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APPROACHES TO THE SYNTHESIS OF AROMATIC DITERPENES OXYGENATED IN RING A: SYNTHESIS OF MARGOCILIN *O*-METHYL ETHER

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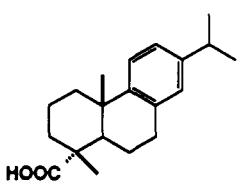
ABSTRACT.—Two approaches for the synthesis of ring-A-oxygenated diterpenes are described. Several routes from natural podocarpic acid aimed at the synthesis of coleon E afforded a wide range of potentially useful chiral derivatives, but the other scheme, which involved a cascade-type cyclization, led to the synthesis of the *O*-methyl ether of (±)-margocilin [**33c**] (recently isolated from *Azadirachta indica*).

The number of simple and complex diterpenes isolated from nature is increasing rapidly as methods of separation and structure elucidation lend themselves to detection of smaller and smaller quantities. Most of the structures of these natural products are proposed from spectroscopic evidence alone, but experience has shown that such assignments are not infallible. Obviously knowledge concerning the occurrence of secondary metabolites is only useful phytochemically if the structures are rigorously proven and, apart from X-ray analysis, the only sure confirmation is still unambiguous synthesis. Ideally, well-known natural substances such as dehydroabietic acid [**1**] and podocarpic acid [**2a**] are the most appropriate starting materials for such syntheses since they lead not only to functionally correct molecules but also to the enantiomerically proper structures. The publications of Cambie (1,2) have shown the versatility of these natural chirons, and Matsumoto and co-workers (3,4) have ably exploited their availability in many of their syntheses.



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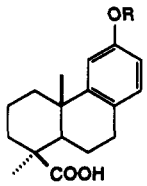
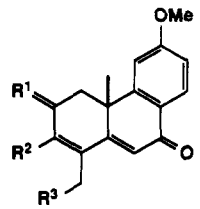


2a R=H
2b R=Me



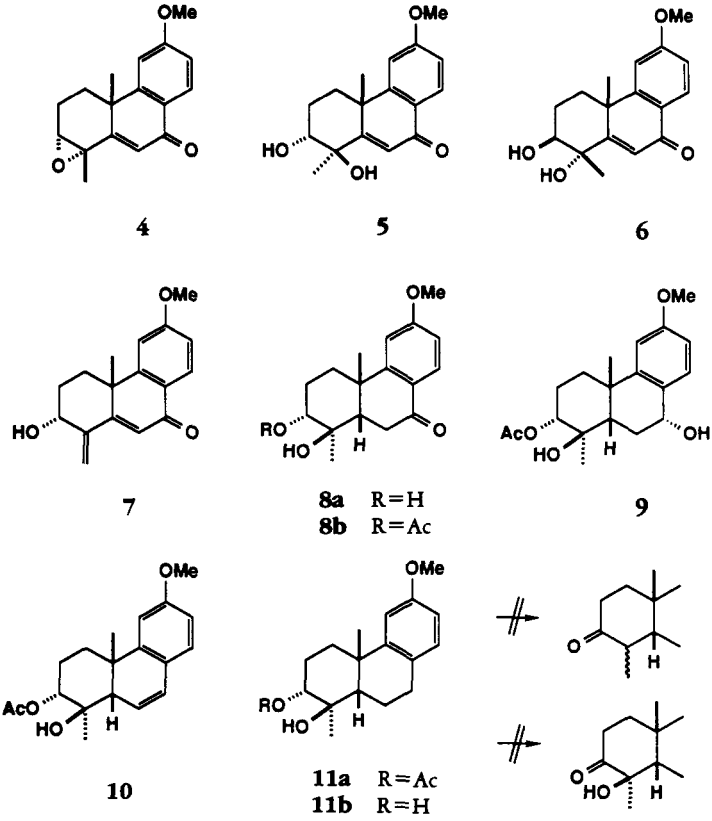
3a $R^1=R^2=R^3=H$
3b $R^1=R^2=H$, $R^3=AcO$
3c $R^1=O$, $R^2=R^3=H$
3d $R^1=O$, $R^2=Br$, $R^3=H$

Following our syntheses of coleon B (5) as the tri-*O*-methyl ether and taxodione (6), it seemed logical to turn our attention to coleon E (7), which appears to contain a hybrid of the two chromophores. As in previous studies, it was felt that either **1** or **2a** would be admirable starting materials since both of them are chiral, commercially available, and inexpensive. However, faced with long and relatively unrewarding sequences, it was found more practical to synthesize a margocillin derivative **33b** in a racemic manner from a simple aromatic precursor and geranyl bromide.

RESULTS AND DISCUSSION

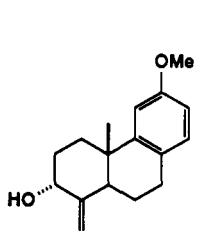
The final products in the coleon B synthesis were chemically interesting but had only been obtained in modest yield, and since these same reactions could also be the final steps in the preparation of coleon E, the efficiency of a variety of reagents was com-

pared to effect the allylic oxidation at C-2 in the conjugated dienone **3a** [easily prepared from **2a** (3)]. The diene-dione **3c** was not readily obtained, and conditions from the literature gave mediocre results. For instance, dichromate in aqueous HOAc (8) gave only 18% (with about a 35% recovery of the starting material), and SeO_2 in HOAc led mostly to the introduction of an acetoxyl at the methyl group on the double bond (**3b**, 41%). The Thomson procedure (9) using wet NBS was the best found, but the highest yield of **3c** was just 52% with another 16% of the 3-bromo derivative **3d**. It was striking that the Nakayama conditions (10) (CrO_3, Ac_2O, HOAc) gave no diene-dione at all but rather resulted in the epoxidation of the remote double bond to form **4**. While it was not the original intention, we decided that due to the diversity of functions, this compound was worth investigating as a useful synthon, especially when it was found that treating the dienone **3a** with *m*-CPBA gave **4** in excellent yield (86%) with just a small amount of the β-epoxide (7%).



Hydrolysis of the epoxide **4** afforded mostly the trans-diol **5** (73%), a minor amount of the other trans-diol **6** (5%), and the hydroxydienone **7** (9%). These last products were unstable, so methods were sought to reduce the number of functions present thus rendering them easier to manipulate. Catalytic hydrogenation of **5** afforded the dihydro derivative **8a** (84%) in which the ring junction is cis, but it contained just enough of the A/B trans isomer (8%) to be troublesome. To remove the remaining function in the B ring the secondary alcohol was first acetylated to give **8b** and then the carbonyl was reduced to give the 7α-HO compound **9**. Dehydration to **10** (95%) and hydrogenation afforded **11a**. After hydrolysis, however, no satisfactory conditions could be found to transform the diol **11b** into a C-3 ketone, with or without the C-4 hydroxyl. For the experimental details for compounds **3** to **11**, see Côté (13).

While seeking an "entry" into podocarpic acid, the known oxidative decarboxylation of the acid in the presence of lead tetracetate (11,12) was re-investigated. Several previous studies described the same olefinic products but in varying proportions. The literature suggested (11,12) and we confirmed that only the tertiary acetate **16a** was easily isolated from the mixture of products (**13**, **14**, **15**, and **16a** mostly) and the remaining positionally isomeric olefins were best separated after treatment with a peracid. Cambie used monoperoxyphthalic acid over several days (12), but only 2 h was required when *m*-CPBA was used for the reaction. Cc allowed the recovery of the least reactive exocyclic olefin **13** unchanged (27%), followed in order by the 4,5-epoxide **18** (22%) and the 3,4-isomer **17** (27%). Subsequently the olefin **13** was subjected to oxidation by SeO_2, and the allylic alcohol **12** was isolated in 68% yield. We found (13) that it was possible to achieve a useful yield (<10%) of this interesting chiron **12** starting from the inexpensive technical "Rimu resin" reagent. The same sequence applied to dehydroabietic acid [**1**] had afforded the analogous synthon in about 20% yield.



