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AN INTEGRATED APPROACH TO THE SYNTHESIS OF CONTIGUOUSLY SUBSTITUTED XANTHOPURPURINS, PACHYBASINS AND PURPURINS.

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Summary - Alkylation, hydroxyalkylation and acylation of 3-methyl-, 3-methoxy- and 3,4-dimethoxycrotonates can be induced to occur exclusively in the α-position Conversion of the products to dienes then provides, through cycloaddition, a wide variety of substitution patterns This approach is illustrated by simplified syntheses of a number of naturally occurring quinones and confirms the structures proposed for vismiaquinone C, 7-geranylemodin, cinnalutein, 4,5-dihydroxydigitolutein, 2-hydroxyislandicin 1-methyl ether and calyculatone 1-methyl ether

Recently, many useful methods have been proposed for effective syntheses of naturally occurring quinones [1,2] Schemes directed towards highly regioselective results, in particular for specifically methylated polyphenolic products, have generally required different approaches for each arrangement of substituents In practice, only dienes derived from a few readily available butenoates can be considered to provide a unified strategy in this area[3] The observation that the reaction of unsaturated ester enolates with electrophiles can be directed preferentially to either the α- or the γ-position has now led to the development of a generalized methodology for the more highly substituted cases

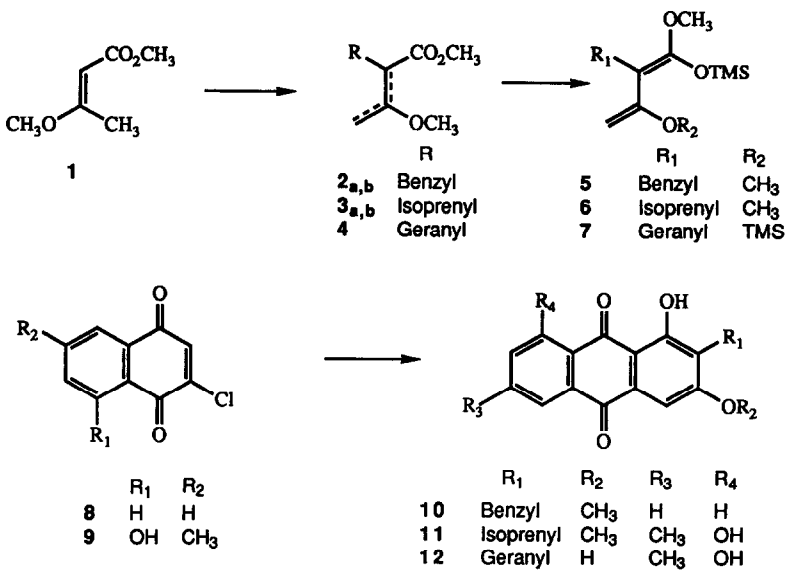
Numerous papers on the alkylation and hydroxyalkylation of crotonic ester enolates have helped to delimit the conditions that favor either α- or γ-substitution[4] A reexamination of some of these methods has suggested the use of an established procedure (LDA, HMPA, THF, –78°C) for the present objective Under these conditions, substitution of 3-methyl, 3-methoxy- and 3,4-dimethoxycrotonates is restricted to the α-position in the only detectable product (a ~ 1 4 mixture of diastereomers in the case of hydroxyalkylation) Thus, the preparation of an array of intermediates for the synthesis of tetra- and pentasubstituted dienes can be envisioned starting from a small number of readily accessible substrates

After this approach had successfully been applied to electrophiles such as methyl[5] and ethyl iodide[6] as well as to acetaldehyde[6], attention was turned to other reagents that could eventually lead to expeditious syntheses of a variety of natural products Benzyl, isoprenyl and geranyl groups were readily introduced into 3-methoxycrotonate **1**, through their

bromides, and afforded intermediates **2-4** in good to excellent yield (70-95%) The products, even in the crude state, showed all the desired characteristics, i e. only monosubstitution had occurred without detectable amounts of the γ-isomer. In most cases, the resultant β-unsaturated esters were partially isomerized during purification, without inconvenience however, since both forms were easily enolized in the next step of the process

Although the use of HMPA for the alkylation could be dispensed with on occasion (as in the case of methyl iodide, but not of acetaldehyde), it was adopted systematically throughout. Subsequent elimination of this additive by washing with a concentrated solution of copper (II) nitrate also resulted, in one case, in extensive hydrolysis of the enol ether However, this occurrence was not inopportune since the ketoester could then be converted to silyl enol ether (**4**) and then affords a more readily deprotected end-product, since β-methoxyanthraquinones are not easily cleaved

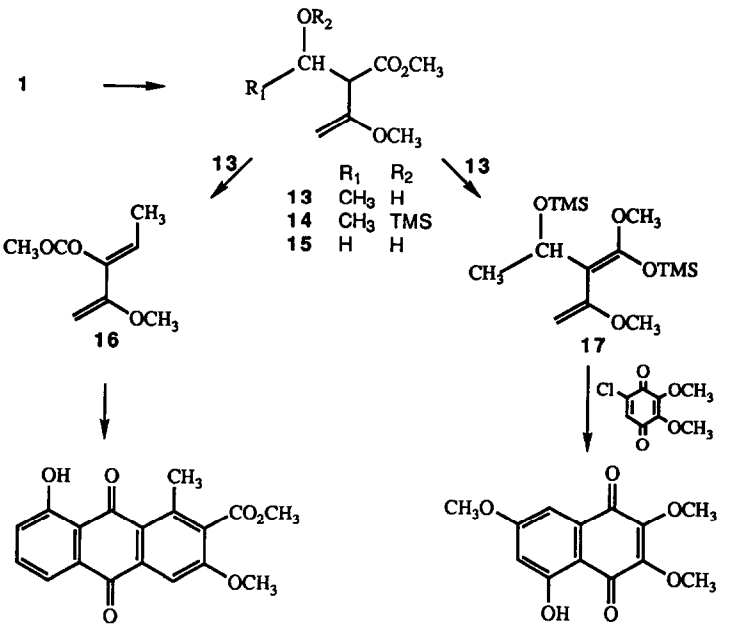
The α- and β-unsaturated esters so obtained were then converted almost quantitatively, by standard procedures[3,7], into the required dienes (**5-7**) and cycloaddition of the latter to appropriate naphthoquinones (**8,9**), followed by aromatization, carried out in 72-84% overall yield The approach then provided a concise preparation of 2-benzylxanthopurpurin 3-methyl ether (**10**) as well as first syntheses of vismiaquinone C[8] (**11**) and 7-geranylemodin[9] (**12**) Attempts to isomerize vismiaquinone C to A[10] (**11**, R_1 = Δ^1-isopentenyl) by the usual means (strong base or rhodium trichloride[11]) were unsuccessful The demethylation of vismiaquinone C to 7-isoprenylemodin[12] (**11**, R_2 = H) using boron tribromide resulted in extensive decomposition while that of 2-benzylxanthopurpurin 3-methyl ether provided a high yield of a homogeneous product[13] that presented somewhat ambiguous characteristics (SCHEME I)



