically. The adduct was then hydrolyzed at room temperature with 12 N HCl in THF in order to minimize the formation of a ubiquitous by-product, the anthraquinone 4-methyl ether. Finally aromatization of the adduct was carried out simply by refluxing the foregoing mixture and the natural product (14) could then be isolated in good yield (76%).

Islandicin (15), *digitopurpone* (16), *erythroglaucin* (17) *and the non-natural* 8-O-*methyldigitopurpone* (19) were prepared in this manner (62-91%) and, by a judicious choice of the most reactive of appropriate substrates (7-11), reaction times were kept within convenient limits (3-45 hours) (SCHEME III). Application of the method to the synthesis of another natural product, 5-O-methylislandicin (18) however presented some difficulties. In a first attempt, 3-chloro-5-methoxynaphthoquinone (8b) seemed particularly unreactive and after 12 days was found upon aromatization

to yield a difficultly separable 10:1 mixture (65%) of 5-O-methylislandicin (18) and 8-O-methyldigitopurpone (19). In order to circumvent this inconvenience, a new technique was devised which confers even greater flexibility to this approach. The free juglone (8a) was used as substrate for the cycloaddition and the resultant adduct was alkylated directly using methyl iodide and silver (I) oxide. The reaction proved to be entirely selective, did not affect the silyl ethers or other sensitive features of the molecule, but did not readily reach completion. After 48 hours, aromatization of the hydrolyzed material gave a mixture of islandicin (15) (7%) and its 5-O-methyl ether (18) (46%) which could easily be separated by chromatography.

The proven reliability of this method, as determined by the synthesis of some natural products with well established structures, prompted the investigation of a few compounds, i.e. ventinone B and the 8-nor-derivative, to which somewhat improbable substitution patterns have been attributed. The required substrate, 2-chloro-5,7-dimethoxynaphthoquinone (11b) had previously been obtained[4] in low yield (20%) by methylation of the crude juglone. It was surmised that the latter was rather unstable in contact with silica gel during the usual work-up. However when aromatization of the adduct was conducted with dilute HCl in THF at room temperature and followed by methylation a much better yield (68%) could be achieved.

Cycloaddition of diene 6b to naphthoquinone 11b led to of an anthraquinone (21) (95%) having physical and spectral properties quite different from those of ventinone B[31] (inconsistently described as orange in color). A reexamination of the extensive data on this substance suggests that it may well be the 4-methyl ether of erythroglaucin. A selective demethylation of quinone 21 using $AlCl_3$ in CH_2Cl_2 gave a product (20), also obtained by cycloaddition of diene 6b to naphthoquinone 11a, which was clearly identical to one obtained earlier by Braun[14]. These results confirm the suspicion that the substance isolated by Lal and Gupta[32] had been incorrectly identified. The lack of information on this substance however prevents any attempt to reassign the structure.



	R_1	R_2	R_3	R_4
7	H	H	H	H
8a	OH	H	H	H
8b	OCH_3	H	H	H
9a	H	H	H	OAc
9b	H	H	H	OCH_3
10	OH	H	OCH_3	H
11a	H	OCH_3	H	OAc
11b	H	OCH_3	H	OCH_3
12	OH	H	CH_3	H

	R_1	R_2	R_3	R_4	R_5
14	CH_3	H	H	H	H
15	CH_3	OH	H	H	H
16	CH_3	H	H	H	OH
17	CH_3	OH	H	OH	H
18	CH_3	OCH_3	H	H	H
19	CH_3	H	H	H	OCH_3
20	CH_3	H	OCH_3	H	OH
21	CH_3	H	OCH_3	H	OCH_3
22	H	OH	H	CH_3	H

SCHEME II

Finally a reaction was also attempted with diene 6a, the lower homologue of the reagent used in the foregoing syntheses. Although the reactivity of naphthoquinone 12, was usually rather high, conversion to the corresponding adduct was very slow. The components, brought together for seven days at room temperature and without solvent provided a low yield (27%) of helminthosporin (22).