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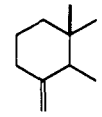

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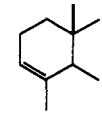

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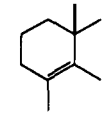

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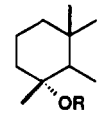
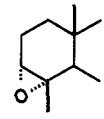


16a R=Ac
16b R=H



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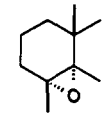

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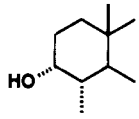

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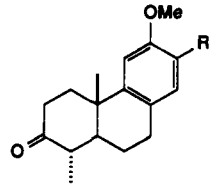
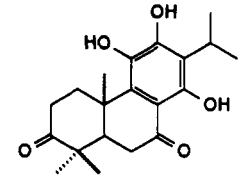


20a R=H
20b R=iPr

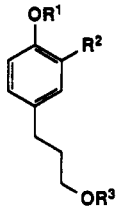


34

Another useful motif for further synthetic development would be the ketone **20a**, which could be prepared from the unsaturated alcohol **12** and also from epoxide **17** as follows. Reduction of epoxide **17** to the secondary alcohol **19** with $LiAlH_4$ in THF was slow (4 days), but in dioxane the yield was similar (60%) after only 15 h. The product contained some of the tertiary alcohol **16b**, which was difficult to remove, but after oxidizing the mixture, the ketone **20a** was easily isolated. Incidentally, Super-hydride® was the most efficient reagent to reduce the epoxide **17**, but it gave exclusively the tertiary alcohol **16b** (86% after 3 h).

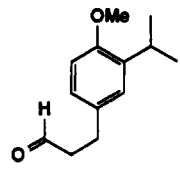
Accumulating a sufficient quantity of this chiral ketone **20a** from the natural material was long and tedious. Inspired by Snider's total synthesis of (±)-podocarpic acid (14) by radical cyclization, we decided to prepare the racemic isopropyl analogue **20b** by total synthesis. Compound **20b** could be a critical model or intermediate in the synthesis of candelabrone [**34**], a diterpenoid diketone recently isolated from *Salvia candelabrum* (15). Some of our results involving cationic cascade cyclizations have already been published (16).

The available starting material was *p*-methoxyphenylpropanol [**21a**], and the first task was to introduce the isopropyl substituent. Friedel-Crafts acylation gave the acetyl derivative **21c** which had of course been acetylated and also partially demethylated (**21d**). Re-methylation was followed by a Grignard reaction which afforded the diol **21e**. Refluxing in glacial HOAc not only dehydrated the tertiary alcohol but also acetylated the primary alcohol in the other sidechain (**21g**), and then catalytic hydrogenation and hydrolysis gave the 4-methoxy-3-isopropylphenylpropanol [**21i**].



	R^1	R^2	R^3
21a	Me	H	H
21b	H	H	CH_2Ph
21c	Me	Ac	Ac
21d	H	Ac	Ac
21e	Me	$C(OH)Me_2$	H
21f	Me	$C(OH)Me_2$	Ac
21g	Me	$C(Me)=CH_2$	Ac
21h	Me	$C(Me)=CH_2$	H
21i	Me	iPr	H

Next the propanol side chain was extended. Oxidation with PCC gave the aldehyde **22**, which reacted with triethyl 2-phosphonopropionate under Horner-Emmons conditions to the necessary *E* isomer of the unsaturated ester **23a** (64%) accompanied by some of the *Z* olefin (8%). Reduction with DIBALH led to the primary alcohol **23b**, which gave an 85% yield of the bromide **23c** on treating with $POBr_3$ in THF. The unsaturated bromide was used as soon as pure since it was susceptible to allylic rearrangement to the isomer with the terminal double bond. It reacted readily with the bis-anion of ethyl 2-methylacetoacetate following Weiler's general method (17), affording the keto-ester **24** (64%). Radically initiated cyclization [$Mn(OAc)_3 \cdot 2H_2O$ in HOAc] gave the racemic tricyclic compound **25a** in which the A/B ring junction is trans and the C-4 ester moiety cis to the angular methyl.



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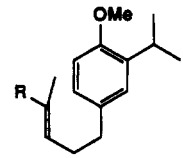
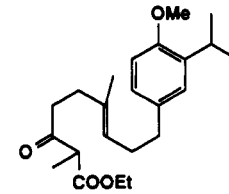


23a R=COOEt
23b R=CH_2OH
23c R=CH_2Br



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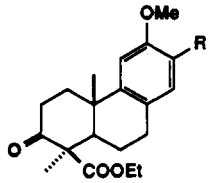
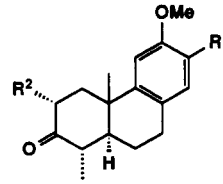
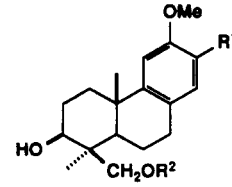


25a R=iPr
25b R=H



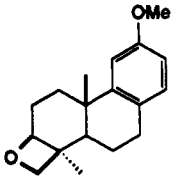
26a R^1=iPr, R^2=H
26b R^1=H, R^2=H
26c R^1=iPr, R^2=Me
26d R^1=H, R^2=Me



27a R^1=iPr, R^2=H
27b R^1=H, R^2=H
27c R^1=iPr, R^2=Ts
27d R^1=H, R^2=Ts

The crux of the approach to candelabrone [**34**] (15) with a carbonyl group at C-3, parsiflorines D, F, and G (18) with acyloxy residues at C-2, or shonanol (19) with a carbonyl group at C-1 was to establish first the *gem*-dimethyl system, because with a quarternary carbon at C-4 preventing reaction in that direction, modification in the A ring would be easy. The first approach was to replace the ester group by a methyl. The β-keto-ester **25a** was deethoxycarbonylated by refluxing with LiI in collidine, thus completing our preparation of ketone **26a** (racemic **20b**). Unfortunately this ketone adamantly refused to be methylated at C-4, always preferring to form the 2-methyl derivative **26d**. For further experimentation the less expensive models **25b** and **26b** (no isopropyl residue at C-13) were also prepared, but despite numerous attempts, alkylation conditions (equilibrating or non-equilibrating) gave no trace of the *gem*-dimethyl compound. It was concluded that the only solution to this impasse was to modify the ester moiety in **25a** (and **25b**) rather than eliminate it. To this end, the model ester **25b** was reduced ($LiAlH_4$, Et_2O), and the primary hydroxyl in the resulting diol **27b** was tosylated to give **27d**. The tosyloxy residue was removed following Fujimoto's method (20) with NaI and Zn in HMPA, but the principal product was the 3,4-oxetano compound **28**. To prevent this undesirable cyclization it could be helpful to oxidize the tosyl derivative **27d** to the ketone **29b**, but when the latter was subjected to the same reduction conditions (LiI, Zn, HMPA), the only product was the cyclopropyl alcohol **30b**. However, refluxing **30b** in C_6H_6 with a trace of *p*-TsOH rearranged it to the C-3 ketone with the adjacent *gem*-dimethyl grouping **31b**.

Among the constituents isolated from *Azadirachta indica* reported recently by Ara *et al.* (21) is the previously unknown diterpene margocillin [**33c**]. The authors report the formation of the *O*-methyl derivative **33b**, and we have now synthesized this derivative. Using the procedures found successful in the model sequence **25b**→**31b**, the keto-ester **25a** was reduced to the diol **27a** which was selectively tosylated at the primary alcohol to **27c**. The remaining C-3 hydroxyl was oxidized to the ketone **29a** which again, on reduction with LiI and Zn, afforded a hydroxycyclopropyl intermediate **30a**. The latter was not isolated but immediately rearranged to the *gem*-dimethyl ketone **31a** by refluxing with TsOH in C_6H_6. The ketone **31a** was reduced to



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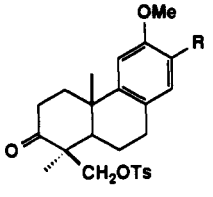
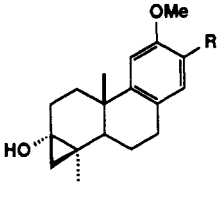
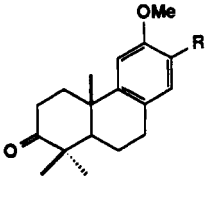


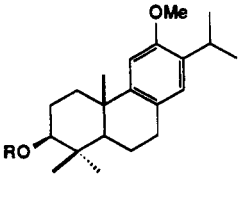
29a R=iPr
29b R=H



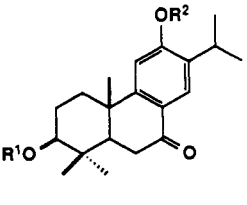
30a R=iPr
30b R=H



31a R=iPr
31b R=H



32a R=H
32b R=Ac



33a R^1=Ac, R^2=Me
33b R^1=H, R^2=Me
33c R^1=R^2=H

the alcohol **32a** and after protection as the acetate **32b**, the substance was oxidized (CrO_3, aqueous HOAc) to the C-7 ketone **33a**. Hydrolysis afforded the alcohol **33b**, (±)-margocillin *O*-methyl ether, identical with the natural product in all respects (except for optical properties of course).

