Phenol Benzylic Epoxide to Quinone Methide Electron Reorganization: Synthesis of (±)-Taxodone

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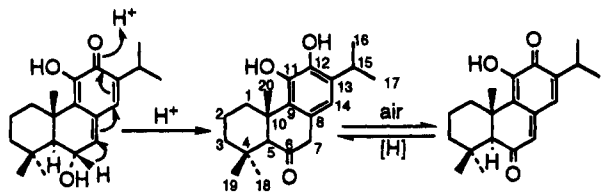
The total synthesis of (±)-taxodone (**1**) is described. The C-ring is formed by the cycloaddition of methyl acrylate with furan **8**, the latter derived from isodrimenin. The C13 isopropyl group was introduced via a sulfur ylide rearrangement followed by reductive cleavage. Compound **1** was synthesized in 61% yield by deprotection and intramolecular oxirane opening of diacetate **31** with potassium *tert*-butoxide and water in THF.

In 1968, the late S. Morris Kupchan and co-workers reported the isolation, structure determination, and basic chemistry of two novel diterpenoid quinone methides, taxodone (**1**) and taxodione (**2**), each of which possesses *in vivo* activity against the Walker intramuscular carcinosarcoma 256 in rats (25 and 40 mg/kg, respectively).[1] In this initial work, Kupchan demonstrated that **1** aromatizes to catechol ketone **3** upon exposure to mild acid. Air oxidation of **3** affords **2** in good yield.



Taxodone (1) **3** **Taxodione (2)**

Taxodone was the first isolated example of a quinone methide[2,3] with a labile hydrogen adjacent to this reactive chromophore. It has been known for over 25 years and its rearrangement/oxidation product, taxodione, has been synthesized numerous times.[4] Taxodone displays higher activity than taxodione and both have subsequently been found in other plants (most recently in 1993).[5,6] Taxodone has never been synthesized previously, nor has any mention of attempted syntheses been found in the literature. Herein we describe the first total synthesis of tricyclic diterpene **1** and its conversion to **2** via the Kupchan protocol. By this approach both biologically active compounds are obtained from a single synthetic venture. It should be noted that while the natural product is synthesized in racemic form,[7] the pure enantiomers of compound **12** have been described in the literature.[8]

Results and Discussion

As taxodone rearranges readily in the presence of mild acids and reacts readily with nucleophiles,[1c] the challenge was to define conditions under which the final conversion to **1** could be accomplished from a suitable precursor. A synthetic plan was formulated that utilized protected epoxide intermediate **4**. It was envisioned that deprotection would induce an electron cascade leading to opening of the epoxide to give taxodone. This approach

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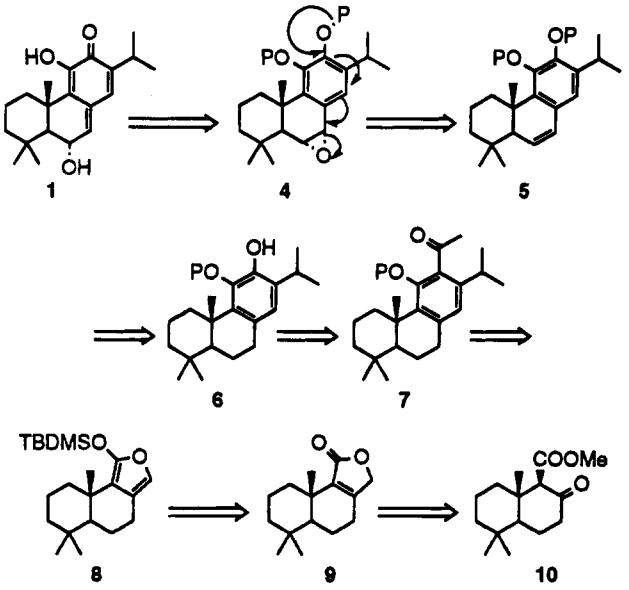
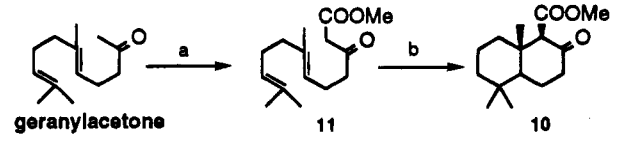
is reminiscent of the early work of Winstein on the synthesis of simple quinone methides.[9]



Disconnection of **4** led to styrene **5**. Styrene **5** should be available from the corresponding saturated derivative **6**, which in turn was expected to arise from Baeyer–Villiger oxidation of **7**. It was anticipated that Diels–Alder reaction of furan **8** would give the C ring of **7** after aromatization. Furan **8** would arise from the insect antifeedant isodrimenin (**9**), itself derived from known β-keto ester **10**.

The synthesis of taxodone commenced with **10**, which was first synthesized by Ragoussis' modification[10] of Eschenmoser's method.[11] While this procedure gave very pure product, it entailed six steps and the first reaction of the series was problematic.

White and co-workers developed a synthesis of **10** via cyclization of **11** with stannic chloride in wet methylene chloride.[12] In this work **11** was prepared from geranyl bromide. A less expensive and more efficacious route was developed in which **11** was prepared from geranylacetone by treatment with sodium hydride and dimethyl carbonate.

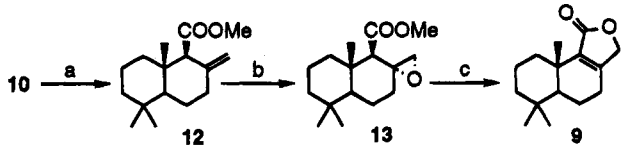


a) NaH, dimethyl carbonate, ether, 82%; b) $SnCl_4$, CH_2Cl_2, 50%.

To prepare **9** from **10** the route of Ragoussis and co-workers[10] was originally followed. Treatment of **10** with a salt-free Wittig reagent obtained from sodium amide and methyltriphenylphosphonium bromide afforded (85%) (±)-methyl albicanate (**12**). It was found that the refluxing toluene used in the original reference could be replaced with THF at room temperature to yield the same results.[13] Resolution is possible at this stage by conversion of **12** to albicanic acid with LiSMe in HMPA[14] or LiI in refluxing collidine, followed by salt formation with enantiomerically pure methylbenzylamine or ephedrine.[8]

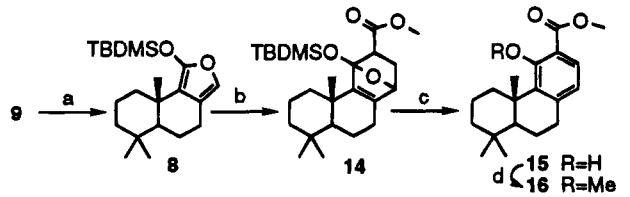
Following Ragoussis' procedure, **12** was epoxidized with MCPBA in methylene chloride at rt but this led to the formation of unidentified byproducts which lowered the yield of epoxide **13**. Beginning the reaction at 0 °C and allowing it to warm slowly to rt afforded epoxide **13** in 80% yield after recrystallization. Using MPPP in place of MCPBA for this epoxidation gave poor results.

Cyclization of epoxide **13** with TsOH in refluxing chloroform by Ragoussis' method to afford drimenin followed by isomerization with sodium methoxide in methanol gave (±)-isodrimenin, **9**, in poor yield in our hands. A direct route[15] to (±)-isodrimenin by treatment of **13** with excess LDA in THF at −78 °C to rt was investigated and found efficacious, affording **9** in 93% yield.



a) $NaNH_2$, Ph_3PMeBr, THF, 85%; b) MCPBA, CH_2Cl_2, 0 °C to RT, 80%; c) LDA, THF, -78 °C to RT, 93%.

