mospheric pressure. The n-dodecane solution is refluxed with stirring for 3 h, and the evolved gases are measured. The quantitative yield is 8.6 mmol of gases identified as a mixture of methane and ethylene by mass spectroscopy.

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Registry No.—Magnesium, 7439-95-4; dimethylmercury, 593-74-8; diphenylmercury, 587-85-9; diethylmagnesium, 557-18-6; *d,l*-benzoin, 579-44-2; 1,2-diphenyl-1,2-propylene glycol, 41728-16-9; 1,2-diphenyl-1-propanone, 67737-73-9; *erythro*-1,2-diphenyl-1-propanol, 56844-75-8; *p*-bromobenzenesulfonyl chloride, 98-58-8; *erythro*-1,2-diphenyl-1-propanol brosylate, 67700-01-0; aniline, 62-53-3; acetone-d_6, 666-52-4; benzylamine, 100-46-9; methyl iodide, 74-88-4.

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Total Synthesis of (±)-Ferruginol and (±)-Hinokione

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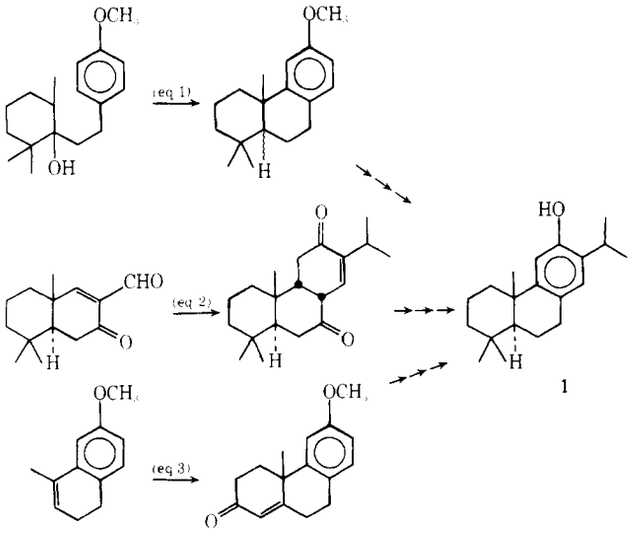
Stereospecific syntheses of (±)-ferruginol and (±)-hinokione were achieved in which the tricyclic ring system was assembled in the order C → BC → ABC. The key features of the approach involve: (1) the utilization of a lactone bridge as part of an enone protecting group in ring A; (2) the installation of an isopropyl group by the regioselective addition of lithium dimethylcuprate to a cross-conjugated dienone; (3) the elimination of the lactone bridge with concomitant aromatization of ring C; and (4) the reductive methylation of the enone in ring A to install the C-4 geminal dimethyl group and to guarantee the trans fusion of the AB rings.

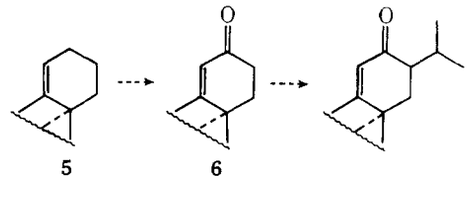
The isolation and structure elucidation[1] of ferruginol (**1**), a major constituent of New Zealand's Miro tree (*Podocarpus ferruginea*), actuated interest in the total synthesis of this phenolic diterpene. Synthetic efforts directed toward ferruginol (**1**) have employed various permutations of the order in which the three rings are assembled. The earliest approach by King[2] utilized the AC → ABC closure shown below (eq 1),



but suffered from a lack of stereoselectivity in the A/B ring fusion.[3] Later approaches by Meyer,[4] who employed an AB → ABC sequence (eq 2), and by Rao,[5] who employed a BC → ABC sequence (eq 3), culminated in stereospecific syntheses of ferruginol (**1**).