The application of these findings to the total synthesis of candelabrone [**34**] and other members of this group of terpenes is currently under investigation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Unless otherwise stated, the conditions used to characterize the products were as follows: melting points, Electrothermal, uncorrected; uv spectra, EtOH solutions (ε in parentheses), Hewlett Packard 8450 A; ir spectra, CCl_4 solutions, Beckman 4250; 200 MHz ^1H and 50 MHz ^{13}C nmr $CDCl_3$ solutions (multiplicity, integrated peak areas, coupling constants in Hz and where necessary assignments in parentheses), "dis. D_2O" signifies that the peak in question disappeared on shaking the solution with a small volume of D_2O, Varian XL-200. The 300 MHz spectra are courtesy of Prof. D.J. Burnell, Memorial University, Newfoundland, and the 400 MHz results come from the Laboratorie régional de rmn à haut champ, Université de Montréal. The assignments result from COSY, HETCOR, and APT experiments which are not described in the text. Ms (Hewlett Packard 5992) and exact mass measurements were made at the Centre régional de spectrométrie de masse, Université de Montréal. Chromatography employed the use of Terochem Si gel (for flash chromatography) with the solvents determined by prior tlc using Whatman Al Sil G/UV precoated aluminium sheets. Reactions were normally carried out under N_2 or argon.

REACTION OF *O*-METHYL PODOCARPIC ACID WITH $Pb(OAc)_4$ AND SEPARATION OF THE OLEFIN MIXTURE.—Treatment of *O*-methyl podocarpic acid [**2b**] [prepared from methyl *O*-methyl podocarpate following the method of Cambie (11,12)] was dissolved in C_6H_6 (35 ml) and refluxed with lead tetracetate (8.40 g) for 3.5 h under N_2. The cooled mixture was filtered, diluted with Et_2O, and washed with dilute HCl. The yellow oil obtained by evaporation gave two fractions by flash chromatography. The first was a mixture (roughly 1:1:1) of the three olefins **13**, **14**, and **15** (1.71 g, 53%) and the other was the tertiary acetate **16a** (480 mg, 12%). The olefin mixture (1.45 g) in $CHCl_3$ (180 ml) was cooled to 0° and treated with *m*-CPBA (870 mg) during 2 h. The mixture was then washed repeatedly with saturated aqueous KI, saturated $NaHCO_3$, and brine. Evaporation gave a pale yellow oil which was flash chromatographed [hexane-EtOAc (80:1)] to afford the following: unchanged **13** (398 mg, 27%), mp 44–47° [after sublimation, lit. (22) 50–52°]; **18** (348 mg, 22%) mp 65–66° [lit. (2) 70–71°]; **17** (405 mg, 27%) mp 123–125° [Et_2O, lit. (2) 123–124°]. *Anal.* calcd for $C_{17}H_{22}O_2$: C 79.03, H 8.58; found C 79.17, H 8.93.

ALLYLIC OXIDATION OF THE EXOCYCLIC OLEFIN **13**.—Following the Matsumoto conditions (23), SeO_2 (48 mg) was added to a solution of the olefin **13** (150 mg) in 95% EtOH (10 ml), and the mixture was refluxed for 2 h. After evaporation the yellow oil was flash chromatographed [hexane-EtOAc (50:1)] to give 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraen-3α-ol [**12**] (110 mg, 68%): ir 3350, 1645, 1605, 1570, 1500 cm^{-1}; ^1H nmr δ 0.99 (s, Me-10), 1.56 (bs, OH-dis. D_2O), 2.76 (dd, J = 11.1 and 3.8 Hz, H-5), 2.90 (m, 2H, H_2-7), 3.78 (s, MeO), 4.37 (bs, H-3), 4.75 and 5.08 (2 bs, H_2C=C), 6.69 (dd, J = 8.6 and 1.2 Hz, H-13), 6.85 (d, J = 1.2 Hz, H-11), 7.14 (d, J = 8.6 Hz, H-14); ms *m/z* $[M]^+$ 258 (100), 225 (96), 173 (29). Exact mass calcd for $C_{17}H_{22}O_2$, 258.1620; found 258.1594.

FORMATION OF THE KETONE **20** FROM EPOXIDE **17**.—The epoxide **17** (127 mg) was reduced by refluxing with $LiAlH_4$ (40 mg) in dioxane (15 ml) during 15 h. H_2O was added, and the product **19** isolated by Et_2O extraction was oxidized with Jones reagent (1 ml) which gave the ketone **20a** (38 mg, 39%) by extraction and flash chromatography. The properties of this compound (as the racemate **26b**) are described later.

REDUCTION OF EPOXIDE **17** WITH SUPER-HYDRIDE®.—To the epoxide **17** (200 mg) in dry THF (8 ml) under argon was added 1.0 M lithium triethylborohydride in THF (5 ml). After 3 h at reflux, H_2O was added to the cooled mixture which was then saturated with K_2CO_3 and the product obtained by Et_2O extraction. Flash chromatography [hexane-EtOAc (4:1)] gave the tertiary alcohol **16b** (172 mg, 86%), mp 103–107° [lit. (24) 108–109°]: ^1H nmr δ 1.16 and 1.23 (2s, Me at C-10 and C-4), 2.85 (m, 2H, H_2-7), 3.78 (s, MeO), 6.67 (dd, J = 8.3 and 2.5 Hz, H-13), 6.80 (d, J = 2.5 Hz, H-11), 6.98 (d, J = 8.3 Hz, H-14); ms *m/z* $[M]^+$ 260 (82), 227 (73), 175 (100).

PREPARATION OF 3-ISOPROPYL-4-METHOXYPHENYLPROPANOL [**21i**].—*Friedel-Crafts acetylation.*—Commercial phenylpropanol **21a** (21.00 g) was purified by conversion to the *O*-benzyl ether (THF, NaH, $PhCH_2Br$), and the product **21b** was distilled in a Kügelrohr (ca. 130° at 0.6 Torr), affording the

pure ether (35.42 g, 95%): ^{1}H nmr δ 1.8–2.0 (2m, 2H, H-6), 2.68 (t, 2H, J = 7.3 Hz, H-7), 3.50 (t, 2H, J = 6.2 Hz, H-5), 3.80 (s, 3H, MeO), 4.52 (s, 2H, CH_2Ph), 6.83 (d, 2h, J = 8.8 Hz), 7.11 (d, 2H, 8.8 Hz, arom H), ca. 7.35 (br s, 5H, benzyl arom H). Exact mass calcd for $C_{17}H_{20}O_2$, 256.1463; found 256.1473.

$AlCl_4$ (39.08 g) was dissolved in CH_2Cl_2 (500 ml), and a solution of phenylpropanol benzyl ether **21b** (25.08 g) and acetyl chloride (23 g) in CH_2Cl_2 (125 ml) was added dropwise at room temperature. Stirring was continued for 26 h, and the mixture was then poured into dilute HCl (5%, 1 liter). The Et_2O extract was washed with dilute HCl, H_2O, and aqueous NaOH, and after drying and concentration the residue was chromatographed [petroleum ether-Et_2O (10:1)] to give the acetyl derivative **21c** (5.20 g, 21%), 3-acetyl-4-methoxyphenypropyl acetate: ir (neat) 1740, 1675, 815 cm^{-1}; ^{1}H nmr δ 1.90 (m, 2H, H-6), 2.04 (s, 3H, AcO), 2.59 (s, 3H, MeCOAr), 2.70 (m, 2H, H-7), 3.87 (s, 3H, MeO), 4.04 (t, 2H, J = 6.2 Hz, H-5), 6.88 (d, 1H, J = 8.4 Hz), 7.26 (dd, 1H, J = 8.4 and 2.2 Hz), 7.55 (d, 1H, J = 2.2 Hz); ms *m/z* [M]$^+$ 250 (12), 235 (15), 191 (5), 177 (8), 175 (100), 163 (24). Exact mass calcd for $C_{14}H_{18}O_4$, 250.1205; found 250.1206.