EXPERIMENTAL

All m.p.s. were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The U.V. spectra were determined on a Hewlett-Packard 8450A spectrophotometer, the I.R. Spectra on a Beckman model IR-4250 instrument and calibrated with a film of polystyrene. N.M.R. spectra were recorded with a Varian XL-200 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck silica gel

$60F_{254}$, for dry column chromatography, was used throughout in a product-to-adsorbent ratio of 1:50-100. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

I. Preparation of dienes

Methyl 4,4-dimethoxybutanoate (3a)

Methyl 4-nitrobutanoate[33] (2a) 25.0 g; 0.17 mol) was introduced dropwise (45 min) into a solution of sodium methylate prepared from sodium (4.30 g; 0.19 mol) and absolute methanol (150 mL). The resultant suspension was added slowly (90 min) to a solution of conc. H_2SO_4 (51.9 mL) and absolute methanol (267 mL) at -10 °C. Stirring was continued for 15 min and the reaction mixture was poured into CH_2Cl_2 (500 mL) and water (500 mL). The organic phase was washed with 1% aqueous NaOH (200 mL), ice water (2 x 250 mL) and saturated NaCl (400 mL). Distillation of the residue afforded ester 3a (23.1 g; 84%), b.p. 86-88 °C/15 mm Hg (lit.[34] 61-64 °C/4 mm Hg); I.R. ν_{max} (film) 1735 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) 1.93 (2H, td, J=7.5, 5.5 Hz, 3-H), 2.39 (2H, t, J=7.5 Hz, 2-H), 3.33 (6H, s, 4,4-OCH_3), 3.68 (3H, s, 1-OCH_3) and 4.40 (1H, t, J=5.5 Hz, 4-H).

Methyl 4,4-dimethoxy-3-methylbutanoate (3b).

In a similar reaction, methyl 3-methyl-4-nitrobutanoate[35] (2b) (32.2 g; 0.20 mol) was reacted with to sodium methylate (0.22 mol) in methanol (175 mL) and added to conc. H_2SO_4 (61 mL) and methanol (253 mL). Isolation of the product as above gave ester 3b (30.3 g; 86%), b.p. 92-94 °C/19.5 mm Hg; I.R. ν_{max} (film) 1735 cm^{-1}; ^{1}H-N.M.R (200 MHz, $CDCl_3$) 0.96 (3H, d, J=6.7 Hz, 3-CH_3), 2.14 (1H, dd, J=14.6, 7.9 Hz, 2-H), 2.21-2.40 (1H, m, 3-H), 2.50 (1H, dd, J=14.6, 5.1 Hz, 2-H), 3.35 and 3.36 (2 x 3H, 2s, 4,4-OCH_3), 3.67 (3H, s, 1-OCH_3) and 4.10 (1H, d, J=6.0 Hz, 4-H); M.S. m/z 145 $(M-CH_3O)^+$. (Found: C, 54.28; H, 9.17. Calc. for $C_8H_{16}O_4$: C, 54.53; H, 9.15).

Methyl 3-methyl-4-oxobutanoate (4b).

A mixture of ester 3b (25.0 g; 0.14 mol) and water (50 mL) was refluxed for 90 min. Methanol was distilled off through a Vigreux column and the residue extracted with methylene chloride (2 x 50 mL). Fractionation of the crude product gave pure ester 4b (16.5 g; 89%), b.p. 87-88 °C/22 mm Hg (lit.[36] 49-51 °C/3 mm Hg); I.R. ν_{max} (film) 1735 and 1725 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 1.20 (3H, d, J=7.0 Hz, 3-CH_3), 2.38 (1H, dd, J=16.1, 5.9 Hz, 2-H), 2.75 (1H, dd, J=16.1, 7.0 Hz, 2-H), 2.80-2.96 (1H, m, 3-H), 3.70 (3H, s, 1-OCH_3) and 9.70 (1H, s, 4-H); M.S. m/z 130 $(M)^+$. 2,4-Dinitrophenylhydrazone, m.p. 136.0-136.5 °C (CH_3OH). (Found: C, 46.64; H, 4.45; N, 17.98. Calc. for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06).