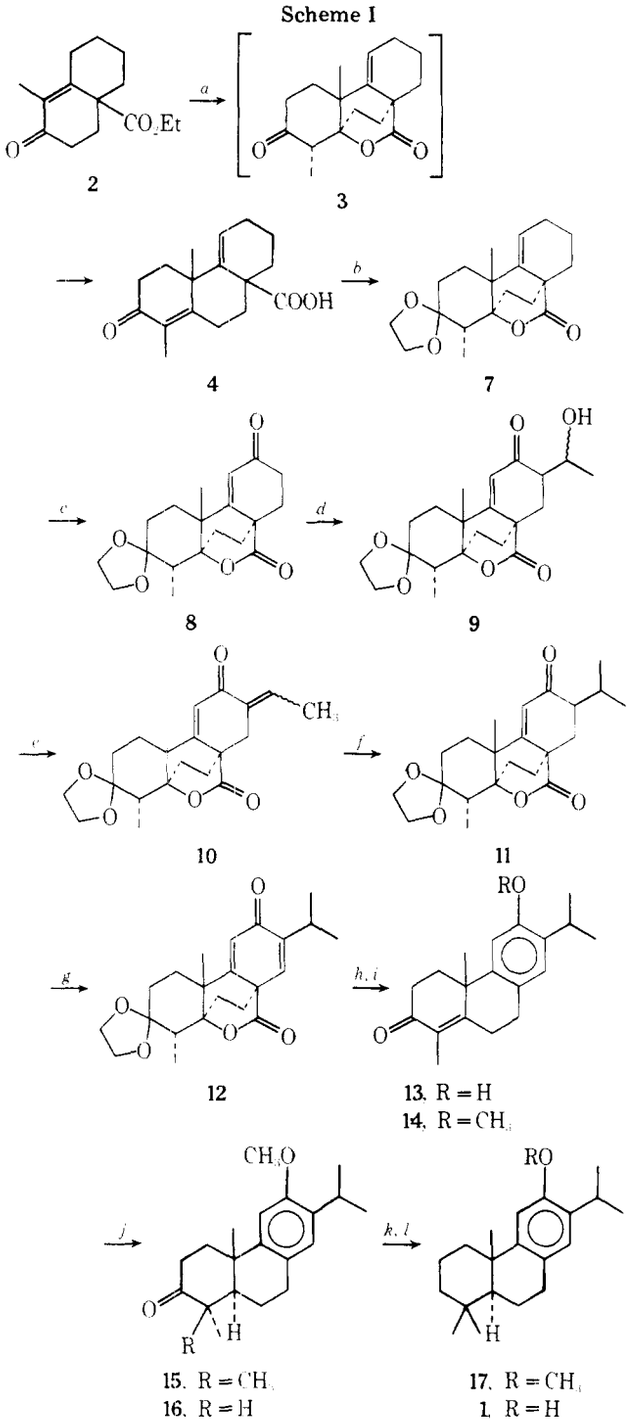
In connection with our interest in diterpenoid synthesis, we recently prepared the tricyclic acid **4** by two successive Robinson annelations of 2-carboethoxycyclohexanone and ethyl vinyl ketone.[6] The cis orientation of the angular methyl and carboxy groups in **4** was in accord with the stereoselective trapping of the enolate of the octalone **2** with ethyl vinyl ketone at the α face of **2** as a result of the directing influence of the C-8β carboethoxy group. To demonstrate the utility of this intermediate acid **4** in diterpenoid synthesis, we wish to report a total synthesis of (±)-ferruginol (**1**) and (±)-hinokione (**18**) as shown in Scheme I.

Having constructed the basic skeleton, we sought to introduce the appropriate functionality in the C ring in a sequential fashion. Prior to generating the enone functionality in the C ring (**5** → **6**), it was necessary to protect the enone



0022-3263/78/1943-4758$01.00/0

Scheme I



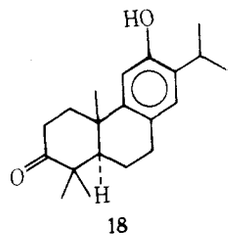
[a] NaOEt, EVK. [b] Ethylene glycol, *p*-TsOH·H_2O. [c] CrO_3·2Py. [d] LDA, $ZnCl_2$, acetaldehyde. [e] *p*-TsOH·H_2O, heat. [f] Me_2CuLi. [g] LDA, PhSeCl followed by H_2O_2. [h] $HClO_4$, THF–H_2O. [i] NaOH, $(CH_3)_2SO_4$. [j] Li, NH_3 followed by CH_3I, THF, HMPA. [k] H_2NNH_2, KOH. [l] BBr_3.

moiety in the A ring. To this end, the ketalization of **4** with ethylene glycol proceeded with concomitant lactonization to secure the bridged δ-lactone **7** in 83% yield as shown in Scheme I. The selection of this approach for protecting the enone was suggested by the isolation of the acid **4** and not the ester in the Robinson annelation of the octalone **2** and ethyl vinyl ketone. It seemed reasonable to assume that this reaction proceeded via the bridged δ-lactone **3**, which suffered base-catalyzed β elimination to give **4**.[7] Consequently, the acid-catalyzed reverse of this process was expected to furnish the ketal **7**. We assumed that equilibration of the intermediate enol of **3** would result in the C-4 methyl group adopting an equatorial orientation as shown.[8]

The chromium trioxide–dipyridine oxidation[9] of **7** furnished the enone **8** in 65% yield. To introduce the isopropyl group at C-13 in **8**; we employed the condensation of the zinc enolate of **8** with acetaldehyde to furnish the β-hydroxy ketone **9** as a mixture of diastereomers.[10] Dehydration of **9** with *p*-toluenesulfonic acid then secured the cross-conjugated dienones **10** as an 8:1 mixture of *E*/*Z* isomers. Migration of the exocyclic double bond in **10** to an endocyclic position was not a problem. The regioselective addition of lithium dimethylcuprate to the s-cis enone portion of **10** completed the introduction of the isopropyl group.[11] The protonation of the copper enolate was presumed to occur from the less-hindered α face to secure the C-13β oriented isopropyl group depicted in **11**.[8] A similar sequence for installing an isopropyl group on a cyclopentanone ring was recently reported by Martin.[12] The entire sequence **8** → **11** was routinely performed without isolation of the intermediates to afford **11** in 53% overall yield from **8**.