Acidification of the NaOH washings from above and extraction with Et_2O afforded the corresponding phenol **21d** (0.349 g, 40%), 4-hydroxy-3-acetylphenylpropyl acetate: ^{1}H nmr δ 1.90 (m, 2H), 2.03 (s, 3H), 2.59 (s, 3H), 2.70 (m, 2H), 4.08 (t, 2H, J = 6.6 Hz), 6.87 (d, 1H, J = 8.4 Hz), 7.27 (dd, 1H, J = 8.4 and 2.2 Hz), 12.09 (s, 1H, dis. D_2O); ms *m/z* [M]$^+$ 236 (14), 221 (2), 177 (8), 163 (6), 161 (100), 149 (44). Exact mass calcd for $C_{13}H_{16}O_4$, 236.1048; found 236.1016.

In a second experiment, the crude mixture of phenol and the *p*-methoxy derivative (0.919 g) from the Friedel-Crafts reaction was methylated by refluxing with MeI (5.3 ml) in Me_2CO (42 ml) in the presence of K_2CO_3 (8.75 g). This afforded **21c** (60%) after chromatography.

Grignard reaction to give the alcohols **21e** *and* **21f**.—To the cooled (5°) Grignard reagent prepared in Et_2O (300 ml) from Mg (8.38 g) and excess MeI (22.24 ml) was added the acetyl compound **21c** (14.38 g) in Et_2O (60 ml). After refluxing for 2 h, the cooled mixture was treated with saturated NH_4Cl solution, and the product obtained by Et_2O extraction was chromatographed to give a small quantity of the acetate **21f** (1.21 g, 8%) and then 3-(1-hydroxy-isopropyl)-4-methoxyphenylpropanol [**21e**] (11.85 g, 92%): ^{1}H nmr δ 1.58 (s, 6H, iPr Me), 1.80 (m, 2H), 2.40 (br s, 1H, dis. D_2O), 2.61 (t, 2H, J = 6.2 Hz), 3.60 (t, 2H, J = 6.6 Hz), 3.85 (s, 3H), 4.30 (br s, 1H, dis. D_2O, tert alcohol), 6.81 (d, J = 8.4 Hz), 7.03 (dd, 1H, J = 8.4 and 2.2 Hz) and 7.13 (d, 1H, J = 2.2 Hz); ms *m/z* [M]$^+$ 224 (14), 209 (100), 191 (21), 163 (78), 161 (10), 149 (31), 134 (10). Exact mass calcd for $C_{13}H_{20}O_3$, 224.1412; found 224.1419.

Dehydration to the isopropenyl derivative with acetylation.—The tert alcohol **21e** (12.502 g) was refluxed for 2.5 h in glacial HOAc (160 ml). The cooled solution was then poured very slowly into 5% aqueous MaOH (300 ml), and the product isolated by Et_2O extraction was 4-methoxy-3-isopropenylphenylpropyl acetate **21g** (12.97 g, 95%): ^{1}H nmr δ 1.90 (m, 2H), 2.06 (s, 3H, AcO), 2.12 (br s, 3H, MeC=C), 2.63 (t, 2H, J = 7.0 Hz), 3.81 (s, 3H), 4.09 (t, 2H, J = 6.6 Hz), 5.05 and 5.14 (2 br s, HC=C), 6.80 (d, 1H, J = 8.4 Hz), 7.05 (m, 2H); ms *m/z* 248 (44), 189 (5), 188 (24), 173 (43), 161 (100). Exact mass calcd for $C_{15}H_{20}O_3$, 248.1412; found 248.1410.

Hydrolysis of the acetate.—The acetate **21g** (12.97 g) was hydrolyzed by stirring for 26 h at room temperature with 5% aqueous NaOH (140 ml) containing MeOH (160 ml). More H_2O was then added and the product extracted into Et_2O, yielding 4-methoxy-3-isopropenylphenylpropanol [**21h**] (10.63 g, 99%): ^{1}H nmr δ 1.90 (m, 2H), 2.14 (t, 3H, J = 1.5 Hz, MeC=C), 2.37 (s, 1H, OH), 2.66 (t, 2H, J = 7.3 Hz), 3.67 (t, 2H, J = 6.6 Hz), 3.81 (s, 3H), 5.08 and 5.16 (2 br s, HC=C), 6.81 (d, 1H, 8.1 Hz), 7.1 (m, 2H); ms *m/z* 206 (37), 191 (8), 161 (100), 147 (8). Exact mass calcd for $C_{13}H_{18}O_2$, 206.1307; found 206.1261.

Hydrogenation to 4-methoxy-3-isopropylphenylpropanol [**21i**].—The isopropenyl compound **21h** (10.63 g) was shaken under H_2 (15 psi) in the presence of 10% Pd/C (0.28 g) for 23 h. The catalyst was removed by filtration over Celite, and concentration and chromatography afforded the alcohol 4-methoxy-3-isopropylphenylpropanol [**21i**] (10.67 g, 95%): ^{1}H nmr δ 1.20 (d, 6H, J = 7.0 Hz, iPr Me), 1.41 (s, 1H, OH), 1.90 (m, 2H), 2.65 (t, 2H, J = 7.3 Hz, CH_2Ar), 3.29 (sept, 1H, J = 7.0 Hz, iPr CH), 3.68 (t, 2H, J = 6.6 Hz, CH_2O), 3.80 (s, 3H, MeO), 6.75 (d, 1H, J = 8.1 Hz), 6.98 (dd, 1H, J = 8.1 and 2.2 Hz), 7.03 (d, 1H, J = 2.2 Hz); ms *m/z* [M]$^+$ 208 (54), 193 (48), 165 (8), 163 (100), 149 (14), 133 (16). Exact mass calcd for $C_{13}H_{20}O_2$, 208.1643; found 208.1452.

PREPARATION OF THE β-KETO ESTER **24** NECESSARY FOR CYCLIZATION.—*4-Methoxy-3-isopropylphenylpropanal* [**22**].—To the stirred solution of PCC (12.55 g) in CH_2Cl_2 (120 ml) was added (dropwise and at room temperature) the alcohol **21i** (8.01 g) in CH_2Cl_2 (80 ml) followed by Celite (3.97 g). The mixture was stirred for 3 h, diluted with petroleum ether, and filtered in a fritted glass funnel containing Si gel. Concentration gave a dark oil which was chromatographed [petroleum ether-ether (15:1)] to give the aldehyde **22** (5.53 g, 70%): ir 2820, 2710, 1720, 800 cm^{-1}; ^{1}H nmr δ 1.20 (d, 6H, J = 7.0 Hz), 2.75

(dt, 2H, J = 7.0 and 1.5 Hz), 2.91 (t, 2H, 7.0 Hz), 3.29 (sept, 1H, J = 7.0 Hz), 3.81 (s, 3H), 6.77 (d, 1H, J = 8.1 Hz), 6.98 (dd, 1H, J = 8.1 and 2.2 Hz), 7.02 (d, 1H, J = 2.2 Hz), 9.82 (t, 1H, J = 1.5 Hz, CHO); ms *m/z* $[M]^+$ 206 (34), 191 (33), 163 (100), 149 (12), 147 (39), 133 (27), 131 (8). Exact mass calcd for $C_{13}H_{18}O_2$, 206.1307; found 206.1308.

