Synthesis of taxodione

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Two syntheses of taxodione are described, as well as some of the model experiments that preceded them. The yields are low but comparable to most other syntheses of this extended quinone.

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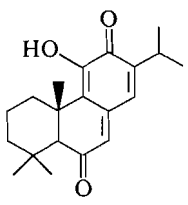
Deux synthèses de la taxodione sont présentées avec quelques séquences réactionnelles qui ont servi comme modèles. Les rendements globaux sont plutôt faibles mais ils sont comparables à ceux de synthèses déjà publiées.

As an extension of certain diterpene syntheses under investigation in our laboratory (1), we were tempted to add our efforts to the several previous taxodione **1** syntheses (2). This extended



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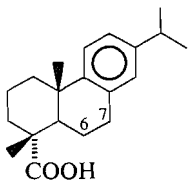

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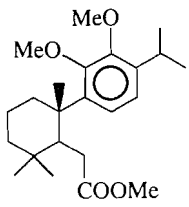

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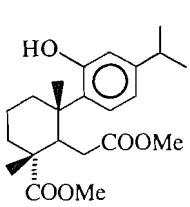
quinone showed interesting biological (3) activity, which precipitated the flurry of methods leading to its synthesis, but in most of the schemes the yields have been low.

During our synthesis and structure correction of 5-dehydronellionol trimethyl ether (1), we converted dehydroabietic acid **2** to the B-seco ester **3** but, for economy of time and effort, we had actually performed the original experimentation without reducing the carboxyl function at C.4 to the methyl. We now describe these transformations because some of the compounds also served as models in the taxodione field. By established procedures, methyl dehydroabietate was oxidized to the C.7 ketone, which, when subjected to Baeyer–Villiger conditions, afforded a 7-membered lactone and the latter, on acid catalysed methanolysis, gave the phenol diester **4**.

As in the previously reported sequence, a second oxygen function was introduced on the aromatic ring by oxidation with phenyl seleninic anhydride (4), which gave mainly the red *o*-quinone **5** and a small quantity of the *p*-quinone **6**. Catalytic hydrogenation of the *o*-quinone **5** gave an intermediate, which was immediately methylated *in situ* (Me_2SO_4, NaOH) under hydrogen to afford the di-*O*-methyl catechol derivative **7***a*. Of the four *O*-methyl groups in the latter, the two ethers and the pivalic type ester at C.4 are stable to aqueous base but the other ester was readily hydrolysed to the acid **7***b*.

Cyclization of the latter in trifluoroacetic anhydride led to the ketone **8***a*. As a taxodione model, the molecule still lacked an oxygen function at C.6, which we intended to introduce by oxygenation in strong base, but, on attempting this reaction on **8***a*, the newly introduced enol, as in **9**, cyclized spontaneously to the lactone **10***a*.

In our original scheme for this synthesis, we had hoped to force the cyclization of the acid **11***c* despite the unfavorable disposition of the substituents and to oxidize the aromatic ring to the *o*-quinone at a later stage. The cyclization, for which several literature equivalents exist (5), gave only the rearranged



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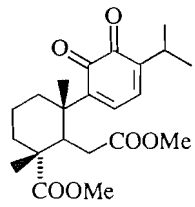

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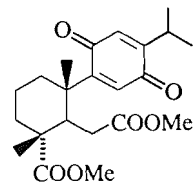

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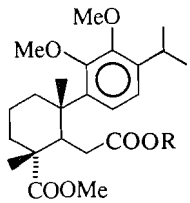
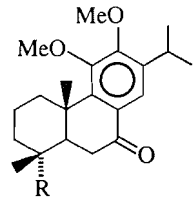
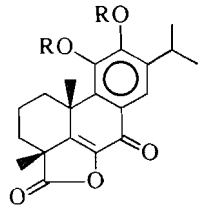


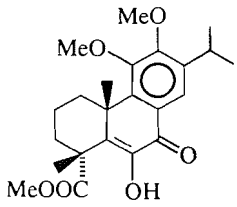
7*a* R = Me
7*b* R = H



8*a* R = COOMe
8*b* R = Me



10*a* R = Me
10*b* R = H



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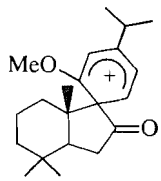

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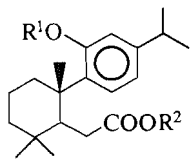
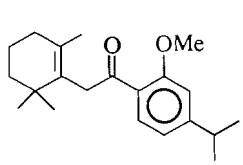


11*a* R^1 = H, R^2 = Me
11*b* R^1 = R^2 = Me
11*c* R^1 = Me, R^2 = H



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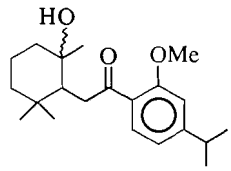

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products **12** and **13**, presumably via the *ipso* substituted intermediate **14** (or its equivalent). The double bond in compound **12** resisted conjugation.

The preparation of the dimethoxy ketone **15**, which we published earlier (1), represented a formal synthesis of taxodione, since this was an intermediate that Matsumoto used to prepare the corresponding $\Delta^{6,7}$-olefin, which in turn was transformed by Mori into taxodione in four steps (2). We felt that this sequence could be improved. Stirring the ketone **15** under oxygen in the presence of potassium *tert*-butylate

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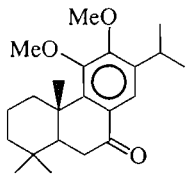

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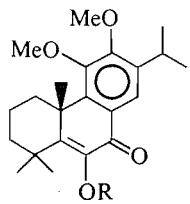
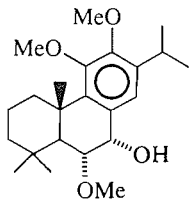