In order to install the *gem*-dimethyl group in the A ring, we first needed to reveal the enone functionality masked in **11**. To avoid generating similar enone subunits in both the A and C rings, the deprotection was delayed to allow for the conversion of **11** to the dienone **12**.[13] At this point, the acid-catalyzed hydrolysis of the ketal in **12** proceeded with concomitant β elimination, decarboxylation, and aromatization to furnish the phenol **13** in 76% yield.

The remaining problem in the synthesis involved the introduction of the *gem*-dimethyl group and the trans fusion of the A/B rings. The reductive methylation procedure of Stork[14] was applied to the phenol **13**, but led predominantly to the *O*-methyl ether **16**. The reductive methylation of **14**, however, under conditions where the enolate was alkylated with methyl iodide in the absence of ammonia, led to the desired ketone **15** in 45% yield. TheWolff–Kishner reduction[15] of **15** and O-demethylation[16] of **17** provided (±)-ferruginol (**1**), which was identical with the natural product. In addition, the O-demethylation[16] of **15** provided (±)-hinokione[17] (**18**), which was also identical with the natural product.



18

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. The abbreviation TF denotes thin film. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. NMR spectra were determined on a Varian EM390 spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga.

Ethyl 4-Methyl-4-octal-3-one-10-carboxylate (2). The procedure of McQuillan and Robinson[18] was modified as follows. To 200 mL of a 2 M solution of sodium ethoxide in ethanol at 0 °C under a nitrogen atmosphere was added 60 g (0.353 mol) of 2-carboethoxycyclohexanone in 200 mL of ethanol over a 15-min period followed by 33 g (0.393 mol) of ethyl vinyl ketone[19] in 200 mL of ethanol over a 1-h period. The mixture was stirred 5 h at 25 °C and 17 h at reflux, cooled, acidified to pH 2 with concentrated hydrochloric acid, and concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The ether solutions were washed with water and brine and dried over anhydrous magnesium sulfate. The crude product containing **2** and the corresponding acid was esterified

by refluxing with 100 mL of ethanol, 2 mL of concentrated sulfuric acid, and 200 mL of benzene for 17 h under a Dean–Stark trap. The product was concentrated under reduced pressure, diluted with ether, washed with water and brine, and dried over anhydrous magnesium sulfate. Distillation afforded 49.5 g (59%) of **2**: bp 109–118 °C (0.3–0.4 mm) [lit.[18] bp 135–136 °C (0.2 mm)]. The esterification sequence improved the yield of **2** from 33 to 59%, indicating that a substantial portion of **2** suffers hydrolysis of the ester group during the aldol portion of the annelation process.

3-Oxo-19-norpodocarp-9(11)-ene-8β,5β-carbolactone Ethylene Ketal (7). A mixture of 103 mg (0.375 mmol) of 3-oxo-16-norpodocarpa-4,9(11)-diene-8β-carboxylic acid[6] (**4**), 233 mg (3.75 mmol, 10 equiv) of distilled ethylene glycol, and ~5 mg of *p*-toluenesulfonic acid monohydrate in 20 mL of benzene were refluxed under a Dean–Stark trap for 30 h. The product was diluted with 50 mL of ether, washed successively with water and brine, and dried over anhydrous magnesium sulfate. The crude product (142 mg) was chromatographed on a 20 × 20 cm Merck silica gel F254 preparative layer plate in ether to afford 100 mg (83%) of **7**: R_f 0.70; IR (KBr) 5.72 μm (lactone); NMR ($CDCl_3$) δ 1.00 (d, J = 7 Hz, 3, $CHCH_3$), 1.07 (s, 3, angular CH_3), 2.48 (q, J = 7 Hz, 1, $CHCH_3$), 3.96 (m, 4, OCH_2CH_2O), and 5.56 (t, $J_{11,12\alpha} = J_{11,12\beta}$ = 4 Hz, C = 11 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 318 (5), 274 (59), 212 (52), 176 (100), 159 (21), 145 (27), and 131 (28).

An analytical sample was prepared by three recrystallizations from ether, mp 146–150 °C. Anal. ($C_{19}H_{26}O_4$) C, H.

On a large scale (0.1 mol), the chromatography was deleted, and pure **7** was isolated in 64–71% yield by simple crystallization from ether.