SCHEME I

In considering alternate electrophiles, epoxides and other cyclic ethers could provide, in principle, convenient means of introducing appropriate substituents although, in view of their weak reactivity, these reagents did not appear very promising In fact, various tries to effect substitution with and without catalysis by Lewis acids such as boron trifluoride were invariably unsuccessful

At this point, the process of hydroxyalkylation applied earlier using acetaldehyde was reexamined The reaction had proceeded smoothly[6], but attempts to enolize the product (**13** or **14**) resulted only in rapid elimination with formation of pentadiene **16**. By restricting the excess of base and carefully eliminating any residual HMPA, enolsilylation was in fact favored and the desired butadiene **17** finally obtained and moreover in almost quantitative yield However, diene **17** proved to be a poor annulating partner; it is particularly unstable, undergoes a sort of retro-aldol process and in a reaction with 5-chloro-2,3-dimethoxybenzoquinone yielded only 2,3,7-trimethoxyjuglone[3] (**18**) Diene **16** on the other hand could constitute an alternative to the previously prepared 4-methoxy-3-methoxycarbonyl-2-trimethylsiloxypentadiene[14] It is more readily available than the vinylogous ketene acetal but shows low reactivity and, in a test with 3-chlorojuglone, gave only 27% of the expected aloesaponarin I 6-methyl ether[15] (**19**) (SCHEME II)



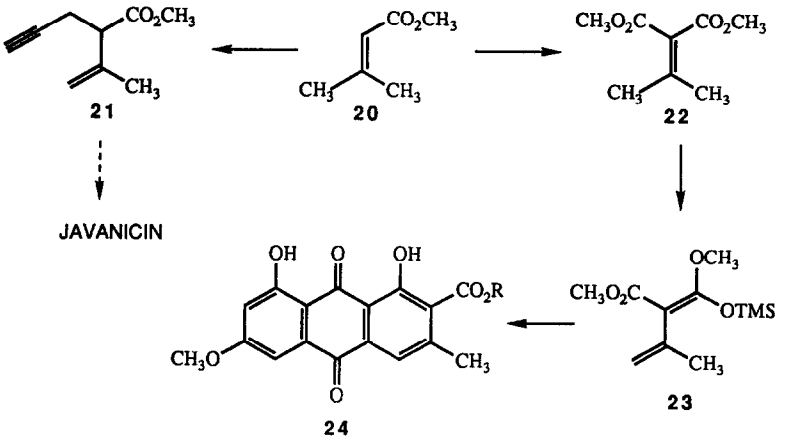
SCHEME II

A similar process using formaldehyde was originally undertaken in order to evaluate the effect of a less hindered substituent. The difficulty of conducting the reaction under anhydrous conditions could be mitigated by the use of a codistillate of the aldehyde and THF obtained after depolymerization of paraformaldehyde by p-toluenesulfonic

anhydride[16] In spite of the low concentration of formaldehyde in the distillate, a 50% yield of the required alcohol **15** was obtained in an initial attempt and could undoubtedly be improved However the unsatisfactory behavior of the corresponding homologous diene **17** effectively forestalls the use of this approach for the synthesis of substituted lucidins

The α-substitution of dienolates by other reagents was then considered using the 3-methyl derivative (**20**), a convenient substrate for a wide range of applications The condensation with propargyl bromide occurred in nearly quantitative yield and the product eventually led to a concise synthesis of javanicin[17] which will be reported elsewhere However the main objective consisted in realizing acylations that would provide easy access to intermediates for the preparation of dienes similar to some obtained earlier but only with considerable difficulty[18] Electrophiles such as carbonates or methyl chloroformate were eventually rejected either because of low reactivity or for giving products contaminated with diisopropylaminoformate. Reactions with cyanoformate[19] proceeded satisfactorily when two equivalents of base are used in order to compensate for deprotonation of the more acidic end-product. Isopropylidenemalonate, i e **22** obtained after spontaneous isomerization of the double bond, is of course available by other means[20], but the better yield, shorter reaction time and more general scope of this approach give it a considerable edge over older methods

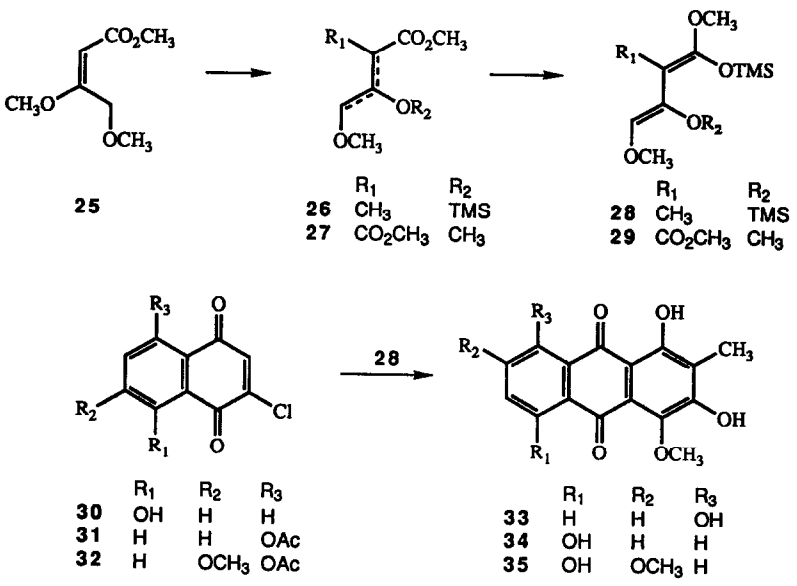
At first, some difficulty was experienced in attempting to enolize substances such as isopropylidenemalonate **22** The use of LDA, with or without TMEDA, invariably gave insoluble and unreactive intermediates Eventually, enolsilylation was carried out straight-forwardly by the consecutive action of NaH and ClTMS The usefulness of diene **23**, much more readily accessible than the previously prepared analogous compound, is illustrated by a first synthesis of the naturally occurring anthraquinone, cinnalutein[21] (**24**, R=H) (SCHEME III)



SCHEME III

Finally, the application of this approach to the enol ether (**25**) of commercially available methyl 4-methoxyacetoacetate has led to the preparation of the first example of pentasubstituted dienes of the type under consideration (vinylketene acetals) The selective alkylation of crotonate **25** by methyl iodide afforded intermediate **26**

and eventually diene **28** The latter, in spite of its high degree of substitution, combined rapidly with chlorojuglones as well as their acetates and could then provide various unusual substitution patterns (selectively methylated polyphenolic arrangements) in an unambiguous fashion. In this way, it was possible to confirm the structures of three natural substances, 4,5-dihydroxydigitolutein[22] (**33**), 2-hydroxyislandicin 1-methyl ether[23] (**34**) and calyculatone 1-methyl ether[23] (**35**) (SCHEME IV) Moreover, the enolate ion of crotonate **25** could be acylated with cyanoformate, as described in a previous case Unfortunately, the corresponding diene **29** was found to be quite inert in cycloaddition processes with quinones



SCHEME IV

Synthetic vismiaquinone C (**11**), 7-geranylemodin (**12**) and cinnalutein (**24**, R=H) were found to be identical with the natural products by direct comparison Aloesaponarin I 6-methyl ether (**19**) was indistinguishable from a sample prepared earlier The spectral and physical characteristics of 4,5-dihydroxydigitolutein (**33**), 2-hydroxyislandicin 1-methyl ether (**34**) and calyculatone 1-methyl ether (**35**) are in good agreement with extensive published data assuming that the m p of compound **34** is the result of a typographical error (authentic samples are as yet unavailable)