16*a* R = H
16*b* R = Me



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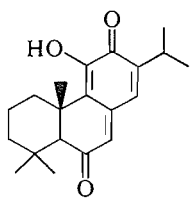


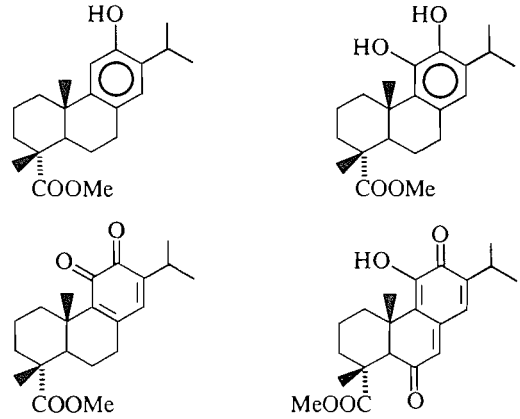
1

afforded the enolized α-diketone **16***a*. We had previously found that hydrogenation of such diketones gives several products, including appreciable quantities of the compound where both oxygen functions are lost by hydrogenolysis, but that this difficulty can be avoided to a large extent by methylation of the enolic carbonyl group (6). So after protecting this hydroxyl group as the methyl ether **16***b*, the product was catalytically hydrogenated to give the 6-methoxy-7-hydroxy compound **17** in which the configurations were assigned using the proton nmr vicinal coupling constants. Upon demethylating this material with boron tribromide and chromatographing the product slowly over silica gel, we obtained taxodione **1** directly in about 20% yield.

Another synthesis of a taxodione analogue described by Ohtsuka and Tahara (7) involves the transformation of an abietatriene type ester by an arduous route into an *o*-quinone, which on slow silica gel chromatography was oxidized directly to the taxodione chromophore in low but interesting yield (14%, see Scheme 1). The authors added that they were unable to prepare the appropriate *o*-quinone (*gem*-dimethyls at C.4) for the synthesis of taxodione itself.

This fortuitous synthesis was appealing so, as a trial system, we demethylated the ester **18***a*, which we had on hand from previous model studies, and subjected the acid **18***b* to oxidation by phenyl seleninic anhydride, which gave an excellent yield of the *o*-quinone **19** (87%). The latter was not too stable so, following the procedure suggested by Tahara *et al.*, we chromatographed it very slowly over silica gel, which caused the colour to change from red to orange to yellow. After further purification, we isolated a 58% yield of the lactone **20**, which showed the same uv absorption as taxodone **21** (8).

When ferruginol **22** was oxidized with phenyl seleninic anhydride the *o*-quinone **23** was isolated in 40% yield accompanied by the quinol **24** (13%). The latter could be dehydrated by refluxing in methanol containing hydrochloric acid but the probable intermediate **28***a* enolized to afford the conjugated olefin **25***a*. It was hoped to integrate the quinol **24** into the synthesis via the olefin **25***a* or the ketone **26**, prepared from it by rearrangement of the 6,7-diol, but their oxidation with phenyl seleninic anhydride led to intractable mixtures, even at low temperature. The *o*-quinone **23** was reduced catalytically and methylated while still under hydrogen, affording both the dimethoxy compound **27***a* and the monomethoxy **27***b*. Of course, the latter gave the former upon further methylation.



SCHEME 1

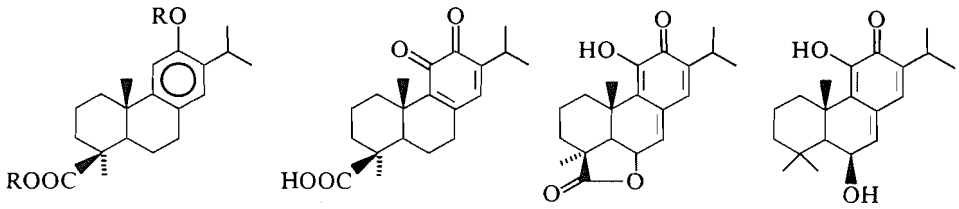
In their synthesis of taxodione, Mori and Matsui bypassed compound **27***a*, which was prepared in a completely different fashion (2*a*).

When the *o*-quinone **23** was slowly chromatographed following the Tahara method, we obtained up to 14% taxodione, but the yield was variable. In an effort to understand this oxidation of the quinone, which must be quite complex, we followed the uv–vis absorption as a function of time. Freshly dissolved in ethanol, the *o*-quinone absorbs at 264 and 424 nm; however, in chloroform there is an intense stable peak at 311 nm, which is exactly like that shown by taxodone **21**. In methanol solution, the 311-nm band diminishes over a period of a few days to the advantage of a peak at 278 nm but, after evaporation, the residue showed only the 311-nm peak, so no irreversible change had occurred. Taxodione has two very intense peaks at 320 and 332 nm (EtOH, ε = 25 000 and 26 000 respectively).

During the slow chromatography the first product we noticed was that showing the peak at 311 nm, and we could isolate this intermediate as a yellow oil in 69% yield after adsorbing the *o*-quinone on a small quantity of silica gel by evaporation of the solvent and then eluting the material from a conventional column. The uv spectrum suggests the taxodone chromophore while absorptions in the ir at 3300 and 1650 cm^{-1} confirmed the presence of a hydroxyl group and a highly conjugated carbonyl. The molecular ion in the mass spectrum at 300 *m/z* showed the new product to be isomeric with the original *o*-quinone, and only the mono-enolized structure **28***b* adequately fits the physical data. The other enol **29** would not only show a different uv absorption but the methyl groups in the sidechain would be displaced from their observed positions of δ 1.13 and 1.14. The stabilizing effect of the hydrogen bonding in **28***b* precludes enolization to the fully aromatic **25***b*. The intermediate **28***b* also gave taxodione on repeated slow chromatography in carbon tetrachloride in yields comparable to those obtained directly from the *o*-quinone.

