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The Total Synthesis of (±)-Megaphyllone Acetate, A Cytotoxic Neolignan

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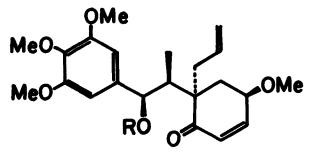
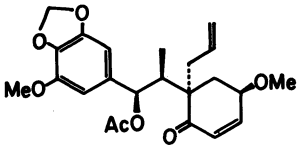
Conversion of 3-methoxy-4,5-methylenedioxybenzaldehyde into (2*RS*,3*SR*,4*RS*)-2-methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-4-butanolide (**11**) was carried out in seven steps *via* 1-acetoxy-1-(3-methoxy-4,5-methylenedioxyphenyl)propanone. The butanolide **11** was further converted into (2*RS*,3*SR*,3a*RS*,5*RS*)-3,3a,4,5-tetrahydro-5-methoxy-2-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-3a-(2-propenyl)-6(2*H*)-benzofuranone (**22**) in eight steps. Reduction of **22** with lithium aluminium hydride followed by acetylation with acetic anhydride in pyridine afforded (±)-megaphyllone acetate.

Three cytotoxic neolignans, megaphone (**1**), megaphone acetate (**2**), and megaphyllone acetate (**3**), have been isolated from the root of *Aniba megaphylla* Mez. (Lauraceae) by Kupchan and his co-workers.[1] Each of these neolignans possesses four asymmetric centers and exhibits an *in vitro* inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB). Recently, the total synthesis of racemic megaphone (**1**) and megaphone acetate (**2**) have been reported independently by four groups, Büchi,[2] Zoretic,[3] Hoye,[4] and ours.[5] As an extension of a previous work,[5] we describe here the stereoselective total synthesis of racemic megaphyllone acetate (**3**) starting from 3-methoxy-4,5-methylenedioxybenzaldehyde (myristicaldehyde)[6] (**5**) which was prepared from 3,4-dihydroxy-5-methoxybenzoic acid[7] (**4**). Our synthetic strategy was essentially the same as that reported in our previous work.



1 R=H
2 R=Ac



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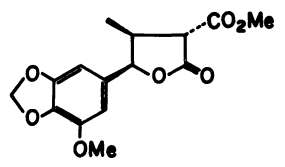
Condensation of **5** with methyl 2-chloropropanoate in tetrahydrofuran in the presence of potassium *t*-butoxide afforded a glycidic ester (**6**), which was hydrolyzed with aqueous sodium hydroxide in ethanol to give a sodium glycidate (**7**). This was decarboxylated with lead tetraacetate and pyridine in refluxing benzene[8] to afford 1-acetoxy-1-(3-methoxy-4,5-methylenedioxyphenyl)propanone (**8**) in 64% overall yield from **5**. Condensation of **8** in tetrahydrofuran with dimethyl malonate in the presence of titanium tetrachloride and pyridine yielded methyl 4-acetoxy-2-methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-2-butenoate (**9**) in 74% yield. The butenoate **9** was refluxed with concentrated hydrochloric acid in methanol to give a butenolide ester (**10**). Reduction of **10** with sodium borohydride in methanol followed by esterification with diazomethane gave a butanolide ester (**11**) in 33% yield along with its stereoisomer (**12**) and a keto diester (**13**) in 3% and 6% yields, respectively. A similar reduction of **13** with sodium borohydride provided **11** and **12** in 33% and 22% yields, respectively. The ^{1}H NMR spectrum of **11** showed a doublet signal due to the C-3 methyl at δ 0.81, while that of **12** showed a corresponding signal at δ 1.17. The appearance of the C-3 methyl signal in **11** in a very high field must be attributable to the shielding effect of the C-4 aromatic ring. Thus, the relative configurations of the methyl and aryl groups in **11** and **12** were assigned to be *cis* and *trans* dispositions, respectively. The *cis*-configurations of the methyl at C-3 and the hydrogen at C-2 in both **11** and **12** were also supported by the NOE measurements: irradiation of the methyl signals at δ 0.81 and 1.17 resulted in 16% and 14% enhancements of the C-2 proton signals at δ 3.35 and 3.39. Michael reaction of **11** in methanol with methyl vinyl ketone in the presence of triethylamine at 0—5 °C yielded a single keto lactone ester (**14**). This was hydrolyzed with aqueous sodium hydroxide in refluxing methanol and then decarboxylated with dilute hydrochloric acid to give a C-2 epimeric mixture of keto lactones (**15**) in 87% overall yield from **11**. Treatment of **15** with 1,2-ethanediol, trimethyl orthoformate, and boron trifluoride in dichloromethane afforded a mixture of the corresponding acetals (**16**) in 87% yield. To introduce an allyl group the acetal **16** was treated with allyl bromide and lithium diisopropylamide in 1,2-dimethoxyethane under a stream of nitrogen. The resulting single product (**17**) was hydrolyzed with dilute hydrochloric acid to give a keto lactone (**18**) in 68% overall yield from **16**. The relative configuration of the C-2 allyl and C-3 methyl groups in **17** was assigned to be *trans* by assuming the