EXPERIMENTAL

All melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected The UV spectra were determined on a Hewlett-Packard Model 8450A spectrophotometer, the IR spectra on a Beckman Model IR-4250 instrument and NMR 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 the aromatization of adducts and ICN SiliTech 32-63 60A for flash chromatography were used throughout in a product-to-adsorbent ratio of 1:50-100 Elemental analyses were carried out by Galbraith Laboratories, Inc , Knoxville, TN Exact masses were provided by the Laboratoire de spectrométrie de masse, Université de Montréal, Qué

I Substitution of Crotonic Esters

General Procedure A To a solution of the LDA-HMPA complex prepared, under nitrogen, from diisopropylamine (0 110 mol) in THF (135 mL), n-butyllithium (0 115 mol) in hexanes at 0°C (25 min) and HMPA (0 110 mol), also in THF (20 mL) at −78°C (20 min) was added crotonic ester **1**, **20** or **25** (0 100 mol) in the same solvent (15 mL) (15-40 min) The mixture was stirred at −78°C (15-30 min), then at 0°C (60-90 min) and again cooled to −78°C when the electrophile (0 175-0 250 mol) in THF (25-40 mL) was added to it (60-90 min) Stirring was continued at the same temperature (2 h) and the solution, upon returning to room temperature, was quenched by addition of saturated aqueous NH_4Cl (200 mL), concentrated under vacuum and extracted with CH_2Cl_2 (3 × 200 mL) The residue, dissolved in ether (200 mL), was washed with 30% aqueous $Cu(NO_3)_2$ (3 × 200 mL), dried ($MgSO_4$) and evaporated

Methyl 2-benzyl-3-methoxy-2- and 3-butenoate (2 a,b)

Ester **2 a,b** was obtained from 3-methoxycrotonate **1** (13 0 g, 0 100 mol) and benzyl bromide (29 7 mL, 0 250 mol), according to general procedure A, as a 3 1 mixture of the 2- and 3-unsaturated isomers, b p 113-115°C/0 3 mmHg (18 4 g, 84%) which was used as such in the next step

Careful fractionation of the mixture afforded pure methyl 2-benzyl-3-methoxy-2-butenoate, IR (film) 1705, 1615 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 45 (3H, s, 4-H), 3 66 (3H, s, 3-OCH_3), 3 70 (2H, s, 2-CH_2), 3 72 (3H, s, 1-OCH_3), and 7 10-7 34 (5H, m, 1'-C_6H_5), MS m/z 220 (17) $(M)^+$, 91 (100)

Separation of the crude product by flash chromatography (CCl_4, then CCl_4-CH_2Cl_2 1 1) gave methyl 2-benzyl-3-methoxy-3-butenoate, IR (film) 1745, 1660, 1620, 1600 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.93-3 24 (2H, AB part of ABX pattern, ν = 26 4 Hz, J = 13 6, 7 7, 7 7 Hz, 2-CH_2), 3 38 (1H, t, J = 7 7, 7 7 Hz, 2-H), 3 55 (3H, s, 3-OCH_3), 3.66 (3H, s, 1-OCH_3), 4 00 (2H, s, 4-H), and 7 14-7 36 (5H, m, 1'-C_6H_5), MS m/z 220 (3) $(M)^+$, 91 (100), exact mass calcd for $C_{13}H_{16}O_3$ 220 1099, found 220 1108

Methyl 2-isoprenyl-3-methoxy-2- and 3-butenoate (3 a,b)

Applying procedure A to substrate **1** (13 0 g, 0 100 mol) and isoprenyl bromide (20.1 mL, 0 175 mol) provided a 1 15 mixture of the 2- and 3-unsaturated ester (**3 a,b**) (17 9 g, 90%), b p 69-89°C/0 4 mmHg [a second fraction (1.0 g, 5%) consisted of a 1 3 mixture of the same isomers], IR (film) 1745, 1660, 1625 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ (for the 2-butenoate) 1 56 and 1 66 (2 × 3H, 2s, 3'-CH_3), 2 43 (3H, s, 4-H), 3 49 (3H, s, 3-OCH_3), 3 64 (3H, s, 1-OCH_3), 4 09 (2H, dd, J = 7 7, 2 9 Hz, 1'-H), and 4 87-5 00 (1H, m, 2'-H), (for the 3-butenoate) 1 62 and 1 68 (2 × 3H, 2s, 3'-CH_3), 2 30-2 60 (2H, d of AB part of ABX pattern, ν = 22 9 Hz, J = 14 3, 7 5, 7 5, 7 2 Hz, 1'-H), 3 07 (1H, t, J = 7 5, 7 5 Hz, 2-H), 3 54 (3H, s, 3-OCH_3), 3 69 (3H, s, 1-OCH_3), 4 05 (2H, s, 4-H), and 5 05 (1H, ~ t, J = 7 2 Hz, 2'-H), MS m/z 198 (4) $(M)^+$, 69 (100), exact mass calcd for $C_{11}H_{18}O_3$ 198 1256, found 198 1244

Methyl 2-geranyl-3-oxobutanoate

The alkylation of ester **1** (13 0 g, 0 100 mol) using geranyl bromide (34 7 mL, 0 175 mol) as in procedure A gave

the hydrolyzed title compound (18 0 g, 71%), b p 113-120°C/0.15 mmHg, IR (film) 1740, 1715, 1615 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.58, 1 61 and 1 66 (3 × 3H, 3s, 3', 7', 7'-CH_3), 1 87-2 16 (4H, m, 4', 5'-H), 2.21 (3H, s, 4-H), 2 55 (2H, t, J = 7.3 Hz, 1'-H), 3.45 (1H, t, J = 7 3 Hz, 2-H), 3.71 (3H, s, 1-OCH_3), and 4.95-5 14 (2H, m, 2', 6'-H), MS m/z 252 (4) $(M)^+$, 69 (100) Anal. Calcd for $C_{15}H_{24}O_3$ C, 71 39, H, 9 59 Found C, 71.31, H, 9.70.