3,12-Dioxo-19-norpodocarp-9(11)-ene-8β,5β-carbolactone 3-Ethylene Ketal (8). To 7.74 g (30 mmol) of chromium trioxide–dipyridine[9] complex in 50 mL of dichloromethane was added 954 mg (3.0 mmol) of **7** in 5 mL of dichloromethane. The mixture was stirred for 17 h at 25 °C. The dichloromethane solution was decanted into 200 mL of ether. The organic solution was successively washed with saturated sodium bicarbonate solution, water, 1 M hydrochloric acid, water, and brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on four 20 × 20 cm Merck silica gel F254 preparative plates in 1:9 ethyl acetate–dichloromethane to afford 648 mg (65%) of **8**: R_f 0.46; IR ($CHCl_3$) 5.73 (lactone), 5.98 (C-12 C=O), and 6.13 μm (C=C); NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3, $CHCH_3$), 1.17 (s, 3, angular CH_3), 3.94 (m, 4, OCH_2CH_2O), and 5.86 (s, 1, C-11 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 332 (2), 288 (7), and 99 (100).

An analytical sample was prepared by two recrystallizations from hexane–dichloromethane, mp 202–206 °C. Anal. ($C_{19}H_{24}O_5$) C, H.

On large scale runs (0.05 mol), the crude product was purified by column chromatography to afford **8** in 61–67% yields.

13-(1ξ-Hydroxyethyl)-3,12-dioxo-19-norpodocarp-9(11)-ene-8β,5β-carbolactone 3-Ethylene Ketal (9). To 30 mmol (2 equiv) of lithium diisopropylamide in 60 mL of anhydrous ether at 0 °C under a nitrogen atmosphere was added 4.98 g (15 mmol) of **8** in 70 mL of anhydrous benzene. To this lithium enolate solution was added sequentially 30 mL of 0.5 M zinc chloride in ether[10] and 4.15 g of acetaldehyde. The solution was stirred for 30 min at 0 °C and 2 h at 25 °C, diluted with 250 mL of 10% dichloromethane–ether, washed successively with two 50-mL portions of saturated ammonium chloride solution and 50 mL of brine, and dried over anhydrous magnesium sulfate. Although the crude β-hydroxy ketones **9** were usually used directly in the next step, the individual diastereomers which we assume differ only in configuration at C-15 were isolated on one occasion by preparative layer chromatography on a 20 × 20 cm Merck silica gel F254 plate in 1:5 ethyl acetate–dichloromethane (two developments).

A band (R_f 0.24) afforded 20 mg (24%) of one diastereomer: mp 194–196 °C (from dichloromethane-hexane); IR (KBr) 2.99 (OH), 5.72 (lactone), 6.01 (C-12 C=O), and 6.12 μm (C=C); NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3, $CHCH_3$), 1.20 (s, 3, angular CH_3), 1.25 (d, J = 7 Hz, 3, $CH(OH)CH_3$), 2.92 (d, 1, OH, exchanges with D_2O), 3.75–4.0 (m, 4, OCH_2CH_2O), 4.05–4.35 (m, 1, $CH(OH)CH_3$), and 5.86 (s, 1, C-11 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 376 (4), 332 (18), and 99 (100).

A band (R_f 0.35) afforded 21 mg (18%) of a second diastereomer: mp 226.5–228 °C (from dichloromethane–hexane); IR (KBr) 2.90 (OH), 5.75 (lactone), 5.99 (C-12 C=O), 6.13 μm (C=C); NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, 3, $CHCH_3$), 1.18 (s, 3, angular CH_3), 1.23 (d, J = 7 Hz, 3, $CH(OH)CH_3$, portion of signal obscured by angular CH_3), 3.75–4.25 (m, 5, OCH_2CH_2O and $CH(OH)CH_3$), 4.31 (m, 1, OH, exchanges with D_2O), and 5.83 (s, 1, C-11 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 376 (5), 332 (28), and 99 (100).

The propensity of the β-hydroxy ketones **9** to dehydrate to **10** on standing precluded obtaining satisfactory analyses and accounted for the low isolated yields on chromatography.

3,12-Dioxo-17,19-dinorabieta-9(11),13(15)-diene-5β,8β-carbolactone 3-Ethylene Ketal (10). The crude β-hydroxy ketones **9** from the preceding experiment and 750 mg of *p*-toluenesulfonic acid monohydrate in 100 mL of benzene were refluxed for 9 h under a Dean–Stark trap. The product was diluted with 200 mL of 20% dichloromethane–ether, washed successively with two 50-mL portions of saturated sodium bicarbonate solution and 50 mL of brine, and dried over anhydrous magnesium sulfate. Although the crude dienones **10** were generally used directly in the next step, it was possible to isolate the *E*/*Z* isomers in an 8:1 ratio by preparative layer chromatography on Merck silica gel F254 in 1:5 ethyl acetate–dichloromethane.

The *E* isomer[12] (R_f 0.55) of **10** had: IR (KBr) 5.72 (lactone), 6.00 (C-12 C=O), 6.12, and 6.20 μm (C=C); UV (ethanol) λ_{max} 255 nm (ε 13 300); NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 3, $CHCH_3$), 1.20 (s, 3, angular CH_3), 3.8–4.1 (m, 4, OCH_2CH_2O), 5.96 (s, 1, C-11 vinyl H), and 6.87 (d of d of q, $J_{15,16}$ = 7.2, $J_{14\alpha,15}$ = 2.4, and $J_{14\beta,15}$ = 1.2 Hz (last two coupling constants could be reversed), 1, C-15 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 358 (20), 313 (7), 302 (3) and 99 (100).