Treatment of **9** with LDA–HMPA followed by TBDMSCl[16] gave rise (100%) to furan **8**. Originally it was hoped that the C12 and C13 functionalities could be introduced simultaneously at this point via a Diels–Alder reaction between **8** and 5-methyl-3-hexen-2-one. However, with the exception of methyl acrylate and *N*-methylmaleimide, compound **8** could not be induced to react with a variety of α,β-unsaturated esters or ketones under a range of conditions (refluxing toluene, 10 kbar in toluene,[17] trityl perchlorate in methylene chloride, lithium perchlorate in ether, $TiCl_4$ in methylene chloride, nitromethane, HMPA). In contrast, methyl acrylate reacted with **8** under several cycloaddition conditions in both nonpolar and polar (nitromethane, HMPA, DMF, acetonitrile) solvents. Reacting **8** with methyl acrylate (4 equiv, $MeNO_2$, 18 h) yielded **14** as a pair of diastereoisomers which were immediately aromatized (MeOH, H_2O, HCl, 4 h) to afford methyl salicylate (**15**) (74% from **9**) and a 15% recovery of **9**. The diastereoisomers **14** could be isolated by chromatography, with some decomposition.



a) LDA, HMPA, TBDMSCl, THF, 100%; b) methyl acrylate, $MeNO_2$, 24 h; c) HCl, MeOH, H_2O, 1 h, 74% from **9**; d) MeI, KOH, DMSO, 1 h, 95%.

The phenol group required protection at this point to avoid side reactions in subsequent transformations.

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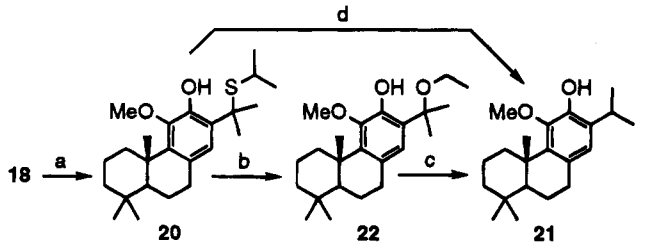
Attempted methylation of **15** with potassium carbonate and dimethyl sulfate in refluxing diethyl ketone (a scheme successful with a substrate containing a methoxy functionality in place of the carbomethoxy of **15**[18]) left the starting material unaffected. Methylation with MeI and KOH in DMSO[19] was successful and gave dimethyl salicylate (**16**) in 95% yield.

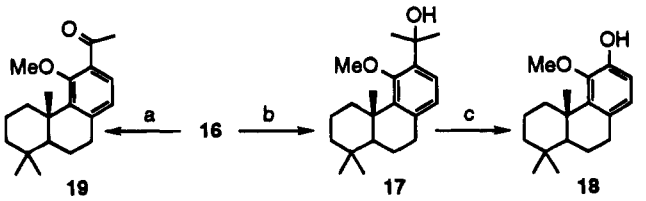
Conversion of **16** into carbinol **17** was first attempted with MeLi but this led to the formation of methyl ketone **19** in approximately the same yield as **17**. Using MeLi in THF at −15 °C (a successful method for a very similar substrate[16]) also resulted in the recovery of substantial methyl ketone. Attempted conversion of this methyl ketone to the acetate of **18** by a Baeyer–Villiger reaction with MCPBA led to a conversion of less than 5% after 24 h. Treatment of **16** with MeLi and $CeCl_3$[20] gave the desired carbinol with minimal enolization and afforded **17** as a oil, which was immediately used in its crude form as it decomposed on standing or on silica gel to the corresponding styrene. Subsequent hydroperoxide rearrangement[21] of crude **17** with hydrogen peroxide in acidic THF yielded (89% from **16**) guaiacol (**18**) as a crystalline solid.



a) i. *i*-Pr_2S, SO_2Cl_2, pyr, -40 °C ii. Et_3N; b) Raney Ni, EtOH, reflux 1 h, 51%; c) H_2, Pd, acid, 100%; d) Raney Ni, EtOH, reflux 1 h, 61% from **18**.

Since introduction of the isopropyl moiety was not achieved at the cycloaddition stage of the sequence, a means to introduce this group had to be devised. Ortho lithiation approaches, Friedel–Craft acylation, and Friedel–Craft alkylations were all unsuccessful in producing the desired ortho isopropylated derivatives in adequate yield. Ultimately the introduction of the C13 alkyl group was best accomplished by the formation and rearrangement of a sulfur ylide followed by reduction. Treatment of **18** with isopropyl sulfide and sulfuryl chloride at −40 °C followed by triethylamine affords benzyl sulfide **20**.[22] Reductive desulfurization of crude **20** with Raney nickel in refluxing ethanol yields (61% from **18**) 11-methoxyferruginol (**21**) and a 20% recovery of **18**.

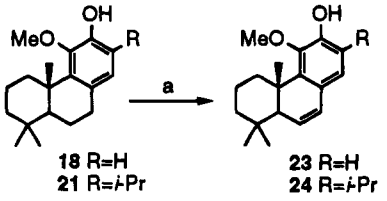
The use of an inadequate excess of Raney nickel led to the isolation of the benzyl ethyl ether **22** in 51% crystallized yield, which was quantitatively converted to **21** by



a) MeLi, THF, -78°C, 46%; b) $CeCl_3$, MeLi, THF, -78°C; c) 30% H_2O_2, TsOH, THF, 89% from **16**.

hydrogenation with palladium in the presence of acid. Substitution of methanol for ethanol gave a mixture of **21** and a new compound that exhibited a singlet at δ = 3.49 as expected for the methyl ether, but the mixture was inseparable by column chromatography. Only starting material was recovered when the sulfide was refluxed in ethanol without Raney nickel.

Either the introduction of the 6,7-double bond or demethylation of the anisole functionality followed by protection of the resulting catechol could have been implemented at this point in the synthetic sequence. The introduction of unsaturation was explored first using DDQ in dioxane on **18** as a model substrate for **21**. This reaction can give styrene **23** in 79% chromatographed yield (containing 7% starting material), but it was not reproducible. Treatment of **21** with DDQ under these conditions afforded a 74% chromatographed yield of an orange gum that decomposed on standing. NMR analysis of this material indicated that it was primarily desired styrene **24**, along with 10% of starting material. No evidence of oxidation of the isopropyl group was observed.



a) DDQ, dioxane, 79% **23**, 74% **24**.

Deprotection of **23** with a variety of reagents followed by protection of the resulting catechol led to low yields of protected styrenes. Because of these difficulties, this sequence was abandoned and a demethylation/protection/C=C introduction sequence was adopted. Since DDQ dehydrogenation only works with unprotected phenols,[23] an alternative 6,7-oxidation scheme was necessary.

Demethylation of **21** was best achieved with boron tribromide to give crude catechol **25** in quantitative yield. Initial plans called for the use of silyl ethers as protecting groups as they can be easily removed with fluoride ion. Lithium sulfide in acetonitrile[24] gave the best yields of silyl ethers when the catechol derivative of **18** was the substrate (the usual basic silylation conditions led to the formation of multiple byproducts), but it was not possible to silylate **25**, presumably because of steric hindrance. Acetate protecting groups were therefore chosen as an alternative to silyl ethers. Initially crude **25** was used in the acetylation reactions, but it often contained an unidentified impurity (not the corresponding *o*-quinone) that severely lowered the yield of diacetate **26**. Chro-

(16) (a) Garver, L. C. Ph.D. Thesis Dissertation, Stanford University, 1982, 179. (b) Garver, L. C.; van Tamelan, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 867.
(17) Special thanks to Professor Barry Trost (Stanford University) for the use of his high-pressure apparatus.
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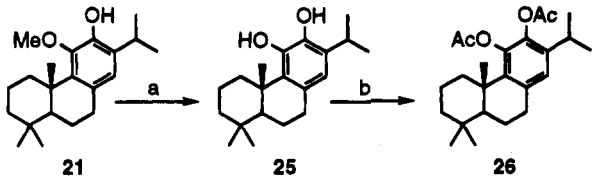
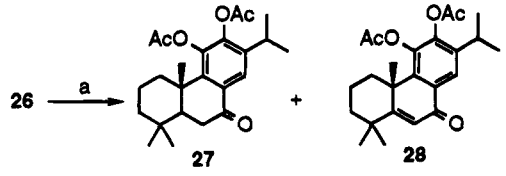
matography of crude **25** gives pure catechol in 95% yield that upon treatment with isopropenyl acetate in refluxing toluene yields diacetate **26** in quantitative yield.