Methyl 2-geranyl-3-trimethylsiloxy-2-butenoate (4)

A mixture of the foregoing keto ester (10 7 g, 0 040 mol), imidazole (0 163 g, 2 40 mmol) and hexamethyldisilazane (9 30 mL; 0 044 mol) was heated to reflux for 4 h, stirred at rt (18 h) and concentrated at 85°C (3 h) under vacuum (0.1 mmHg) The residue (12 9 g, 99%) consisted of an essentially pure 5 1 mixture (used without further purification) of the Z- and E-isomers of enol ether **4**, IR (film) 1710, 1620, 1250, 830 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ (Z-isomer) 0 24 (9H, s, 3-OTMS), 1 58 and 1 66 (3H, 6H, 2s, 3', 7', 7'-CH_3), 1 88-2 16 (4H, m, 4', 5'-H), 2 27 (3H, s, 4-H), 2 97 (2H, d, J = 6 6 Hz, 1'-H), 3 67 (3H, s, 1-OCH_3), and 4 96-5 15 (2H, m, 2', 6'-H), MS m/z 324 (6) $(M)^+$, 73 (100)

Methyl 3-methyl-2-propargyl-3-butenoate (21)

3-Methylcrotonate **20** (11 4 g, 0 100 mol) and propargyl bromide (16 7 mL of an 80% solution in toluene, 0 150 mol), as in preceding cases but quenching at –78°C, provided crude ester **21** (15 7 g) Distillation of the latter (3 32 g) gave pure butenoate **21** (2 52 g, 78%), b p 64-65°C/10 mmHg, IR (film) 3290, 2100, 1740, 1640 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 75 (3H, dd, J = 1 4, 0 8 Hz, 3-CH_3), 1.98 (1H, t, J = 2 6 Hz, 3'-H), 2 39-2 79 (2H, d of AB part of ABX pattern, ν = 41 6 Hz, J = 16 9, 7 7, 7 7, 2 6 Hz, 1'-H), 3 27 (1H, t, J = 7 7, 7 7 Hz, 2-H), 3 71 (3H, s, 1-OCH_3), 4 93 (1H, dq, J = 1 4, 0 8 Hz, 4-H), and 4 96 (1H, dq, J = 1 4, 1 4 Hz, 4-H), MS m/z 152 (3) $(M)^+$, 91 (100) Anal Calcd for $C_9H_{12}O_2$ C, 71 03, H, 7 95 Found C, 71 38, H, 8 15

Methyl 2-methoxycarbonyl-3-methyl-2-butenoate (22)

The condensation of 3-methylcrotonate **20** (11 4 g, 0 100 mol) with methyl cyanoformate (11 9 mL, 0.150 mol) as per method A, using two equivalents of the LDA-HMPA complex and quenching the reaction mixture after 16 h at rt, afforded diester **22**, b p 58-71°C/0 4 mmHg (12 2 g, 71%), IR (film) 1730, 1635 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 04 (6H, s, C-CH_3), and 3 74 (6H, s, OCH_3), MS m/z 172 (8) $(M)^+$, 141 (100)

Methyl 4-methoxy-2-methyl-3-oxobutanoate

The substitution of methyl 3,4-dimethoxy-2-butenoate (**25**) (16 0 g, 0 100 mol) with methyl iodide (9 4 mL, 0.15 mol) was carried out as in method A, omitting the HMPA and the subsequent treatment by $Cu(NO_3)_2$, and was followed by hydrolysis of the crude enol ether in 10% aqueous HCl (250 mL) and THF (200 mL) at 25°C (20 h) Evaporation of the solvent, extraction by CH_2Cl_2 (3 × 150 mL) and distillation of the crude product gave the corresponding oxobutanoate (12 5 g, 78%), b p 68-72°C/2 mmHg, IR (film) 1745, 1720 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 34 (3H, d, J = 7 2 Hz, 2-CH_3), 3 40 (3H, s, 4-OCH_3), 3 67 (1H, q, J = 7 2 Hz, 2-H), 3 72 (3H, s, 1-OCH_3), and 4 11 (2H, s, 4-H), MS m/z 160 (16) $(M)^+$, 59 (100) Anal Calcd for $C_7H_{12}O_4$ C, 52 49, H, 7 55 Found C, 52 72, H, 7 58

Methyl 4-methoxy-2-methyl-3-trimethysiloxy-2-butenoate (26)

The foregoing keto ester (6 41 g, 40 0 mmol) was enolsilylated according to the method used for compound **4** The reaction mixture was evaporated at 10 mmHg and the residue, upon distillation provided enol ether **26** (8 20 g, 88%), b p 66-72°C/0 5 mmHg, IR (film) 1700, 1610, 1270, 835 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0 22 (9H, s, 3-OTMS), 1 80 (3H, s, 2-CH_3), 3 31 (3H, s, 4-OCH_3), 3 69 (3H, s, 1-OCH_3), and 4 40 (2H, s, 4H), MS m/z 232 (7) $(M)^+$, 73 (100) Anal Calcd for $C_{10}H_{20}O_4Si$ C, 51 69, H, 8 68 Found C, 51 33, H, 8 77

Methyl 3,4-dimethoxy-2-methoxycarbonyl-3-butenoate (27)

As in the preparation of ester **22**, 3,4-dimethoxycrotonate **25** (16 0 g, 0 100 mol) was acylated using methyl cyanoformate[19] (11 9 mL; 0 150 mol). A portion (5.0 g) of the crude product (17 9 g) in CH_2Cl_2 (150 mL) was extracted with water (2 × 200 mL) and saturated brine (200 mL) then, after purification by flash chromatography (AcOEt - petroleum ether, b p. 35-60°C 1 4 followed by 1 2), yielded diester **27** (3 02 g, 50%) as a 3·1 mixture of the Z- and E-isomers; IR (KBr) (Z-isomer) 1745 (sh), 1735 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ (Z-isomer) 3 53 and 3 56 (2 × 3H, 2s, 3, 4-OCH_3), 3.77 (6H, s, 1, 1'-OCH_3), 4.65 (1H, s, 2-H), and 5 90 (1H, s, 4-H), (E-isomer) 3.63 (3H, s, 3-OCH_3), 3.77 (6H, s, 1, 1'-OCH_3), 3.80 (3H, s, 4-OCH_3), 3.92 (1H, s, 2-H), and 5 66 (1H, s, 4-H), MS m/z 218 (15) $(M)^+$, 159 (100); exact mass calcd for $C_9H_{14}O_6$: 218.0790, found 218 0797 Anal. Calcd. C, 49 54; H, 6 47 Found· C, 49 48; H, 6.56

II Formation of dienes

General Procedure B: To a 10% excess of LDA in THF (– 15 mL per 0 01 mol of ester) at –78°C and under N_2 was added the substituted crotonate (**2a,b**, **3a,b**, **4**, **13**, **21**, **22**, **26** or **27**) (15-50 mmol) in 10-20 mL of the same solvent (20 min). After 15 min, the temperature was raised to O°C for 0.75-2 h and again lowered to –78°C A 50% excess of CITMS in THF (10-15 mL) was then introduced into the mixture (40-75 min) which was stirred at the same temperature for 1 h and at rt for 1 h, concentrated under vacuum, diluted with petroleum ether, b p. 35-60°C (250 mL), filtered and evaporated (this step can be repeated until salts no longer separate) The dienes are sensitive, were not analyzed, but used directly

2-Benzyl-1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene (5)

When applied to the 3.1 mixture of 2- and 3-butenoates **2 a,b** (6.6 g; 0 030 mol), general prodecure B afforded essentially pure diene **5** (8.7 g; 99%) as a single isomer; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.26 (9H, s, 1-OTMS), 3 49 and 3.54 (2 × 3H, 2s, 1,3-OCH_3), 3 53 (2H, s, 2-CH_2), 4.07 (2H, s, 4-H), and 7 13-7 32 (5H, m, 1'-C_6H_5)

2-Isoprenyl-1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene (6)

