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APPROACHES TO THE SYNTHESIS OF AROMATIC DITERPENES OXYGENATED IN THE A RING. SYNTHESIS OF MARGOCIN

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ABSTRACT.—The structure of margocin [**24**] is confirmed by its synthesis from useful synthons encountered during transformations exploring the utility of dehydroabietic acid as a chiral starting material for natural product synthesis.

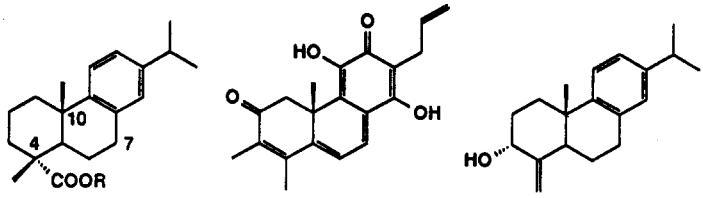
Newer and more sensitive methods for elucidating the structures of natural products have resulted in the reporting of many new compounds including aromatic diterpenes. Much of the argument on which these structures are based is spectroscopic, and while the data itself is irrefutable, it can be inadvertently misinterpreted. This means that some new natural substances are incorrectly described in the literature. If their presence is worth recording, these structures must be beyond suspicion, and other than X-ray diffraction, the only unambiguous corroboration is by partial or total synthesis. Logic dictates that the preparation of a proposed compound from another well-known natural substance of unquestionable structure and stereochemistry would represent the most believable proof of identity. With this in mind a search was undertaken to find useful synthons available from abundant chiral natural products.

Many uses of dehydroabietic acid [**1a**] and the closely related podocarpic acid as chiral starting materials for the synthesis of more complex, highly oxygenated diterpenes are described in the literature. Thus syntheses of coleon U (1), coleon C (2), taxodione (3), and maytenoquinone (4) have been reported. The list of similar natural products with oxygen functions in the A ring is increasing rapidly, but most of the synthetic approaches used previously do not lend themselves to the introduction of functions beyond the quarternary centers at C-4 and C-10. Examples such as coleon F [**2**] (5) and parsiflorines D, F, and G (6) have oxygens at C-2, while others such as candelabrone (7) or the simpler hinokiol are functionalized at C-3, and some such as shonanol (8) have the ketone or alcohol at C-1.

RESULTS AND DISCUSSION

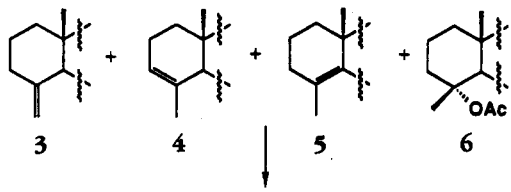
Originally two different general approaches were planned to synthesize several of these diterpenes from **1a**. Using the aromatic ring to activate the benzylic C-7 position, one could extend a conjugation from there into the A ring with elimination of the carboxylic residue at C-4. Some results in this area are published separately (9).

The alternate route involved direct entry into ring A by the known oxidative decarboxylation of dehydroabietic acid [**1a**] by lead tetraacetate, which affords three isomeric olefins **3**, **4**, and **5** and the tertiary acetate **6**. The yields and proportions of the latter given in the literature vary considerably (10–12). In our hands, the olefins were obtained in 50% yield in the ratio 2:2:1 (for **3**, **4**, and **5**). The quantity of the acetate **6**, if reported, also varies from none (10,11) to as high as 22% (this study). Since the olefins are virtually inseparable, Cambie and Deny (13) converted the mixture to the epoxides by reaction with mono peroxyphthalic acid during 4 days which left the less reactive exocyclic double bond in **3** untouched. The use of *m*-CPBA for this step gave better results after just 2 h, when chromatography afforded the exocyclic olefin **3** (35%), a small amount of the corresponding epoxide **7** (8%), the 3,4-epoxide **8** (19%), the 4,5-epoxide **9** (30%), a trace of retene (1-methyl-7-isopropylphenanthrene, ca. 1%), and the interesting allylic alcohol **10** (5%). The epoxide **8** can also be transformed to **10** by

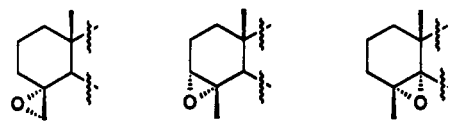


1a R=H
1b R=Me

2 **10**



3 **4** **5** **6**



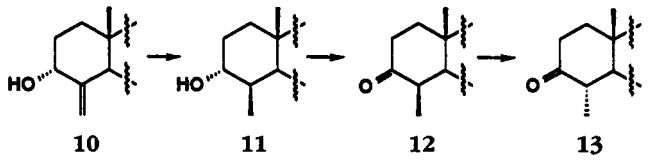
7 **8** **9**

lithium diisopropylamide in virtually quantitative yield (14). Moreover, when the exocyclic olefin **3** was oxidized with SeO_2, the principal product (54%) was the alcohol **10**. Combining the product from the three sources, the allylic alcohol **10** could be obtained in over 20% yield from the inexpensive, technical grade dehydroabietic acid.

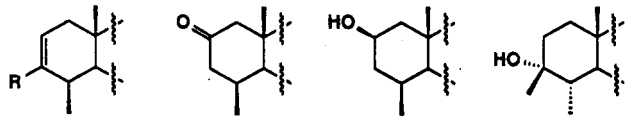
To explore the potential of the allylic alcohol **10** as an intermediate to establish the functions in the A ring (necessary for coleon F [**2**] for example), the double bond was hydrogenated and the product **11** was oxidized to ketone **12**. The stereochemistry at C-4 obviously placed the methyl group in the latter in the less stable axial orientation, since refluxing in C_6H_6 with a trace of acid quantitatively epimerized the product to **13**. Alcohol **11** could also be used to establish a carbonyl or hydroxyl group at C-2 by exploiting the highly regioselective dehydration effected by phosphorus oxychloride in pyridine, which gives exclusively the 2,3-olefin **14a** (94%). The unsaturation in the latter was exploited to introduce oxygen functions to give products such as the ketone **15** and the alcohol **16**. Only a few of these compounds are mentioned in the text and described in the experimental: for more ample details see Côté (15).