Methyl E- and Z-4-trimethylsiloxybut-3-enoate (5a)

To a suspension of powdered anhydrous $ZnCl_2$ (400 mg) in dry triethylamine (22.2 g; 0.22 mol) were added ester 4a[25] (11.6 g; 0.10 mol) in dry benzene (30 mL) (18 min) and then $ClSiMe_3$ (21.7 g; 0.20 mol) (20 min). The reaction mixture was stirred for 30 min, then kept at 40 °C for 17 h. Volatile fractions were evaporated under vacuum and petroleum ether (b.p. 35-60 °C) (250 mL) was added. The insoluble material was filtered off and the filtrate was concentrated (this process was repeated until salts no longer precipitated). Distillation of the residue gave unsaturated ester 5a as a 1:2.9 mixture of the E- and Z-isomers (14.6 g; 78%), b.p. 42-45 °C/0.55-0.60 mm Hg, I.R. ν_{max} (film) 1740, 1660, 1250 and 840 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 0.18 (s, Z-4-OTMS), 0.20 (s, E-4-OTMS), 2.92 (dd, J=7.6, 1.3 Hz, E-2-H); 3.15 (dd, J=7.0, 1.6 Hz, Z-2-H), 3.67 (s, E-1-OCH_3), 3.68 (s, Z-1-OCH_3), 4.70 (td, J=7.0, 5.7 Hz, Z-3-H), 5.08 (dt, J=12.1, 7.6 Hz, E-3-H), 6.29 (dt, J=5.7, 1.6 Hz, Z-4-H) and 6.30 (dt, J=12.1 and 1.3 Hz, E-4-H). (Found: C, 50.97; H, 8.43. Calc. for $C_8H_{16}SiO_3$: C, 51.03; H, 8.56).

Methyl E- and Z-3-methyl-4-trimethylsiloxybut-3-enoate (5b).

Under conditions analogous to those of the preceding paragraph, ester 4b (13.0 g; 0.10 mol) provided enol ether 5b (18.4 g; 91%) as a 4:5 mixture of the E- and Z-forms, b.p. 42-45 °C/0.3 mm Hg; I.R. ν_{max} (film) 1740, 1675, 1255 and 845 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 0.16 and 0.18 (2s, 4-OTMS), 1.61 (d, J=1.3 Hz, Z-3-CH_3), 1.65 (d, J=1.3 Hz, E-3-CH_3), 2.87 (d, J=1.0 Hz, E-2-H), 3.11 (br s, Z-2-H), 3.67 (s, 1-OCH_3) and 6.15 (m, 4-H). (Found: C, 53.41; H, 9.11; Si, 13.59. Calc. for $C_9H_{18}SiO_3$: C, 53.43; H, 8.97; Si, 13.88).

1-Methoxy-1,4-bistrimethylsiloxy-1,3-butadiene (6a).

To a solution of dry diisopropylamine (8.60 g; 85.0 mmol) in anhydrous THF at 0 °C, was added under nitrogen a 1.60 M solution of n-BuLi (53.0 mL; 85.0 mmol) in hexane. The mixture was

stirred for 15 min then cooled to -78 °C and to it were added successively $ClSiMe_3$ (12.6 g; 0.12 mol) (10 min) and a solution of ester 5a (14.6 g; 77.0 mmol) in THF (25 mL) (75 min). The mixture was stirred for 15 min, allowed to come to room temperature, concentrated under vacuum, diluted with petroleum ether (b.p. 35-60 °C) (250 mL), and filtered (this operation is repeated until salts no longer precipitated). Distillation of the residue yielded diene 6a (17.1 g; 85%) as a 0.9: 1.0: 2.9 mixture of the E,Z-, Z-E- and Z,Z-isomers, b.p. 75-77 °C/0.7 mm Hg; I.R. ν_{max} (film) 1665, 1610, 1250 and 845 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 0.18 and 0.27 (2s, 1,4-OTMS); E,Z-isomer: 3.60 (s, 1-OCH_3), 4.69 (dd, J=10.5, 1.1 Hz, 2-H), 5.31 (dd, J=10.5, 5.9 Hz, 3-H) and 5.96 (dd, J=5.9, 1.1 Hz, 4-H); Z,E-isomer: 3.54 (s, 1-OCH_3), 4.35 (d, J=11.2 Hz, 2-H), 5.79 (dd, J=12.1, 11.2 Hz, 3-H) and 6.26 (d, J=12.1 Hz, 4-H); Z,Z-isomer: 3.57 (s, 1-OCH_3), 4.76 (dd, J=10.8, 1.1 Hz, 2-H), 5.35 (dd, J=10.8, 5.9 Hz, 3-H) and 5.94 (dd, J=5.9, 1.1 Hz, 4-H).