From the 1 15 mixture of 2- and 3-butenoates **3 a,b** (7 9 g, 0 040 mol), according to procedure B, was obtained quite pure diene **6** as a single isomer (10 7 g, 99%); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0 20 (9H, s, 1-OTMS), 1 61 (3H, s, 3'-CH_3), 1 66 (3H, d, J = 1 5 Hz, 3'-CH_3), 2.82 (2H, d, J = 7.0 Hz, 1'-H), 3.51 and 3.53 (2 × 3H, 2s, 1.3-OCH_3), 4 07 (1H, d, J = 1 8 Hz, 4-H), 4.09 (1H, d, J = 1 8 Hz, 4-H), and 5 06 (1H, dq, J = 7 0; 1 5 Hz, 2'-H)

2-Geranyl-1-methoxy-1,3-bistrimethylsiloxy-1,3-butadiene (7)

To a solution of LDA (16 5 mmol) in THF (20 mL) at –78°C was added (20 min) CITMS (2 9 mL, 23 mmol) in the same solvent (3 mL) and, after 30 min, butenoate **4** (4 87 g; 15 0 mmol) in THF (10 mL) (75 min) The reaction mixture was stirred at –78°C (40 min), at –25°C (40 min) and at rt (30 min) then evaporated, treated as in method B and gave quite pure diene **7** (5 89 g, 99%) in a 1.9 ratio of stereomers, ^{1}H-NMR (200 MHz, $CDCl_3$) δ (principal isomer) 0 18 and 0.22 (2 × 9H, 2s, 1,3-OTMS), 1 58, 1 63 and 1 66 (3 × 3H, 3s, 3', 7', 7'-CH_3), 1 88-2 17 (4H, m, 4', 5'-H), 2 79 (2H, d, J = 7 0 Hz, 1'-H), 3 52 (3H, s, 1-OCH_3), 4 26 and 4 35 (2 × 1H, 2s, 4-H), and 5 01-5 22 (2H, m, 2', 6'-H)

2-Methoxy-3-methoxycarbonyl-1,3-pentadiene (16)

A mixture of ester **13** (13 9g, 80 0 mmol) and HMPA (2 1 mL, 0 012 mol) in THF (45 mL) was added (30 min) to a suspension of LDA (0 19 mol) in the same solvent (120 mL) at –78°C and was followed, after 60 min, by CITMS

(30 5 mL, 0.240 mol) in THF (40 mL) (40 min). The mixture was stirred at −78°C (40 min), allowed to cool to rt (60 min), concentrated under vacuum and treated with petroleum ether as in method B A portion (5.99 g) of the crude product (17 5 g) was purified by flash chromatography on neutral alumina (CCl_4-CH_2Cl_2 8 1, then 5 1) and provided pentadiene **16** (2 98 g, 70%), b p 64-76°C/0 75 mmHg; IR (film) 1710, 1635, 1610 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 84 (3H, d, J = 7 1 Hz, 5-H), 3 58 (3H, s, 2-OCH_3), 3 69 (3H, s, 3-CO_2CH_3), 4 02 (1H, d, J = 2 2 Hz, 1-H), 4 33 (1H, d, J = 2 2 Hz, 1-H), and 6 96 (1H, q, J = 7 1 Hz, 4-H), MS m/z 156 (53) $(M)^+$, 59 (100), exact mass calcd for $C_8H_{12}O_3$, 156 0786, found 156 0774

1,3-Dimethoxy-1-trimethylsiloxy-2-(1-trimethylsiloxyethyl)-1,3-butadiene (17)

In a reaction similar to the foregoing – but omitting the HMPA – ester **13** (3 48 g, 20 0 mmol) in THF (10 mL) was added (20 min) to LDA (0 044 mol) in the same solvent (30 mL) (30 min at −78°C, 40 min at −35°C) CITMS (7 6 mL, 0 060 mol) in THF (10 mL) was introduced (40 min), at −78°C, into the mixture which was kept at this temperature (60 min) and at 25°C (30 min) then concentrated under vacuum After treatment with petroleum ether as in method B, the residue afforded diene **17** (6 31 g, 99%) as one quite pure isomer; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0 09 (9H, s, 1'-OTMS), 0 23 (9H, s, 1-OTMS), 1 21 (3H, d, J = 6 4 Hz, 2'-H), 3 54 and 3 58 (2 × 3H, 2s, 1,3-OCH_3), 4 09 (1H, d, J = 1 4 Hz, 4-H), 4 19 (1H, d, J = 1 4 Hz, 4-H), and 4 68 (1H, q, J = 6 4 Hz, 1'-H)

1-Methoxy-2-methoxycarbonyl-3-methyl-1-trimethylsiloxy-1,3-butadiene (23)

A solution of isopropylidenemalonate **22** (8 61 g, 50 0 mmol) in THF (20 mL) was added (45 min) to a suspension of 97% NaH (1 86 g, 75 0 mmol) in the same solvent (70 mL) at 0°C and under N_2 The mixture was stirred at this temperature (20 min), at 25°C (60 min) and finally under reflux (75 min) To the cooled solution (0°C), was added CITMS (9 5 mL, 75 mmol) in THF (15 mL) (40 min) and stirring was continued at the same temperature (60 min) then at rt (75 min) The mixture was then concentrated, diluted with petroleum ether (b p 35-60°C) (250 mL), filtered and again evaporated Distillation of the residue gave diene **23** (10 2 g, 83%) as a 1 1 mixture of isomers, b p 64-66°C/0 25 mmHg, IR (film) 1700, 1640, 1580, 1250, 850 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ (mixture) 0 31 (9H, s, 1-OTMS), 1 84 (3H, ~ t, J = 1 3 Hz, 3-CH_3), 3 61, 3 65 and 3 71 (3H, 1 5H, 1 5H, 3s, 1,2-OCH_3), 4 75 (1H, q, J = 1 3 Hz, 4-H), and 5 05 (1H, q, J = 1 3 Hz, 4-H), MS m/z 244 (10) $(M)^+$, 112 (100) Anal Calcd for $C_{11}H_{20}O_4Si$ C, 54 07, H, 8 25 Found C, 53 75, H, 8 32

1,4-Dimethoxy-2-methyl-1,3-bistrimethylsiloxy-1,3-butadiene (28)

The procedure used in the case of diene **7** was applied to butenoate **26** (3 49 g, 15 0 mmol) and gave diene **28** (4 52 g, 99%) as a 1 1 mixture of isomers, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0 13 and 0 15 (2 × 9H, 2s, 3-OTMS), 0 20 and 0 21 (2 × 9H, 2s, 1-OTMS), 1 61 and 1 65 (2 × 3H, 2s, 2-CH_3), 3 46, 3 52 and 3 55 (3H, 6H, 3H, 3s, 1,4-OCH_3), and 5 76 (2 × 1H, s, 4-H)

1,3,4-Trimethoxy-2-methoxycarbonyl-1-trimethylsiloxy-1,3-butadiene (29)

In a preparation analogous to that of diene **23**, butenoate **27** (3 27 g, 15 0 mmol) in THF (10 mL), KH (0 903 g, 22 5 mmol) also in THF (25 mL) and later CITMS (2 9 mL, 0 023 mol) in the same solvent (5 mL) gave essentially pure diene **29** (3 98 g, 91%) as a single isomer; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0 34 (9H, s, 1-OTMS), 3 46 and 3 47 (2 × 3H, 2s, 3,4-OCH_3), 3 65 (6H, s, 1,2-OCH_3), and 5 89 (1H, s, 4-H)