Because these compounds stem from the olefin mixture arising from the decarboxylation, they are in effect norditerpene derivatives. Having placed an oxygen function in ring A, one now has to reintroduce the missing carbon. Addition of methyl lithium to the carbonyl in **13** gave the two tertiary alcohols **17** (71%) and its epimer (9%), and dehydration of the former with thionyl chloride in C_6H_6 afforded **14b**, the olefin with the 2,3-double bond. Hydrolysis (Me_2CO, H_2SO_4) of the epoxide of the latter afforded diol **18** (90%). Ten minutes at 0° with Jones reagent gave the hydroxyketone **19** (83%), and the desired coleon F motif for ring A was finally obtained by dehydrating ($SOCl_2$, pyridine) to the conjugated enone **20**.

As this route to coleon F appeared laborious, it was abandoned, but the allylic alcohol **10** has been used to synthesize margocin [**24**], a diterpene recently isolated from *Azadirachta indica* (16). A more convenient preparation of the exocyclic olefin **3** by

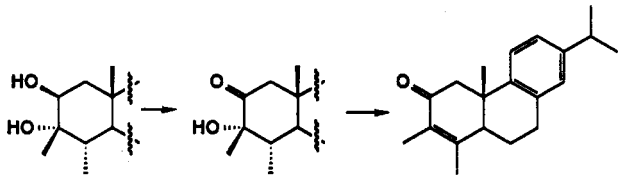


10 **11** **12** **13**



14a R=H
14b R=Me

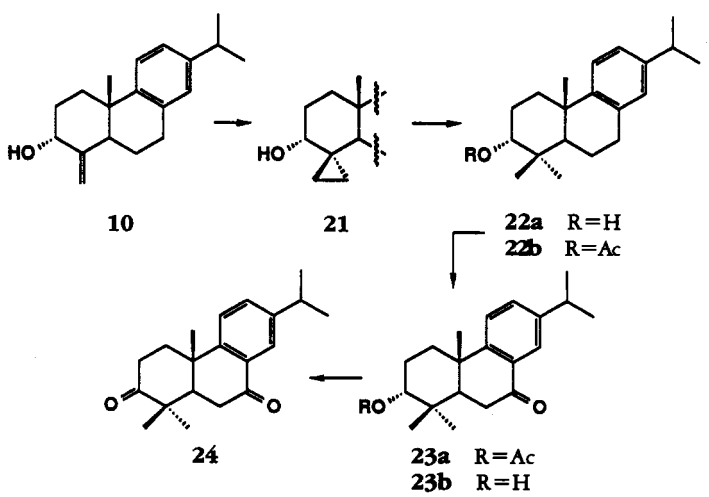
15 **16** **17**



18 **19** **20**

Matsumoto *et al.* (17) involves methyl dehydroabietate **1b**, which is converted to the diphenyl carbinol in a Grignard reaction (about 65%). This sterically strained compound eliminates benzophenone when heated in C_6H_6 with lead tetracetate and $CaCO_3$, affording the olefin **3** (92%). Recently Cambie *et al.* (18) have published yet another route. As before, allylic oxidation provides the 3α-hydroxy compound **10** (54% or about 20% overall from commercial dehydroabietic acid).

One promising route to the *gem*-dimethyl moiety of margocin involved the cyclopropyl intermediate **21**, which was obtained in excellent yield from **10** by a modified Simmons-Smith procedure (19). Hydrogenolytic opening of the three-membered ring proved more difficult than anticipated, and most conditions found efficient in similar cases (20,21) also hydrogenated the aromatic ring. Despite this, enough of the *gem*-dimethyl compound **22a** was accumulated to continue the synthesis. The hydroxyl was protected as the acetate derivative **22b**, and the C-7 benzylic position was oxidized



10 **21**

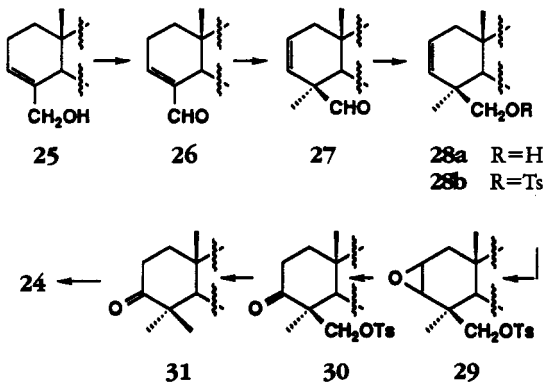
22a R=H
22b R=Ac

24

23a R=Ac
23b R=H

to the ketone **23a**. After hydrolysis of the acetate to the alcohol **23b**, Jones oxidation gave the diketone **24**, margocin. Comparison showed the synthesized material to be identical with the natural product.

Margocin was synthesized by another sequence starting from the olefin **3** or its derived epoxide **7**. Isomerization of the latter with LDA gave exclusively the allylic alcohol **25**, which was oxidized to the conjugated aldehyde **26**. Alkylation created the *gem*-dimethyl grouping at C-4, moving the double bond to the 2,3 position, and the product **27** was reduced to the primary alcohol **28a** and protected as the tosylate **28b**. Reaction of the double bond with *m*-CPBA afforded a mixture of epoxides (**29**), which after reductive cleavage with $LiAlH_4$ and Jones oxidation gave just one ketone **30**. The tosyloxy residue was reduced, affording the *gem*-dimethyl ketone **31**. As before, benzylic oxidation with PCC gave margocin **24**.



EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Unless otherwise stated, the conditions used to characterize the products were as follows: mp's, 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 assignments resulted from COSY, HETCOR, and APT experiments which are not described in the text); ms, Hewlett Packard 5992, and exact mass measurements at the Centre régional de spectrométrie de masse, Université de Montréal. Cc implies 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 are normally carried out under N_2 or argon.

LEAD TETRACETATE DECARBOXYLATION OF DEHYDROABIETIC ACID [**1a**].—Following the method of Bennett *et al.* (12), pyridine (2 ml) and then $Pb(OAc)_4$ (8.4 g) were added to a C_6H_6 (25 ml) solution of the acid **1a** (5.0 g) under N_2. The mixture was refluxed for 3 h, cooled, filtered through Celite, and concentrated. Cc (hexane) gave an oil containing the three olefins **3**, **4**, and **5** (2:2:1 from the ^1H nmr, 2.08 g, 49%), and elution with C_6H_6 afforded the tertiary acetate **6** (1.08 g, 22%).

The olefin mixture (from above, 24.90 g) was added to a solution of *m*-CPBA (14.11 g) in $CHCl_3$ (2.5 liters) at 0°, and the mixture was stirred for 2 h. The excess peroxy acid was decomposed by washing with saturated KI, saturated $NaHCO_3$, and saturated NaCl, and the dried solution was evaporated. Cc afforded unreacted olefin **3** [8.59 g, 35%, $[\alpha]^{25}D$ 199.3 (*c*=1.12, $CHCl_3$)], retene (302 mg, 1%), the 4,5-epoxide **9** (7.97 g, 30%), exocyclic epoxide **7** (2.02 g, 8%), the 3,4-epoxide **8** (4.98 g, 19%), and the allylic alcohol **10** (1.28 g, 5%).