1-Methoxy-3-methyl-1,4-bistrimethylsiloxy-1,3-butadiene (6b).

In a procedure similar to the foregoing, $ClSiMe_3$ (14.5 g; 133 mmol) and then a solution of methyl 3-methyl-4-trimethylsiloxy-3-butenoate (5b) (18.0 g; 89.0 mmol) in THF (25 mL) were added to lithium diisopropylamide (98.0 mmol) [prepared from diisopropylamine (9.90 g; 98.0 mmol) and 1.55 M n-BuLi in hexane (63 mL; 98.0 mmol)] in anhydrous THF (100 mL). Distillation of the crude product through a short Vigreux column provided diene 6b (22.0 g; 90%) as a 4:5 mixture of the Z,E- and Z,Z-isomers, b.p. 69-70 °C/0.3 mm Hg; IR ν_{max} (film) 1655, 1615, 1250 and 840 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) 0.16 (s, Z,Z-4-OTMS), 0.17 (s, Z,E-4-OTMS), 0.24 (s, Z-E-1-OTMS), 0.27 (s, Z,Z-1-OTMS), 1.74 (d, J=1.6 Hz, Z,Z-3-CH_3), 1.78 (d, J=1.3 Hz, Z,E-3-CH_3), 3.53 (s, 1-OCH_3), 4.25 (d, J=1.0 Hz, Z,E-2-H), 4.86 (d, J=1.0 Hz, Z,Z-2-H), 5.79-5.81 (m, Z,Z-4-H) and 6.21-6.23 (m, Z,E-4-H).

II Syntheses of 2-methylquinizarins

General method A: To a solution or supension of the chloronaphthoquinone (1.00 mmol) in anhydrous benzene (3 mL) is added (3-5 min) at room temperature, diene 6b (549 mg; 2.00 mmol) in the same solvent (2 mL). The mixture is stirred for 1 h at 25 °C, heated to reflux (until t.l.c. indicated disappearance of the naphthoquinone), cooled and evaporated under vacuum. Conc. HCl (2 mL) is added to a solution of the crude adduct in THF (10 mL) which is stirred for 1 h at 25 °C, refluxed for 1 h (3 h in the case of acetoxynaphthoquinones) and poured into a mixture of ether (250 mL) and water (150 mL). The organic phase is extracted with 2% aqueous NaOH (3 x 60 mL); the basic extracts acidified with 6 N HCl and extracted with dichloromethane (2 x 200 mL). After washing the organic solution with water (2 x 150 mL), drying and evaporating, the residue is purified by chromatography on silica gel.

General method B: As in method A except that, after refluxing, the THF -conc. HCl solution is poured into water (250 mL) and the crude anthraquinone extracted with dichloromethane (2 x 200 mL). The organic phase is washed with water (3 x 125 mL), dried and evaporated. After triturating with petroleum ether, b.p. 35-60 °C (250 mL), the crude solid is purified by chromatography (the small amount of product dissolved in the petroleum ether can be recovered by evaporation of the solvent, extraction with 2% NaOH, and acidification in the usual way).

1,4-Dihydroxy-2-methylanthraquinone (2-Methylquinizarin) (14).