introduction of the allyl group from the less hindered side of the molecule. Intramolecular aldol condensation of **18** with potassium *t*-butoxide in refluxing benzene was carried out and the crude product was immediately refluxed with *p*-toluenesulfonic acid in benzene to give an α,β-unsaturated ketone (**19**) in 66% yield. Subsequently, the introduction of a hydroxyl group at C-5 in **19** was carried out as follows.[9] The enone **19** in 1,2-dimethoxyethane was treated with chlorotrimethylsilane and lithium diisopropylamide under a stream of nitrogen to give a silyl enol ether. This was oxidized with *m*-chloroperbenzoic acid in dichloromethane in the presence of sodium hydrogencarbonate and then treated with triethylammonium fluoride to give the desired hydroxy enone (**20**) and its C-5 epimer (**21**) in 60% and 5% yields, respectively. In the ^{1}H NMR spectrum of the major alcohol **20**, a methine proton adjacent to the hydroxyl group exhibits both axial-axial (J=12 Hz) and axial-equatorial (J=5.5 Hz) vicinal coupling; while the corresponding proton in the minor alcohol **21** exhibits two equatorial-equatorial (J=5.5 and 3 Hz) vicinal coupling. Consequenly the hydroxyl groups in **20** and **21** are pseudoequatorial and pseudoaxial respectively. From these spectral data, the relative configurations of the hydroxyl and allyl groups in **20** and **21** were assigned respectively to be *trans* and *cis* dispositions. Methylation of **20** with diazomethane in ether in the presence of silica gel[10] afforded a methoxy enone (**22**) in 74% yield. This was reduced[11] with lithium aluminium hydride in refluxing tetrahydrofuran and the resulting alcohol was immediately acetylated with acetic anhydride in pyridine under a stream of nitrogen to give an acetate (**3**) in 71% yield. The ^{1}H NMR spectrum of the synthetic **3** was in good agreement with that published for natural megaphyllone acetate. A similar reduction of the enone **19** with lithium aluminium hydride followed by acetylation gave the corresponding acetate (**23**) in 82% yield.



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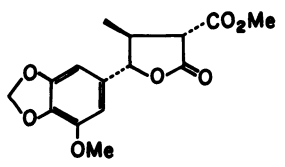

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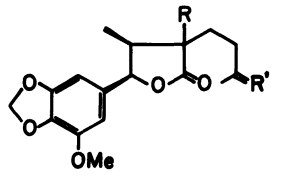
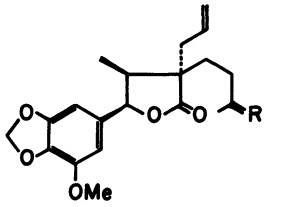
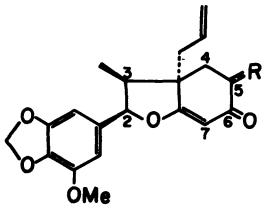


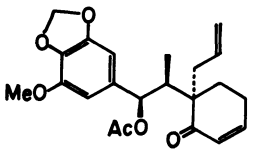
14 R=CO_2Me, R'=O
15 R=H, R'=O
16 R=H, R'=O(CH_2)$_2$O



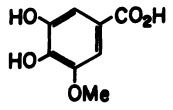
17 R=O(CH_2)$_2$O
18 R=O



19 R=H_2
20 R= α-H, β-OH
21 R= α-OH, β-H
22 R= α-H, β-OMe



23



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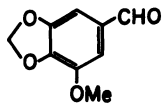

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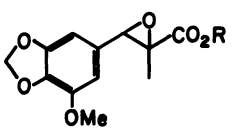
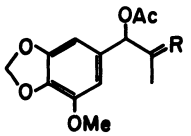
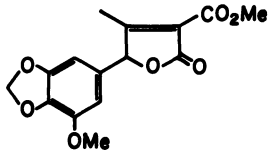


6 R=Me
7 R=Na



8 R=O
9 R=C(CO_2Me)$_2$



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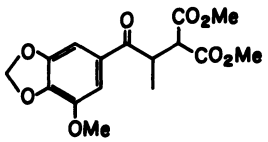

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Experimental

All melting points are uncorrected. The IR spectra were measured in chloroform and the ^{1}H NMR spectra in deuteriochloroform at 90 MHz, with tetramethylsilane as an internal standard, unless otherwise stated; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, t: triplet, dt: double triplet, q: quartet, bq: broad quartet, m: multiplet. The column chromatography was performed using Merck silica gel (0.063 mm).

Methyl 3,4-Dihydroxy-5-methoxybenzoate. According to the method of Scheline,[7] 3,4-dihydroxy-5-methoxybenzoic acid (**4**) was prepared from gallic acid.