III Formation of anthraquinones

2-Benzyl-1-hydroxy-3-methoxy-9,10-anthraquinone (10)

To a suspension of 2-chloronaphthoquinone (**8**) (0.385 g, 2 00 mmol) in dry benzene (6 mL) at ~ 6°C, was added an excess of diene **5** (1 5 mL; ~ 6 mmol) in the same solvent (2 mL) (15 min). The mixture was stirred at the same temperature (60 min) and at rt (3 h), then diluted with CCl_4 (8 mL) and percolated through a column of silica gel (100 g) (C_6H_6 - CCl_4 1 1) Purification of the crude product by flash chromatography (dry column) (CH_2Cl_2 - hexanes 1 1) gave anthraquinone **10** (0.482 g, 70%), m p 182 0-182.5°C (1,2-dichloroethane - petroleum ether, b p 90-120°C), IR (KBr) 1670, 1630 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4 02 (3H, s, 3-OCH_3), 4 10 (2H, s, 2-CH_2), 7 08-7 40 (5H, m, 1'-C_6H_5), 7 42 (1H, s, 4-H), 7 68-7.84 (2H, m, 6,7-H), 8 20-8 34 (2H, m, 5,8-H), and 13 05 (1H, s, 1-OH), MS m/z 344 (12) $(M)^+$, 91 (100). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73, H, 4.68 Found C, 76 60, H, 4.96.

A second band consisted of 2-benzyl-1,3-dimethoxyanthraquinone (0 099 g; 14%), m p 174.5-175 0°C (1,2-dichloroethane - petroleum ether, b p 90-120°C) (lit.[13] m p 176 5-177 5°C), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3 80 and 4 01 (2 × 3H, 2s, 1,3-OCH_3), 4 14 (2H, s, 2-CH_2), 7.08-7.32 (5H, m, 1'-C_6H_5), 7 64-7 84 (2H, m, 6,7-H), 7 68 (1H, s, 4-H), and 8 18-8 34 (2H, m, 5,8-H); MS m/z 358 (2) $(M)^+$, 91 (100) Anal Calcd for $C_{23}H_{18}O_4$ C, 77 08, H, 5 06 Found C, 76 91, H, 5 32

1,8-Dihydroxy-2-isoprenyl-3-methoxy-6-methyl-9,10-anthraquinone (vismiaquinone C) (11)

The product obtained from 3-chloro-7-methyljuglone[3] (**9**) (0 455 g, 2 00 mmol) and diene **6** (1 2 mL, ~ 4 mmol), as in the preceding preparation, was separated by flash chromatography (CH_2Cl_2 - ligroine 1.1) A first zone provided anthraquinone **11** (0 343 g; 49%), m p. 206-207°C (1,2-dichloroethane - petroleum ether, b p. 90-120°C) (lit [8] m p 215-217°C), UV λ_{max} (CH_3OH) (log ε) 220 (4 49), 274 (4 46), 304 (sh) (3 97), and 434 (4 09) nm, IR (KBr) 1670, 1625, 1600, 1560 cm^{-1},^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 68 and 1.79 (2×3H, 2s, 3'-CH_3), 2 44 (3H, s, 6-CH_3), 3 42 (2H, d, J = 7 2 Hz, 1'-H), 4 01 (3H, s, 3-OCH_3), 5 19 (1H, t, J = 7 2 Hz, 2'-H), 7 06 (1H, d, J = 1 5 Hz, 7-H), 7 40 (1H, s, 4-H), 7 61 (1H, d, J = 1 5 Hz, 5-H), 12 14 and 12 42 (2 × 1H, 2s, 1,8-OH), ^{13}C-NMR (50 3 MHz, $CDCl_3$) δ 17 87, 22.14, 25 80, 56 25, 103 33, 110 64, 113 65, 120 57, 121 12, 124 18, 124 39, 132 78, 132 97, 133 15, 148 27, 161 69, 162 41, 163 53, 182 07, and 191 23, MS m/z 352 (31) $(M)^+$, 309 (100) Anal Calcd for $C_{21}H_{20}O_5$ C, 71 58, H, 5 72 Found C, 71 37, H, 5 88

A second band afforded 8-hydroxy-2-isoprenyl-1,3-dimethoxy-6-methylanthraquinone (0.254 g, 35%), m p 183 5°C (1,2-dichloroethane - petroleum ether, b p 90-120°C), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 67 and 1 80 (2 × 3H, 2s, 3'-CH_3), 2 43 (3H, s, 6-CH_3), 3 46 (2H, d, J = 7 2 Hz, 1'-H), 3 89 and 4 02 (2 × 3H, 2s, 1,3-OCH_3), 5 14 (1H, t, J = 7 2 Hz, 2'-H), 7 08 (1H, d, J = 1 1 Hz, 7-H), 7 57 (1H, d, J = 1 1 Hz, 5-H), 7 62 (1H, s, 4-H), and 13 09 (1H, s, 8-OH), MS m/z 366 (50) $(M)^+$, 53 (100) Anal Calcd for $C_{22}H_{22}O_5$ C, 72 11, H, 6 05 Found C, 71 82, H, 6 09

2-Geranyl-1,3,8-trihydroxy-6-methyl-9,10-anthraquinone (7-geranylemodin) (12)

A mixture of naphthoquinone[3] **9** (0 113 g, 0 500 mmol) in dry THF (4 mL) and diene **7** (0 4 mL, ~ 1 mmol) in the same solvent (1 mL) was stirred at 0°C (90 min) and at rt (3 h) then cooled again to 0°C and treated with 10% aqueous HCl (5 mL) The solution was stirred at the same temperature (30 min) and at 25°C (3 h) then poured into water Extraction of the crude product with CH_2Cl_2 (2 × 200 mL) and purification by flash chromatography (dry column) ($CHCl_3$ then $CHCl_3$ - Et_2O 1 1) gave anthraquinone **12** (146 mg, 72%), m p 209-210°C (1,2-dichloroethane - petroleum ether, b p 90-120°C) (lit.[9] m p 208-210°C), UV λ_{max} (CH_3OH) (log ε) 218 (4 53), 249 (4 16), 282 (4 43), and 438 (4 08) nm, IR (KBr) 3370 (br), 1665, 1605 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 59, 1 66 and 1 83 (3 × 3H, 3s, 3', 7', 7'-CH_3), 2 09 (4H, br s, 4', 5'-H), 2 44 (3H, s, 6-CH_3), 3 52 (2H, d, J = 7 1 Hz, 1'-H), 4 98-5 10 (1H, m, 6'-H), 5 28 (1H, t, J = 7 1

Hz, 2'-H), 6 38 (1H, s, 3-OH), 7 07 (1H, s, 7-H), 7 29 (1H, s, 4-H), 7.61 (1H, s, 5-H), 12 14 and 12 74 (2 × 1H, 2s, 1,8-OH); ^{13}C-NMR (50.3 MHz, DMSO-d_6) δ 15.92, 17 42, 21.45, 25 34, 26.05, 108.01, 108.54, 113 24, 120.27, 120 61, 120.98, 123 65, 123 94, 130 59, 131 93, 132 68, 135 14, 148 07, 161 28, 161 87, 162 70, 181 07, and 189 92; MS m/z 406 (13) $(M)^+$, 283 (100) Anal. Calcd for $C_{25}H_{26}O_5$· C, 73.87; H, 6 45 Found· C, 73 52, H, 6.59.