The reaction of 2-chloronaphthoquinone (7)[37] (193 mg; 1.00 mmol) with diene 6b (549 mg; 2.00 mmol) according to method A (138 h) (an equal portion of diene in 1 mL of benzene was added after 95 h), after purification by chromatography (C_6H_6-CCl_4, 1:1), provided 2-methylquinizarin (14) (200 mg; 79%), m.p. 178 °C ($CHCl_3$-CH_3OH) (lit[38] m.p. 175-176 °C; [6] 178-179 °C; [7] 170 °C; UV λ_{max}-(CH_3OH) (log ε) 226 (4.32), 231 (4.32), 249 (4.60), 284 (4.03), 323 (sh) (3.41), 454 (sh) (3.93), 480 (3.98), 500 (sh) (3.82) and 512 (3.76) nm; IR ν_{max} (KBr) 1625 and 1580 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 2.37 (3H, d, J=0.7 Hz, 2-CH_3), 7.16 (1H, br s, 3-H), 7.78-7.86 (2H, m, 6,7-H), 8.30-8.38 (2H, m, 5,8-H), 12.96 (1H, s, 4-OH) and 13.35 (1H, s, 1-OH); M.S. m/z 254 $(M)^+$. (Found: C, 70.64; H, 3.81. Calc. for $C_{15}H_{10}O_4$: C, 70.86; H. 3.96).

1,4,5-Trihydroxy-2-methylanthraquinone (Islandicin) (15).

An analogous reaction applied to diene 6b (2.00 mmol) and 3-chlorojuglone (8a)[37] (209 mg; 1.00 mmol) using method A (3h) gave isladicin (15) (209 mg; 79%, m.p. 218.5-219.0 °C ($CHCl_3$-CH_3OH) (lit.[39] m.p. 218 °C;[14] 215-217 °C;[15] 219-220 °C); UV λ_{max} (CH_3OH) (log ε) 231 (4.61), 252 (4.39),

290 (3.97), 464 (sh) (4.07), 4.78 (sh) (4.13), 490 (4.17), 508 (sh) (4.03) and 524 (3.98) nm; IR ν_{max} (KBr) 3130 (br) and 1595 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 2.38 (3H, d, J=1.1 Hz, 2-CH_3), 7.16 (1H, br s, 3-H), 7.30 (1H, dd, J=8.4, 1.5 Hz, 6-H), 7.69 (1H, ~ t, J=8.4, 7.7 Hz, 7-H), 7.89 (1H, dd, J=7.7, 1.5 Hz, 8-H), 12.28 and 12.32 (2 x 1H, 2s, 4,5-OH) and 13.48 (1H, s, 1-OH); M.S. m/z 270 $(M)^+$. (Found: C, 66.51; H, 3.52. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73).

1,4,8-Trihydroxy-2-methylanthraquinone (Digitopurpone) (16).

Application of method A (32h) to diene 6b (2.00 mmol) and 2-chlorojuglone acetate (9a)[40] (251 mg; 1.00 mmol) (an extra 0.5 mmol of diene in 1 mL of benzene was added after 25h) and purification as before afforded digitopurpone (16) (235 mg; 87%), m.p. 211-212 °C; ($CHCl_3$-CH_3OH) (lit.[41] m.p. 209-211 °C; [11] 210.5-212 °C; [15] 209-210 °C); UV λ_{max} (CH_3OH) (log ε) 231 (4.66), 250 (4.40), 289 (4.01), 462 (sh) (4.10), 476 (sh) (4.15), 490 (4.20), 508 (sh) (4.06) and 522 (4.01) nm; IR ν_{max} (KBr) 3150 (br) and 1595 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 2.37 (3H, d, J=1.5 Hz, 2-CH_3), 7.18 (1H, br s, 3-H), 7.30 (1H, dd, J=8.2, 1.5 Hz, 7-H), 7.70 (1H, ~ t, J=8.2, 7.6 Hz, 6-H), 7.88 (1H, dd, J=7.6, 1.5 Hz, 5-H), 12.33 and 12.71 (2H, 2s, 4,8-OH) and 13.09 (1H, s, 1-OH); M.S. m/z 270 $(M)^+$. (Found: C, 66.72; H, 3.67. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73).

1,4,5-Trihydroxy-7-methoxy-2-methylanthraquinone (Erythroglaucin) (17).