A mixture of the crude **4** (57 g) and concentrated sulfuric acid (6.0 ml) in methanol (250 ml) was refluxed for 6 h with a water separator containing 4-Å Molecular Sieves. The mixture was concentrated to a half volume, diluted with

brine, and extracted with ether. The ether extract was washed, successively, with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from benzene to give methyl 3,4-dihydroxy-5-methoxybenzoate (52 g: 76% from gallic acid), mp 115—118 °C, IR: 3550, 3350, 1713, 1622, 1521 cm^{-1}; ^1H NMR (60 MHz): δ=3.90 (6H, s, $-CO_2CH_3$ and $-OCH_3$), 5.4—6.4 (2H, br, 2-OH), 7.18 (1H, d, J=2 Hz) and 7.32 (1H, d, J=2 Hz) (aromatic protons).

3-Methoxy-4,5-methylenedioxybenzaldehyde (5). *a)*: Anhydrous potassium fluoride (88 g) was added to a stirred solution of methyl 3,4-dihydroxy-5-methoxybenzoate (50.0 g) in *N,N*-dimethylformamide (500 ml) and the mixture was stirred for 15 min. After the addition of dibromomethane (25.4 ml), the stirred mixture was refluxed for 2.5 h, cooled, diluted with ether, and then filtered. The filtrate was washed, successively, with brine, aqueous sodium hydroxide, and brine. The dried solution was evaporated *in vacuo* to give the crude methyl 3-methoxy-4,5-methylenedioxybenzoate (49.7 g). ^1H NMR (60 MHz): δ=3.89 (3H, s) and 3.95 (3H, s) ($-CO_2CH_3$ and $-OCH_3$), 6.04 (2H, s, $-OCH_2O-$), 7.17 (1H, d, J=2 Hz) and 7.28 (1H, d, J=2 Hz) (aromatic protons).

b): Lithium aluminium hydride (9.0 g) was added portionwise to a stirred solution of the above crude ester (49.7 g) in tetrahydrofuran (350 ml) with cooling in an ice-water bath. The mixture was refluxed for 2 h, cooled, poured into a mixture of ice and aqueous ammonium chloride, and then filtered. The filtrate was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude 3-methoxy-4,5-methylenedioxybenzyl alcohol (41.0 g). ^1H NMR (60 MHz): δ=3.28 (1H, s, -OH), 3.85 (3H, s, $-OCH_3$), 4.46 (2H, s, $-C\underline{H}_2OH$), 5.90 (2H, s, $-OCH_2O-$), 6.46 (2H, s, aromatic protons).

c): Pyridinium dichlorochromate (186 g) was added to a stirred solution of the above crude alcohol (41.0 g) in dichloromethane (657 ml). The mixture was stirred at room temperature for 2 h and then filtered from a tarry residue, which was washed with ethyl acetate. The combined organic solution was washed with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from methanol to give **5** (26.0 g), mp 130—132 °C (lit,[6] mp 130—131 °C); IR: 1692, 1637, 1604 cm^{-1}; ^1H NMR (60 MHz): δ=3.98 (3H, s, $-OCH_3$), 6.10 (2H, s, $-OCH_2O-$), 7.04 (1H, d, J=2 Hz) and 7.12 (1H, d, J=2 Hz) (aromatic protons), 9.78 (1H, s, -CHO).

1-Acetoxy-1-(3-methoxy-4,5-methylenedioxyphenyl)propanone (8). *a)*: Potassium *t*-butoxide (50.50 g) was added to a stirred solution of 3-methoxy-4,5-methylenedioxybenzaldehyde (**5**) (54.05 g) and methyl 2-chloropropanoate (55.17 g) in tetrahydrofuran (810 ml) with cooling in an ice-water bath over a 10-min period. The mixture was stirred at 0—5 °C for 1.5 h and then at room temperature for 3 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude glycidic ester (**6**) (82.67 g) as an oil; IR: 1727, 1628 cm^{-1}; ^1H NMR (60 MHz): δ=1.36 (3H, s, $-\underset{|}{C}CH_3$), 3.80 (3H, s) and 3.90 (3H, s) ($-CO_2CH_3$ and $-OCH_3$), 4.22 (1H, s, $-\underset{|}{C}H-O-$), 5.97 (2H, s, $-OCH_2O-$), 6.47 (2H, s, aromatic protons).

b): Aqueous sodium hydroxide (13.2 g in 135 ml of water) was added, dropwise, to a stirred solution of the above crude **6** (82.67 g) in ethanol (1800 ml) with cooling in an ice-water bath. The mixture was stirred at room temperature for 3 h. The precipitates were collected by filtration and washed with ethanol to give a sodium glycidate (**7**) (68.00 g) as a colorless solid. Some additional **7** (8.00 g) was obtained from the filtrate.