3a-Hydroxy-19-norabieta-4(18),8,11,13-tetraene [**10**].—Mp 63–66° (petroleum ether/$CHCl_3$) [lit. (14) 60–61°]; $[\alpha]^{26}D$ 150.0 (*c*=0.75, $CHCl_3$); ir 3265 cm^{-1}; ^1H nmr δ 0.98 (s, Me-10), 1.24 [d, *J*=7.0 Hz, iPr(Me)], 1.52 (br s, OH, dis. D_2O), 2.84 [sept, 1H, *J*=7.0 Hz, iPr(CH)], 2.70 to 3.00 (m, 3H, H_2-7 and H-5), 4.34 (d, *J*=2.6 Hz, H-3), 4.74 (dd, *J*=3.3 and 1.5 Hz, H-18), 5.07 (dd, *J*=3.3 and 1.5 Hz, H-18), 6.94 (d, *J*=1.5 Hz, H-14), 7.02 (dd, *J*=8.1 and 1.5 Hz, H-12), 7.22 (d, *J*=8.1 Hz, H-11); ms *m/z* $[M]^+$ 270

(25), 255 (7), 237 (100), 195 (30), 167 (13), 153 (10). *Exact mass* calcd for $C_{19}H_{26}O$, 270.1984; found 270.1977.

ISOMERIZATION OF THE EPOXIDE **8** TO ALCOHOL **10**.—A solution of *n*-BuLi (0.5 ml of 10 M) was added to diisopropylamine (2.5 ml) in anhydrous Et_2O (8 ml). After stirring for 10 min, the epoxide **8** (485 mg) was introduced in Et_2O (3 ml), and the mixture was refluxed for 4 h. The cooled solution was poured into ice-H_2O, and the product was obtained by Et_2O extraction. Cc [petroleum ether/EtOAc (4:1)] of the solid residue after evaporation gave the allylic alcohol **10** (474 mg, 98%), identical in all respects with that described above.

ALLYLIC OXIDATION OF OLEFIN **3**.—Based on Matsumoto's method (22), SeO_2 (1.70 g) was added to the olefin **3** (5.50 g) in 95% EtOH (200 ml), and the solution was refluxed for 2 h with efficient stirring, then cooled, filtered, and evaporated. The yellow oil was chromatographed [petroleum ether-EtOAc (8:1)], affording the allylic alcohol **10** (3.19 g, 54%), identical with that described above.

HYDROGENATION OF ALLYLIC ALCOHOL **10**.—The alcohol **10** (300 mg) in MeOH (50 ml) was shaken with 10% Pd/C (120 mg) under H_2 (45 psi) for 2 h. After filtering and evaporating, the residue was chromatographed [petroleum ether-EtOAc (8:1)] to give alcohol **11** (292 mg, 97%): mp 121° (hexane/Et_2O) [lit. (11) 119–120°], $[\alpha]^{25}D$ 66.4 (c=0.92, $CHCl_3$); ^1H nmr δ 1.00 (d, J=7.6 Hz, Me-4), 1.16 (s, Me-10), 1.49 (s, OH, dis. D_2O), 2.44 [d, 6H, J= 57.0 Hz, iPr(Me)], 2.82 [sept, J=7.0 Hz, iPr(CH)], 2.90 (m, H_2-7), 3.85 (d, J=2.2 Hz, H-3), 6.89 (d, J=1.6 Hz, H-14), 6.99 (dd, J=7.9 and 1.6 Hz, H-12), 7.16 (d, J=7.9 Hz, H-11); ms m/z $[M]^+$ 272 (15), 257 (16), 239 (100), 197 (8), 186 (8), 171 (18), 155 (17), 141 (20). *Anal.* calcd for $C_{19}H_{28}O$, C 83.77, H 10.36; found C 83.88, H 10.35.

OXIDATION TO THE KETONE **12**.—Agitation at room temperature (5 min) of the alcohol **11** (900 mg) in Me_2CO (15 ml) with Jones reagent (3 ml, introduced dropwise) followed by the usual workup and cc [petroleum ether-EtOAc (32:1)] afforded 3-oxo-18-norabieta-8,11,13-triene [**12**] (723 mg, 81%): mp 71–73° (petroleum ether); ^1H nmr δ 1.21 (d, 3H, J=7.9 Hz, Me-4), 1.23 [d, 6H, J=7.0 Hz, iPr(Me)], 1.33 (s, 3H, Me-10), 2.85 [sept, 1H, J=7.0 Hz, iPr(CH)], 2.90 (m, 2H, H_2-7), 6.92 (d, 1H, J=1.9 Hz, H-14), 7.02 (dd, 1H, J=7.9 and 1.9 Hz, H-12), 7.19 (d, 1H, J=7.9 Hz, H-11); ms m/z $[M]^+$ 270 (37), 255 (90), 213 (100), 199 (18), 186 (31), 183 (29), 171 (46), 159 (43). *Anal.* calcd for $C_{19}H_{26}O$, C 84.32, H 9.69; found C 84.42, H 9.74. If the stirring was continued longer, appreciable quantities of the epimer **13** were isolated.

EPIMERIZATION OF KETONE **12** TO KETONE **13**.—p-TsOH (50 mg) was added to the ketone **12** (683 mg) in EtOAc (20 ml), and the mixture was refluxed for 40 min. Washing, evaporation, and cc (as above) gave 3-oxo-19-norabieta-8,11,13-triene [**13**] (636 mg, 93%): $[\alpha]^{26}D$ 74.9 (c=0.81, $CHCl_3$); ^1H nmr δ 1.11 (d, 3H, J=6.7 Hz, Me-4), 1.22 [d, 6H, J=7.0 Hz, iPr(Me)], 1.35 (s, 3H, Me-10), 2.87 [sept, 1H, J=7.0 Hz, iPr(CH)], 2.90 (m, 2H, H_2C-7), 6.93 (d, 1H, J=1.9 Hz, H-14), 7.02 (dd, 1H, J=7.9 and 1.9 Hz, H-12), 7.23 (d, 1H, J=7.9 Hz, H-11); ms m/z $[M]^+$ 270 (42), 255 (100), 213 (39), 183 (24), 159 (31), 129 (25). *Exact mass* calcd for $C_{19}H_{26}O$, 270.1984; found 270.1944.