An analytical sample was prepared by three recrystallizations from ethyl acetate–hexane, mp 192.5–193.5 °C. Anal. ($C_{21}H_{26}O_5$) C, H.

The *Z* isomer[12] (R_f 0.57) of **10** had: IR (KBr) 5.72 (lactone), 6.01 (C-12 C=O), 6.16, and 6.22 μm (C=C); UV (ethanol) λ_{max} 252 nm (ε 9840); NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 3, $CHCH_3$), 1.18 (s, 3, angular CH_3), 3.8–4.1 (m, 4, OCH_2CH_2O), 5.87 (s, 1, C-11 vinyl H), and 5.85–6.05 (m, 1, C-15 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 358 (28), 313 (10), and 99 (100).

An analytical sample was prepared by three recrystallizations from ethyl acetate–hexane, mp 170.5–172.5 °C. Anal ($C_{21}H_{26}O_5$) C, H.

3,12-Dioxo-19-norabiet-9(11)-ene-8β,5β-carbolactone 3-Ethylene Ketal (11). To a solution of 3.0 equiv of lithium dimethylcuprate in 200 mL of anhydrous ether at 0 °C under a nitrogen atmosphere was added the crude dienone **10** from the preceding experiment in 60 mL of anhydrous benzene. The mixture was stirred for 1 h at 0 °C and 2.5 h at 25 °C. The product was diluted with 150 mL of 20% dichloromethane–ether and washed successively with three 200-mL portions of 1:9 concentrated ammonium hydroxide–saturated ammonium chloride solution, 175 mL of water, and 175 mL of brine. The crude product (6.2 g) was chromatographed on 200 g of Merck silica gel 60 using an ethyl acetate–dichloromethane progression (0–20% in 5% steps) to afford 3.0 g (54% overall from **8**) of **11**: IR (KBr) 5.71 (lactone), 6.00 (C-12 C=O), and 6.11 μm (C=C); NMR ($CDCl_3$) δ 0.8–1.1 (three d, 9, $CH(CH_3)_2$ and $CHCH_3$), 1.17 (s, 3, angular CH_3), 3.95 (m, 4, OCH_2CH_2O), and 5.82 (s, 1, C-11 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 374 (5), 332 (29), 287 (5), and 99 (100).

An analytical sample was prepared by recrystallization from ether–dichloromethane, mp 248–250 °C. Anal. ($C_{22}H_{30}O_5$) C, H.

In small but variable amounts, we also isolated a product more polar than **11**, but with a similar NMR: δ 0.8–1.1 (three d, 9, $CH(CH_3)_2$ and $CHCH_3$), 1.78 (s, 3, angular CH_3), 3.97 (m, 4, OCH_2CH_2O), and 5.92 (s, 1, C-11 vinyl H). This product is presumably the C-13 epimer of **11**.

3,12-Dioxo-19-norabieta-9(11),13-diene-8β,5β-carbolactone 3-Ethylene Ketal (12). To 0.62 mmol (1.5 equiv) of lithium diisopropylamide in 2 mL of anhydrous THF at −78 °C under a nitrogen atmosphere was added 155 mg (0.41 mmol) of **11** in 3 mL of anhydrous THF and 0.5 mL of hexamethylphosphoramide. After stirring 30 min, a solution of 126 mg (0.66 mmol, 1.6 equiv) of phenylselenyl chloride in 2 mL of anhydrous THF was introduced. The mixture was stirred for 90 min and then poured into 25 mL of 0.5 M hydrochloric acid and 50 mL of 20% dichloromethane–ether. The organic layer was washed successively with water, saturated sodium bicarbonate solution, and brine and dried over anhydrous magnesium sulfate. Solvents were evaporated to afford 318 mg of yellow oil. To the crude selenation product in 5 mL of dichloromethane at 25 °C was added 35 mg (1.03 mmol, 2.5 equiv) of 30% hydrogen peroxide in 0.5 mL of H_2O. The mixture was stirred for 45 min and then diluted with 50 mL of 20% dichloromethane–ether. The organic layer was washed successively with saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. The crude product (185 mg) was chromatographed on three 20 × 20 cm Merck silica gel F254 preparative layer plates in 1:9 dichloromethane–ethyl acetate to afford 105 mg (69%) of **12**: R_f 0.31; IR ($CHCl_3$) 5.74 (lactone), 6.02 (C-12 C=O), and 6.15 μm (C=C); UV (EtOH) λ_{max} 249 nm (ε 13 800); NMR ($CDCl_3$) δ 0.95–1.35 (m, 12, C-16, -17, -18, and -20 CH_3), 3.95 (m, 4, OCH_2CH_2O), 6.16 (s, 1, C-11 vinyl H), and 6.92 (s, 1, C-14 vinyl H);

mass spectrum (70 eV) *m/e* (rel intensity) 372 (1) and 99 (100).