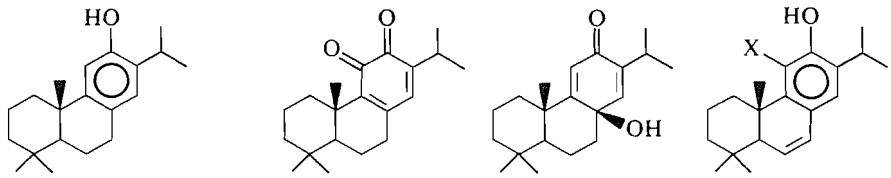
Experimental

Unless otherwise stated, the conditions and instruments used to characterize the products were melting points, Electrothermal, uncorrected; ultraviolet spectra, ethanol solutions (log ε in parentheses), Hewlett Packard 8450 A; infrared spectra, carbon tetrachloride solutions, Beckman 4250 and Perkin Elmer 457; proton magnetic resonance spectra, deuteriochloroform solutions, TMS internal standard (multiplicity, integrated peak areas, coupling constants, and assignments in parentheses), Bruker HX 90; carbon-13 magnetic resonance spectra, deuteriochloroform solutions, TMS internal standard, Bruker WP 80; mass spectra, Hewlett Packard 5992. Elemental analyses were by Galbraith Laboratories, Knoxville. The high resolution mass spectra were recorded on an A.E.I. MS-30. Unless otherwise stated, dry



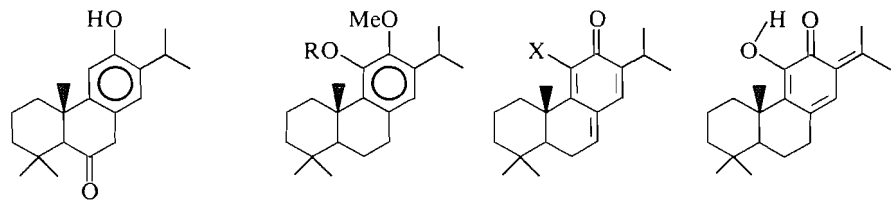
18*a* R = Me
18*b* R = H

19 **20** **21**



22 **23** **24**

25*a* X = H
25*b* X = OH



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27*a* R = Me
27*b* R = H

28*a* X = H
28*b* X = OH

29

column chromatography implies the use of Merck Kieselgel 60F (70–230 mesh) and elution with hexane – ethyl acetate (proportions determined by prior thin-layer chromatography using Machery–Nagel Polygram precoated plastic sheets).

Ortho-quinone **5**

The phenol diester **4** (1.24 g, prepared following essentially the procedure described by Pelletier and Ohtsuka (9)) was dissolved in anhydrous THF (50 mL) and this solution was added dropwise to a suspension of freshly sublimed phenyl seleninic anhydride (2.60 g) in THF (50 mL) warmed to 50–60°C. After 60 min the mixture was poured into ice-water and extracted with ether, which was then well washed with a saturated sodium bicarbonate solution. The reddish crude product was chromatographed (silica gel; benzene – ethyl acetate 9:1) affording diphenyl diselenide (730 mg, yellow solid, mp 50–55°C), the *p*-quinone **6** (270 mg; 21%), and the *o*-quinone **5** (900 mg; 70%) as a viscous dark red oil; uv λ_{max}: 275 (sh), 414 (1800), and 580 (weak) nm; ir (CCl_4): 1730, 1685, 1675, and 1660 cm^{-1}; ^1H nmr δ: 1.11 (d, J = 7 Hz, iso-Pr methyls), 1.18 and 1.23 (2s, C.4-Me and C.10-Me), 2.26 and 2.28 (d, J = 5 Hz, CH_2—COOMe), 2.94 (sept, J = 7 Hz, iso-Pr CH), 3.51 (dd, J = 6 and 5 Hz, C.5-H), 3.59 and 3.75 (2s, COOMe), 6.72 (s, 2H, =CH); ^{13}C nmr: see Table 1; mass spectrum, m/z: 392 (M + 2), 390 (M^+), 362, 360, 332, and 181 (base). *Exact Mass* (hrms) calcd. for $C_{22}H_{30}O_6$: 390.2042; found: 390.2034.

The yellow *p*-quinone **6** was identified by comparison with a sample prepared in another context: ^{13}C nmr, see Table 1.

Reduction and methylation

The *o*-quinone (900 mg) in methanol (20 mL) was added to prehydrogenated Adams catalyst (40 mg) in methanol (10 mL) and hydrogenated at atmospheric pressure. When the red solution had become colorless, without opening to the atmosphere, sodium hydroxide (30% aqueous solution, total 18 mL) and dimethyl sulfate (total 7 mL) were added 1 mL at a time at intervals over a period of 50 h. After filtering and washing the catalyst, the organic solvent was evaporated to give the crude product **7***a*, which was purified by dry column chromatography (705 mg; 70%); ir (CCl_4): 1740 cm^{-1}; ^1H nmr δ: 1.18 (d, J = 7 Hz, iso-Pr methyls), 1.26 and 1.32 (2s, C.4-Me and C.10-Me respectively), 2.22 (d, J = 6 Hz, -CH_2COOMe), 3.28 (sept, J = 7 Hz, iso-Pr CH), 3.36 and 3.47 (2s, COOMe), 3.66 (t, J = 6 Hz, C.5-H), 3.79 and 4.09 (2s, Ar-OMe), 6.89 (ABq, $\Delta\nu$ = 11.7, J = 8.5 Hz, arom. H); ^{13}C nmr, see Table 1; mass spectrum, m/z: 420 (M^+), 405, and 389. *Anal.* calcd. for $C_{24}H_{36}O_6$: C 68.54, H 8.63; found: C 68.26, H 8.02.