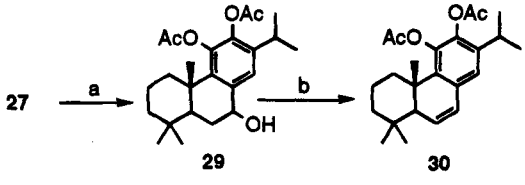
a) BBr_3, CH_2Cl_2, -78 °C to RT, 95%; b) isopropenyl acetate, TsOH, PhMe, reflux, 8 h,100%.

As acetoxylation or bromination at C7 followed by elimination gave poor results, a benzylic oxidation/reduction/elimination scheme was investigated to introduce a double bond to **26**. A variety of benzylic oxidation systems (PCC in refluxing benzene,[25] PCC/*tert*-butyl hydroperoxide (TBHP),[20] PDC/TBHP,[26] chromium pillared clay (CrPILC) in CH_2Cl_2[27]) were investigated with poor results. Only two methods gave usable yields of **27**. Reaction of **26** with chromium hexacarbonyl and TBHP in refluxing benzene[28] gives a 71% yield of **27** after chromatography. A byproduct elutes immediately after **27** that was identified as the α,β-unsaturated ketone **28** (4%). Ketone **27** could also be prepared in 61% yield by oxidation of **26** with chromium trioxide in acetic acid.



a) TBHP, $Cr(CO)_6$, PhH, reflux, 28 h, 71% **27**, 4% **28**.

A variety of reduction methods (Al–Ni,[29] lithium pyrrolidinoborohydride,[30] and sodium borohydride in methanol at 0 °C) were explored for reducing **27** with poor results. In the end, sodium borohydride in water and THF gave the best yield (100% crude) of alcohol **29**. Elimination of **29** was accomplished by refluxing in toluene with TsOH to give alkene **30** in 85% yield. The addition of isopropenyl acetate at the end of this reaction reverses the small amount of acetate hydrolysis that occurs.

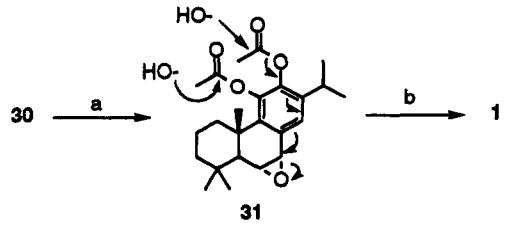


a) $NaBH_4$, THF, H_2O, 100%; b) TsOH, PhMe, reflux, 1 h, 85%.

The key intermediate in our proposed synthetic route was a 6,7-epoxide with suitable (base-sensitive) protection of the catechol functionality. While the acetates on C11 and C12 fulfill the latter need, introduction and isolation of the oxirane was a different matter. The vast majority of literature on systems of this type indicate that a 6,7-epoxide is rarely stable enough for isolation. We are aware of only one example of an epoxide of similar structure (**4**, P = Bz) isolated in pure form (an analytical sample prepared by crystallization in unstated yield).[2d] It is significant that this isolated epoxide derivative is protected with ester functionalities as is **31**. The electron withdrawal of the ester functionality para to C7 destabilizes the C7 carbocation that leads to rearrangement of the epoxide. Related epoxide intermediates with electron-donating protecting groups (such as alkoxy functionalities) are very difficult to isolate in pure form, even when dimethyldioxirane is the epoxidation agent, due to the ease with which they rearrange.[31] Other research groups have reported syntheses of taxodione (**2**) that have employed synthetic intermediates similar to the epoxide precursor to taxodone presented here. These epoxide intermediates were invariably prepared with MCPBA and rearranged to the C6 keto compounds without purification of the epoxide (this rearrangement often beginning in the acidic medium of the epoxidation reaction). In several cases the rearrangement was carried out (or continued) by elution of the crude epoxide through silica gel.

Dimethyldioxirane has proven to be a particularly mild epoxidation agent and a series of sensitive molecules have been prepared through its use.[32] In the event, treatment of **30** with dimethyldioxirane[33] in acetone gives crude **31** in quantitative yield. Surprisingly the crude epoxide was stable enough to be quickly chromatographed in 81% yield but the best overall yield of **1** was achieved with crude **31**.

The stage was now set for the final deprotection/electron reorganization step. The acetate functionalities of **31** proved to be surprisingly resistant to hydrolysis and a series of deprotection agents (K_2CO_3 in aqueous THF, K_2CO_3 in aqueous IPA, KOH with 18-crown-6 in benzene, DIBAL, Super Hydride, Selectride) gave poor results. After much experimentation, Gassman's "anhydrous hydroxide" (*t*-BuOK and water in THF)[34] was found to work well. Concomitant deprotection and oxirane opening of crude **21** with *t*-BuOK and water in THF gave (±)-**1** in 61% yield as a golden foam whose spectral properties (IR, MS, ^1H and ^{13}C NMR) were identical to those of an authentic sample of (+)-taxodone.



a) dimethyldioxirane, acetone, 30 min, 100%; b) KO^{t}Bu, H_2O, THF 61%.

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Treatment of **1** with hydrochloric acid and MeOH at 45 °C for 15 min gave a mixture of **1** and **3** plus one other major unidentified compound whose NMR spectra had representative downfield resonances in the following relative proportions: **1** (singlet at 7.49 ppm, 25%), **3** (singlet at 6.40 ppm, 35%), unknown compound (singlet at 7.09 ppm, 40%). Employing Kupchan's procedure, this mixture was refluxed with hydrochloric acid/MeOH to give **3**, which was converted to (±)-taxodione by air oxidation on silica gel in benzene in 54% overall yield.

In conclusion, (±)-taxodone has been synthesized in 3.5% overall yield and 16 steps from geranylacetone. Novel elements of the synthesis, in addition to the isolation of epoxide **31** and its reorganization to **1**, include compound **18** in which the sterically most demanding C11 phenol functionality is in a protected form while C12 is unprotected and the protocol for introduction of the C13 alkyl group on **18**. These new intermediates and protocols may be of interest in future tricyclic diterpene synthetic ventures.

Experimental Section

General. Melting point determinations are uncorrected. Infrared spectra were recorded as thin films on salt plates. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were obtained in $CDCl_3$ at 250 and 62 MHz, respectively. Sample fragmentation for mass spectra was induced by electron ionization unless otherwise indicated by CI (chemical ionization). Combustion analyses for carbon and hydrogen were performed by the staff at Atlantic MicroLabs, Norcross, GA.

Flash chromatography (FC) was performed on Merck Grade 60, 230–400-mesh silica gel using hexane/ethyl acetate (H/E) as solvent.

Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether (hereafter referred to as ether) were distilled from sodium benzophenone ketyl immediately prior to use. For anhydrous reactions, dichloromethane and hexanes were distilled from calcium hydride. Toluene and benzene were distilled from sodium and stored over sodium. HMPA and DMF were distilled from calcium hydride and stored over molecular sieves. Nitromethane was dried with calcium chloride, distilled, and stored over molecular sieves. Triethylamine and diisopropylamine were distilled over calcium hydride and stored over KOH. Alkyllithiums were titrated with 1,3-diphenylacetone *p*-tosylhydrazone.[35] All other chemicals were used as purchased.

All reactions requiring nonaqueous conditions were performed in oven-dried glassware under nitrogen or argon. Solvent extractions were dried with $MgSO_4$.