Decomposition of this product on standing precluded obtaining an elemental analysis.

12-Hydroxy-19-norabieta-4,8,11,13-tetraen-3-one (13). To 87 mg (0.23 mmol) of **12** in 5 mL of THF under a nitrogen atmosphere was added 1.5 mL of 25% perchloric acid in water. The solution was stirred at 60 °C for 2 h, and then diluted with 50 mL of 20% dichloromethane–ether. The organic layer was washed successively with water and brine and dried over anhydrous magnesium sulfate. The crude product (91 mg) was chromatographed on two 20 × 20 cm Merck silica gel F254 preparative layer plates in 1:9 dichloromethane–ethyl acetate (two developments) to afford 50 mg (76%) of **13:** IR ($CHCl_3$) 2.78 (OH), 6.06 (C=O), and 6.17 μm (C=C); NMR ($CDCl_3$) δ 1.20 and 1.25 (two d, J = 7 Hz, 6, $CH(CH_3)_2$), 1.50 (s, 3, angular CH_3), 1.87 (s, 3, vinyl CH_3), 3.19 (heptet, 1, $CH(CH_3)_2$), 5.53 (s, 1, OH, exchanges with D_2O), and 6.71 and 6.91 (two s, 2, C-11, C-14 aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 284 (52), 269 (100), 241 (15), 195 (6), and 82 (67).

The benzoate derivative of **13** was prepared in the usual fashion in 80% yield and was purified by chromatography on a 20 × 20 cm Merck silica gel F254 plate twice in 1:15 ethyl acetate–dichloromethane: R_f 0.52; mp 63–66 °C; IR ($CHCl_3$) 5.75 (ester C=O), 6.06 (C-3 C=O), 6.19 C=C), and 6.25 μm (aromatic); NMR ($CDCl_3$) δ 1.22 and 1.24 (two d, J = 7 Hz, 6, $CH(CH_3)_2$), 1.54 (s, 3, angular CH_3), 1.89 (s, 3, vinyl CH_3), 7.08 and 7.10 (two s, 2, C-11, C-14 aromatic H), and 7.32–8.33 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 388 (5), 122 (44), 106 (100), 84 (72), and 78 (47). Anal. ($C_{26}H_{28}O_3$) C, H.

12-Methoxy-19-norabieta-4,8,11,13-tetraen-3-one (14). To 193 mg (0.67 mmol) of **13** in 70 mL of anhydrous acetone was added 14 g of anhydrous potassium carbonate and 850 mg (6.7 mmol, 10 equiv) of dimethyl sulfate. The mixture was refluxed under a nitrogen atmosphere for 2 h, filtered, and condensed. The crude product was diluted with 150 mL of ether, washed successively with 75 mL of 1 M hydrochloric acid, three 75-mL portions of water, and 75 mL of brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on five 20 × 20 cm Merck silica gel F254 preparative layer plates in 1:25 ethyl acetate–dichloromethane to afford 200 mg (100%) of **14:** R_f 0.49; IR (TF) 6.00 (C=O), 6.19 (C=C), 6.35 (aromatic), and 8.00 μm (C–O); NMR ($CDCl_3$) δ 1.16 and 1.19 (two d, J = 7 Hz, 6, $CH(CH_3)_2$), 1.52 (s, 3, angular CH_3), 1.86 (s, 3, vinyl CH_3), 3.25 (heptet, 1, $CH(CH_3)_2$), 3.79 (s, 3, OCH_3), 6.71 and 6.90 (two s, 2, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 298 (54), 283 (100), and 255 (11).

A sample of **14** was recrystallized three times from methanol–water, mp 91–92 °C (lit.[21] mp 92–94 °C).

12-Methoxy-8,11,13-abietatrien-3-one (15). To a solution of 40 mg (5.6 mmol, 7.0 equiv) of lithium in 25 mL of anhydrous liquid ammonia under a slow stream of nitrogen in a 100 mL three-neck flask equipped with a dry ice–acetone condenser was added 120 mg (0.40 mmol) of **14** in 3 mL of anhydrous THF. The blue solution was stirred for 1 h. The addition of ~0.1 mL of methyl iodide discharged the blue color. The dry ice–acetone condenser was replaced by a water-jacketed condenser, and the ammonia was evaporated with a water bath under a stream of nitrogen. The remaining traces of ammonia (and THF) were removed under high vacuum to afford a white salt. Unless precautions were taken to remove the ammonia, the yield of **15** was substantially reduced and **16** was the major product. To the lithium enolate salt in 5.5 mL of 1:10 anhydrous HMPA–THF was added 2.84 g (20 mmol, 50 equiv) of methyl iodide. The solution was stirred under a nitrogen atmosphere for 18 h at 25 °C and for 4 h at 40 °C. The crude product was diluted with 25 mL of 20% dichloromethane–ether and 25 mL of water. The aqueous layer was extracted with an additional 25 mL of 20% dichloromethane–ether. The combined organic solutions were washed successively with four 25-mL portions of water and 25 mL of brine and dried over anhydrous magnesium sulfate. The crude product (139 mg) was purified by liquid–liquid chromatography on a 9 mm × 1.5 m (diameter × length) column of Woelm silica gel (flow rate = 4.3 mL/min) using 1:2 hexane–benzene to afford 55.6 mg (45%) of **15:** retention time 30 min; IR (KBr) 5.90 (C=O), 6.21 (aromatic), and 8.03 μm (C–O); NMR ($CDCl_3$) δ 1.04–1.37 (m, 15, C-4 geminal CH_3, angular CH_3 and $CH(CH_3)_2$), 3.21 (heptet, 1, $CH(CH_3)_2$), 3.74 (s, 3, OCH_3), 6.65 and 6.81 (two s, 2, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 299 (80), 257 (39), 215 (20), and 173 (13). This product **15** had spectra identical with a sample of (+)-hinokione methyl ether[21b] provided by Dr. Cambie.