Hydrolysis ester **7**a → **7**b

To the ester **7***a* (570 mg) in methanol (25 mL) was added potassium hydroxide solution (25 mL of 10% aqueous) and the mixture was refluxed for 140 min. Most of the methanol was then evaporated under vacuum and the aqueous solution washed with ether to remove neutral materials. After acidification (concentrated HCl), ether extraction afforded the acid **7***b* as a yellow solid (538 mg; 97%), mp 112–114°C; ir (KBr): 3600–2400 (v br), 1730, and 1710 cm^{-1}; ^1H nmr δ: 1.17 (d, J = 7 Hz, iso-Pr Me), 1.24 and 1.29 (2s, C.4-Me and C.10-Me respectively), 2.25 (d, J = 6 Hz, -CH_2COOMe), 3.26 (sept, J = 7 Hz, iso-Pr CH), 3.36 (s, COOMe), 3.60 (t, J = 6 Hz, C.5-H), 3.76 and 4.00 (2s, Ar-OMe), 6.88 (ABq, $\Delta\nu$ = 12.1, J = 8 Hz, arom. H), 9.80 (bs, D_2O, COOH); ^{13}C nmr, see Table 1; mass spectrum, m/z: 406 (M^+), 374, and 160 (base). *Anal.* calcd. for $C_{23}H_{34}O_6$: C 67.95, H 8.43; found: C 68.41, H 8.74.

Cyclization to the ketone **8**a

The acid **7***b* (300 mg) was stirred in trifluoroacetic anhydride (3 mL) for 12 h at room temperature. The mixture was poured into ice-water and the ether extract was washed with sodium bicarbonate solution until neutral, then evaporated and taken up in methanol (30 mL) and aqueous potassium hydroxide (3 mL of 10%). After 2 h at room temperature the product was obtained by adding water and extracting with ether. The ketone **8***a* was obtained as a wax (253 mg; 83%); ir (CCl_4): 1730 and 1690 cm^{-1}; uv λ_{max}: 272 (8000) nm; ^1H nmr δ: 1.22 and 1.25 (two d, J = 7 Hz, iso-Pr Me), 1.34 and 1.42 (2s, C.4-Me and C.10-Me respectively), 2.69 (d, J = 11 Hz, —CH_2—C(=O)—), 3.28 (sept, J = 7 Hz, iso-Pr CH), 3.68 and 3.87 (2s, Ar-OMe), 7.79

TABLE 1. ^{13}C nuclear magnetic resonance data[a]

	Compound															
Carbon	**4**	**5**	**7***a*	**7***b*	**10***a*	**11***c*	**12**	**13**	**16***a*	**16***b*	**18***b*	**20**	**23**	**24**	**25***a*	**28***b*
1	34.8	34.4	36.2	35.7	37.8	36.1	39.5	40.0	29.6	29.4	40.4	35.6	36.1	39.9	36.2	36.9
2	19.2	18.6	18.9	19.0	18.7	19.5	19.7	20.7	18.3	18.2	20.8	18.1	18.1	17.1	19.1	18.5
3	32.9	33.1	35.2	34.5	36.7	41.5	43.4	43.5	36.7	37.5	38.5	43.1	33.4	37.9	29.7	41.9
4	46.5	46.8	46.8	46.2	47.6	34.6	32.7	35.3	36.7	37.5	44.3	31.5	41.6	41.9	47.0	33.0
5	40.0	40.2	41.1	41.0	44.5	44.4	130.7	52.0	142.4	142.2	53.7	48.7	51.4	55.0	51.1	50.7
6	34.1	33.5	33.5	33.1	36.5	33.1	34.2	41.5	143.9	144.0	22.2	73.0	20.0	20.3	124.8	26.8
7	175.0	173.9	173.9	179.6	197.5	181.0	200.1	204.2	180.1	181.0	31.8	132.8	33.4	34.3	127.5	136.2
8	128.6	134.9	119.5	119.6	128.3	128.3	130.5	130.9	124.0	125.0	126.7	143.8	145.1	69.4	127.3	144.1
9	131.0	148.8	141.6	141.7	145.5	134.4	127.6	127.2	145.6	144.0	147.2	123.2	146.9	169.0	147.4	127.5
10	41.3	42.3	42.2	42.2	40.2	42.7	131.6	73.2	41.4	42.4	39.1	43.1	38.1	41.9	41.2	38.9
11	155.4	181.3	153.1	153.1	151.5	158.8	158.6	158.6	151.0	150.8	112.5	144.4	181.5	122.1	109.7	140.7
12	115.9	180.6	151.5	151.5	156.8	111.0	110.0	110.0	156.1	155.5	153.4	191.9	180.5	187.5	167.1	181.6
13	148.5	147.8	139.0	139.0	141.7	148.5	154.8	155.0	143.4	144.3	133.0	132.9	147.9	142.2	131.1	131.9
14	118.0	133.0	123.4	123.4	121.5	118.1	119.0	119.0	118.0	119.8	127.3	136.0	137.9	145.5	125.0	148.9
15	33.4	27.4	26.9	26.9	27.1	33.7	34.6	34.5	27.2	27.3	26.9	26.4	26.9	25.7	26.9	26.0
16	23.9	21.5	23.5	23.5	23.4	23.9	23.8	23.7	23.6	23.6	23.0	21.4	21.4	21.8	22.7	21.5
17	23.9	21.5	23.5	23.5	23.1	23.9	23.8	23.7	23.3	23.3	23.0	21.4	21.4	21.8	22.7	21.9
18	21.7	178.2	178.5	178.5	178.1	33.7	28.2	32.7	31.8	31.7	32.0	32.3	33.8	33.5	33.1	33.4
19	178.5	21.5	20.2	20.2	16.7	21.4	28.2	22.8	28.1	29.4	179.4	181.9	21.7	21.4	20.3	22.2
20	23.9	23.9	23.5	23.9	20.4	22.8	20.6	21.6	29.9	29.4	23.7	21.8	18.9	18.7	37.9	19.0
Other	51.7	52.2	51.7	51.4	52.2	55.1	55.5	55.6	59.9	59.6						
	51.6	51.8	51.1	59.6	60.0				60.3	59.9						
			59.6	59.9	60.2					60.3						
			60.0													

[a]In ppm from TMS.