A condensation analogous to the foregoing, with diene 6b (2.00 mmol) and 3-chloro-7-methoxyjuglone[4] (10) (239 mg; 1.00 mmol) (method A-45h) (0.5 mmol of the diene in 1 mL of benzene was added after 25h), after purification in the usual way gave erythroglaucin (17) (186 mg; 62%), m.p. 206.5-207.5 °C ($CHCl_3$-CH_3OH) (lit.[42,14] m.p. 205.0-206.0; [10] 204 °C; UV λ_{max} (CH_3OH) (log ε) 230 (4.61), 255 (4.31), 275 (4.29), 304 (4.06), 460 (sh) (4.10), 476 (sh) (4.17), 488 (4.22), 508 (sh) (4.10) and 520 (4.04) nm; IR ν_{max} (KBr) 1595 and 1575 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 2.37 (3H, d, J=1.1 Hz; 2-CH_3), 3.95 (3H, s, 7-OCH_3), 6.71 (1H, d, J=2.6 Hz, 6-H), 7.14 (1H, br s, 3-H), 7.42 (1H, d, J=2.6 Hz, 8-H), 12.38 and 12.46 (2 x 1H, 2s, 4,5-OH) and 13.38 (1H, s, 1-OH); M.S. m/z 300 $(M)^+$. (Found: C, 64.22; H, 3.94). Calc. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03).

1,4-Dihydroxy-5-methoxy-2-methylanthraquinone (5-O-Methylislandicin) (18).

To a solution of 3-chlorojuglone (8a) (209 mg; 1.00 mmol) in dry methylene chloride (3 mL) was added dropwise (10 min) diene 6b (549 mg; 2.00 mmol) dissolved in the same solvent (2 mL). The mixture was stirred at r.t. for 35 h and evaporated under vacuum. To the residue taken up in chloroform (20 mL) were added freshly prepared silver (I) oxide (2.3 g; 9.9 mmol) and iodomethane (1.0 mL; 16 mmol - similar portions were added after 12 and 24 h). The mixture was stirred at r.t. for 76 h [additional amounts of silver oxide (1.2 g) and iodomethane (0.5 mL) were introduced after 56 h] filtered and evaporated. Aromatization of the methylated adduct was conducted according to method B and separation of the crude products by chromatography (C_6H_6) yielded islandicin (15) (20 mg; 7%) as a first fraction. Elution of a second zone (C_6H_6 - AcOEt 20:1) provided 5-O-methylislandicin (18) (130 mg; 46%), m.p. 195 °C (C_6H_6 - petroleum ether, b.p. 65-110 °C) (lit.[11] m.p. 193.5-195.0 °C;[20] 194-195 °C; [21] 194.0-196.5 °C); UV λ_{max} (CH_3OH) (log ε) 230 (4.54), 249 (4.32), 287 (3.93), 387 (sh) (3.43), 468 (sh) (4.01), 478 (sh) (4.01), 492 (4.02) and 526 (3.75) nm; IR ν_{max} (KBr) 1610 and 1575 cm^{-1}; ^{1}H-N.M.R. (200 MHz; $CDCl_3$) δ 2.35 (3H, d, J=1.5 Hz, 2-CH_3), 4.08 (3H, s, 5-OCH_3), 7.15 (1H, br s, 3-H), 7.37 (1H, dd, J=8.4, 1.3 Hz, 6-H), 7.76 (1H, dd, J=8.4, 7.6 Hz, 7-H), 8.04 (1H, dd, J=7.6, 1.3 Hz, 8-H) and 13.32 and 13.33 (2H, 2s, 1,4-OH); M.S. m/z 284 $(M)^+$. (Found: C, 67.65; H, 4.38. Calc. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25).

1,4-Dihydroxy-8-methoxy-2-methylanthraquinone (8-O-Methyldigitopurpone) (19).