DEHYDRATION OF ALCOHOL **11**.—The alcohol **11** (300 mg) was refluxed with $POCl_3$ (0.5 ml) in pyridine (4.7 ml) for 1 h, and the cooled mixture was poured into cold dilute HCl. Et_2O extraction and cc (petroleum ether) gave 18-norabieta-2,8,11,13-tetraene [**14a**] (270 mg, 94%): ^1H nmr δ 1.04 (d, J=7.6 Hz, Me-4), 1.21 (s, Me-10), 1.22 [d, J=7.0 Hz, iPr(Me)], 2.13 (d, J=16.5 Hz, H_α-1), 2.52 (dd, J=16.5 and 4.5 Hz, H_β-1), 2.84 [m, 3H, H_2-7 and iPr(CH)], 5.69 (m, 2H, H-2 and H-3), 6.89 (d, J=1.9 Hz, H-14), 7.01 (dd, J=7.9 and 1.9 Hz, H-12), 7.17 (d, J=7.9 Hz, H-11); ms m/z $[M]^+$ 254 (21), 239 (22), 197 (11), 186 (100), 171 (40), 159 (21), 155 (17), 143 (23). *Exact mass* calcd for $C_{19}H_{26}$, 254.2034; found 254.1989.

KETONE **15** VIA THE EPOXIDE AND ALCOHOL **16**.—Treating the major bromohydrin obtained from **14a** (NBS, DMSO, H_2O) with KOH in MeOH afforded the epoxide (37 mg, 84%): ^1H nmr δ 1.15 (d, J=7.6 Hz, Me-4), 1.22 [d, 6H, J=7.0 Hz, iPr(Me)], 1.30 (s, Me-10), 2.80 (m, 2H, H_2C-7), 2.82 [sept, J=7.0 Hz, iPr(CH)], 3.34 (m, 2H, H-2 and H-3), 6.86 (d, J=1.9 Hz, H-14), 7.01 (dd, J=7.9 and 1.9 Hz, H-12) and 7.16 (d, J=7.9, Hz, H-11); ms m/z $[M]^+$ 270 (44), 255 (49), 237 (53), 195 (98), 171 (49), 169 (99), 155 (69), 141 (100). *Exact mass* calcd for $C_{19}H_{26}O$, 270.1984; found 270.1977.

The epoxide (28 mg) was reduced with excess $LiAlH_4$ in Et_2O (4 ml) at room temperature during 1.5 h. After destroying excess reagent with H_2O, the product obtained by extraction with Et_2O was chromatographed [hexane-EtOAc (16:1)] to give 2β-hydroxy-18-norabieta-8,11,13-triene [**16**] (24 mg, 86%): ir 3380 cm^{-1}; ^1H nmr δ 1.22 [d, 6H, J=7.0 Hz, iPr(Me)], 1.23 (d, J=9.5 Hz, Me-4), 1.43 (s, Me-10), 1.62 (br s, OH, dis. D_2O), 2.44 (dd, J=14.3 and 3.5 Hz, H_β-1), 2.82 [sept, J=7.0 Hz, iPr(CH)], 2.90 (m, 2H, H_2-7), 4.33 (m, H-2), 6.89 (d, J=1.6 Hz, H-14), 7.00 (dd, J=8.3 and 1.6 Hz, H-12) and 7.16 (d, J=8.3 Hz, H-11); ms m/z $[M]^+$ 272 (28), 257 (48), 239 (100), 197 (59), 183 (15), 159 (62), 143 (52). *Exact mass* calcd for $C_{19}H_{28}O$, 272.2140; found 272.2167.

The alcohol **16** (21 mg) in Me_2CO (3 ml) at 0° was vigorously stirred for 10 min with Jones reagent (5 drops), and after the usual Et_2O extraction, washing, drying, and cc [petroleum ether-EtOAc (30:1)] this afforded 2-oxo-18-norabieta-8,11,13-triene [**15**] (13 mg: 63%): ir 1705 cm^{-1}; ^1H nmr δ 1.05 (d, J=7.3 Hz, Me-4), 1.19 (s, Me-10), 1.23 [d, 6H, J=7.0 Hz, iPr(Me)], 2.83 [sept, J=7.0 Hz, iPr(CH)], 3.00 (m, 3H, H_2-7 and H_β-1), 6.94 (d, J=1.0 Hz, H-14), 7.05 (s, 2H, H-11 and H-12); ms *m/z* $[M]^+$ 270 (8), 255 (100), 213 (60), 185 (76). *Exact mass* calcd for $C_{19}H_{26}O$, 270.1984; found 270.1984.

REACTION OF METHYL LITHIUM ON KETONE **13**.—Methyl lithium (1.5 ml, 1.55 M in hexane) was added to the ketone **13** (411 mg) in Et_2O (35 ml), and stirring was continued at room temperature for 3 h. H_2O was added, the solution was neutralized with 10% aqueous HCl, and cc of the residue obtained by extraction gave first [petroleum ether-EtOAc (11:1)] the alcohol **17** (311 mg, 71%) and then [petroleum ether-EtOAc (8:1)] the epimer (41 mg, 9%).

3α-Hydroxy-3β-methyl-19-norabieta-8,11,13-triene [**17**].—Mp 70–73°; ^1H nmr δ 0.98 (d, 3H, J=6.0 Hz, Me-4), 1.08 (s, 3H, Me-10), 1.22 [d, 6H, J=7.0 Hz, iPr(Me)], 1.24 (s, 3H, Me-3), 2.86 [sept, 1H, J=7.0 Hz, iPr(CH)], 6.91 (d, 1H, J=1.6 Hz, H-14), 6.99 (dd, 1H, J=8.2 and 1.6 Hz, H-12), 7.20 (d, 1H, J=8.2 Hz, H-11); mass *m/z* $[M]^+$ 286 (11), 271 (6), 253 (100), 213 (8), 159 (11), 129 (11). *Exact mass* calcd for $C_{20}H_{30}O$, 286.2297; found 286.2283.

3β-Hydroxy-3α-methyl-19-norabieta-8,11,13-triene.—^1H nmr δ 0.96, 1.08, 1.13 (s, 3H, Me-3), 1.22, 2.87, 6.93, 7.0, 7.19 (compare with **17** above); ms *m/z* $[M]^+$ 286 (28), 271 (17), 253 (100), 213 (43). *Exact mass* calcd for $C_{20}H_{30}O$, 286.2297; found 286.2260.