An analytical sample was prepared by three recrystallizations from ether, mp 132–133 °C (lit.[21a] mp 119–121 °C). Anal. ($C_{21}H_{30}O_2$) C, H.

The chromatography conditions were critical to separate **15** from a slightly more polar byproduct (retention time ~35 min), which was identified as the simple reduction product **16** largely on the basis of the NMR spectrum, which displayed a doublet at δ 0.91 for the C-4 methyl group after removing the C-3 ketone in a Wolff–Kishner reaction.

(±)-Ferruginyl Methyl Ether (17).[5] To 34.5 mg (0.110 mmol) of **15** and 0.1 g of hydrazine hydrochloride was added under a nitrogen atmosphere 5 mL of distilled triethylene glycol and 1 mL of 99% hydrazine hydrate. The reaction was stirred at 125 °C for 4.5 h, 0.4 g of potassium hydroxide was added, and then the temperature was slowly increased to 210 °C in order to remove water and excess hydrazine. The reaction was stirred at 195 °C for an additional 4 h, cooled, and diluted with 50 mL of cold 20% dichloromethane–ether and 50 mL of 1 M hydrochloric acid. The aqueous layer was extracted with an additional 50 mL of 20% dichloromethane ether. The combined organic solutions were washed successively with three 50-mL portions of water and 50 mL of brine and dried over anhydrous magnesium sulfate. The crude product (41.0 mg) was chromatographed on a 20 × 20 cm Merck silica gel F254 preparative layer plate in hexane (two developments). A band (R_f 0.45) was eluted to afford 18.7 mg (57%) of **17**:[5] IR ($CHCl_3$) 6.20 (aromatic), 8.02 μm (C–O); NMR ($CDCl_3$) δ 0.92 (s, 6, C-4 geminal CH_3), 1.18, 1.20 (two s, 6, $CH(CH_3)_2$), 3.21 (heptet, 1, $CH(CH_3)_2$), 3.77 (s, 3, OCH_3), and 6.69 and 6.80 (two s, 2, aromatic H).

The identity of **17** was also established by comparison with a sample of ferruginyl methyl ether prepared from (+)-ferruginol (**1**). The procedure described in the preparation of **14** was repeated using 15 mg of (+)-ferruginol (**1**), 66 μL of dimethyl sulfate, and 1.4 g of potassium carbonate in 7 mL of acetone (reflux, 4 h) to afford, after chromatography on a 20 × 20 cm Merck silica gel F254 analytical plate in 1:15 ethyl acetate–hexane, 6 mg (38%) of ferruginyl methyl ether (R_f 0.67). Since **17** has already been converted to **1** by Rao,[5] at this stage the total synthesis of **1** was formally completed.

(±)-Ferruginol (1). To 8.4 mg (0.028 mmol) of **17** in 0.5 mL of anhydrous dichloromethane at −78 °C was added 4 drops of boron tribromide.[16] The light brown solution was stirred at −78 °C for 10 min and at 25 °C for 30 min. The boron tribromide was quenched by adding several drops of water. The product was diluted with 25 mL of 20% dichloromethane–ether, washed successively with 25 mL of 1 M hydrochloric acid, three 25-mL portions of water, and 25 mL of brine, and dried over anhydrous magnesium sulfate. The crude product (10.8 mg) was chromatographed on a 20 × 20 cm Merck silica gel F254 analytical plate in 1:5 ethyl acetate–hexane to afford 5.6 mg (70%) of (±)-ferruginol (**1**), R_f 0.65. The spectra of (±)-**1** were identical with an authentic sample of (+)-ferruginol (**1**).

An authentic sample of (+)-ferruginol (**1**) was prepared by chromatographing the crude oils kindly provided by Professors Meyer and Wenkert on Merck silica gel F254 in 1:25 ethyl acetate–dichloromethane (R_f 0.77) and then in 1:15 ethyl acetate-hexane (two developments, R_f 0.47) to afford (+)-**1** as a glass. The identity of this material was established by conversion to the crystalline benzoate derivative having spectra identical with those provided by Professor Matsumoto. Saponification of the benzoate (NaOH, 95% ethanol, reflux, 1 h) provided a pure sample of (+)-ferruginol (**1**).