Application of method B to 2-chlorojuglone methyl ether (9b)[43] (223 mg; 1.00 mmol) and diene 6b (2.00 mmol + 0.50 mmol after 24h), and chromatography of the crude product (C_6H_6-AcOEt 20:1) provided 8-O-methyldigitopurpone (19) (258 mg; 91%), m.p. 211.5-212.0 °C; (AcOEt) (lit.[11] 208.0-210.5 °C; [12] 218 °C; [21] 209-211 °C); UV λ_{max} (CH_3OH) (log ε) 231 (4.53), 248 (4.32), 285 (3.95), 389 (sh) (3.48), 470 (sh) (4.03), 476 (4.03), 492 (4.03) and 526 (3.76) nm; IR ν_{max} (KBr) 1615 and 1575 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 2.36 (3H, d, J=0.8 Hz, 2-CH_3), 4.08 (3H, s, 8-OCH_3), 7.11 (1H, q, J=0.8 Hz, 3-H), 7.36 (1H, dd, J=8.4, 1.1 Hz, 7-H), 7.76 (1H, dd, J=8.4, 7.8 Hz, 6-H), 8.02 (1H, dd, J=7.8, 1.1 Hz; 5-H), 12.95 (1H, s, 4-OH) and 13.69 (1H, s, 1-OH); M.S. m/z 284 $(M)^+$. (Found: C, 67.55; H, 4.38. Calc. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25).

2-Chloro-5,7-dimethoxy-1,4-naphthoquinone (11b).

To 2,5-dichlorobenzoquinone (531 mg; 3.00 mmol) in dry THF (25 mL) was added 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene[8] (668 mg; 3.30 mmol) in the same solvent (5 mL). The solution was stirred at 25 °C for 2h and diluted with 5% aqueous HCl (6 mL). After stirring at the same temperature for 88h, the mixture was poured into water (200 mL) and extracted with dichloromethane (2 x 100 mL). The organic extracts were then washed with water (3 x 75 mL), dried and evaporated. Methylation of the residue [Ag_2O (2.0 g; CH_3I (1.0 mL), $CHCl_3$ (50 mL) - 23h] and purification of the crude product by chromatography (C_6H_6-AcOEt 10:1) afforded naphthoquinone 11b (518 mg; 68%), m.p. 187.5-188.0 °C (C_6H_6) (lit.[9] 185-187 °C, [10] 187.5-188.5 °C).

1,4-Dihydroxy-6,8-dimethoxy-2-methylanthraquinone (21).

Purification by chromatography (C_6H_6-AcOEt 20:1) of the crude product obtained from naphthoquinone 11b (253 mg; 1.00 mmol) and diene 6b (2 mmol + 0.5 mmol in 1 mL benzene after 26h) according to method B (70h) gave anthraquinone (21) (300 mg; 95%), m.p. 220.5 °C ($CHCl_3$-CH_3OH); UV λ_{max} (CH_3OH) (log ε) 230 (4.58), 275 (4.30), 299 (4.03), 476 (4.06), 488 (sh) (4.05), 512 (sh) (3.87) and 524 (sh) (3.75) nm; IR ν_{max} (KBr) 1610, 1580 and 1560 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) 2.36 (3H, s, 2-CH_3), 4.00 (3H, s, 6-OCH_3), 4.04 (3H, s, 8-OCH_3), 6.80 (1H, d, J=2.4 Hz, 7-H), 7.08 (1H, br s, 3-H), 7.52 (1H, d, J=2.4 Hz, 5-H), 12.89 (1H, s, 4-OH) and 13.85 (1H, s, 1-OH); M.S. m/z 314 $(M)^+$. (Found: C, 64.80; H, 4.48. Calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49).

5-Acetoxy-2-chloro-7-methoxynaphthoquinone (11a).