DEHYDRATION OF ALCOHOL **17** WITH THIONYL CHLORIDE IN C_6H_6.—The alcohol **17** (280 mg) was stirred with $SOCl_2$ (2 ml) in C_6H_6 (16 ml) for 3 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and the Et_2O extracted as usual. Cc (petroleum ether) gave first the 2,3-olefin **14b** (108 mg, 42%), then the axial chloro derivative (103 mg, 35%) followed by the equatorial isomer (10 mg, 3%).

3-Methyl-19-norabieta-2,8,11,13-tetraene [**14b**].—^1H nmr δ 1.07 (s, 3H, Me-10), 1.09 (d, 3H, J=8.4 Hz, Me-4), 1.23 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.70 (s, 3H, Me-3), 2.10 (dd, 1H, J=16.8 and 1.5 Hz, H_α-1), 2.45 (dd, 1H, J=16.8 and 6.2 Hz, H_β-1), 2.85 [m, 3H, H_2-7 and iPr(CH)], 5.44 (dd, 1H, J=6.2 and 1.5 Hz, H-2), 6.91 (s, 1H, H-14), 7.01 (d, 1H, J=8.0 Hz, H-12), 7.20 (d, 1H, J=8.0 Hz, H-11); ms *m/z* $[M]^+$ 268 (8), 253 (16), 200 (6), 186 (100), 143 (18). *Exact mass* calcd for $C_{20}H_{28}$, 268.2191; found 268.2172.

3α-Chloro-3β-methyl-19-norabieta-8,11,13-triene.—^1H nmr δ 1.05 (d, 3H, J=6.2 Hz, Me-4), 1.08 (s, 3H, Me-10), 1.23 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.63 (s, 3H, Me-3), 2.87 [sept, 1H, J=7.0 Hz, iPr(CH)], 2.90 (m, 2H, H_2-7), 6.92 (d, 1H, J=1.5 Hz, H-14), 7.00 (dd, 1H, J=8.0 and 1.5 Hz, H-12), 7.20 (d, 1H, J=8.0 Hz, H-11); ms *m/z* 306 (6) $[M]^+$ 304 (12), 291 (14), 289 (47), 268 (18), 253 (72), 211 (23), 186 (100). *Exact mass* calcd for $C_{20}H_{29}{}^{35}Cl$, 304.1958; found 304.1971.

3β-Chloro-3α-methyl-19-norabieta-8,11,13-triene.—^1H nmr δ 1.12 (d, J=6.7 Hz), 1.16, 1.23, 1.46 (s, 3H, 3-Me), 2.87, 2.90, 6.92, 7.00, 7.16 (compare with 3α isomer above); ms *m/z* 306 (6), 304 (11), 291 (13), 289 (43), 253 (100), 211 (26), 186 (37).

Slow cc of the chloro derivatives over Si gel (petroleum ether) gave a mixture of **14b**, the $\Delta^{3,4}$ isomer, and the exocyclic olefin in the ratio 30:7:4 (82%). The total yield of the 2,3-olefin from alcohol **17** was 61%.

DIOL **18** VIA EPOXIDATION OF OLEFIN **14b**.—To *m*-CPBA (203 mg) in $CHCl_3$ (20 ml) at 0° was added the olefin **14b** (241 mg). Vigorous stirring for 2 h and workup as described previously gave after cc [petroleum ether-EtOAc (40:1)] the epoxide (245 mg, 96%): ^1H nmr δ 1.11 (d, 3H, J=1.0 Hz, Me-10), 1.17 (d, 3H, J=6.3 Hz, Me-4), 1.22 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.38 (s, 3H, Me-3), 1.76 (d, 1H, J=14.9 Hz, H_α-1), 2.50 (dd, 1H, J=14.9 and 6.3 Hz, H_β-1), 2.75 (m, 2H, H_2-7), 2.82 [sept, 1H, J=7.0 Hz, iPr(CH)], 3.13 (d, 1H, J=6.3 Hz, H-2), 6.88 (d, 1H, J=1.9 Hz, H-14), 7.00 (dd, 1H, J=7.9 and 1.9 Hz, H-12), 7.17 (d, 1H, J=7.9 Hz, H-11); ms *m/z* $[M]^+$ 284 (31), 269 (100), 251 (23), 225 (13), 209 (35), 171 (28). *Exact mass* calcd for $C_{20}H_{28}O$, 284.2140; found 284.2141.

The epoxide (146 mg) was stirred in Me_2CO-H_2O (2:1) (30 ml) with H_2SO_4 (2 ml) for 2.5 h at room temperature. The product was obtained by extraction and cc [petroleum ether-EtOAc (40:1)]. 2β,3α-Dihydroxy-3β-methyl-19-norabieta-8,11,13-triene [**18**] (140 mg, 90%): ^1H nmr δ 1.00 (d, 3H, J=8.1 Hz, Me-4), 1.22 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.28 (s, 3H, Me-10), 1.32 (s, 3H, Me-3), 2.10 (dd, 1H, H_α-1), 2.32 (dd, 1H, J=14.6 and 2.2 Hz, H_β-1), 2.82 [sept, 1H, J=7.0 Hz, iPr(CH)], 2.85 (m, 2H, H_2-7), 3.76 (m, 1H, H-2), 6.91 (br s, 1H, H-14), 6.98 (br d, J=8.1 Hz, H-12), 7.18 (d, 1H, J=8.1 Hz, H-11); ms *m/z* $[M]^+$ 302 (19), 287 (28), 269 (88), 251 (22), 209 (57). *Exact mass* calcd for $C_{20}H_{30}O_2$, 302.2246; found 302.2257.

Enone **20** *via ketol* **19**.—Jones reagent (1.5 ml) was added to the diol **18** (70 mg) in Me_2CO (10 ml)

at 0°. After stirring vigorously for 10 min, the product was isolated as above and purified by cc [petroleum ether-EtOAc (4:1)] to give 2-oxo-3-methyl-19-norabieta-3,8,11,13-tetraene [**19**] (58 mg, 83%): ir 3440 and 1700 cm^{-1}; ^1H nmr δ 1.02 (s, 3H, Me-10), 1.14 (d, 3H, J=6.6 Hz, Me-4), 1.23 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.35 (s, 3H, Me-3), 2.83 (d, 1H, J=12.1 Hz, H_α-1), 2.90 [m, 3H, H_2-7 and iPr(CH)], 3.16 (d, 1H, J=12.1 Hz, H_β-1), 6.94 (d, 1H, J=1.8 Hz, H-14), 7.02 (dd, 1H, J=8.4 and 1.8 Hz, H-12), 7.12 (d, 1H, J=8.4 Hz, H-11); ms *m/z* $[M]^+$ 300 (18), 267 (41), 239 (46), 213 (23). *Exact mass* calcd for $C_{20}H_{28}O_2$, 300.2089; found 300.2091.