Horner-Emmons reaction to give the ester **23a**.—As described by B.B. Snider (Brandeis University, personal communication), a solution of triethyl 2-phosphonopropionate (7.34 g) in THF (30 ml) was slowly added to NaH (1.234 g, degreased with hexane), and stirring was continued for 80 min. The aldehyde **22** (5.23 g) in THF (30 ml) was introduced dropwise over 20 min, and the mixture was stirred for 2.5 h and then poured cautiously into H_2O. Et_2O extraction gave an oil which was chromatographed [petroleum ether-Et_2O (25:1)] to give first the *Z* isomer (0.867 g, 11%) and then the required *E* isomer ethyl (*E*)-5-(4-methoxy-3-isopropylphenyl)-2-methylpent-2-enoate [**23a**] (5.284 g, 68%): ir 1705, 1640, 1260, 805 cm^{-1}; ^1H nmr δ 1.21 (d, 6H, J = 7.0 Hz, iPr Me), 1.29 (t, 3H, J = 7.3 Hz, CH_3CH_2-), 1.77 (d, 3H, J = 1.5 Hz, MeC=C), 2.46 (q, 2H, J = 7.3 Hz, CH_2C=C), 2.70 (t, 2H, J = 7.3 Hz, CH_2Ar), 3.30 (sept, 1H, iPr CH), 3.81 (s, 3H, MeO), 4.19 (q, 2H, -O-CH_2CH_3), 6.77 (d, J = 8.1 Hz), 6.83 (t broadened by allylic coupling, 1H, J = 7.3 Hz, HC=C), 6.98 (dd, 1H, J = 8.1 and 2.2 Hz), 7.01 (d, 1H, J = 2.2 Hz); ms *m/z* $[M]^+$ 290 (12), 245 (5), 164 (94), 163 (100), 161 (14), 148 (20), 147 (27), 133 (77). Exact mass calcd for $C_{18}H_{26}O_3$, 290.1882; found 290.1870.

For the *Z* isomer: ^1H nmr δ 1.20 (d, 6H, J = 7.0 Hz), 1.29 (t, J = 7.0 Hz), 1.89 (d, 3H, J = 1.5 Hz), 2.75 (m, 4H), 3.29 (sept, 1H, J = 7.0 Hz), 3.80 (s, 3H), 4.19 (q, 2H, J = 7.0 Hz), 5.96 (t broadened by allylic coupling, 1H), 6.76 (d, 1H, J = 8.1 Hz), 6.98 (dd, 1H, J = 8.1 and 1.8 Hz), 7.01 (d, 1H, J = 1.8 Hz). Exact mass calcd for $C_{18}H_{26}O_3$, 290.1882; found 290.1885.

Reduction of the E *ester*.—The unsaturated ester **23a** (*E* isomer, 4.16 g) in toluene (40 ml) was added very slowly to 25 ml of a solution of DIBALH (31.25 ml, 1.5 M in toluene) and cooled to −78°. The mixture was allowed to warm to room temperature and stirred for 21 h when MeOH was added cautiously to destroy excess reagent. After pouring into dilute HCl (210 ml, 0.1 N), m the product was obtained as a colorless oil by EtOAc extraction and purified by chromatography (*E*)-5-(4-methoxy-3-isopropylphenyl)-2-methylpent-2-en-1-ol [**23b**] (3.78 g, 95%): ir 3380–3280 (br), 3020, 1660, 1600, 1500, 1000, 805 cm^{-1}; ^1H nmr δ 1.22 (d, 6H, J = 7.0 Hz, iPr Me), 1.59 (br s, 1H, OH), 1.63 (d, 3H, J = 1.1 Hz, MeC=C), 2.34 (q, 2H, J = 7.0 Hz, CH_2C=C), 2.63 (t, 2H, J = 7.0 Hz, CH_2Ar), 3.32 (sept, J = 7.0 Hz, iPr CH), 3.81 (s, 3H, MeO), 3.99 (br s, CH_2O), 5.48 (t broadened by allylic coupling, 1H, J = 7.0 Hz, HC=C), 6.78 (d, J = 8.1 Hz), 6.98 (dd, J = 8.1 and 2.2 Hz), 7.03 (d, J = 2.2 Hz); ms *m/z* $[M]^+$ 248 (5), 163 (100), 148 (3), 147 (4), 133 (13). Exact mass calcd for $C_{16}H_{24}O_2$, 248.1776; found 248.1774.

Formation of the primary bromide **23c**.—The alcohol **23b** (3.245 g) was cooled to 5° in THF (35 ml), and a solution of PBr_3 (7.09 g) in THF (40 ml) was introduced. Cooling and stirring were continued for 35 min. The reaction mixture was then poured into ice-H_2O, extracted with Et_2O, washed, dried, and evaporated before chromatography [petroleum ether-Et_2O (15:1)], which gave the bromide (*E*)-1-bromo-5-(4-methoxy-3-isopropylphenyl)-2-methylpent-2-ene [**23c**] (3.02 g, 74%): ^1H nmr δ 1.22 (d, 6H, J = 7.0 Hz, iPr Me), 1.72 (d, 3H, J = 1.1 Hz, MeC=C), 2.33 (q, 2H, J = 7.0 Hz, CH_2C=C), 2.63 (t, 2H, J = 7.0 Hz, CH_2Ar), 3.31 (sept, 1H, J = 7.0 Hz, iPr CH), 3.81 (s, 3H, MeO), 3.97 (br s, 2H, CH_2Br), 5.65 (t, broadened by allylic coupling, J = 7.0 Hz, HC=C), 6.77 (d, J = 8.1 Hz), 6.97 (dd, J = 8.1 and 2.9 Hz), 7.01 (d, J = 2.9 Hz); ms *m/z* $[M]^+$ 312 and 310 (9), 231 (32), 189 (33), 164 (100). Note: this product was used promptly in the following reaction to avoid its degradation by allylic rearrangment.

Coupling with the acetoacetate moiety to give **24**.—NaH (0.096 g, 60% suspension) was degreased with hexane and then suspended in THF (3 ml) at 5°. Ethyl 2-methylacetoacetate (0.298 g) in THF (3 ml) was introduced over a 10 min period, and stirring was continued for 30 min before adding *n*-BuLi (1.02 ml, 1.6 M in hexanes) again during 10 min followed by 10 min stirring. Over 15 min, the bromo compound **23c** (0.663 g) in THF (6 ml) was added and the mixture was then stirred at 0° for 45 min. The mixture was poured slowly into saturated NH_4Cl (40 ml) and extracted with Et_2O, and the product was chromatographed [petroleum ether-Et_2O (30:1)] giving first some un-reacted bromide **23c** (201 mg) and then the coupled product ethyl (*E*)-9-(4-methoxy-3-isopropylphenyl)-3-oxo-2,6-dimethylnon-6-enoate [**24**] (460 mg, 83%): ir 1745, 1715, 1640, 1610, 1500, 1245, 810 cm^{-1}: ^1H nmr (400 MHz Me_2CO-d_6) δ (numbered as a cyclized diterpene): 1.20 (d, 6H, J = 6.86 Hz, iPr Me), 1.26 (t, J = 7.06 Hz, CH_3CH_2O), 1.32 (d, 3H, J = 7.05 Hz, 4-Me), 1.52 (d, 3H, J = 1.26 Hz, MeC=C), 2.15–2.25 (m, 4H, H-1 and H-6), 2.54 (t, 2H, J = 7.27 Hz, H-7), 2.60–2.80 (m, 2H, H-2), 3.27 (sept, 1H, J = 6.86 Hz, iPr CH), 3.64 (q, 1H, J = 7.05 Hz, H-4), 3.78 (s, 3H, MeO), 4.13 (q, 2H, J = 7.06 Hz, CH_3MeCH_2O), 5.19 (qt, 1H, J = 7.14 and 1.26 Hz, HC=C), 6.80 (d, J = 8.28 Hz), 6.95 (dd, J = 8.28 and 2.26 Hz), 7.02 (d, J = 2.26 Hz); ms *m/z* 374 (6), 163 (100), 133 (6).