(s, arom. H at C.14); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 388 (M^+, 100%), 373, 358, 329, and 313. *Anal.* calcd. for $C_{23}H_{32}O_5$: C 70.33, H 8.08; found: C 70.10, H 8.30.

Formation of the lactone ***10****a*

At room temperature the ketone ***8a*** (240 mg) in *tert*-butanol (20 mL) was added to the solution resulting from dissolving potassium (1.5 g) in *tert*-butanol (40 mL). Oxygen was bubbled through the solution for 4 h, the reaction mixture was then acidified with 10% hydrochloric acid, and the product obtained by ether extraction. The ester **9** and the lactone ***10a*** are both present at this stage (tlc and spectra) in the ratio 3:7 but during the silica gel chromatography (benzene–EtOAc 9:1) the former disappears and only lactone ***10a*** was isolated (165 mg; 72%) as a white solid, mp 182–183°C: uv λ(EtOH): 251 (9600), 269 (11 600), and 306 (10 000) nm; ir (KBr): 1810 (lactone), 1680, 1660, and 1600 cm^{-1}; ^{1}H nmr δ: 1.27 and 1.29 (2d, total 6H, J = 7 Hz, nonequivalent iso-Pr Me), 1.67 and 1.69 (2s, C-Me at C.4 and C.10), 3.35 (sept, J = 7 Hz, iso-Pr CH), 3.89 and 3.95 (2s, Ar-OMe), 8.03 (s, arom. H at C.14); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 370 (M^+), 342 (100%), and 327. *Anal.* calcd. for $C_{22}H_{26}O_5$: C 71.33, H 7.08; found: C 71.50, H 7.12.

Demethylation of ***10****a to give* ***10****b*

A solution of boron tribromide (0.4 mL) in dichloromethane (1.0 mL) was added very slowly (during 3 h), with stirring, to the lactone ***10a*** (20 mg) in dichloromethane (2 mL) at room temperature. After 11 h, the solvent was removed by evaporation, the residue taken up in water, and ether extracted. Chromatography (silica gel; hexane – ethyl acetate 6:4) gave some starting material (3 mg) and then the catechol ***10b*** (14 mg; 76%), mp 268–270°C (yellow crystals); uv: 262 (9400), 340 (2700), and 424 (3600) nm; ir (KBr): 3470, 3420, 1800, 1670, 1645, and 1610 cm^{-1}; ^{1}H nmr δ: 1.25 (d, J = 7 Hz, iso-Pr Me), 1.59 and 1.67 (2s, C-Me), 3.1 (m, iso-Pr CH), 6.6 (br, 2H, D_2O), and 7.84 (s, arom. H); (in acetone-d_6: 1.26, 1.66, 1.78, 3.3, and 7.82); mass spectrum, *m/z*: 342 (M^+), 314, 299, 298, and 286 (100%). *Exact Mass* (hrms) calcd. for $C_{20}H_{22}O_5$: 342.1467; found: 342.1466.

Preparation of the acid ***11****c*

The phenol ester ***11a*** (described earlier (*1c*), 0.86 g), dimethyl sulfate (8.4 g), and anhydrous potassium carbonate (9.0 g) were refluxed in acetone (100 mL) for 20 h. Water was added to destroy excess dimethyl sulfate and most of the acetone was then evaporated before extracting the solution with ether. Chromatography (silica gel; hexane – ethyl acetate 9:1) afforded the methoxy ester ***11b*** (0.71 g; 80%); ir: 1740 cm^{-1}; ^{1}H nmr δ: 3.20 ($COOCH_3$) and 3.89 (Ar-OCH_3); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 346 (M^+), 315, 303, and 117 (100%), which was hydrolysed without further purification.

To the methoxy ester ***11b*** (2.44 g) in methanol (85 mL) was added sodium hydroxide (85 mL, 10% aqueous) and the mixture was refluxed for 20 h. Most of the methanol was evaporated and the product obtained by ether extraction. Chromatography (silica gel; hexane – ethyl acetate 4:1) gave the acid ***11c*** as a low-melting solid (1.78 g; 79%), mp 46–50°C; ir: 3200–2500 (acid), 1710, and 1610 cm^{-1}; ^{1}H nmr δ: 0.89, 0.97 and 1.31 (3s, Me-C), 1.20 (d, J = 7 Hz, iso-Pr Me), 1.89 (dd, J = 16 and 5 Hz, -C*H*—CO), 2.17 (dd, J = 16 and 6 Hz, CH—CO), 2.70 (sept, J = 7 Hz, iso-Pr CH), 3.50 (dd, J = 6 and 5 Hz, C.5-H), 3.84 (s, Ar, OMe), 6.7 and 7.16 (arom. H), 11.4 (bs, COO*H*, D_2O); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 332 (M^+, 100%), 317, and 289. *Anal.* calcd. for $C_{21}H_{32}O_3$: C 75.86, H 9.70; found: C 75.95, H 9.94.

ipso *Cyclization of acid* ***11****c*

The methoxy acid (308 mg) was stirred in trifluoroacetic anhydride (4 mL) at room temperature for 6 h. The mixture was decomposed with ice-water and the product obtained by ether extraction and well washed with aqueous potassium hydroxide. Chromatography (silica gel; hexane – ethyl acetate 4:1) afforded two products:

Nonconjugated enone ***12*** (162 mg; 56%); uv λ_{max}: 253 (10 000) and 304 (5200) nm; ir (film): 1680 and 1600 cm^{-1}; ^{1}H nmr δ: 0.91 and 1.49 (2s, Me-C), 1.23 (d, J = 7 Hz, iso-Pr Me), 2.85 (sept, iso-Pr CH), 3.64 (s, 2H, C═C—CH_2—C═O), 3.83 (s, Ar, OMe), 6.88, 6.94 (m), and 7.61 (d, J = 8 Hz, arom. H); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 314 (M^+), 299, 287, 272 and 177 (100). *Exact Mass* (hrms) calcd. for $C_{21}H_{30}O_2$: 314.2246; found: 314.2244.