Methyl 7,11,11-Trimethyl-3-oxo-6,10-dodecadienoate (11). Dimethyl carbonate (46.9 g, 0.52 mol) was added to NaH (1.36 g, 0.57 mol) in dry ether (200 mL). After the mixture was refluxed for 10 min, geranylacetone (50 g, 0.26 mol) in ether (50 mL) was added dropwise over 4 h. After refluxing for an additional 2 h, the mixture was cooled and the reaction quenched with MeOH (50 mL) in ether (250 mL). The suspension was poured into an ice (400 g)/concentrated HCl (100 mL) mixture, extracted with ether (3×), washed with $NaHCO_3$ solution (2×), dried, and concentrated to yield a red fragrant oil (61.2 g, 94%). Vacuum distillation afforded 53.3 g of **11** (82%) as a clear oil: bp 146–52 °C/3.5 Torr; ^{1}H NMR δ 1.58, 1.60 and 1.67 (3 H, s), 2.0 (4 H, m), 2.27 (2 H, m), 2.54 (2 H, m), 3.47 (2 H, s), 3.72 (3 H, s), 5.06 (2 H, m).

Methyl (1β,4aα,8aβ)-Decahydro-5,5,8a-trimethyl-2-oxonaphthalene-1-carboxylate (10). Tin(IV) chloride (5.17 g, 80 mmol) was added to a solution of diene ester **11** (1 g, 4.0 mmol) in methylene chloride (30 mL) at 0 °C. The temperature of this golden solution was allowed to reach rt after 1 h and then stirred overnight. The next day the red solution was washed with 10% HCl (3×), $NaHCO_3$ solution, and brine, dried, and concentrated to yield a golden oil (818 mg, 82%). Adding hexane and storing the solution in the freezer for 48 h yielded 150 mg (15%) of **10** as clear crystals. FC (9:1 H/E) of the mother liquor gave an additional 350 mg (35%) of **10** as pale yellow crystals. An analytical sample was recrystallized from hexane: mp 84–5 °C (lit.[8] mp 83–84.5 °C); ^{1}H NMR δ 0.84, 0.92 and 1.10 (3 H each, s), 1.2–2.2 (9 H, m), 2.29 and 2.44 (1 H each, m), 3.17 (1 H, s), 3.63 (3 H, s); ^{13}C NMR δ 14.78, 18.59, 21.74, 23.03, 33.49, 39.14, 41.22, 41.85, 41.96, 51.39, 53.12, 69.90, 168.65, 205.48; IR 2950, 1700, 1630 cm^{-1}.

Methyl (1β,4aα,8aβ)-Decahydro-5,5,8a-trimethyl-2-methylenenaphthalene-1-carboxylate ((±)-Methyl Albicanate) (12). $NaNH_2$ (2 g, 51 mmol) and Ph_3PCH_3Br (14.3 g, 40 mmol) were added to a 2-neck flask. THF (250 mL) was added with efficient stirring. The mixture turned yellow in a few minutes. Stirring was continued for 1 h and the suspension was allowed to settle for 15 min. The clear yellow supernatant was decanted via cannula through a glass frit onto a solution of β-keto ester **10** (5 g, 20 mmol) dissolved in THF (50 mL) with stirring. The reaction was followed by TLC or GC and was usually done within 12 h. Upon complete reaction, the solution was concentrated and the resulting residue triturated thoroughly with hexane. The hexane solution was chilled overnight, filtered to remove the precipitated triphenylphosphine, and concentrated to an oil. MPLC (18:1 H/E) of the oil gave **12** (4.27 g, 85%) as a colorless oil: ^{1}H NMR δ 0.83, 0.87 and 1.05 (3 H each, s), 1.1–2.5 (9 H, m), 2.39 and 2.44 (1 H each, dd, J = 2.1, 4.5 Hz), 2.80 (1 H, s), 3.64 (3 H, s), 4.65 (1 H, d, J = 0.9 Hz), 4.82 (1 H, br s); MS m/z 250 (M$^+$, 5), 235-(4), 176 (4), 137 (100), 123 (10), 114 (8), 95 (7); IR 1739, 1648, 1164 cm^{-1}.

Methyl [1β,4aα,8aβ,2(1′)α]-Octahydro-5,5,8a-trimethylnaphthalene-2(1*H*)-spiro-2′-oxirane-1-carboxylate (13). A solution of MCPBA (85% purity, 3.16 g, 15 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 10 min to a solution of **12** (3.66 g, 14.6 mmol) in CH_2Cl_2 (30 mL) stirred in an ice bath. The ice bath was allowed to melt over the course of 1 h and was then removed. The reaction was complete (GC indicated <1% starting material) after stirring for 6 h. Ether (150 mL) was added to the reaction mixture, which was then washed consecutively with $NaHCO_3$ solution (3×), water (2×), and brine. The organic phase was dried and concentrated to give a crude white solid (3.79 g, 97%) which was crystallized from hexane to give **13** (3.13 g, 80%) as clear prisms: mp 94–6 °C (lit.[10] mp 94–6 °C); ^{1}H NMR δ 0.85, 0.90 and 1.13 (3 H each, s), 0.9–2.0 (11 H, m), 2.59 (1 H, d, J = 5.1 Hz), 2.66 (1 H, s), 3.35 (1 H, dd, J = 1.7, 4.8 Hz), 3.58 (3 H, s); MS (CI) m/z 235 (100).

(5aα,9aβ)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphtho[1,2-c]furan-1(3*H*)-one ((±)-Isodrimenin) (9). A solution of **13** (4.13 g, 15.4 mmol) in THF (20 mL) was added to an LDA solution (77 mmol) in THF (200 mL) stirred in a dry ice/acetone bath. The bath was allowed to warm up to room temperature over 1 h and was then removed. After 3 h at room temperature, the dark red reaction mixture was poured into 1 M HCl (150 mL) and separated, and the organic layer was washed with 1 M HCl and brine (2×), dried, and concentrated to give a yellow solid (3.66 g, 102%) which was recrystallized from hexane (10 mL) to give **9** (3.35 g, 93%) as pale yellow crystals melting at 89–91 °C. An analytical sample was recrystallized from hexane to give colorless

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prisms: mp 91–2 °C (lit.[36] mp 91–2 °C); ^{1}H NMR δ 0.88, 0.92 and 1.13 (3 H each, s), 1.2–1.7 (11 H, m), 4.54 and 4.55 (1 H each, s); MS *m/z* (CI) 235 (M^{+1}, 100), 233 (2), 219 (2), 69 (1). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.89; H, 9.50.

4,5,5a,6,7,8,9,9a-Octahydro-1-(*tert*-butyldimethylsiloxy)-6,6,9a-trimethylnaptho[1,2-*c*]furan (8). A 100-mL two-neck flask was charged with THF (40 mL) and immersed in a ice bath. Diisopropylamine (1.3 g, 12.9 mmol) was added, followed by *n*-BuLi (12.9 mmol, 5.16 mL of a 2.5 M solution in hexane). After 15 min the ice bath was replaced by a dry ice/ethanol bath and HMPA (2.54 g, 14.2 mmol) was added to the LDA solution. After 30 min **9** (2 g, 8.6 mmol, dissolved in THF (4 mL)) was added. Thirty minutes later TBDMSCl (1.92 g, 14.2 mmol) in THF (2 mL) was added and the bath removed. Two hours later the reaction mixture was poured into ice–water (60 mL) containing AcOH (2 mL) and extracted with hexane (3 × 50 mL). The extracts were washed with water (2 × 50 mL) and brine (50 mL), dried, concentrated at room temperature, and placed on the vacuum pump for 1 h to yield TBDMS furan **8** (2.97 g, 100%) as a yellow oil that was used immediately for the next step: ^{1}H NMR δ 0.237 and 0.247 (3 H each, s), 0.89, 0.93 and 1.16 (3 H each, s), 0.99 (9 H, s), 1.2–1.9 (9 H, m), 6.49 (1 H, s); ^{13}C NMR δ 4.07, 19.13, 19.65, 21.73, 22.06, 25.74, 33.82, 37.96, 42.18, 53.00, 106.78, 122.50, 125.01, 149.77.