Lead tetraacetate (112 g) was added to a stirred suspension of **7** (54.874 g) and pyridine (21.8 ml) in dry benzene (2000 ml) under a stream of nitrogen. The mixture was stirred at room temperature for 30 min, refluxed for 5 h, and then cooled. After the addition of 1,2-ethanediol (20 ml), the mixture was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (1200 g), using ether-benzene (1:99) as the eluent, to give **8** (34.254 g: 64.3% from **5**) as an oil. IR: 1743, 1731, 1639 cm^{-1}; ^1H NMR: δ=2.11 (3H, s) and 2.17 (3H, s) ($-COCH_3$ and $-OCOCH_3$), 3.91 (3H, s, $-OCH_3$), 5.87 (1H, s, $-C\underline{H}(OAc)-$), 6.00 (2H, s, $-OCH_2O-$), 6.59 (2H, s, aromatic protons). Found: C, 58.50; H, 5.34%. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30%.

Methyl 4-Acetoxy-2-methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-2-butenoate (9). A solution of **8** (26.638 g), dimethyl malonate (22.9 ml), and pyridine (145.3 ml) in dry tetrahydrofuran (270 ml) was added (over a 15-min period) to a stirred solution of titanium tetrachloride (65.9 ml) in dry tetrahydrofuran (850 ml) with cooling in an ice-water bath under a stream of nitrogen. The mixture was stirred at room temperature for 3.5 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (600 g), using ether-benzene (2:98) as the eluent, to give **9** (28.046 g: 73.7%) as an oil. IR: 1730, 1640 cm^{-1}; ^1H NMR (60 MHz): δ=1.95 (3H, s), and 2.15 (3H, s) ($=\underset{|}{C}CH_3$ and $-OCOCH_3$), 3.78 (3H, s), 3.84 (3H, s), and 3.90 (3H, s) ($2-CO_2CH_3$ and $-OCH_3$), 5.95 (2H, s, $-OCH_2O-$), 6.65 (2H, s, aromatic protons), 6.87 (1H, s, $-C\underline{H}(OAc)-$). Found: C, 56.77; H, 5.18%. Calcd for $C_{18}H_{20}O_9$: C, 56.84; H, 5.30%.

2-Methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-2-buten-4-olide (10). A mixture of **9** (3.783 g) and concentrated hydrochloric acid (1.0 ml) in methanol (38 ml) was refluxed for 4 h. The mixture was concentrated and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude **10** (2.953 g) as a solid, which was used without purification in the next reaction. IR: 1775, 1760 sh, 1720, 1633 cm^{-1}; ^1H NMR (60 MHz): δ=2.23 (3H, s, $=\underset{|}{C}CH_3$), 3.89 (6H, s, $-CO_2CH_3$ and $-OCH_3$), 5.60 (1H, s, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.33 (1H, d, J=2 Hz) and 6.37 (1H, d, J=2 Hz) (aromatic protons).

Reduction of 10 with Sodium Borohydride. Sodium borohydride (0.376 g) was added to a stirred solution of the crude **10** (2.953 g) in methanol (38 ml) with cooling in an ice-water bath over a 5 min period. The mixture was stirred at room temperature for 30 min, poured into ice-dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was

methylated with diazomethane in ether and the crude product was repeatedly chromatographed on silica gel, using ether–benzene (2:98) as the eluent, to give the following three compounds: **13**, **11**, and **12** in the order of elution.

a): Methyl 2-methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-4-oxobutanoate (**13**) (0.201 g: 6.0%), which was recrystallized from methanol, mp 83—85 °C. IR: 1747, 1728, 1672, 1628, 1602 cm^{-1}; ^1H NMR: δ= 1.18 (3H, d, J=7 Hz, $-CH(C\underline{H}_3)-$), 3.67 (3H, s) and 3.80 (3H, s) ($2-CO_2CH_3$), 3.94 (3H, s, $-OCH_3$), 3.5—4.3 (2H, m, $-C\underline{H}(CH_3)C\underline{H}(CO_2CH_3)_2$), 6.07 (2H, s, $-OCH_2O-$), 7.19 (1H, d, J=1.5 Hz) and 7.30 (1H, d, J=1.5 Hz) (aromatic protons). Found: C, 56.64; H, 5.57%. Calcd for $C_{16}H_{18}O_8$: C, 56.80; H, 5.36%.

b): (2*RS*,3*SR*,4*RS*)-2-Methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-4-butanolide (**11**) (0.999 g: 32.6%), which was recrystallized from methanol, mp 91.5—92.5 °C. IR: 1782, 1738, 1640 cm^{-1}; ^1H NMR: δ= 0.81 (3H, d, J=7 Hz, C_3-CH_3), 3.17 (1H, m, C_3-H), 3.35 (1H, d, J=6.5 Hz, C_2-H), 3.83 (3H, s) and 3.90 (3H, s) ($-CO_2CH_3$ and $-OCH_3$), 5.65 (1H, d, J=6.5 Hz, C_4-H), 5.98 (2H, s, $-OCH_2O-$), 6.38 (2H, s, aromatic protons). Found: C, 58.60; H, 5.41%. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23%.

c): (2*RS*,3*SR*,4*SR*)-2-Methoxycarbonyl-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-4-butanolide (**12**) (0.084 g: 2.7%) as an oil. IR: 1782, 1738, 1640 cm^{-1}; ^1H NMR: δ=1.17 (3H, d, J=7 Hz, C_3-CH_3), 2.84 (1H, m, C_3-H), 3.39 (1H, d, J=12 Hz, C_2-H), 3.83 (3H, s) and 3.91 (3H, s) ($-CO_2CH_3$ and $-OCH_3$), 4.78 (1H, d, J=9.5 Hz, C_4-H), 5.99 (2H, s, $-OCH_2O-$), 6.55 (2H, s, aromatic protons). Found: C, 58.74; H, 5.22%. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23%.