RADICAL CYCLIZATION TO **25a**.—Manganese triacetate [$Mn(OAc)_3 \cdot 2H_2O$, 1.65 g] was vigorously stirred in glacial HOAc (15 ml) containing two drops of Ac_2O for 15 min before adding the keto-ester **24**

(1.151 g) in HOAc (5 ml). After stirring at room temperature for 90 min, the mixture was poured into ice-H_2O and the product obtained by Et_2O extraction was chromatographed [petroleum ether-Et_2O (19:1)]. Some unreacted ester **24** (150 mg) was followed by the cyclized product ethyl 3-oxo-12-methoxy-13-isopropylpodocarpa-8,11,13-trienate [**25a**] (732 mg, 74%): mp 117–118°; ir 1725, 1710, 1610, 1500, 1240, 1040 cm^{-1}; ^1H nmr δ 1.17 and 1.19 (2d, 6H, $J = 6.6$ Hz, iPr Me), 1.27 (t, 3H, $J = 7.0$ Hz, $MeCH_2O$), 1.36 (s, 3H, Me-10), 1.45 (s, 3H, Me-4), 1.7–1.95 (m, 2H, H_{ax}-1 and H-5), 2.1–2.25 (m, 2H, H-6), 2.5–2.65 (m, 2H, H_{eq}-1 and H_{eq}-2), 2.72 (ddd, 1H, H_{eq}-7), 2.90 (dt, H_{eq}-7), 3.15 (dt, 1H, $J = 14.8$ and 6.4 Hz, H_{ax}-2), 3.22 (sept, 1H, $J = 6.6$ Hz, iPr CH), 3.79 (s, 3H, MeO), 4.17 (q, 2H, $J = 7.0$ Hz, $MeCH_2$-O), 6.71 (s, 1H, H-11), 6.87 (s, 1H, H-14); ms *m/z* $[M]^+$ 372 (40), 357 (11), 327 (11), 311 (8), 299 (11), 283 (18), 255 (18). Exact mass calcd for $C_{23}H_{32}O_4$, 372.2300; found 372.2326.

MODEL TRICYCLIC ESTER **25b**.—The model ester, mp 88–89°, described by Snider *et al.* (14) was prepared from *p*-methoxyphenylpropanol, employing the same reactions and conditions that led to **25a**. In general, yields were comparable although the cyclization never afforded more than 61%.

DECARBOXYLATION OF MODEL ESTER **25b**.—To a refluxing solution of $LiI \cdot 2H_2O$ (0.424 g prepared from anhydrous LiI by the addition of the stoichimetric quantity of H_2O) in 2,4,6-collidine (5 ml) was added the keto-ester **25b** (270 mg) in collidine (3 ml). After refluxing for 6.5 h, the mixture was poured into 10% aqueous HCl containing ice and extracted with Et_2O which was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The dried solution was evaporated and the yellowish solid chromatographed [petroleum ether-Et_2O (19:1)] to give the product 12-methoxy-19-norpodocarpa-8,11,13-trien-3-one [**26b**] (149 mg, 70%): mp 102°; ir 1700 cm^{-1}; ^1H nmr (400 MHz) δ 1.09 (d, 3H, $J = 6.6$ Hz, Me-4), 1.35 (s, 3H, Me-10), 1.6–1.73 (m, 2H, H-6 and H-5), 1.86 (dt, 1H, H_{ax}-1), 1.9–2.1 (m, 1H, H-6), 2.4–2.48 (m, 1H, H-4), 2.48–2.60 (m, 2H, H_{eq}-1 and H_{eq}-2), 2.6–2.7 (m, 1H, H_{ax}-2), 2.7–2.95 (m, 2H, H-7), 3.77 (s, 3H, MeO), 6.69 (dd, $J = 8.4$ and 2.6 Hz, H-13), 6.83 (d, $J = 2.6$ Hz, H-11), 6.99 (d, $J = 8.4$ Hz, H-14); ms *m/z* $[M]^+$ 258 (100), 243 (37), 225 (15), 201 (33), 199 (11), 187 (21), 170 (54). Exact mass calcd for $C_{17}H_{22}O_2$, 258.1620; found 258.1606. *Anal.* calcd for $C_{17}H_{22}O_2$: C 79.03, H 8.58 (found C 79.04, H 8.60).

METHYLATION OF THE MODEL KETONE **26b**.—All conditions under kinetic or thermodynamic control gave the same 2,4-dimethylated products **26c** and **26d**. The following, using a method described by Wharton and Sundin (25), is just one example.

NaH (27.1 mg, 60% disp in oil) was added to the ketone (159 mg) in DME (4 ml) followed by excess MeI (0.2 ml). After 2.5 h, the mixture was poured into H_2O, most of the DME was removed by evaporation, and the product was extracted into Et_2O and chromatographed [petroleum ether-Et_2O (20:1)] to yield some starting material (14 mg) and then the 2,4-dimethyl compound 12-methoxy-2α-methyl-19-norpodocarpa-8,11,13-trien-3-one [**26d**] (70 mg: 46%): ir 1700 cm^{-1}; ^1H nmr (400 MHz) δ 1.10 (d, 3H, $J = 6.5$ Hz, Me-4), 1.12 (d, 3H, $J = 6.4$ Hz, Me-2), 1.43 (d, 3H, $J = 0.6$ Hz, 10-Me coupled with H_α-1), 1.57 (dq, 1H, $J = 13.1$, 13.1, and 0.6 Hz, H_{ax}-1), 1.59 (dt, 1H, $J = 12.4$, 12.4, and 2.6 Hz, H-5), 1.68 (ddt, 1H, $J = 12.4$, 12.4, 10.9, and 6.7 Hz, H_{ax}-6), 1.9–2.0 (m, 1H, H_{eq}-6), 2.44–2.52 (m, 1H, $J = 6.5$ and 1.2 Hz, H_{ax}-4), 2.57 (dd, 1H, $J = 13.1$ and 5.8 Hz, H_{eq}-1), 2.65–2.80 (m, 1H, H_{ax}-7), 2.89 (ddd, 1H, $J = 17.2$, 6.7, and 2.1 Hz, H_{eq}-7), 3.80 (s, 3H, MeO), 6.71 (dd, 1H, $J = 8.4$ and 2.7 Hz, H-13), 6.87 (d, 1H, $J = 2.7$ Hz, H-11), 7.00 (d, 1H, $J = 8.4$ Hz, H-14). Exact mass calcd for $C_{18}H_{24}O_2$, 272.1776; found 272.1762.

TRANSFORMATION OF THE C-4 ESTER TO A METHYL GROUP.—The experimental conditions for the model and the isopropyl series were the same and will be given for the former only.

Reduction of the ester **25b** *to the diol* **27b**.—The keto-ester **25b** (300 mg) in Et_2O (30 ml) was added to a suspension of $LiAlH_4$ (100 mg) in Et_2O at 5°. After stirring for 30 min, the temperature was allowed to rise to ambient during 3 h after which excess hydride was destroyed by the cautious addition of H_2O (4 ml). After 20 min the cloudy mixture separated into a clear liquid and a white precipitate which was filtered off and well washed with Et_2O. The combined organic phase was dried and evaporated, affording the crystalline diol **27b** (264 mg, quant.): mp 154–155° (not improved by chromatography): ir 3380–3200 (br) cm^{-1}; ^1H nmr (300 MHz) δ 1.15 and 1.30 (2s, each 3H, 4-Me, 10-Me), 1.42 (dd, 1H, $J = 12.4$ and 1.3 Hz, H-5), 2.29 (dt, 1H, $J = 13.2$, 3.3, and 3.3 Hz, H_{eq}-1), 2.76 (ddd, 1H, $J = 16.8$, 11.1 and 6.9 Hz, H_{ax}-7), 2.88 (dd, 1H, $J = 16.8$ and 5.7 Hz, H_{eq}-7), 3.75 (s, 3H, MeO), 4.30 (d, 1H, $J = 11.1$ Hz, CH_2OH), 6.66 (dd, 1H, $J = 8.4$ and 2.6 Hz, H-13), 6.76 (d, 1H, $J = 2.6$ Hz, H-11), 6.94 (d, 1H, $J = 8.4$ Hz, H-14). After D_2O was added, a 4H multiplet extending from δ 3.30 to 3.60 simplified to show 3.40 (d, 1H, $J = 11.1$ Hz, H-19) and 3.48 (dd, 1H, $J = 11.4$ and 4.8 Hz, H_{ax}-3); ms *m/z* $[M]^+$ 290 (91), 257 (9), 239 (23), 227 (11), 199 (20). Exact mass calcd for $C_{18}H_{26}O_3$, 290.1882; found 290.1877.