Methyl 5-Hydroxy-1,2,3,4,4a,9,10,10a-octahydro-1,1,-4aβ-trimethyl-6-phenanthroate (15). Methyl acrylate (4 mL) was added to **8** (prepared from 17.2 mmol **9**) followed by nitromethane (10 mL). After 18 h the mixture was concentrated, the residue dissolved in MeOH (10 mL), and 10% HCl (10 mL) added. After stirring for 1 h, the mixture was filtered to yield **15** (2.80 g, 54%) as a pale yellow powder used for the next step without further purification. FC (18:1 H/E) of the mother liquors yielded an additional 1.03 g (20%) of **15**. Crystallization of an analytical sample from MeOH yielded white flakes: mp 131.5–132.5 °C; ^{1}H NMR δ 0.95, 0.98 and 1.37 (3 H each, s), 1.2–1.9 (8 H, m), 2.84 (2 H, m), 3.31 (1 H, dm, J = 13.2 Hz), 3.91 (3 H, s), 6.56 (1 H, d, J = 8.1 Hz), 7.57 (1 H, d, J = 8.4 Hz), 11.64 (1 H, s); ^{13}C NMR δ 18.67, 19.31, 19.40, 22.27, 33.68, 33.87, 36.07, 39.73, 41.58, 52.12, 53.21, 58.12, 109.56, 120.40, 126.59, 136.76, 145.93, 161.65, 171.72; MS *m/z* 302 (M^+, 24), 287 (350), 256 (23), 255 (100), 217 (198), 205 (36), 199 (13), 191 (46), 187 (16), 186 (13), 185 (32), 173 (23), 159 (26), 69 (38); IR 2920, 1664, 1613, 1571 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.35; H, 8.72.

Further elution (9:1 H/E) of the column recovered 600 mg (15%) of **9**.

Diels–Alder Product of 8 and Methyl Acrylate (14). The unaromatized intermediate **14** could be isolated as a pair of diastereoisomers by FC (18:1 H/E) of the residue prior to acid treatment to give a 40% yield of a yellow oil that decomposed on standing: major isomer (55%) ^{1}H NMR δ 0.15 and 0.24 (3 H each, s), 0.86, 0.89 and 1.15 (3 H each, s), 0.95 (9 H, s), 1.2–1.9 (9 H, m), 2.81 (1 H, dd, J = 4.5, 9 Hz), 3.63 (3 H, s), 4.41 (1 H, d, J = 5.1 Hz); minor isomer (45%) ^{1}H NMR δ 0.07 and 0.13 (3 H each, s), 0.81, 0.86 and 1.16 (3 H each, s), 0.91 (9 H, s), 1.2–1.9 (9 H, m), 2.74 (1 H, dd, J = 4.2, 8.1 Hz), 3.68 (3 H, s), 4.54 (1 H, d, J = 4.8 Hz).

Methyl 5-Methoxy-1,2,3,4,4a,9,10,10a-octahydro-1,1,-4aβ-trimethyl-6-phenanthroate (16). After stirring a suspension of finely powdered KOH (standard 85% assay, 312 mg, 4.72 mmol) in DMSO (3 mL) for 5 min, finely powdered **15** (357 mg, 1.18 mmol) was added, followed by MeI (335 mg, 2.36 mmol) and the heterogenous mixture (**15** is very poorly soluble in DMSO) was stirred for 1 h. The mixture was poured into brine (30 mL), extracted with CH_2Cl_2 (4×), washed with water (4×), dried, and concentrated to yield a colorless viscous oil (378 mg, 101%) that solidified after 5 h under high vacuum. Crystallization from MeOH (2 mL) yielded **16** (293 mg, 78%) as a white solid. FC (18:1 H/E) of the mother liquors yielded an additional 64 mg (17%) of **16**. An analytical sample was recrystallized from MeOH to yield a white solid: mp 77–80 °C; ^{1}H NMR δ 0.93, 0.95 and 1.32 (3 H each, s), 1.2–1.9 (8 H, m), 3.06 (1 H, dm, J = 13.0 Hz), 3.75 (3 H, s), 3.89 (3 H, s), 6.78 and 7.47 (1 H each, d, J = 8 Hz); ^{13}C NMR δ 18.73, 19.46, 21.47, 22.18, 33.02, 33.86, 37.4,9 40.08, 41.26, 52.18, 52.51, 62.27, 121.82, 124.39, 128.65, 142.87, 143.21, 160.57, 167.83; MS *m/z* 316 (M^+, 18), 301 (13), 270 (18), 269 (100), 231 (11), 219 (9), 205 (30), 201 (12), 69 (18); IR 3026, 3001, 2922, 1722, 1592, 1469, 1427, 1265 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.86; H, 8.91.

5-Methoxy-6-(2-hydroxyprop-2-yl)-1,2,3,4,4a,9,10,10a-octahydro-1,1,4a-trimethylphenanthrene (17). THF (120 mL) was added to anhydrous $CeCl_3$ (8.56 g, 24.7 mmol) and the suspension sonicated for 1 h. The flask was immersed in a dry ice/EtOH bath and MeLi (17 mL of 1.4 M ether solution, 24.7 mmol) was added. After 30 min crude **16** (2.6 g, 8.23 mmol) in THF (15 mL) was added and 4.5 h later the reaction was quenched with aqueous NH_4Cl. The mixture was filtered through Celite, the filter cake was washed with ether, the filtrate was separated, and the aqueous phase was extracted with ether (2×), dried, and concentrated to give crude **17** (195 mg, 98%) as an oil which was used without purification for the next step: ^{1}H NMR δ 0.93, 0.96 and 1.38 (3 H each, s), 1.2–1.9 (8 H, m), 1.59 and 1.63 (3 H each, s), 2.88 (2 H, m), 2.98 (1 H, dm, J = 12.9 Hz), 3.84 (3 H, s), 5.41 (1 H, s), 6.81 and 7.03 (1 H each, d, J = 8 Hz).

5-Methoxy-6-hydroxy-1,2,3,4,4a,9,10,10a-octahydro-1,1,-4aβ-trimethylphenanthrane (18). A solution of H_2O_2 (30%, 8.95 g, 82 mmol) and *p*-TsOH (151 mg, 0.82 mmol) in THF (10 mL) was added to crude **17** (prepared from 8.23 mmol of **16**). After stirring the heterogeneous reaction for 21 h, it was neutralized with $NaHCO_3$ solution and concentrated, water added to the residue, and it was extracted with CH_2Cl_2 (4×), dried, and concentrated to yield a pale yellow solid (2.42 g, 108%). Crystallization from hexane yielded **18** (1.71 g, 76%) as a white solid. FC (18:1 H/E) of the mother liquor yielded an additional 293 mg (13%) of **18**. An analytical sample was recrystallized from hexane: mp 111.5–112 °C; ^{1}H NMR δ 0.95, 0.97 and 1.32 (3 H each, s), 1.2–1.9 (8 H, m), 2.83 (2 H, m), 2.99 (1 H, dm, J = 12.9 Hz), 3.80 (3 H, s), 5.25 (1 H, br s), 6.72 and 6.76 (1 H each, d, J = 8 Hz); ^{13}C NMR δ 19.27, 19.52, 22.08, 22.30, 31.82, 33.84, 37.74, 41.41, 52.09, 62.88, 114.04, 125.58, 129.42, 142.62, 146.42, 147.46; IR 3320, 2930, 1384, 1293 cm^{-1}; MS *m/z* 274 (M^+, 67), 259 (17), 203 (8), 189 (29), 177 (64), 163 (100), 137 (6), 97 (6), 83 (11), 69 (32), 57 (23), 56 (12). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.55; H, 9.78.