Reduction of 13 with Sodium Borohydride. A solution of **13** (920 mg) in methanol (9.5 ml) was reduced with sodium borohydride (103 mg) as described above. The crude product was chromatographed on silica gel (50 g), using ether–benzene (2:98) as the eluent, to give the recovered **13** (85 mg: 9.2%), **11** (204 mg: 24.4%), and a 1:2.5 mixture of **11** and **12** (259 mg: 30.9%).

Michael Condensation of 11 with Methyl Vinyl Ketone. Triethylamine (1.40 ml) was added to a stirred solution of **11** (6.125 g) and methyl vinyl ketone (2.43 ml) in methanol (120 ml) with cooling in an ice-water bath. The mixture was allowed to stand in a refrigerator for 23 h, poured into ice-dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude keto lactone ester (**14**) (7.592 g), which was used without purification in the next reaction. IR: 1773, 1715, 1633 cm^{-1}; ^1H NMR: δ=0.65 (3H, d, J=7.5 Hz, C_3-CH_3), 2.00—2.48 (2H, m, $-C\underline{H}_2CH_2CO-$), 2.14 (3H, s, $-COCH_3$), 2.48—3.08 (3H, m, $-C\underline{H}_2COCH_3$ and C_3-H), 3.74 (3H, s) and 3.89 (3H, s) ($-CO_2CH_3$ and $-OCH_3$), 5.66 (1H, d, J=6.5 Hz, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.43 (1H, d, J=1.5 Hz) and 6.46 (1H, d, J=1.5 Hz) (aromatic protons).

Hydrolysis and Decarboxylation of 14. A mixture of the crude **14** (7.592 g) and 10% aqueous sodium hydroxide (5.0 ml) in methanol (86 ml) was refluxed for 3 h. The mixture was cooled, acidified with dilute hydrochloric acid, and then allowed to stand at room temperature for 30 min. After the methanol had been removed *in vacuo*, the residue was diluted with brine, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (200 g), using ether–benzene (1:9) as the eluent, to give a mixture of (2*RS*,3*SR*,4*RS*)- and (2*SR*,3*SR*,4*RS*)-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-2-(3-oxobutyl)-4-butanolide (**15**) (5.537 g: 87.0% from **11**); IR: 1771, 1716, 1637 cm^{-1}. The ^1H NMR spectrum of the mixture suggested the ratio of two C-2 epimers to be 57:43. ^1H NMR of the major compound: δ=0.78 (3H, d, J=6.5 Hz, C_3-CH_3), 2.16 (3H, s, $-COCH_3$), 3.88 (3H, s, $-OCH_3$), 5.45 (1H, d, J=7 Hz, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.33 (2H, s, aromatic protons). ^1H NMR of the minor compound: δ=0.58 (3H, d, J=7 Hz, C_3-CH_3), 2.16 (3H, s, $-COCH_3$), 3.88 (3H, s, $-OCH_3$), 5.38 (1H, d, J=5.5 Hz, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.42 (1H, d, J=2 Hz) and 6.46 (1H, d, J=2 Hz) (aromatic protons). Found: C, 63.49; H, 6.22%. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29%.

Acetalization of 15. A mixture of **15** (6.495 g), 1,2-ethanediol (11.3 ml), trimethyl orthoformate (22.0 ml), and boron trifluoride etherate (0.6 ml) in dichloromethane (130 ml) was stirred at room temperature for 12.5 h. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (200 g), using ether–benzene (1:9) as the eluent, to give a C-2 epimeric mixture of acetals (**16**) (6.395 g: 86.6%); IR: 1770, 1637 cm^{-1}. ^1H NMR of the major compound: δ=0.77 (3H, d, J=6.5 Hz, C_3-CH_3), 1.32 (3H, s, $-\underset{|}{C}CH_3$), 3.89 (3H, s, $-OCH_3$), 3.94 (4H, s, $-OCH_2CH_2O-$), 5.45 (1H, d, J=7 Hz, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.36 (2H, s, aromatic protons). ^1H NMR of the minor compound: δ=0.58 (3H, d, J=7 Hz, C_3-CH_3), 1.32 (3H, s, $-\underset{|}{C}CH_3$), 3.89 (3H, s, $-OCH_3$), 3.94 (4H, s, $-OCH_2CH_2O-$), 5.39 (1H, d, J=4 Hz, C_4-H), 5.97 (2H, s, $-OCH_2O-$), 6.43 (1H, d, J=2 Hz) and 6.47 (1H, d, J=2 Hz) (aromatic protons). Found: C, 62.69; H, 6.70%. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64%.