Tertiary alcohol ***13*** (44 mg; 14%); uv λ_{max}: 253 (14 700) and 302 (6000) nmr; ir: 3460, 1670, and 1600 cm^{-1}; ^{1}H nmr δ: 0.86 (6H), 1.14 (2s, 3 × Me-C), 1.24 (d, J = 7 Hz, iso-Pr Me), 2.12 (dd, J = 6 and 5 Hz, C.5-H), 2.24 (s, OH, D_2O), 2.86 (sept, J = 7 Hz, iso-Pr CH), 3.83 (s, Ar-OMe), 6.84, 6.92 (m), and 7.59 (d, J = 8 Hz) (3 × arom. H); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 332 (M^+), 317, 314, 299, 289, and 177 (100). *Anal.* calcd. for $C_{21}H_{32}O_3$: C 75.86, H 9.70; found: C 76.02, H 9.89.

NOTE: When the alcohol **13** (91 mg) was refluxed in methanol (20 mL) containing hydrochloric acid (5 mL, 50%) for 5 h, the product was the tetraene **12** (83 mg; after chromatography: 96%).

Oxygenation of the ketone ***15*** *(→ diosphenol* ***16****a)*

Potassium (2.0 g) was dissolved in *tert*-butanol (50 mL) and stirred for 12 h. The ketone **15** (290 mg) dissolved in *tert*-butanol (25 mL) was then added at room temperature and oxygen was bubbled through the solution for 2 h. The mixture was then acidified with dilute hydrochloric acid (5%) and the weak acid product was extracted into ether and finally crystallized from hexane, affording the diosphenol ***16a*** (253 mg; 84%), mp 115–117°C (colorless plates, hexane); uv λ_{max}: 243 (8000), 279 (9600), and 322 (10 500) nm; ir: 3370, 3340, 1640, 1625, and 1585 cm^{-1}; ^{1}H nmr δ: 1.25, 1.29 (two d, J = 7 Hz, iso-Pr Me), 1.48 (6H) and 1.66 (3s, Me-C at C.4 and C.10 respectively), 3.33 (sept, J = 7 Hz, iso-Pr CH), 3.87, 3.94 (2s, Ar-OMe), 7.14 (s, enol OH, D_2O), 7.92 (s, arom. H); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 358 (M^+), 343, 330, 327, 315, and 273 (100). *Anal.* calcd. for $C_{22}H_{30}O_4$: C 73.71, H 8.44; found: C 73.75, H 8.31.

Methylation of the diosphenol ***16****a (→* ***16****b)*

The diosphenol (159 mg) was dissolved in ethanol (10 mL) and water (10 mL), and aqueous sodium hydroxide (8.0 mL of 30%) was added, followed by dimethyl sulfate (4.0 mL, dropwise). The mixture was stirred for 21 h and then more sodium hydroxide (4 mL of 30%) and dimethyl sulfate (2.0 mL) were added. After 26 h the solution was diluted with water and the product obtained by ether extraction. Chromatography (silica gel; hexane – ethyl acetate 19:1) gave some starting material (29 mg; 18%) and then the methylated product ***16b*** (89 mg; 54%), mp 104–106°C (from hexane): uv λ_{max}: 243 (20 000), 274 (30 000), and 299 (27 000) nm; ir: 1650 and 1600 cm^{-1}; ^{1}H nmr δ: 1.23, 1.26 (two d, J = 7 Hz, iso-Pr Me), 1.43 (6H) and 1.65 (2s, 3 × Me-C), 3.30 (sept, iso-Pr CH), 3.85 (6H) and 3.92 (2s, 3 × OMe), 7.92 (s, arom. H); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 372 (M^+), 357, 341, 329, and 287 (100). *Anal.* calcd. for $C_{23}H_{32}O_4$: C 74.16, H 8.66; found: C 74.01, H 8.76.

Hydrogenation of the methylated enol ***16****b (→* ***17****)*

The methylated product ***16b*** (22 mg) in methanol (15 mL) was introduced into a hydrogenation apparatus containing prehydrogenated 10% palladium on carbon (25 mg) in methanol (10 mL). After stirring under hydrogen for 12 h, the catalyst was filtered off, and the solution diluted with water and extracted with ether. After chromatography (silica gel; carbon tetrachloride – ethyl acetate 9:1) the colorless solid **17** was crystallized from hexane, mp 92–95°C (19.5 mg; 88%); ir: 3620, 3380, and 1615 cm^{-1}; ^{1}H nmr δ: 1.03, 1.17, and 1.60 (3s, C-Me), 1.21 (d, J = 7 Hz, iso-Pr Me), 2.28 (d, J = 12 Hz, C.5-H), 3.24 (sept, J = 7 Hz, iso-Pr CH), 3.58 (s, OMe at C.6), 3.74, 3.82 (2s, Ar-OMe), 3.98 (d, J = 5 Hz, C*H*OH), 4.56 (dd, J = 12 and 5 Hz, C*H*-OMe), 7.30 (s, arom. H); mass spectrum, *m/z*: 376 (M^+, 100), 361, 358, and 343. *Anal.* calcd. for $C_{23}H_{36}O_4$: C 73.36, H 9.64; found: C 73.11, H 9.64.