(±)-Hinokione (18). The procedure described for the preparation of (±)-**1** from **17** was repeated using 21.3 mg of **15** and 7 drops of boron tribromide in 1 mL of anhydrous dichloromethane at −78 °C to afford, after chromatography on a 20 × 20 cm Merck silica gel F254 analytical plate in 1:2 hexane–ether, 12.6 mg (62%) of (±)-hinokione (**18**): R_f 0.63; mp 146–149 °C (from hexane–ether). The spectra of (±)-**18** were identical with an authentic sample of (+)-hinokione (**18**).

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Registry No.—(+)-**1**, 514-62-5; (±)-**1**, 10219-82-6; **2**, 67938-38-9; **3**, 67938-39-0; **4**, 67938-40-3; **7**, 67938-41-4; **8**, 67938-42-5; **9** isomer 1, 67938-43-6; **9** isomer 2, 67999-01-3; (*E*)-**10**, 67938-44-7; (*Z*)-**10**,

67999-02-4; **11**, 67938-45-8; **12**, 67938-46-9; **13**, 67938-47-0; **13** benzoate, 67938-48-1; **14**, 167999-03-5; **15**, 67999-04-6; (+)-**17**, 10064-26-3; (±)-**17**, 64199-80-0; **18**, 67999-05-7; 3,12-dioxo-19-norabiet-9(11)-ene-5β,8β-carbolactone 3-ethylene ketal phenylselenyl derivative, 67938-49-2; 2-carboethoxycyclohexanone, 1655-07-8; ethyl vinyl ketone, 1629-58-9; acetaldehyde, 75-07-0; phenylselenyl chloride, 5707-04-0.

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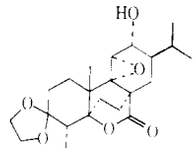

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Synthesis of Harringtonine, a *Cephalotaxus* Antitumor Alkaloid[1]

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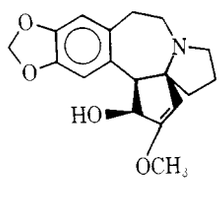
Harringtonine (**10a**), one of the antitumor alkaloid esters from *Cephalotaxus harringtonia*, has been synthesized from cephalotaxine (**1**) by an indirect approach involving a series of cyclic ketal and hemiketal intermediates. A Claisen condensation of $(CH_3)_2C{=}CHCH_2CO_2Et$ (**3**) with diethyl oxalate gives $(CH_3)_2C{=}CHCH(COCO_2Et)(CO_2Et)$ (**4**). This substituted oxalacetate affords methyl 2-methoxy-5,5-dimethyltetrahydro-2-furoate (**6**) on aqueous acid hydrolysis followed by reaction with HCl–MeOH. Cyclic ketal **6** is then converted by a series of transformations to cephalotaxyl 2-hydroxy-5,5-dimethyltetrahydro-2-furoate (**9**) as a mixture of two diastereomers. Treatment of this mixture with methyl bromoacetate and zinc via the Reformatsky procedure yields harringtonine (**10a**) and its acyl C-2 epimer, epiharringtonine (**10b**).

Cephalotaxus harringtonia plant material contains small amounts of a number of ester alkaloids which have shown significant activity in several experimental tumor systems in mice.[2,3] Prominent in this active alkaloid group are harringtonine and homoharringtonine. Harringtonine[4] is an ester composed of the alkaloid (−)-cephalotaxine (**1**) esterified with the 2*R* enantiomer of acid **2**, and homoharringtonine contains an additional methylene group in the acyl side chain.[4] More recently, clinical testing with mixtures of these two alkaloids has given promising results with leukemia patients in the People's Republic of China.[5] However, a scarcity of plant material has halted testing of these alkaloid esters in the United States at the preclinical stage.



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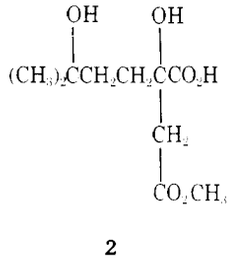

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Cephalotaxus plant material usually contains appreciably more unesterified cephalotaxine (**1**) than its active esters. Since cephalotaxine has also been synthesized,[6] it is desirable to have an effective method of converting **1** to its active esters. All attempts to acylate **1** directly with fully elaborated acid moieties,[7] such as **2**, have failed due to (a) severe steric hindrance at the reaction site, (b) difficulties in unmasking hydroxyl functions and generating the carbomethoxymethylene side chain at the terminal stage, and (c) problems associated with instability of α-keto esters having a $-C(O-)CCC(=O)-C(=O)O-$ grouping. The sequence we employed[8] in synthesizing harringtonine, shown in Scheme I, deals with all of these problems in some degree by utilizing intermediates which cyclize readily to form ketals or hemiketals in a way reminiscent of common reducing sugars.