Thionyl chloride (2 ml) was added to the ketol **19** (20 mg) in pyridine (8 ml), and the mixture was stirred for 15 min at room temperature. Cc [petroleum ether-EtOAc (16:1)] of the crude product (isolated as described above) afforded 2-oxo-3-methyl-19-norabieta-3,8,11,13-tetraene [**20**] (14 mg, 74%): uv λ max 249 (4100) nm; ir 1655 cm^{-1}; ^1H nmr δ 1.09 (s, 3H, Me-10), 1.24 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.86 (br s, 3H, Me-3), 2.0 (br s, 3H, Me-4), 2.30 (m, 1H, H-6), 2.48 (d, 1H, J=16.2 Hz, H_α-1), 2.75 (m, 1H, H-5), 2.85 [sept, 1H, J=7.0 Hz, iPr(CH)], 3.00 (m, 2H, H_2-7), 3.13 (d, 1H, H_β-1), 6.96 (br s, 1H, H-14), 7.04 (d, 1H, J=8.1 Hz, H-12), 7.14 (d, 1H, J=8.1 Hz, H-11); ^{13}C nmr δ (from C-1 to C-20) 51.4, 198.1, 131.0, 155.1, 46.2, 21.3, 29.8, 134.0, 146.5, 39.4, 127.0, 124.2, 33.6, 24.0, 24.0, 11.4, 18.3 (now 3-Me), 29.5; ms *m/z* $[M]^+$ 282 (26), 267 (34), 239 (25), 199 (35). *Exact mass* calcd for $C_{20}H_{26}O$, 282.1984; found 282.1913.

CYCLOPROPANATION OF ALLYLIC ALCOHOL **10**.—To the allylic alcohol **10** (370 mg, 1.37 mmol) in dry toluene (1.5 ml) under N_2 was added diethyl zinc (12.5 ml of 1.1 M in toluene, 13.75 mmol). After stirring at room temperature for 30 min the solution was cooled to 0° and diiodomethane (freshly distilled over Cu, 1.2 ml, 14.9 mmol) was added and stirring continued for 20 h. After a brief reflux (50 min), H_2O (12 ml) was introduced and the product obtained by Et_2O extraction. The Et_2O was washed (dilute HCl, saturated $NaHCO_3$, saturated NaCl), dried over $MgSO_4$, evaporated and the residue chromatographed [petroleum ether-Et_2O (7:3)] to give the cyclopropyl derivative **21** (370 mg, 95%): mp 89–90°; $[\alpha]^{25}D$ 38.7 (c=0.97, $CHCl_3$); ^1H nmr δ 0.17, 0.38, and 0.65 (3m, 1H, 1H, and 2H respectively, cyclopropyl protons), 1.20 (s, 3H, Me-10), 1.25 [d, 6H, iPr(Me_2)], 1.62 (br s, 1H, OH), 2.38 (dd, 1H, J=10.6 and 4.4 Hz, H-5), ca. 2.85 [m, 3H, H_2-7 and iPr(CH)], 3.00 (m, 1H, H-3), 6.92 (br s, 1H, H-14), 7.03 (dd, 1H, J=8.0 and 1.4 Hz, H-12), 7.25 (d, 1H, J=8.0 Hz, H-11); *ms* m/z $[M]^+$ 284 (34), 269 (22), 251 (100), 241 (58), 223 (28), 213 (25), 199 (25), 186 (23), 181 (26). *Exact mass* calcd for $C_{20}H_{28}O$, 284.2140; found 284.2139.

HYDROGENOLYSIS OF THE CYCLOPROPYL DERIVATIVE **21**.—Compound **21** (106 mg) in glacial HOAc (20 ml) was stirred under H_2 (rubber balloon) with PtO_2 (22 mg) for 18 h. The mixture was diluted with Et_2O, well washed with saturated aqueous $NaHCO_3$ and NaCl, dried, evaporated, and chromatographed [petroleum ether-Et_2O (4:1)] giving first some starting material (48 mg) then the *gem*-dimethyl compound **22a** (30 mg, 52% after subtracting the recovered **21**), $[\alpha]^{25}D$ 23.8 (c=0.65, $CHCl_3$): ^1H nmr δ 0.95 (s, 3H, Me_β-4), 1.03 (s, 3H, Me_α-4), 1.20 (s, 3H, Me-10), 1.22 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.52 (br s, 1H, OH), 1.65–2.30 (m, 7H), 2.82 [sept, 1H, J=7.0 Hz, iPr(CH)], 2.88 (m, 2H, H_2-7), 3.50 (m, 1H, H-3), 6.89 (br s, H-14), 6.99 (dd, 1H, J=8.0 and 1.8 Hz, H-12), 7.18 (d, 1H, J=8.1 Hz, H-11); mass *m/z* $[M]^+$ 286 (13), 254 (24), 253 (100), 171 (22), 155 (19), 143 (29), 141 (30), 129 (36), 128 (40), 115 (22). *Exact mass* calcd for $C_{20}H_{30}O$, 286.2297; found 286.2293.

The acetate **22b** was prepared in the usual manner: ir 1735 and 1240 cm^{-1}; ^1H nmr δ 0.94 (s), 1.01 (s) 1.21 (s), 1.23 (6H), 1.98 (s, 3H, Me-C=O), 2.87 (sept), 2.91 (m), 4.74 (dd, 1H, J=2.9 and 2.6 Hz, H-3), 6.92 (d), 7.01 (dd), 7.18 (d); mass *m/z* $[M]^+$ 328 (8), 254 (23), 253 (100). *Exact mass* calcd for $C_{22}H_{32}O$, 328.2402; found 328.2435.