Taxodione ***1*** (demethylation and oxidation of **17**)

To the trimethoxy derivative **17** (27 mg) in dry dichloromethane (5 mL) cooled to 0°C was added boron tribromide (0.5 mL of 1 *M* solution in dichloromethane). After 2 h, more boron tribromide solution (0.5 mL) was added and the reaction stirred for 12 h at room temperature. The reaction mixture was poured into ice-water and extracted with ether that was well washed with saturated sodium

bicarbonate solution. The crude oily orange product (26 mg) was slowly chromatographed over silica gel in carbon tetrachloride, twice, affording a fraction of pure taxodione (3.0 mg; 13%); ir: 3320, 1675, 1640, 1628, 1618, and 1600 cm^{-1}; mass spectrum, *m/z*: 314 (M^+), 299, 286, 271, and 149 (100). *Exact Mass* (hrms) calcd. for $C_{20}H_{26}O_3$: 314.1882; found: 314.1875.

Comparison of the product with an authentic sample obtained from Prof. Takashi Matsumoto (Hiroshima University) showed the two to be identical (ir, tlc; two solvent systems).

Synthesis of lactone ***20*** *(via o-quinone* ***19****)*

The methyl *O*-methyl-13-isopropylpodocarpate **18***a* (323 mg, prepared as described previously (1*a*) was dissolved in methylene chloride (20 mL) and, at −10°C and under nitrogen, boron tribromide (5 mL) in methylene chloride (10 mL) was rapidly added. After stirring for 1 h, water was added and the volatile solvent removed *in vacuo*. Ether extraction gave a brownish oil from which chromatography (silica gel; ethyl acetate) gave the substituted podocarpic acid **18***b* (256 mg; 83%), mp 252°C (colorless needles); ir: 3600–2400 (very br), 1690, 1600, 1575, and 1500 cm^{-1}; ^1H nmr, acetone-d_6, δ: 1.12 and 1.30 (2s, 2 × Me-C), 1.21 (d, *J* = 7 Hz, iso-Pr Me), 3.23 (sept, *J* = 7 Hz, iso-Pr CH), 6.81 and 6.86 (2s, arom. H at C.11 and C.14); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 316 (84, M^+), 301 (54), 255 (73), 213 (100), 199 (23), 185 (22), 171 (39), 157 (59), and 147 (55). *Anal.* calcd. for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 75.79, H 9.02.

Phenyl seleninic anhydride (466 mg) was suspended in anhydrous THF (50 mL) and warmed to 50°C. The phenol **18***b* (200 mg) in anhydrous THF (20 mL) was added drop by drop and stirring was continued for 2 h. The reaction mixture was diluted with chloroform (200 mL) and the solution washed many times with aqueous sodium bicarbonate and then with brine. The organic phase gave a red oil, which was chromatographed rapidly over silica gel to give the unstable red *o*-quinone **19** (182 mg; 87%); ^1H nmr δ: 1.12 and 1.19 (2d, 6H, *J* = 7 Hz, iso-Pr Me), 1.17 and 1.32 (2s, Me-C), 2.29 (m, iso-Pr CH), 6.46 (s, C.14-H).

The *o*-quinone **19** (182 mg) was adsorbed on a small quantity of silica gel by evaporation, introduced at the top of a silica gel column, and, very slowly, the product was eluted with carbon tetrachloride. The color changed from red to orange to dark yellow. This slow chromatography was repeated a second time and gave the lactone **20** (105 mg; 58%), mp 100–104°C (yellow needles, ethanol–water); uv: 268 (13 000), 311 (26 500), and 378 (2900) nm; ir: 3340, 1765 (lactone), 1645, 1625, and 1615 cm^{-1}; ^1H nmr δ: 1.16 and 1.18 (2d, 6H, *J* = 7 Hz, iso-Pr Me), 1.22 and 1.38 (2s, Me-C), 2.13 (d, *J* = 5 Hz, C.5-H), 3.08 (sept, *J* = 7 Hz, iso-Pr CH), 5.19 (dd, *J* = 5 and 5 Hz, C.6-H), 6.61 (d, *J* = 5 Hz, C.7-H), 6.92 (s, C.14-H), and 7.22 (s, OH, D_2O); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 328 (29, M^+), 300 (49), 285 (51), 272 (35), 257 (93), 229 (38), and 218 (100). *Anal.* calcd. for $C_{20}H_{24}O_4$: C 73.14, H 7.37; found: C 73.21, H 7.70.

Oxidation of ferriginol ***22*** *to o-quinone* ***23***

Ferruginol (300 mg) in anhydrous THF (20 mL) was oxidized by adding to a suspension of phenyl seleninic anhydride (760 mg) in THF (40 mL) warmed to 50°C as described above. Chromatography over silica gel afforded first the *o*-quinone **23** (127 mg; 40%), mp 143–144°C (dark red needles from hexane); uv: 264 (6100) and 424 (1750) nm; ir: 1670 and 1655 cm^{-1}; ^1H nmr δ: 0.90 and 0.94 (2s, *gem* Me), 1.11 (d, *J* = 7 Hz, iso-Pr Me), 1.24 (s, Me-C.10), 2.83 (sept, *J* = 7 Hz, iso-Pr CH), 6.42 (s, olefinic H); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 302 (8, *M* + 2), 300 (11, M^+), 258 (8), 257 (25), 231 (31), 229 (44), 217 (43), and 204 (65). *Anal.* calcd. for $C_{20}H_{20}O_2$: C 79.95, H 9.39; found: C 80.12, H 9.52.

A second fraction from the column contained the quinol **24** (40 mg; 13%), mp 177–179°C (lit. (2*c*) mp 181–182°C); ^{13}C nmr, see Table 1.