5-Methoxy-6-acetyl-1,2,3,4,4a,9,10,10a-octahydro-1,1,-4a-trimethylphenanthrene (19). Anisole **17** (100 mg, 0.32 mmol) in ether was added to MeLi (0.8 mmol, 570 μL of a 1.4 M solution in ether) in ether at 0 °C. The reaction mixture was warmed to rt over an hour, washed with H_2O (3×), dried, and concentrated to afford 98 mg of a pale yellow oil. FC (18:1 H/E) of this material gave the corresponding oily styrene (39 mg, 41%) as a byproduct, followed by methyl ketone **19** (44 mg, 46%) as an oil. Crystallization of an analytical sample of **19** from wet MeOH gave pale yellow prisms of **19**: mp 71.5–72.5 °C; ^{1}H NMR δ 0.94, 0.97, and 1.33 (3 H each, s), 1.2–1.9 (8 H, m), 2.59 (3 H, s), 2.86 (1 H, d, J = 4.1 Hz), 2.90 (1 H, d, J = 4.5 Hz), 3.04 (1 H, dm, J = 12.0 Hz), 3.68 (3 H, s), 6.81 and 7.22 (1 H each, d, J = 8 Hz); ^{13}C NMR δ 18.76, 19.50, 21.63, 22.15, 29.71, 32.89, 33.80, 37.58, 40.06, 41.29, 52.50, 63.31, 124.91, 126.75, 132.22, 142.70, 159.68, 202.44; IR 2921, 1680, 1592, 1393, 1264, 1056 cm^{-1}; MS *m/z* 300 (M^+, 52), 285 (100), 215 (23), 203 (18), 189 (20). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.81; H, 9.30.

5-Methoxy-6-hydroxy-1,2,3,4,4a,10a-hexahydro-1,1,4aβ-trimethylphenanthrane (23). DDQ (50 mg, 0.22 mmol) was added to a solution of **18** (50 mg, 0.182 mmol) in dioxane (4 mL). After 2 h the supernatant was decanted and the residue washed with benzene (3×). The combined solutions were concentrated to yield an orange gum (49.6 mg, 100%) which was subjected to FC (18:1 H/E) to afford a pale orange solid (39 mg, 79%) that contained approximately 7% starting material (by NMR analysis). Crystallization from hexane (2×) gave **23** (23 mg, 46%) as pale yellow needles which slowly

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turned amber upon standing: mp 116–7 °C; ^{1}H NMR δ 0.98, 1.05 and 1.18 (3 H each, s), 1.2–1.9 (5 H, m), 2.16 (1 H, t, J = 2.8 Hz), 2.75 (1 H, m), 3.76 (3 H, s), 5.59 (1 H, s), 5.85 (1 H, dd, J = 2.8 and 9.6 Hz), 6.44 (1 H, dd, J = 3.1 and 9.6 Hz), 6.75 and 6.79 (1 H, d, J = 8.1 Hz); ^{13}C NMR δ 19.33, 22.69, 32.98, 33.35, 36.22, 40.81, 41.12, 51.19, 61.33, 113.16, 123.97, 127.68, 127.81, 140.16, 144.63, 149.35; MS m/z 272 (M^+, 39), 190 (44), 187 (30), 173 (23), 157 (21), 97 (22), 85 (26), 83 (38), 81 (39), 73 (26), 71 (45), 70 (22), 69 (100), 67 (20), 57 (76), 56 (25), 55 (65).

11-Methoxy-12-hydroxyabieta-6,8,11,13-tetraene ((±)-6,7-Dehydro-11-methoxyferruginol) (24). The procedure above was applied to **21** (35 mg, 0.11 mmol) to give an orange residue (34.1 mg, 98%) which was subjected to FC (18:1 H/E) to yield **24** (25.6 mg, 74%) as a pale orange gum that rapidly darkened on standing: NMR δ 0.97 (3 H, s), 1.06 (3 H, s), 1.18 (3 H, s), 1.21 (3 H, d, J = 6.9 Hz), 1.23 (3 H, d, J = 6.8 Hz), 1.1–1.8 (5 H, m), 2.16 (1 H, t, J = 2.8 Hz), 2.73 (1 H, dm, J = 12.9 Hz), 3.23 (1 H, sep, J = 6.9 Hz), 3.76 (3 H, s), 5.85 (1 H, dd, J = 2.7 and 9.5 Hz), 6.45 (1 H, dd, J = 3.1 and 9.5 Hz), 6.70 (1 H, s); ^{13}C NMR δ 19.34, 22.24, 22.66, 27.07, 32.98, 36.22, 40.75, 51.42, 61.36, 121.06, 127.41, 128.14, 132.53, 134.50, 137.06, 144.15, 146.54

11-Methoxy-12-hydroxy-15-(2-propylthio)abieta-8,11,-13-triene (20). SO_2Cl_2 (217 mg, 1.61 mmol) was added dropwise to a solution of **18** (400 mg, 1.46 mmol), pyridine (144 mg, 1.82 mmol), a trace of BHT, and i-Pr_2S (190 mg, 1.61 mmol) in CH_2Cl_2 cooled in a dry ice/acetonitrile bath. After 15 min triethylamine (740 mg, 7.3 mmol) in hexane (1 mL) was added to the mixture over 2 min. After 5 min, the cooling bath was removed and, once at room temperature, the solution was concentrated. The resulting residue was dissolved in ether, washed with water, dried, and concentrated to give 639 mg (>100%) of crude **20** as a viscous orange oil (containing mostly desired product with some starting material and other impurities) which was used without purification for the next reaction. FC (18:1 H/E) of a sample gave **20** as a clear colorless oil: ^{1}H NMR δ 0.93, 0.96 and 1.31 (3 H each, s), 1.14 and 1.16 (3 H each, d, J = 11 Hz), 1.2–1.9 (8 H, m), 1.69 and 1.70 (3 H each, s), 2.57 (1 H, sep, J = 7 Hz), 2.77 (2 H, m), 3.04 (1 H, dm, J = 13.0 Hz), 3.86 (3 H, s), 6.59 (1 H, s), 8.21 (1 H, s).

Raney Nickel. Al–Ni alloy (30 g) was added over 30 min to a solution of NaOH (39 g) in water (150 mL) at 80 °C. The mixture was stirred an additional 30 min, the nickel allowed to settle, and the supernatant decanted. The nickel was washed with water until the washings were neutral and was then stored under ethanol.

11-Methoxy-12-hydroxyabieta-8,11,13-triene ((±)-11-Methoxyferruginol) (21). Crude **20** (prepared from 1.46 mmol of **18**) was dissolved in ethanol (50 mL) and Raney nickel (5 g prepared as above) was added with vigorous stirring. The reaction solution was refluxed for 2 h, cooled, and filtered through a cotton plug, and the nickel was washed with CH_2Cl_2, filtered through a silica gel plug, and concentrated to afford 427 mg of a white solid. FC (18:1 H/E) gave **21** (280 mg, 61% from **18**) as a white solid. An analytical sample was recrystallized from hexane: mp 145.5–146 °C; ^{1}H NMR δ 0.94, 0.95 and 1.31 (3 H each, s), 1.2–1.9 (8 H, m), 1.21 and 1.24 (3 H each, d, J = 4.8 Hz), 2.82 and 2.94 (1 H each, m), 2.93 (1 H, dm, J = 13.2 Hz), 3.15 (1 H, sep, J = 7 Hz), 3.78 (3 H, s), 5.31 (1 H, br s), 6.66 (1 H, s); ^{13}C NMR δ 19.37, 19.52, 22.03, 22.42, 22.49, 27.10, 31.83, 33.83, 37.86, 39.59, 41.48, 52.03, 61.01, 122.49, 128.11, 133.11, 139.46, 144.94, 145.88; IR 3378, 2952, 1416, 1053 cm^{-1}; MS m/z 317 (25), 316 (M^+, 100), 302 (11), 301 (49), 231 (31), 219 (42), 205 (92), 179 (11), 86 (20), 69 (11). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.46; H, 10.21.

Further elution of the column recovered 78 mg of **18** (20%).