8-Hydroxy-3-methoxy-2-methoxycarbonyl-1-methyl-9,10-anthraquinone (aloesaponarin I 6-methyl ether) (19)

The adduct obtained when the mixture of 3-chlorojuglone[24] (**30**) (0 313 g; 1.50 mmol) and diene **16** (0.351 g, 2.25 mmol) in benzene (14 mL) was kept at 25°C (1 h) and heated to reflux (48 h) – an extra portion of diene (0 117 g; 0.750 mmol) being added after 10 h – was aromatized by stirring at rt (24 h) with freshly prepared MnO_2 (0 52 g, 6 0 mmol) Separation of the crude product by flash chromatography (CH_2Cl_2-AcOEt 20.1) yielded anthraquinone **19** (0 131 g, 27%), m p 199-200°C (benzene - petroleum ether, b p 90-120°C) (lit[15] m p 210-212°C), IR (KBr) 1725, 1660, 1625 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 74 (3H, s, 1-CH_3), 3 97 and 4 01 (2 × 3H, 2s, 2-CO_2CH_3, 3-OCH_3), 7 30 (1H, dd, J = 8 0, 1 1 Hz, 7-H), 7 62 (1H, ~ t, J = 8 0 Hz, 6-H), 7 76 (1H, s, 4-H), 7 78 (1H, dd, J = 8 0; 1 1 Hz, 5-H), and 12 89 (1H, s, 8-OH), ^{13}C-NMR (50 3 MHz, $CDCl_3$) δ 20 09, 52 75, 56 52, 107 53, 116 88, 119 00, 124 98, 131 24, 132 50, 133.80, 137 45, 135 80, 141 47, 159 85, 162 43, 167 47, 182 37, and 189 68, MS m/z 326 (83) $(M)^+$, 311 (100)

1,8-Dihydroxy-6-methoxy-2-methoxycarbonyl-3-methyl-9,10-anthraquinone (24; R = CH_3)

The mixture of 3-chloro-7-methoxyjuglone[3] (0.239 g, 1 00 mmol) and diene **23** (0 4 mL, 1 5 mmol) in dry benzene (4 mL) was stirred at ~ 6°C (60 min) and at 25°C (2 h) then heated to reflux (10 h) – a supplemental portion of diene (0 20 mL, 0 75 mmol) in the same solvent (1 mL) being added after 6 h. After evaporation of the solvent, the residue was dissolved in THF (10 mL) and treated at 0°C with 10% aqueous HCl (10 mL) This solution was stirred at 0°C (30 min) and at 25°C (3 h) then poured into water and extracted with CH_2Cl_2 (2 × 200 mL) A suspension of the crude product in dry CH_2Cl_2 (35 mL) containing anhydrous $AlCl_3$ (1 33 g, 10 0 mmol) was stirred at rt (2 5 h) and hydrolyzed in the usual way [ice (150 g), conc. HCl (30 mL), H_2O (150 mL) - 12 h] Extraction with CH_2Cl_2 (3 × 300 mL) and purification by flash chromatography (dry column) (CH_2Cl_2 - AcOEt 20 1) followed by trituration in ether afforded anthraquinone **24** (R = CH_3) (0 213 g, 62%), m p 220-221°C (1,2-dichloroethane - petroleum ether, b p 90-120°C) (lit.[21] m p 225°C), IR (KBr) 1720, 1670, 1615 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 42 (3H, s, 3-CH_3), 3 93 and 3 98 (2 × 3H, 2s, 2-CO_2CH_3 and 6-OCH_3), 6 67 (1H, d, J = 2 4 Hz, 7-H), 7 34 (1H, d, J = 2 4 Hz, 5-H), 7 62 (1H, s, 4-H), 12 14 and 12 48 (2 × 1H, 2s 1,8-OH), ^{13}C-NMR (50 3 MHz, $CDCl_3$) δ 20 35, 52 70, 56 15, 106 83, 108 75, 110 04, 114 01, 121 36, 129 02, 133 33, 134 91, 145 44, 159 45, 165 39, 166 56, 166 83, 181 38, and 190 37, MS m/z 342 (32) $(M)^+$, 310 (100) Anal Calcd for $C_{18}H_{14}O_7$ C, 63 16, H, 4 12 Found C, 63 15, H, 4 22

2-Carboxy-1,8-dihydroxy-6-methoxy-3-methyl-9,10-anthraquinone (cinnalutein) (24; R = H)

A mixture of the foregoing methyl ester (**24**, R = CH_3) (34 mg, 0 10 mmol), methanol (1 mL) and 25% methanolic NaOH (1 mL) was stirred at rt (3 h) and refluxed (20 h) then acidified and extracted with AcOEt. Purification of the crude product by flash chromatography on deactivated silica gel (Et_2O) gave cinnalutein (**24**, R = H) (32 mg; 98%), m p 264-265°C (acetone - petroleum ether, b p 70-90°C) (lit.[21] m p 277°C), UV λ_{max} (CH_3OH) (log ε) 224 (4 51), 255 sh (4 26), 267 (4 29), 279 sh (4 28), 434 (4 10), and 580 (2 19) nm, IR (KBr) 2900 (br), 1685, 1670, 1590 cm^{-1}, ^{1}H-NMR (200 MHz, DMSO-d_6) δ 2 40 (3H, s, 3-CH_3), 3 92 (3H, s, 6-OCH_3), 6 87 (1H, d, J = 2 4 Hz, 7-H), 7 17 (1H, d, J = 2 4 Hz, 5-H), 7 56 (1H, s, 4-H), 12 07 and 13 00 (2 × 1H, 2s, 1,8-OH); MS m/z 328 (30) $(M)^+$, 310 (100), exact mass calcd for $C_{17}H_{12}O_7$ 328 0583, found 328 0566

1,3,8-Trihydroxy-4-methoxy-2-methyl-9,10-anthraquinone (4,5-dihydroxydigitolutein) (33)

A mixture of 3-chlorojuglone[24] (**30**) (0.105 g; 0 500 mmol) in THF (4 mL) and diene **28** (0.3 mL, ~ 0 8 mmol) in the same solvent (2 mL) was stirred at 0°C (60 min) and at rt (2h) then cooled to 0°C. After addition of anhydrous NaOAc (0 082 g; 1 00 mmol), the suspension was stirred at 0°C (15 min) and at rt (2 h) then heated to reflux (20 min) and poured into water. The residue of a CH_2Cl_2 extract (2 × 200 mL) was dissolved at 0°C in THF (25 mL) and 10% aqueous HCl (25 mL) and the solution was stirred at the same temperature (60 min) and at rt (3 h) then poured into water Finally, the crude product isolated by extraction with $CHCl_3$ (2 × 150 mL) and purified by flash chromatography (dry column) (C_6H_6 - AcOEt 5.1) yielded anthraquinone **33** (99 mg, 66%), m p 230-231°C (1,2-dichloroethane - petroleum ether, b p 90-120°C) (lit.[25] m.p. 239-242°C, [22] 244°C), UV λ_{max} (CH_3OH) (log ε) 253 (4 35), 267 (4 31), 286 (4 18), and 450 (4.10) nm, IR (KBr) 3360 (br), 1665, 1615 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6) δ 2 11 (3H, s, 2-CH_3), 3.74 (3H, s, 4-OCH_3), 7.29 (1H, d, J = 7 9 Hz, 7-H), 7 66 (1H, t, J = 7 9 Hz, 6-H), 7 77 (1H, d, J = 7.9 Hz, 5-H), 10.74 (1H, s, 3-OH), 11 99 and 13 13 (2H, 2s, 1,8-OH), MS m/z 300 (100) $(M)^+$, exact mass calcd for $C_{16}H_{12}O_6$. 300.0634, found. 300 0662.