Dehydration of the quinol ***24***

The quinol (90 mg) was gently refluxed in methanol (50 mL) containing concentrated hydrochloric acid (1 mL) for 3 h. Dilution with water, removal of most of the methanol by evaporation, and then ether extraction afforded some starting material (10 mg) and then the olefin **25***a* (42 mg; oil, 50%, identical with the product obtained by boron tribromide demethylation of the known methyl ether); ir: 3600, 3385, 3030, 1650, and 1610 cm^{-1}; uv: 278 (10 500) nm; ^1H nmr δ: 0.97 and 1.04 (2s, *gem* Me), 1.20 and 1.24 (2d, *J* = 7 Hz, iso-Pr Me), 1.27 (s, Me-C), 3.17 (m, iso-Pr CH), 5.88 (dd, *J* = 9 and 3 Hz, olefinic H at C.6), 6.60 (s, arom. H at C.11), 6.88 (dd, *J* = 9 and 3 Hz, olefinic H at C.7), and 6.91 (s, arom. H at C.14); ^{13}C nmr, see Table 1.

Formation of the ketone ***26***

Following the Défaye–Duchateau procedure (10), a solution of the olefin **25***a* (84 mg) in acetone (30 mL) was treated with osmic acid (50 mg) in carbon tetrachloride (5 mL). The mixture was protected from light with aluminium foil and stirring was continued at room temperature for 1.5 days. The solvents were then evaporated and the black residue taken up in methanol (30 mL) and reduced by adding excess sodium borohydride and stirring for 24 h. After dilution with water and acidification with concentrated hydrochloric acid, the crude product (mixture of *cis*-diols) was obtained by ether extraction. The residue was taken up in dry benzene (35 mL) containing *p*-toluenesulfonic acid (4 mg) and then refluxed for 2 h. Extraction and chromatography gave the ketone **26** (43 mg; 48% from the olefin **25***a*): ir (film): 3380, 1690, and 1620 cm^{-1}; ^1H nmr δ: 1.12 and 1.18 (2s, *gem* Me), 1.28 (d, *J* = 7 Hz, iso-Pr Me), 1.34 (s, Me-C), 2.43 (s, C.5-H), 3.22 (m, iso-Pr CH), 3.61 (s, 2H, C.7-H), 5.08 (s, OH, D_2O), 6.81 and 6.92 (2s, arom. H); mass spectrum, *m/z*: 300 (100, M^+), 285 (92), 257 (36), 240 (63), 217 (22), 215 (36), and 201 (63).

NOTE: Attempts to oxidize this phenolic ketone **26** and the preceding olefin **25***a* with phenyl seleninic anhydride led to the complete destruction of the substrates.

Reduction and methylation of the o-quinone ***23***

The *o*-quinone **23** (59 mg) in methanol (50 mL) was introduced into an atmospheric hydrogenation apparatus containing prehydrogenated palladium on charcoal (20%, 50 mg) suspended in methanol (25 mL). Agitation under hydrogen rapidly changed the solution from red to colorless and then, without opening to the air, sodium hydroxide (2 mL of 30%) was added, followed by dimethyl sulfate (1 mL). The addition of base and dimethyl sulfate was repeated every half hour (total 8 mL and 4 mL respectively). After 24 h the reaction mixture was filtered, diluted with water, concentrated, and extracted with ether. Chromatography gave two products, first the *dimethoxy compound* **27***a* (15 mg; 23%); ir: 1615, 1570, and 1500 cm^{-1}; ^1H nmr δ: 0.95 (s, 6H, *gem* Me), 1.15 (d, *J* = 7 Hz, iso-Pr Me), 1.30 (s, Me-C), 3.75 and 3.80 (2s, O-Me), 6.68 (s, arom. H); mass spectrum: 330 (M^+). These properties are identical with those given by Mori and Matsui (2*a*).

The second fraction was the *monomethylated compound* **27***b* (28 mg; 45%); ir: 3500, 1615, and 1495 cm^{-1}: ^1H nmr δ: 0.97 (s, 6H, *gem* Me), 1.18 (d, *J* = 7 Hz, iso-Pr Me), 1.30 (s, Me-C), 3.75 (s, O-Me), 5.83 (s, OH, D_2O), 6.33 (s, arom. H); mass spectrum: 316 (M^+).

Methylation of **27***b* (NaOH, dimethyl sulfate) afforded **27***a*.

Formation of taxodione by slow chromatography

The *o*-quinone **23** (35 mg) was adsorbed by evaporation of the solvent onto a small quantity of silica gel and then introduced to the top of a conventional column of silica gel and slowly eluted with carbon tetrachloride. Evaporation of the eluate afforded a yellow oil, **28***b* (24 mg; 69%) uv:316 (7000) and 370 (1600) nm; ir (film): 3300, 1650, 1620, 1610, and 1560 cm^{-1}; ^1H nmr δ: 0.92 and 0.97 (s, 6H, *gem* Me), 1.13 and 1.14 (2d, 6H, *J* = 7 Hz, iso-Pr Me), 1.18 (s, Me-C), 3.07 (m, iso-Pr CH), 6.81 (m, 2H, C.7-H and C.14-H), and 7.48 (s, OH, D_2O); ^{13}C nmr, see Table 1; mass spectrum, *m/z*: 300 (35, M^+), 232 (35), 231 (50), 229 (70), 218 (45), 215 (40), and 204 (90).

When either the *o*-quinone **23** or the mono-enolized form **28***b* was subjected to repeated, slow chromatography (as described above), taxodione (identical with that described above) was formed in yields up to 15%. Attempts to accelerate this process by bubbling air through a solution of the *o*-quinone for 2 days produced no permanent change. Although the uv–vis spectrum of the solution showed an intense peak

at 311 nm, upon evaporation of the methanol only the *o*-quinone chromophore was evident. Bubbling oxygen through a methanol solution of the *o*-quinone led to its complete and rapid decomposition.

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