(2SR,3SR,4RS)-2-(3,3-Ethylenedioxybutyl)-4-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-2-(2-propenyl)-4-butanolide (17). A solution of butyllithium in hexane (1.6 mol dm^{-3}, 9.38 ml) was added to a stirred solution of diisopropylamine (2.10 ml) in dry tetrahydrofuran (43 ml) at −70 °C under a stream of nitrogen. The mixture was stirred at −70 °C for 25 min and a solution of **16** (2.186 g) in dry tetrahydrofuran (6.0 ml) was added over a 5-min period. After 30 min, allyl bromide (3.57 ml) was added. The mixture was stirred at −70 °C for 25 min and then at −5—0 °C for 75 min, quenched with water, diluted with aqueous ammonium chloride, poured into dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed, successively, with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude **17** (2.624 g), which was used without purification in the next reaction. IR: 1760, 1633 cm^{-1}; ^1H NMR (60 MHz): δ=0.67 (3H, d, J=7.5 Hz, C_3-CH_3), 1.29 (3H, s, $-\underset{|}{C}CH_3$), 2.47 (2H, bd, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 3.88 (7H, bs, $-\underset{|}{O}CH_3$ and $-OCH_2CH_2O-$), 4.95—5.35 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.54 (1H, d, J=6 Hz, C_4-H), 5.6—6.1 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.94 (2H, s, $-OCH_2O-$), 6.37 (2H, bs, aromatic protons).

(2SR,3SR,4RS)-4-(3-Methoxy-4,5-methylenedioxyphenyl)-3-

methyl-2-(3-oxobutyl)-2-(2-propenyl)-4-butanolide (18). A mixture of the crude **17** (2.624 g) and 5% hydrochloric acid (1.3 ml) in methanol (26 ml) was stirred at room temperature for 3 h. The mixture was poured into brine and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using ether–benzene (5:95) as the eluent, to give **18** (1.463 g: 67.6% from **16**). This was recrystallized from chloroform–hexane, mp 114—114.5 °C IR: 1765, 1715, 1638 cm^{-1}; ^1H NMR: δ=0.68 (3H, d, J=7.5 Hz, C_3–CH_3), 1.42—2.13 (2H, m, $-C\underline{H}_2CH_2CO-$), 2.16 (3H, s, $-COCH_3$), 2.43 (2H, bd, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 2.26—3.10 (3H, m, C_3–H and $-CH_2C\underline{H}_2CO-$), 3.90 (3H, s, $-OCH_3$), 5.04—5.33 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.54 (1H, d, J=7 Hz, C_4–H), 5.56—6.03 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.97 (2H, s, $-OCH_2O-$), 6.40 (1H, d, J=1.5 Hz) and 6.45 (1H, d, J=1.5 Hz) (aromatic protons). Found: C, 66.94; H, 6.72%. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71%. Further elution with ether–benzene (1:9) gave the recovered **15** (0.222 g).

(2RS,3SR,3aSR)-3,3a,4,5-Tetrahydro-2-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-3a-(2-propenyl)-6(2H)-benzofuranone (19). Potassium *t*-butoxide (0.875 g) was added, portionwise, to a stirred solution of **18** (2.162 g) in dry benzene (22 ml) with cooling in an ice-water bath. The mixture was stirred at the same temperature for 5 min and then refluxed for 3 h. The mixture was cooled, poured into ice-dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give an oily product.

A mixture of the above oily product and *p*-toluenesulfonic acid monohydrate (50 mg) in benzene (40 ml) was refluxed for 1 h, cooled, and diluted with ethyl acetate. The ethyl acetate solution was washed with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using ether–benzene (1:9) as the eluent, to give **19** (1.351 g: 65.8%). This was recrystallized from chloroform–hexane, mp 134—135 °C, IR: 1628 cm^{-1}; ^1H NMR: δ=0.53 (3H, d, J=7.5 Hz, C_3–CH_3), 2.56 (2H, d, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 3.91 (3H, s, $-OCH_3$), 5.12—5.38 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.54 (1H, s, C_7–H), 5.64—6.11 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.78 (1H, d, J=5.5 Hz, C_2–H), 5.97 (2H, s, $-OCH_2O-$), 6.42 (2H, s, aromatic protons). Found: C, 69.90; H, 6.52%. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%.

Hydroxylation of 19. A solution of butyllithium in hexane (1.6 mol dm^{-3}: 1.56 ml) was added dropwise to a stirred solution of diisopropylamine (0.42 ml) in dry 1,2-dimethoxyethane (6.8 ml) at −15 °C under a stream of nitrogen. The mixture was stirred at −15 °C for 15 min and a solution of **19** (342 mg) in dry 1,2-dimethoxyethane (3.0 ml) was added. After 15 min, chlorotrimethylsilane (0.64 ml) was added at −15 °C. The mixture was further stirred at room temperature for 2 h and the solvent was evaporated *in vacuo* under a stream of nitrogen. The residue was dissolved in dry hexane (30 ml) and then filtered. The filtrate was evaporated *in vacuo* under a stream of nitrogen to give a crude silyl enol ether.