In the same manner the ester **25a** (202 mg) ws reduced to diol 12-methoxyabieta-8,11,13-triene-3β,19-diol [**27a**] (155 mg, 86%): ^1H nmr δ 1.20 (m, 9H, 10-Me and iPr), 1.32 (s, 3H, 4-Me), 3.25

(sept, 1H, iPr CH), 3.45 (m, 4H, H_{ax}-3, -CH_2OH, two OH), 3.80 (s, 3H, MeO), 4.33 (d, 1H, J = 12.5 Hz, H-19), 6.70 (s, 1H, H-11), 6.85 (s, 1H, H-14). After shaking with D_2O: 3.42 (d, 1H, J = 12.5 Hz, H-19), 3.45 (m, 1H, H_{ax}-3); ms *m/z* $[M]^+$ 332 (100), 299 (24), 281 (15), 239 (24). Exact mass calcd for $C_{21}H_{32}O_3$, 332.2351; found 332.2398.

Tosylation of diol **27b**.—*p*-Tosyl chloride (727 mg) was added to the diol **27b** (554 mg) in dry pyridine (8 ml). After the mixture was stirred for 40 h, it was poured into dilute aqueous HCl (50 ml, 10%) containing some ice chips. The Et_2O extract was well washed with dilute HCl and then with aqueous $NaHCO_3$ before drying and evaporating. The crude product was chromatographed [petroleum ether-Et_2O (10:1 increasing to 1:1)]. The first eluted product was the ditosylate (371 mg, 32%): mp 120–122°. Exact mass calcd for $C_{32}H_{38}O_7S_2$, 598.2059; found 598.2053. This product was hydrolyzed and recycled.

Further elution afforded the monotosylate **27d** (340 mg, 40%): mp 160–161°; ir 3350 cm^{-1}; ^1H nmr δ 1.07 and 1.18 (2s, 6H, 4-Me and 10-Me), 1.40 (dd, 1H, J = 2.0 Hz, H-5), 1.5 to 1.8 (m, 2H, H-6 and H_{ax}-1), 1.8 to 2.1 (m, 3H, H_2-2 and H-6), 2.28 (dt, 1H, H_{eq}-1), 2.44 (s, 3H, MeAr), 2.70 (ddd, 1H, H_{ax}-7), 2.88 (dd, 1H, H_{eq}-7), 3.37 (dd, J = 10.8 and 2.5 Hz, H_{ax}-3), 3.75 (s, 3H, MeO), 4.19 (d, 1H, J = 10.3 Hz, H-19), 4.30 (d, 1H, H-19), 6.66 (dd, 1H, J = 8.3 and 2.8 Hz, H-13), 6.73 (d, 1H, J = 2.8 Hz, H-11), 6.95 (d, 1H, J = 8.3 Hz, H-14), 7.35 and 7.81 (2d, 2H each, J = 7.9 Hz, ArH tosyl); ms *m/z* $[M]^+$ 444 (16), 272 (34), 257 (5), 243 (5), 239 (23), 215 (34), 91 (100). Exact mass calcd for $C_{25}H_{32}O_5S$, 444.1970; found 444.1996.

In the same way, the tosylate **27c** was obtained in 49% yield: mp 130–132°; ^1H nmr δ (cf. **27d** above) 1.10 (3H), 1.19 (3H), 1.16 and 1.19 (2d, 6H, J = 6.9 Hz, iPrMe), 1.42 (1H, 1.5–1.6 (m, 1H, H_{ax}-1), 1.65–1.9 (m, 3H, H_2-2 and H_{ax}-6), 2.28 (1H), 2.46 (3H, 2.70 (1H), 2.84 (1H), 3.21 (sept, J = 6.9 Hz, iPr C-H), 3.36 (1H), 3.77 (3H), 4.20 (1H), 4.33 (1H), 6.64, 6.83 (2s, 1H each, ArCH), 7.36 and 7.81 (2d, 2H each, ArH tosyl); ms *m/z* $[M]^+$ 486 (17), 314 (39), 299 (26), 281 (13), 257 (11), 91 (100). Exact mass calcd for $C_{28}H_{38}O_{56}S$, 486.2440; found 486.2364.

Oxidation of the hydroxytosylate to **29b** *and* **29a**.—At 5° the model tosylate **27d** (125 mg) in CH_2Cl_2 (5 ml) was added to a solution of PCC (91 mg) in CH_2Cl_2 (5 ml), and stirring was continued for 30 min at 5° and then 4 h at room temperature. The mixture was then diluted with petroleum ether (10 ml) and filtered through a bed of Si gel which was washed with Et_2O. After drying, the solvent was evaporated leaving the pure product 19-tosyloxy-12-methoxypodocarpa-8,11,13-trien-3-one [**29b**]: mp 154–155°; ir 1705 cm^{-1}; ^1H nmr δ 1.16 (s, 3H, 4-Me), 1.24 (s, 3H, 10-Me), 1.7–2.1 (m, 4H, H_2-6, H-5 and H_{ax}-1), 2.44 (s, 3H, MeAr), 2.4 to 2.65 (m, 3H, H_2-2 and H_{eq}-1), 2.75 (ddd, 1H, H_{ax}-7), 2.90 (dd, 1H, H_{eq}-7), 3.75 (s, 3H, MeO), 4.09 (d, 1H, J = 9.9 Hz, H-19), 4.41 (d, 1H, J = 9.9 Hz, H-19), 6.68 (dd, J = 8.4 and 2.2 Hz, H-13), 6.73 (d, J = 2.2 Hz, H-11), 6.97 (d, 1H, J = 8.4 Hz, H-14), 7.34 and 7.76 (2d, 2H each, J = 8.1 Hz, ArH tosyl); ms *m/z* $[M]^+$ 442 (6), 227 (5), 215 (10), 91 (100). Exact mass calcd for $C_{25}H_{30}O_5S$, 442.1814; found 442.1833. *Anal.* calcd C 67.85, H 6.83 (found C 67.51, H 6.80).

The isopropyl analogue **27c** was oxidized in the same manner to afford 19-tosyloxy-12-methoxy-abieta-8,11,13-trien-3-one [**29a**] (75%): ^1H nmr δ (cf. **29b** above) 1.16 (3H), 1.16 and 1.18 (2d, 6H, J = 6.6 Hz, iPr Me), 1.25 (3H), 1.7–2.1 (m, 4H), 2.45 (3H), 2.4–2.65 (3H), 2.75 (1H), 2.90 (1H), 3.21 (sept, J = 6.6 Hz, iPr CH), 3.77 (3H), 4.10 (1H), 4.43 (1H), 6.63 (s, 1H, H-11), 6.84 (s, 1H, H-14), 7.34 and 7.77 (2d, 2H each); ms *m/z* $[M]^+$ 484 (16), 269 (6), 255 (9), 91 (100). Exact mass calcd for $C_{28}H_{36}O_5S$, 484.2283; found 484.2250.