BENZYLIC OXIDATION TO **23a**.—To a solution of CrO_3 (134 mg) in 80% aqueous HOAc (8.8 ml) was added drop by drop the acetate **22b** (115 mg) in HOAc (4.4 ml). After stirring for 65 h at room temperature, the mixture was diluted with Et_2O, washed with H_2O, $NaHCO_3$, and brine. The residue from evaporation of the dried organic phase was chromatographed [petroleum ether-Et_2O (4:1)], giving some starting material and then the 7-ketone **23a** (42 mg, 42% allowing for the recuperated **22b**), $[\alpha]^{26}D$ −38.3 (c=0.42, $CHCl_3$); ir 1730, 1680, 1240 cm^{-1}; ^1H nmr δ 0.92, 1.08, 1.25 (3s, 3H each, Me_2-4 and Me-10), 1.25 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.99 (s, 3H, Me-C=O), 2.34 (dd, 1H, J=10.6 and 7.7 Hz, H-5), 2.93 [sept, 1H, J=7.0 Hz, iPr(CH)], 4.78 (br s, 1H, H-3), 7.30 (d, 1H, J=8.1 Hz, H-11), 7.42 (dd, J=8.1 and 1.8 Hz, H-12), 7.89 (d, 1H, J=1.8 Hz, H-14); ms *m/z* $[M]^+$ 342 (15), 282 (18), 268 (40), 267 (100), 200 (20), 187 (25). *Exact mass* calcd for $C_{22}H_{30}O$, 342.2195; found 342.2171.

HYDROLYSIS OF ACETATE **23a** TO **23b**.—The acetate **23a** (44 mg) was hydrolyzed by stirring overnight at room temperature in MeOH (7 ml) containing aqueous NaOH (5%, 4 ml). The mixture was acidified with dilute HCl and extracted with Et_2O to give the alcohol **23b** (36 mg, 93%): $[\alpha]^{24}D$ 5.7 (c=0.72, $CHCl_3$) 3400, 1675 cm^{-1}; ^1H nmr δ 0.99, 1.00, and 1.23 (3s, 3H each, Me-4 and Me-10), 1.23 [d, 6H, J=7.0 Hz, iPr(Me_2)], 2.07 (br s, OH), 2.33 (dd, 1H, J=12.1 and 6.0 Hz, H-5), 2.63 (d, 1H, J=6.0

Hz, H_α-6), 2.66 (d, 1H, J=12.1 Hz, H_β-6), 2.90 [sept, 1H, J=7.0 Hz, iPr(CH)], 3.55 (m, 1H, H-3), 7.29 (d, 1H, J=8.0 Hz, H-11), 7.38 (dd, 1H, J=8.0 and 2.0 Hz, H-12), 7.84 (d, 1H, J=2.0 Hz, H-14); ^{13}C nmr δ (from C-1 to C-20) 30.6, 25.5, 75.1, 37.5, 42.7, 35.7, 199.5, 130.6, 153.4, 37.5, 123.6, 132.4, 146.6, 124.8, 33.62, 23.9, 23.8, 27.5, 21.7, 23.4; mass *m/z* $[M]^+$ 300 (15), 268 (21), 267 (100), 199 (21), 187 (11), 185 (10), 159 (14), 157 (12). *Exact mass* calcd for $C_{20}H_{28}O_2$, 300.2089; found 300.2064.

OXIDATION TO MARGOCIN.—The alcohol **23b** (35 mg) in Me_2CO (4 ml) was cooled to 0° before adding freshly prepared Jones reagent (0.4 ml) and stirring for 10 min. The mixture was poured into H_2O and extracted with Et_2O. The latter was well washed (H_2O, $NaHCO_3$, NaCl) dried, evaporated, and chromatographed [petroleum ether-Et_2O (7:3)] to afford margocin [**24**] (27.5 mg, 79%): mp 119–122°; $[\alpha]^{28}D$ −15.5 (*c*=0.90, $CHCl_3$); uv λ max 252 (10,900), 298 (3400) nm; ir 1705, 1675 cm^{-1}; ^{1}H nmr δ 1.13 and 1.20 (2s, 3H each, Me-4), 1.24 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.43 (s, 3H, Me-10), 2.00 (ddd, 1H, J=13.5, 13.5, 5.5 Hz, H_α-1), 2.31 (dd, 1H, J=13.5 and 4.4 Hz, H-5), 2.92 [sept, 1H, J=7.0 Hz, iPr(CH)], 7.27 (d, 1H, J=8.0 Hz, H-11), 7.42 (dd, 1H, J=8.0 and 2.2 Hz, H-12), 7.89 (d, 1H, J=2.2 Hz, H-14); ^{13}C nmr δ (from C-1 to C-20) 36.9, 34.6, 214.2, 47.3, 49.5, 36.4, 198.1 130.3, 151.0, 37.4, 124.1, 132.8, 147.3, 125.0, 33.7, 23.8, 23.8, 25.1, 21.5, 22.8; ms *m/z* $[M]^+$ 298 (29), 283 (11), 241 (21), 213 (14), 202 (10), 199 (15), 159 (10), 128 (14), 125 (100). *Exact mass* calcd for $C_{20}H_{26}O_2$, 298.1933; found 298.1913. Alcohol **22a** was also oxidized directly to margocin using PCC, Celite in dry C_6H_6. The yield was at best mediocre.

SYNTHESIS OF MARGOCIN FROM THE EPOXIDE **7**.—Olefin **3** obtained by Matsumoto's more recent method (17) was epoxidized to **7** as described earlier. To the epoxide **7** (1.912 g) in dry toluene (50 ml) was added aluminium isopropoxide (4.5 g), and the mixture was refluxed for 24 h. The cooled solution was poured onto ice/10% HCl and Et_2O extracted. After washing, drying, and evaporating the residue was chromatographed [petroleum ether-Et_2O (7:3)] to give alcohol **25** (1.544 g, 81%): ^{1}H nmr δ 1.11 (s, 3H, Me-10), 1.32 [d, 6H, J=7.0 Hz, iPr(Me_2)], 4.12 and 4.25 (2d, 1H ea, J=12.5 Hz, CH_2OH), 5.81 (br s, 1H, H-3), 7.04 (br s, H-14), 7.08 (dd, 1H, J=8.1 and 1.8 Hz, H-12), 7.32 (d, 1H, J=8.1 Hz, H-11); ms *m/z* $[M]^+$ 270 (90), 257 (53), 255 (93), 239 (72), 237 (54), 199 (38), 195 (100), 167 (42), 148 (68), 128 (61). *Exact mass* calcd for $C_{19}H_{26}O$, 270.1984; found 270.1970.