A solution of the above crude product in dichloromethane (2.0 ml) was added to a stirred mixture of *m*-chloroperbenzoic acid (purity>90%: 326 mg) and sodium hydrogencarbonate (151 mg) in dichloromethane (20 ml) at −15 °C. The mixture was stirred at room temperature for 1 h, diluted with chloroform, and washed with aqueous sodium hydrogencarbonate. The dried solution was evaporated *in vacuo*. The residue was dissolved in dichloromethane (3.0 ml) and the resulting solution was added to a stirred solution of triethylammonium fluoride (484 mg) in dichloromethane (20 ml). The mixture was stirred at room temperature for 13.5 h, diluted with chloroform, and then washed successively with aqueous sodium hydrogencarbonate, dilute hydrochloric acid, and aqueous sodium hydrogencarbonate. The dried solution was evaporated *in vacuo*. The crude product was repeatedly chromatographed on silica gel (Merck 0.040—0.063 mm), using hexane–chloroform (4:6) as the eluent, to give the starting **19** (33.6 mg: 9.8%) and the following two alcohols.

(2*RS*,3*SR*,3a*RS*,5*RS*)-3,3a,4,5-Tetrahydro-5-hydroxy-2-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-3a-(2-propenyl)-6(2*H*)-benzofuranone (**20**) (213.5 mg: 59.6%), which was recrystallized from chloroform–hexane, mp 160—161.5 °C. IR: 3480br, 1656sh, 1637sh, 1625 cm^{-1}; ^1H NMR: δ=0.54 (3H, d, J=7.5 Hz, C_3–CH_3), 1.81 (1H, t, J=12 Hz) and 2.37 (1H, dd, J=12 and 5.5 Hz) ($-C\underline{H}_2CH(OH)-$), 2.61 (2H, d, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 3.52 (1H, bs, -OH), 3.90 (3H, s, $-OCH_3$), 4.34 (1H, dd, J=12 and 5.5 Hz, C_5–H), 5.15—5.43 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.63 (1H, s, C_7–H), 5.70—6.18 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.83 (1H, d, J=5.5 Hz, C_2–H), 5.98 (2H, s, $-OCH_2O-$), 6.40 (2H, s, aromatic protons). M^+, 358. Calcd for $C_{20}H_{22}O_6$: M^+, 358.

(2*RS*,3*SR*,3a*RS*,5*SR*)-3,3a,4,5-Tetrahydro-5-hydroxy-2-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-3a-(2-propenyl)-6(2*H*)-benzofuranone (**21**) (17.6 mg: 4.9%), which was recrystallized from chloroform–hexane, mp 166—168 °C. IR: 3575, 3400br, 1637sh, 1624 cm^{-1}; ^1H NMR: δ=0.54 (3H, d, J=7.5 Hz, C_3–CH_3), 2.07 (1H, dd, J=15 and 5.5 Hz) and 2.22 (1H, dd, J=15 and 3 Hz) ($-C\underline{H}_2CH(OH)-$), 2.57 (1H, dd, J=13.5 and 8 Hz, $-C\underline{H}_AH_BCH=CH_2$), 2.86 (1H, dd, J=13.5 and 6 Hz, $-CH_A\underline{H}_BCH=CH_2$), *ca.* 2.6 (1H, m, C_3–H), 2.92 (1H, br, -OH), 3.91 (3H, s, $-OCH_3$), 4.10 (1H, dd, J=5.5 and 3 Hz, C_5–H), 5.11—5.40 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.61 (1H, s, C_7–H), 5.89 (1H, d, J=5.5 Hz, C_2–H), 5.67—6.25 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.79 (2H, s, $-OCH_2O-$), 6.40 (2H, bs, aromatic protons). M^+, 358. Calcd for $C_{20}H_{22}O_6$: M^+, 358.

(2RS,3SR,3aRS,5RS)-3,3a,4,5-Tetrahydro-5-methoxy-2-(3-methoxy-4,5-methylenedioxyphenyl)-3-methyl-3a-(2-propenyl)-6(2H)-benzofuranone (22). A cold solution of diazomethane (*ca.* 100 mmol) in ether (200 ml) was added to a stirred mixture of **20** (179.0 mg) and silica gel (9.0 g: Merck 0.040—0.063 mm) in dry tetrahydrofuran (15 ml) with cooling in an ice-water bath. Afer stirring at 0—5 °C for 30 min and then at room temperature for 1.5 h, the mixture was filtered to remove silica gel, which was washed well with chloroform. The filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give **22** (101.0 mg: 54.1%), mp 154—155 °C. The mother liquor of recrystallization was evaporated *in vacuo* and the residue was chromatographed on silica gel (10 g: Merck 0.040—0.063 mm), using hexane–chloroform (6:4) as the eluent, to give an additional **22** (26.9 mg: 19.8%). IR: 1659sh, 1636, 1632 cm^{-1}; ^1H NMR: δ=0.54 (3H, d, J=7.5 Hz, C_3–CH_3), 1.88 (1H, t, J=12 Hz) and 2.28 (1H, dd, J=12 and 5.5 Hz) ($-C\underline{H}_2CH(OMe)-$), 2.33—