Reduction of tosylates **29b** *and* **29a**.—Using essentially the Matsumoto procedure (26), the model tosylate **29b** (160 mg) was dissolved in dry DMF (7 ml) and to this stirred solution was added dried NaI (271 mg) and after 15 min Zn powder [236 mg, activated and dried (27)]. The reaction mixture was heated at 125° for 7 h and then diluted with Et_2O, and the unreacted Zn was filtered and well washed over Celite. The combined organic phase was washed (H_2O and saturated NaCl) and evaporated. The ^1H nmr of this crude material (113 mg) revealed the cyclopropyl moiety, δ 0.39 (d, 1H, J = 5.86 Hz) and 0.81 (d, 1H, J = 5.86 Hz), so it was taken up in C_6H_6 (10 ml) acidified with a trace of *p*-TsOH. After distilling 1–2 ml of the solvent, the mixture was refluxed for 90 min. The cooled solution was washed, dried, and concentrated. Chromatography of the residue [petroleum ether-Et_2O (20:1)] afforded the gem-dimethyl product (50 mg, 68%) and with more polar eluent some starting tosylate **29b** (40 mg). 12-Methoxy-podocarpa-8,11,13-trien-3-one [**31b**]: mp 71–72°: ir 1700 cm^{-1}; ^1H nmr (400 MHz) δ 1.14, 1.17, and 1.31 (3s, 3H each, 4-Me and 10-Me), 1.7–1.86 (m, 2H, H_2-6), 1.91 (dd, 1H, J = 11.8 and 2.7 Hz, H-5), 1.97 (dddq, 1H, J = 13.3, 10.0, 7.7, and 0.8 Hz, H_{ax}-1), 2.46 (ddd, 1H, J = 13.3, 7.5, and 4.2 Hz, H_{eq}-1), 2.60 (ddd, 1H, J = 15.8, 7.7, and 4.2 Hz, H_{eq}-2), 2.71 (ddd, 1H, J = 15.8, 10.0, and 7.5 Hz, H_{ax}-2), 2.81 (ddd, 1H, J = 16.4, 11.6, and 6.9 Hz, H_{ax}-7), 2.93 (ddd, 1H, J = 16.4, 5.4, and 2.2 Hz, H_{eq}-7), 3.79 (s, 3H, MeO), 6.71 (dd, 1H, J = 8.4 and 2.6 Hz, H-13), 6.79 (d, 1H, J = 2.6 Hz, H-11), 7.00 (d, 1H, J = 8.4 Hz, H-14); ms *m/z* $[M]^+$ 272 (16), 257 (3), 215 (8), 201 (2), 187 (3), 171 (7). Exact mass calcd for $C_{18}H_{24}O_2$, 272.1776; found 272.1798.

In exactly the same way the tosylate **29a** (64 mg) gave first a cyclopropyl intermediate **30a** [^1H-nmr

peaks at 0.38 (d, 1H) and 0.82 (d, 1H)] and then 12-methoxy-abieta-8,11,13-trien-3-one [**31a**] (22 mg, 53% for the two steps): mp 118–120°; ^{1}H nmr δ 1.13 and 1.16 (2s, 3H each, Me_2-4), 1.18 and 1.21 (2d, 3H each, J = 7.0 Hz, iPr Me), 1.30 (s, 3H, 10-Me), 1.68–1.83 (m, 2H, H_2-6), 1.85–1.96 (dd, 1H, H-5), 1.95–2.05 (m, 1H, H_{ax}-1), 2.55–2.70 (m, 2H, H_2-2), 2.70–2.90 (m, 2H, H_2-7), 3.23 (sept, 1H, J = 7.0 Hz, iPr CH), 3.79 (s, 3H, MeO), 6.68 (s, 1H, H-11), 6.86 (s, 1H, H-14); ms *m/z* $[M]^+$ 314 (100), 299 (73), 257 (56), 243 (6), 229 (12), 227 (10), 213 (49). Exact mass calcd for $C_{21}H_{30}O_2$, 314.2246; found 314.2235.

(±)-O-*Methyl margocillin* [**33b**].—To the ketone **31a** (22 mg) in Et_2O (5 ml) was added at 5° a suspension of $LiAlH_4$ (15 mg) in Et_2O (3 ml). After 30 min the temperature was allowed to rise to ambient, and 90 min later, H_2O was cautiously introduced. Stirring was continued for several min until the supernatant liquid was clear. After filtering, the organic phase was dried and concentrated to afford the equatorial alcohol **32a** (20 mg, 90%): ^{1}H nmr δ 0.89 and 1.06 (2s, 3H each, 4-Me_2), 1.17 and 1.19 (2d, 3H each, J = 7.0 Hz, iPr Me), 1.21 (s, 3H, Me-10), 1.30–200 (m, 6H, H_2-2, H-5, H_{ax}-1 and H_2-6), 2.20–2.35 (dt, 1H, H_{eq}-1), 2.65–3.00 (m, 2H, H_2-7), 3.21 (sept, 1H, J = 7.0 Hz, iPr CH), 3.26–3.34 (m, 1H, H_{ax}-3), 3.78 (s, 3H, MeO), 6.69 (s, 1H, H-11), 6.84 (s, 1H, H-14).

The alcohol **32a** (20 mg) was acetylated by stirring overnight in pyridine (3 ml) and Ac_2O (2 ml) at room temperature. Extraction gave the acetate **32b** (24 mg, quant): ^{1}H nmr δ 0.95 and 0.96 (2s, 3H each, 4-Me_2), 1.18 and 1.21 (2d, 3H each, J = 6.96 Hz, iPr Me), 1.22 (s, 3H, 10-Me), 1.30–2.00 (m, 6H), 2.07 (s, 3H, MeC=O), 2.20–2.35 (m, 1H, H_{eq}-1), 2.65–3.00 (m, 2H, H_2-7), 3.21 (sept, 1H, J = 6.96 Hz, iPr CH), 3.78 (s, 3H, MeO), 4.54 (dd, 1H, J = 10.3 and 5.13, H_{ax}-3), 6.67 (s, 1H, H-11), 6.84 (s, 1H, H-14).

A solution of CrO_3 (15 mg) in 80% aqueous HOAc (5 ml) was added drop by drop to the acetate **32b** (24 mg) in glacial HOAc (2 ml). After stirring overnight the mixture was poured into H_2O (10 ml), and the keto acetate **33a** (24 mg) was obtained by extraction. ^{1}H nmr δ 0.92 and 1.03 (2s, 3H each, 4-Me_2), 1.16–1.26 (m, 9H each, iPr Me and 10-Me), 1.70–2.10 (m, 4H, H_2-2, H_{ax}-1 and H-5), 2.07 (s, 3H, MeC=O), 2.20–2.40 (m, 1H, H_{eq}-1), 2.60–2.70 (m, 2H, H_2-6), 3.23 (sept, 1H, iPr CH), 3.87 (s, 3H, MeO), 4.50–4.56 (m, 1H, H-3), 6.68 (s, 1H, H-11), 7.87 (s, 1H, H-14).

The acetate **33a** (24 mg) was hydrolyzed by stirring in MeOH (7 ml) containing 5% aqueous NaOH (4 ml) at room temperature overnight. After most of the organic solvent was evaporated, the product was obtained by extraction and purified by flash chromatography, 3β-hydroxy-12-methoxyabieta-8,11,13-trien-7-one (margocillin methyl ether) [**33b**] (15 mg, yield for the four steps 65%): mp 193–194°; ir 3430, 3020, 1650, 1600, 1500, 1450, 1380, 1260, 1040, 1060 cm^{-1}; ^{1}H nmr (400 MHz) δ 0.98 (s, 3H, 4β-Me), 1.05 (s, 3H, 4α-Me), 1.19 and 1.22 (2d, 3H each, J = 6.9 Hz, iPr Me), 1.26 (s, 3H, 10-Me), 1.63 (br s, 1H, OH), 1.74 (dt, 1H, J = 12.5, 12.5, and 4.0 Hz, H_{ax}-1), 1.80–2.00 (m, 3H, H_2-2 and H-5), 2.36 (dt, 1H, J = 12.5, 3.3, and 3.3 Hz, H_{eq}-1), 2.60–2.80 (m, 2H, H_2-6), 3.24 (sept, 1H, J = 6.9 Hz, iPr CH), 3.36 (dd, 1H, J = 10.3 and 3.7 Hz, H_{ax}-3), 3.90 (s, 3H, MeO), 6.71 (s, 1H, H-11), 7.89 (s, 1H, H-14); ^{13}C nmr δ (C-1 to C-20, respectively) 36.18, 27.50, 78.02, 38.85, 48.77, 35.55, 197.86, 123.79, 155.28, 37.92, 104.47, 161.63, 135.48, 125.57, 26.50, 22.28, 22.43, 23.18, 14.93, 27.44, MeO 55.33: ms *m/z* $[M]^+$ 330 (82), 315 (100), 297 (23), 271 (6), 243 (11), 229 (48). Exact mass calcd for $C_{21}H_{30}O_3$, 330.2195; found 330.2213.

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