To a suspension of PCC (2.093 g), NaOAc (162 mg), and Celite in CH_2Cl_2 (30 ml) as described by Corey and Suggs (23), was added at room temperature the alcohol **25** (1.688 g) in CH_2Cl_2 (20 ml). After 1 h the mixture was filtered over Celite and evaporated, and the residue was chromatographed [petroleum ether-Et_2O (9:1)] to give first the aldehyde with no double bond (259 mg, 15%, arising from Cannizaro disproportionation) and then the conjugated aldehyde **26** (720 mg, 43%): uv λ max 216 (18,500) nm; ir 1685 cm^{-1}; ^{1}H nmr δ 1.06 (s, 3H, Me-10), 1.26 [d, 6H, J=7.0 Hz, iPr(Me_2)], 2.41 (d, 1H, J=12.5 Hz, H-5), 2.87 [sept, 1H, J=7.0 Hz, iPr(CH)], 6.85 (br s, H-14), 7.02 (d, 1H, J=8.0 Hz, H-12), 7.24 (d, 1H, J=8.0 Hz, H-11), 9.52 (s, 1H, CHO); ms *m/z* $[M]^+$ 268 (51), 253 (100), 211 (38), 195 (35), 165 (29), 155 (25), 141 (42), 128 (46). Among other spectral data, the saturated aldehyde showed ir 1730 cm^{-1}, nmr δ 9.55 (d, 1H, J=4.4 Hz, CHO), and ms *m/z* $[M]^+$ 270 (39).

The conjugated aldehyde **26** (582 mg) was added to a solution of *t*-BuOK (1 g) in dry C_6H_6 (23 ml) and heated at 80° for 30 min. After cooling, MeI (1.3 ml) was added, and refluxing was resumed for 2 h. The cooled solution was diluted with Et_2O and well washed before evaporation, and cc [petroleum ether-Et_2O (19:1)] gave the required aldehyde **27** (417 mg, 68%) followed by a small quantity of the methyl enol ether of the starting aldehyde (47 mg, 8%). 19-oxo-abieta-2,8,11,13-tetraene [**27**]: mp 63–67°, $[\alpha]^{28}D$ 219 (*c*=1.08, $CHCl_3$): ^{1}H nmr δ 1.19 (s, 3H, Me-10), 1.25 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.26 (s, 3H, Me-4), 2.66 (dd, 1H, J=17.0 and 5.9 Hz, H_β-1), 2.85 [sept, 1H, J=7.0 Hz, iPr(CH)], 5.69 (br d, J=9.9 Hz, H-3), 5.95 (ddd, 1H, J=9.9, 5.9 and 1.8 Hz, H-2), 6.93 (br s, 1H, H-14), 7.05 (dd, 1H, J=8.0 and 1.8 Hz, H-12), 7.20 (d, 1H, J=8.0 Hz, H-11), 9.86 (s, 1H, CHO); ms *m/z* $[M]^+$ 282 (35), 253 (35), 186 (20), 173 (100), 159 (45), 129 (20). *Exact mass* calcd for $C_{20}H_{26}O$, 282.1984; found 282.1997.

To a suspension of $LiAlH_4$ (76 mg) in Et_2O (6 ml) at 0° was added dropwise the aldehyde **27** (463 mg) in Et_2O (10 ml). The mixture was stirred overnight at room temperature, and excess hydride was then destroyed by cautious addition of dilute HCl (to a pH of 3) when the product was extracted into Et_2O and washed. Evaporation and cc afforded the alcohol **28a** (407 mg, 87% crude) converted immediately (TsCl, pyridine, catalytic DMAP, 3 days) to the tosylate **28b** (537 mg, 94%): ^{1}H nmr δ 1.10 and 1.11 (2s, 3H each, Me-10 and Me-4), 1.21 [d, 6H, J=7.0 Hz, iPr(Me_2)], 1.92 (m, 1H, H-5), 2.10 (br d, 1H, J=17.0 Hz, Hα-1), 2.44 (s, 3H, Me-Ar), 2.78 [sept, J=7.0 Hz, iPr(CH)], 3.97 and 4.11 [2d, 1H each, J=9.2 Hz, H_2C(19)-O-Ts], 5.52 (dd, H-3), 5.73 (ddd, H-2), 6.87 (br s, 1H, H-14), 7.01 (dd, 1H, H-11), 7.13 (d, 1H, J=8.1 Hz, H-12), 7.13 and 7.79 (2d, 2H each, J=8.1 Hz, Ar-H tosyl); ms *m/z* $[M]^+$ 438 (5), 209 (19), 186 (100), 173 (37), 171 (27), 159 (29), 155 (32).

The tosylate **28b** (107 mg) in C_6H_6 (1 ml) was cooled to 0°, and *m*-CPBA (5 ml, 0.072 M in C_6H_6) was added. Stirring was continued for 24 h, and the solution was diluted with Et_2O and washed ($NaHSO_3$,

$NaHCO_3$, NaCl), dried, and chromatographed [petroleum ether-Et_2O (7:3)] giving some starting material (12 mg) and then the epoxides **29** (79 mg, 3:1 mixture). The latter (70 mg) was reduced in Et_2O (1.5 ml) with $LiAlH_4$ (12.5 mg) at 0° for 5 h. The product (65 mg), a mixture of epimeric C-3 alcohols, was taken up in Me_2CO (6 ml) and oxidized with Jones reagent (0.3 ml) at 0° for 15 min. The mixture was diluted with H_2O, extracted into Et_2O, and chromatographed to afford a keto tosylate **30** (44 mg, 63% for the last two steps): ir 1710 cm^{-1}; ^1H nmr δ 1.16 (s), 1.21 (d, J=7.0 Hz), 1.22 (s), 2.44 (s, Me-Ar), 2.81 (sept, J=7.0 Hz), 2.94 (m, 2H, H_2-7), 4.10 and 4.42 (2d, J=9.9 Hz, CH_2-OR), 6.89 (d), 699 (br s), 7.13 (d), 7.34 and 7.76 (2d, Ar-H tosyl); ms *m/z* $[M]^+$ 454 (13), 267 (42), 239 (33), 227 (39), 225 (54), 197 (36). Exact mass calcd for $C_{27}H_{34}SO_4$, 454.2178; found 454.2155.

Following the Matsumoto procedure (24) the tosyl derivative **30** (56 mg) in DMF (2.5 ml) was treated with oven-dried NaI (95 mg) and activated Zn (25) (81 mg) by refluxing for 6 h. The cooled mixture was filtered through Celite, extracted into Et_2O, washed (H_2O, brine), and chromatographed [petroleum ether-ether (9:1)] to give 2-oxo-abieta-8,11,13-triene [**31**] (22 mg, 62%): $[\alpha]^{25}D$ 98.7 (c=0.73, $CHCl_3$); spectral data as described previously. Benzylic oxidation gave margocin **24**.

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