This compound was prepared as in the procedure used for naphthoquinone 11b; however the crude intermediate 2-chloro-5-hydroxy-7-methoxynaphthoquinone was isolated and recrystallized twice ($CHCl_3$-95% C_2H_5OH). Acetylation of this material (385 mg; 54%) in the usual way [Ac_2O (5 mL); H_2SO_4; 1h] occurred in nearly quantitative yield and provided the acetate 11a (447 mg), m.p. 198.0-199.0 °C (AcOEt); UV λ_{max} (CH_3OH) (log ε) 267 (4.29) and 385 (3.41) nm; IR ν_{max} (KBr) 1765, 1690, 1655, 1610 and 1590 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 2.43 (3H, s, 5-$OCOCH_3$), 3.96 (3H, s, 7-OCH_3), 6.88 (1H, d, J=2.9 Hz, 6-H), 7.03 (1H, s, 3-H) and 7.60 (1H, d, J=2.9 Hz, 8-H); MS m/z 280/282 $(M)^+$ (4,2%) and 238/240 $(M-CH_2CO)^+$ (100, 33%).

1,4,8-Trihydroxy-6-methoxy-2-methylanthraquinone (20).

A: Cycloaddition of diene 6b (2.00 mmol + 0.50 mmol after 24h) to naphthoquinone 11a (281 mg; 1.00 mmol), hydrolysis and aromatization of the adduct according to method B (72h) provided, after chromatography (CH_2Cl_2), anthraquinone 20 (203 mg; 68%), m.p. 257.0-257.5 °C (C_6H_6) (lit.[11] 256-257 °C); UV λ_{max} (CH_3OH) (log ε) 231 (4.63), 252 (4.28), 268 (sh) (4.24), 277 (4.31), 305 (4.06), 460 (sh) (4.13), 474 (sh) (4.18), 486 (4.22), 506 (4.10) and 516 (4.04) nm; IR ν_{max} (KBr) 1595 and 1580 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) 2.37 (3H, d, J=1.1 Hz, 2-CH_3), 3.95 (3H, s, 6-OCH_3), 6.71 (1H, d, J=2.6 Hz, 7-H), 7.14 (1H, br s, 3-H), 7.42 (1H, d, J=2.6 Hz, 5-H), 12.44 and 12.78 (2 x 1H, 2s, 4,8-OH) and 13.00 (1H, s, 1-OH); M.S. m/z 300 $(M)^+$. (Found: C, 63.94; H, 4.14. Calc. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03).

B: A suspension of anthraquinone 21 (100 mg; 0.32 mmol), anhydrous $AlCl_3$ (0.4 g; 3.2 mmol) and dry CH_2Cl_2 (10 mL) was stirred at 25 °C (75 min) then poured into a mixture of ice (50 g), water (50 mL) and conc. HCl (10 mL) and again stirred for 6h. The crude product was extracted with CH_2Cl_2 (3 x 150 mL) and the organic solution washed with water (2 x 150 mL), dried and evaporated. Chromatography ($CHCl_3$) of the residue gave anthraquinone 20 (77 mg; 81%).

1,5,8-Trihydroxy-3-methylanthraquinone (Helminthosporin) (22).

Adaptation of method B (7 days; without solvent) to 3-chloro-7-methyljuglone (12)[9] (0.50 mmol) and diene 6a (2.00 mmol + 2.00 mmol after 3 days) followed by chromatography (C_6H_6-CCl_4 1:1) of the crude product afforded helminthosporin (22) (37 mg; 27%), m.p. 227.5-228.5 °C; ($CHCl_3$-CCl_4) (lit.[12] 225-226 °C; [13] 226-227 °C; [14] 228-229 °C; UV λ_{max} (CH_3OH) (log ε) 229 (4.64), 254 (4.30), 287 (3.96), 295 (sh) (3.92), 462 (sh) (4.05), 478 (4.10), 486 (4.12), 506 (sh) (4.00) and 520 (3.89) nm; IR ν_{max} (KBr) 1595 and 1570 cm^{-1}; ^{1}H-N.M.R. (200 MHz, $CDCl_3$) δ 2.49 (3H, s, 3-CH_3), 7.12 (1H, br s, 2-H), 7.30 (2H, s, 6,7-H), 7.70 (1H, br s, 4-H), 12.14 and 12.32 (2 x 1H, 2s, 1,8-OH) and 13.01 (1H, s, 5-OH); M.S. m/z 270 $(M)^+$. This substance is indistinguishable from a sample prepared earlier[9] (IR, mixture m.p. and tlc in 4 solvent systems).

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