2.83 (3H, m, $-C\underline{H}_2CH=CH_2$ and C_3-H), 3.60 (3H, s, C_5-OCH_3), 3.91 (3H, s, $-OCH_3$), 3.98 (1H, dd, J=12 and 5 Hz, C_5-H), 5.17—5.43 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.56 (1H, s, C_7-H), 5.70—6.18 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.80 (1H, d, J= 5.5 Hz, C_2-H), 5.98 (2H, s, $-OCH_2O-$), 6.40 (2H, s, aromatic protons). Found: C, 67.47; H, 6.65%. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50%.

(±)-Megaphyllone Acetate (3). Lithium aluminium hydride (9.5 mg) was added to a stirred solution of **22** (93.1 mg) in dry tetrahydrofuran (5.0 ml) at room temperature. The mixture was refluxed for 2 h, cooled, poured into ice-water containing 15% hydrochloric acid (1.0 ml), and extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo* under a stream of nitrogen. The residue was immediately acetylated with acetic anhydride (0.5 ml) in pyridine (5.0 ml) at 50 °C for 15 h in an atmosphere of nitrogen. After the usual work-up, the crude product was chromatographed on silica gel (20 g: Merck 0.040—0.063 mm), using hexane–chloroform (1:1) as the eluent, to give **3** (73.8 mg: 70.9%) as an oil, whose spectral data were identical with those reported for natural megaphyllone acetate. IR (CCl_4): 1745, 1676, 1636 cm^{-1}; ^1H NMR: δ=0.90 (3H, d, J=7 Hz, $-CH(C\underline{H}_3)-$), 1.87 (1H, dd, J=14 and 10 Hz) and 2.27 (1H, d of dd, J=14, 6, and 2 Hz) ($-C\underline{H}_2CH-(OCH_3)-$), 2.09 (3H, s, $-OCOCH_3$), 2.34 (2H, bd, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 2.51 (1H, bq, J=7 Hz, $-C\underline{H}(CH_3)-$), 3.44 (3H, s, $-CH(OC\underline{H}_3)-$), 3.91 (3H, s, $-OCH_3$), 4.04—4.30 (1H, m, $-C\underline{H}(OCH_3)-$), 4.87—5.12 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.35—5.82 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.67 (1H, bs, $-C\underline{H}-(OCOCH_3)-$), 5.93 (2H, s, $-OCH_2O-$), 6.00 (1H, dd, J=10 and 2 Hz, $-COC\underline{H}=CH-$), 6.49 (1H, d, J=1.5 Hz) and 6.55 (1H, d, J=1.5 Hz) (aromatic protons), 6.89 (1H, dt, J=10 and 2 Hz, $-COCH=C\underline{H}-$). Found: C, 66.07; H, 6.88%; M^+, 416. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78%; M^+, 416.

(±)-Demethoxymegaphyllone Acetate (23). Reduction of a solution of **19** (250 mg) in dry tetrahydrofuran (20 ml) with lithium aluminium hydride (27.7 mg), followed by acetylation with acetic anhydride (2.5 ml) in pyridine (20 ml), was carried out as described regarding the preparation of **3**. The crude product was recrystallized from methanol to give **23** (179 mg: 63.2%), mp 115.5—116.5 °C. The mother liquor of recrystallization was evaporated *in vacuo* and the residue was chromatographed on silica gel (10 g), using ether–benzene (5:95) as the eluent, to give an additional **23** (51.3 mg: 18.2%). IR: 1737, 1666, 1640 cm^{-1}; ^1H NMR: δ=0.88 (3H, d, J=7.5 Hz, $-CH(C\underline{H}_3)-$), 2.09 (3H, s, $-OCOCH_3$), 2.33 (2H, bd, J=7 Hz, $-C\underline{H}_2CH=CH_2$), 2.47 (1H, bq, J=7.5 Hz, $-C\underline{H}(CH_3)-$), 3.91 (3H, s, $-OCH_3$), 4.83—5.11 (2H, m, $-CH_2CH=C\underline{H}_2$), 5.37—5.86 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.71 (1H, bs, $-C\underline{H}(OCOCH_3)-$), 5.93 (2H, s, $-OCH_2O-$), 5.98 (1H, dt, J=10 and 2 Hz, $-COC\underline{H}=CH-$), 6.51 (1H, d, J=1.5 Hz) and 6.57 (1H, d, J= 1.5 Hz) (aromatic protons), 6.86 (1H, dt, J=10 and 4 Hz, $-COCH=C\underline{H}-$). Found: C, 68.44; H, 6.88%. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78%.

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