1,3,5-Trihydroxy-4-methoxy-2-methyl-9,10-anthraquinone (2-hydroxyislandicin 1-methyl ether) (34)

The cycloaddition of diene **28** (0 60 mL, ~ 1 6 mmol) to 2-chlorojuglone acetate[26] (**31**) (0 250 g; 1.00 mmol) was conducted as for 2-geranylemodin (**12**) – a second portion of diene (0 10 mL, ~ 0 25 mmol) being added after 3.5 h, at 0°C (30 min), and the reaction completed at rt (30 min) Aromatization of the adduct was carried as in the case of **12** and hydrolysis of the resulting acetate achieved by refluxing (7 h) in methanol (100 mL) and 10% aqueous HCl (10 mL) The crude product recovered by dilution with H_2O (200 mL) and extraction with $CHCl_3$ (2 × 150 mL) was separated by flash chromatography (dry column) on deactivated silica gel (CH_2Cl_2) and gave anthraquinone **34** (57 mg, 19%), m p 241-242°C (1,2-dichloroethane - petroleum ether, b p 90-120°C) (lit.[23] m p 210°C), UV λ_{max} (CH_3OH) (log ε) 235 (4.19), 252 (4 23), 274 (4.21), 292 (4 04), and 444 (3 99) nm; IR (KBr) 3340 (br), 1605 cm^{-1}, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 27 (3H, s, 2-CH_3), (3H, s, 4-OCH_3), 6 94 (1H, s, 3-OH), 7 27 (1H, dd, J = 7 8, 1 1 Hz, 6-H), 7 64 (1H, t, J = 7 8 Hz, 7-H), 7 82 (1H, dd, J = 7 8, 1 1 Hz, 8-H), 12 90 and 14 01 (2 × 1H, 2s, 1,5-OH), MS m/z 300 (100) $(M)^+$ Anal Calcd for $C_{16}H_{12}O_6$ C, 64 00; H, 4 03 Found C, 63 79, H, 4.14

A second zone (CH_2Cl_2 - AcOEt 5 1) consisted of 9a-chloro-3,5-dihydroxy-4-methoxy-2-methyl-1-oxo-1,4,4a,9a-tetrahydro-9,10-anthraquinone (125 mg), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1 92 (3H, s, 2-CH_3), 3 07 (3H, s, 4-OCH_3), 3 86 and 3 95 (2 × 1H, 2d, J = 2 5 Hz, 4,4a-H), 6 10-6 30 (1H, br s, 3-OH), 7 34 (1H, dd, J = 6 8, 1.3 Hz, 6-H), 7 66-7 75 (2H, m, 7,8-H), and 11 95 (1H, s, 5-OH), MS m/z 336 (12) $(M)^+$, 300 (100) A mixture of this modified adduct and K_2CO_3 (1 23 g, 8 9 mmol) in THF (200 mL) was stirred at rt (6 h), diluted with H_2O (200 mL), acidified with 10% HCl and extracted with $CHCl_3$ (2 × 200 mL) The product, purified as indicated above, was identical with anthraquinone **34** (0 114 g; 38% - total yield 57%)

1,3,5-Trihydroxy-4,7-dimethoxy-2-methyl-9,10-anthraquinone (calyculatone 1-methyl ether) (35)

In an approach similar to the preceding one, 2-chloro-7-methoxyjuglone acetate[27] (**32**) (0 196 g, 0 700 mmol) was allowed to react with an excess of diene **28** (0.6 mL, ~ 1 6 mmol) Aromatization of the adduct was promoted by the addition of NaOAc (0 115 g; 1 4 mmol) to the reaction mixture at 0°C followed by acidification with 10% HCl as described for compound **33**. The corresponding acetate was hydrolyzed in the usual way [10% aqueous HCl (10 mL), CH_3OH (200 mL), at reflux (7 h)] and the crude product (recovered as in the preceding preparation) after purification by

flash chromatography (dry column) on deactivated silica gel ($CHCl_3$ - Et_2O 10:1) afforded anthraquinone **35** (84 mg, 36%), m p 251-252°C (1,2-dichloroethane - petroleum ether, b.p 90-120°C) (lit.[23] m p. 253°C); UV λ_{max} (CH_3OH) (log ε) 230 (4.40), 257 (4 21), 283 (4 43), 321 (4 02), and 438 (4 10) nm, IR (KBr) 3400 (br), 1605 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 25 (3H, s, 2-CH_3), 3 92 and 3.98 (2 × 3H, 2s, 4,7-OCH_3), 6 67 (1H, d, J = 2 6 Hz, 6-H), 6 96 (1H, s, 3-OH), 7.36 (1H, d, J = 2.6 Hz, 8-H), 13.18 and 13 95 (2 × 1H, 2s, 1,5-OH), MS m/z 330 (100) $(M)^+$, exact mass calcd for $C_{17}H_{14}O_7$ 330 0739, found. 330 0752 Anal. Calcd. C, 61 82, H, 4 27 Found· C, 61 48, H, 4.58.

A second fraction consisted of the corresponding 1-methyl ether (15 mg, 6%), m.p 216-217°C (1,2-dichloroethane - petroleum ether, b p 90-120°C), ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2 30 (3H, s, 2-CH_3), 3 87, 3 91 and 3 98 (3 × 3H, 3s, 1,4,7-OCH_3), 6.64 (1H, d, J = 2 5 Hz, 6-H), 6 85 (1H, s, 3-OH), 7 28 (1H, d, J = 2 5 Hz, 8-H), and 12 97 (1H, s, 5-OH), MS m/z 344 (100) $(M)^+$

Continued elution ($CHCl_3$ - Et_2O 2.1) provided the modified adduct 9a-chloro-3,5-dihydroxy-4,7-dimethoxy-2-methyl-1-oxo-1,4,4a,9a-tetrahydro-9,10-anthraquinone (60 mg) Silica gel for flash chromatography (50 g) was added to a CH_2Cl_2 - AcOEt solution of this compound and the mixture was evaporated to dryness The residue was allowed to stand at rt (8 h) and repeatedly extracted with $CHCl_3$ and Et_2O Purification of this material as indicated above gave an additional portion of quinone **35** (47 mg, 21% - total yield 57%)

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