11-Methoxy-12-hydroxy-15-ethoxyabieta-8,11,13-triene ((±)-11-Methoxy-15-ethoxyferruginol) (22). Chromatographed **20** (80 mg, 0.02 mmol, 77% pure by GC) was dissolved in absolute ethanol (7 mL) and Raney nickel (200 mg) added. After being refluxed for 2 h, the mixture was cooled, filtered, and concentrated to yield a white solid (75 mg, 104%). Crystallization from hexane yielded **22** (37 mg, 51%) as white needles: mp 140–1 °C; ^{1}H NMR δ 0.02, 0.94, 1.31, 1.58, and 1.61 (3 H, s), 1.1–1.8 (8 H, m), 1.21 (3 H, t, J = 7 Hz), 2.75 (2 H, m), 2.99 (1 H, dm, J = 12.9 Hz), 3.37 (2 H, q, J = 7 Hz), 3.87 (3 H, s), 6.47 (1 H, s), 8.61 (1 H, s); ^{13}C NMR δ 15.61, 19.37, 19.58, 21.54, 22.12, 26.80, 27.07, 32.46, 33.85, 37.28, 39.84, 41.44, 52.60, 58.84, 60.02, 121.65, 127.14, 127.65, 147.19; IR 3284, 2920, 1296, 1055 cm^{-1}; MS m/z 360 (M^+, 37), 314 (100), 299 (30). Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.73; H, 10.04.

Hydrogenolysis of **22** in the presence of palladium, H_2, and acid gave pure **21**.

When **20** was treated as above using MeOH in place of ethanol, a crude product (single spot by TLC) was obtained consisting of **21** and a new compound (21% by GC and NMR analysis) that demonstrated a resonance in NMR (δ 3.20 ppm) indicative of an aliphatic methoxy group. This mixture was hydrogenolyzed in the presence of palladium, H_2, and acid to give pure **21**.

11,12-Dihydroxyabieta-8,11,13-triene ((±)-11-Hydroxyferruginol) (25). BBr_3 (2.55 mL of a 1 M solution in CH_2Cl_2, 2.55 mmol) was added dropwise to a solution of **21** (200 mg, 0.63 mmol) in CH_2Cl_2 cooled in a dry ice/ethanol bath. After 30 min the bath was removed and the solution allowed to warm to room temperature. The solution was concentrated under vacuum (0.1 Torr) and immersed in a cooling bath again. Water and CH_2Cl_2 were added and the mixture was allowed to come to room temperature. The layers were separated and the aqueous phase was further extracted with CH_2Cl_2. The organic extracts were washed with $NaHCO_3$ solution, dried, and concentrated to give an amber foam (192 mg, 100%). FC (9:1 hexane/EtOAc) yielded **25** (182 mg, 95%) as an light amber semicrystalline solid: ^{1}H NMR δ 0.93, 0.95 and 1.35 (3 H each, s), 1.2–1.9 (8 H, m), 1.24 and 1.26 (3 H each, d, J = 6.8 Hz), 2.80 (2 H, m), 3.04 (2 H, m), 4.70 (1 H, br s), 5.68 (1 H, s), 6.46 (1 H, s); ^{13}C NMR δ 19.41, 20.31, 22.18, 22.55, 22.79, 27.30, 32.53, 33.82, 36.82, 39.25, 41.45, 52.88, 117.35, 129.78, 131.57, 133.20, 138.25, 142.97.

11,12-Diacetoxyabieta-8,11,13-triene (26). Isopropenyl acetate (282 mg, 2.81 mmol) and TsOH (21 mg, 0.11 mmol) were added to **25** (170 mg, 0.56 mmol) in toluene (10 mL). After refluxing for 1 h, GC analysis indicated equal amounts of **26** and an intermediate (probable monoacetoxy compound) and no **25**. After an additional 1 h, 14% of the intermediate was present. TLC indicated a single spot throughout the reaction. After refluxing for 10 h, the solution was concentrated, the residue triturated (9:1 hexane/EtOAc), and the supernatant run though a silica gel plug and concentrated to yield **26** (220 mg, 100%) as an off-white foam. An analytical sample was prepared by recrystallization from hexane: mp 163 °C; ^{1}H NMR δ 0.92, 0.96 and 1.24 (3 H, s), 1.17 and 1.20 (3 H each, d, J = 7 Hz), 1.2–1.9 (9 H, m), 2.28 and 2.29 (3 H each, s), 2.83–2.92 (3 H, m), 6.90 (1 H, s); ^{13}C NMR δ 19.03, 19.33, 20.48, 21.19, 21.74, 22.00, 22.86, 23.06, 27.36, 32.31, 33.62, 33.74, 36.9, 39.46, 40.97, 51.55, 124.84, 135.77, 138.48, 139.38, 140.76, 168.69, 168.81; IR 2959, 1776, 1369, 1209, 1179, 1015 cm^{-1}; MS m/z 386 (M^+, 19), 344 (22), 303 (25), 302 (100), 287 (22), 205 (18). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.69; H, 8.94.

11,12-Diacetoxyabieta-8,11,13-trien-7-one (27). Method A. CrO_3 (68 mg, 0.68 mmol) was added to a solution of **26** (75 mg, 0.19 mmol) in acetic acid. After 27 h water was added, and the mixture was extracted with ether (4×), dried, and concentrated to afford a semicrystalline residue (85.1 mg, 110%). FC (4:1 H/E) yielded **27** (47 mg, 61%) as an off-white solid.

Method B. *tert*-Butyl hydroperoxide (TBHP, 937 μL of a 3 M 2,2,4-trimethylpentane solution, 2.81 mmol) was added to a solution of crude **26** (217 mg, 0.56 mmol) in benzene (6 mL) followed by $Cr(CO)_6$ (37 mg, 0.17 mmol). After being refluxed for 15 h, the golden solution was concentrated. The residue was dissolved in 9:1 H/E and run through a silica gel plug followed by 4:1 H/E. The eluant was concentrated to yield a yellow foam (240 mg, 91%). FC (4:1 H/E) yielded **27** (160 mg, 71% from **25**) as an off-white solid. An analytical sample was recrystallized from MeOH: mp 173–175.5 °C; ^{1}H NMR δ 0.94, 0.97, and 1.32 (3 H each, s), 1.19 and 1.22 (3 H each, d, J = 6.9 Hz), 1.2–1.8 (6 H, m), 1.92 (1 H, dd, J = 3.9 and 13.6 Hz),

2.30 and 2.31 (3 H each, s), 2.62 (1 H, d, J = 13.6 Hz), 2.69 (1 H, d, J = 3.9 Hz), 2.91 (1 H, q, J = 6.9 Hz), 8.02 (1 H, s); ^{13}C NMR δ 18.99, 20.22, 20.42, 21.03, 21.44, 22.67, 22.85, 27.63, 32.9, 33.56, 35.61, 40.63, 40.82, 49.50, 124.31, 130.83, 140.34, 144.67, 167.84, 168.51, 197.89, 222.56; IR 2965, 2870, 1778, 1688, 1371, 1309, 1199, 1174, 1143, 1016 cm^{-1}; MS m/z 400 (M$^+$, 37), 358 (20), 316 (100), 301 (25). Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.06; H, 8.08.

11,12-Diacetoxyabieta-5,8,11,13-tetraen-7-one (28). Further elution of the column above (method B) gave **28** (9 mg, 4%) as a pale yellow semicrystalline residue: ^{1}H NMR δ 1.22 (3 H, d, J = 7 Hz), 1.23 (3 H, d, J = 7.4 Hz), 1.28, 1.36 and 1.57 (3 H each, s), 2.32 and 2.36 (3 H each, s), 2.95 (1 H, sep, J = 6.9 Hz), 6.52 (1 H, s), 8.14 (1 H, s); ^{13}C NMR δ 18.93, 20.48, 21.15, 22.78, 22.93, 27.76, 28.05, 30.05, 32.83, 35.04, 38.19, 38.96, 40.65, 41.93, 122.69, 124.32, 129.32, 130.67, 140.08, 140.94, 142.95, 144.68, 144.99, 167.84, 168.03, 174.85, 184.11, 184.51; MS m/z 399 (95), 398 (M$^+$, 100), 356 (82), 314 (100), 287 (88).

11,12-Diacetoxyabieta-8,11,13-trien-7-ol (29). A solution of $NaBH_4$ (217 mg, 0.57 mmol) in THF/ water (4 mL:1 mL) at 0 °C was added to **27** (153 mg, 0.38 mmol) in THF (4 mL) cooled in an ice bath. After 15 min the bath was removed, and 3.5 h later acetic acid (4 drops) was added, the solution was concentrated, water was added, and the mixture was extracted with CH_2Cl_2, dried, and concentrated to give **29** (154 mg, 100%) as a yellow foam which was used in the next step without further purification: ^{1}H NMR δ 0.92, 0.95 and 1.43 (3 H each, s), 1.18 and 1.21 (3 H each, d, J = 6.6 Hz), 1.2–1.9 (9 H, m), 2.27 and 2.28 (3 H each, s), 2.86 (1 H, sep, J = 6.9 Hz), 4.72 (1 H, m) and 7.49 (1 H, s).

11,12-Diacetoxyabieta-6,8,11,13-tetraene (30). A solution of crude **29** (76.8 mg, 0.19 mmol), BHT (3 mg), and p-TsOH (7.3 mg, 0.04 mmol) in toluene (6 mL) was refluxed for 1 h. Isopropenyl acetate (100 μL) was added and the solution refluxed an additional 15 min. The solution was concentrated, and the residue was triturated with 9:1 H/E, run through a silica gel plug, and concentrated to yield a pale yellow foam (74.3 mg, 97%). FC (18:1 H/E) yielded **30** (62 mg, 85%) as an off-white foam. An analytical sample was recrystallized from hexane: mp 138.5–139.5 °C; ^{1}H NMR δ 0.96, 1.02 and 1.12 (3 H each, s), 1.16 and 1.21 (3 H each, d, J = 6.9 Hz), 1.2–1.8 (6 H, m), 2.24 (1 H, t, J = 2.9 Hz), 2.28 and 2.29 (3 H each, s), 2.88 (1 H, sep, J = 6.9 Hz), 5.99 (1 H, dd, J = 2.8 and 9.6 Hz), 6.50 (1 H, dd, J = 3.1 and 9.6 Hz), 6.89 (1 H, s); ^{13}C NMR δ 18.86, 19.23, 20.46, 21.06, 22.52, 22.67, 23.15, 27.38, 32.78, 33.23, 35.77, 40.39, 40.80, 50.55, 122.57, 127.67, 130.47, 133.32, 136.89, 139.05, 168.58, 169.04, 222.55; MS m/z 384 (M$^+$, 40), 343 (28), 342 (100), 301 (20), 300 (87), 260 (22), 218 (38); IR 2963, 2870, 1770, 1372, 1207, 1188 cm^{-1}. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.96; H, 8.41.

6,7-Epoxy-11,12-diacetoxyabieta-8,11,13-triene (31). Dimethyldioxirane (4.44 mL of a 0.054 M solution in acetone, 0.24 mmol) was added to **30** (46 mg, 0.12 mmol) and BHT (4 mg) in acetone (10 mL). After 1 h the solution was concentrated, dissolved in 4:1 H/E, run through a SG plug, and concentrated to yield **31** (52 mg, 100%) as a pale yellow foam. This product could be further purifed by FC (9:1 H/E) to give an 81% yield of **31**, but the best overall yield of **1** was obtained with crude epoxide: mp = 97–100 °C; ^{1}H NMR δ 1.10, 1.13 and 1.29 (3 H each, s), 1.17 and 1.23 (3 H each, d, J = 6.9 Hz), 1.2–1.8 (6 H, m), 1.43 (1 H, d, J = 4.5 Hz), 2.25 and 2.28 (3 H each, s), 2.90 (1 H, sep, J = 6.9 Hz), 3.51 (1 H, dd, J = 4.5 and 4.5 Hz), 3.85 (1 H, d, J = 4.5 Hz), 7.41 (1 H, s); ^{13}C NMR δ 19.15, 20.43, 21.00, 22.32, 22.60, 23.10, 27.43, 32.65, 33.81, 40.38, 41.02, 53.14, 54.00, 58.57, 127.55, 131.29, 139.46, 139.93, 140.98, 158.87, 168.30, 168.82; IR 2964, 1778, 1770, 1368, 1207, 1187 cm^{-1}; MS m/z 400 (M$^+$, 18), 358 (22), 316 (100), 301 (15), 273 (13).

(±)-Taxodone (1). THF (8 mL), water (240 μL of a 1 M solution in THF, 0.24 mmol), and BHT (4 mg) were added to crude **31** (48 mg, 0.12 mmol) and argon was bubbled through the solution for 10 min. After cooling in an ice bath, t-BuOK (480 μL of a 1 M solution in THF, 0.48 mmol) was added dropwise over 10 min, turning the solution deep red. After stirring for 1 h, the reaction was quenched with AcOH (29 mg, 0.48 mmol), turning the red solution golden. Concentration, trituration (4:1 H/E), elution through a SG plug, and concentration gave crude **1** (55 mg, 135%) as a red-orange foam. FC (18:1 to 9:1 H/E) afforded **1** (23 mg, 61% from **30**) as an orange foam identical by MS, IR, and NMR to an authentic sample of (+)-taxodone: ^{1}H NMR δ 1.13 and 1.15 (3 H each, d, J = 7 Hz), 1.14, 1.20 and 1.21 (3 H each, s), 1.1–1.7 (5 H, m), 2.90 (1 H, m), 3.05 (1 H, sep, J = 7 Hz), 4.70 (1 H, m), 6.55 (1 H, d, J = 2.7 Hz), 6.81 (1 H, br s), 7.49 (1 H, s); ^{13}C NMR δ 18.98, 20.97, 21.57, 21.90, 22.98, 26.88, 34.24, 36.86, 37.88, 40.89, 43.37, 58.16, 70.20, 126.42, 130.58, 135.90, 142.13, 143.58, 149.36, 181.87; MS m/z 316 (M$^+$, 100), 298 (27), 273 (19), 229 (37), 220 (42).

11,12-Dihydroxyabieta-8,11,13-trien-6-one (3). A drop of concentrated hydrochloric acid was added to a solution of **1** (10 mg, 0.03 mmol) in MeOH (2 mL) and the solution heated to 45 °C for 15 min. Cooling and concentration gave a mixture of **1** and **3** plus at least one other unidentified compound whose NMR spectra had representative downfield resonances in the following relative proportions: **1** (singlet at 7.49 ppm, 25%), **3** (singlet at 6.40 ppm, 35%), unknown compound (singlet at 7.09 ppm, 40%). This mixture was resubjected to the above reaction conditions at reflux to afford crude **3** (10 mg, 100%) as an orange residue that was about 90% pure by NMR (containing about 5% of the intermediate displaying a singlet at 7.09 ppm): ^{1}H NMR δ 1.02, 1.27 and 1.35 (3 H each, s), 1.24 and 1.26 (3 H each, d, J = 6.9 Hz), 1.1–1.8 (5 H, m), 2.65 (1 H, s), 3.01 (1 H, sep, J = 6.9 Hz), 3.20 (1 H, dm, J = 11.9 Hz), 3.37 and 3.70 (1 H each, d, J = 20 Hz), 6.40 (1 H, s).

(±)-Taxodione (2). Crude **3** from the above experiment was dissolved in benzene and placed on a silica gel column for 24 h. Elution and concentration afforded **2** (5.4 mg, 54%) as a golden orange residue with ^{1}H NMR spectra identical to the published spectra[1] of (+)-taxodione: ^{1}H NMR (benzene-d_6) δ 1.03 and 1.08 (3 H each, d, J = 7 Hz), 1.2–1.8 (5 H, m), 1.23, 1.32 and 1.45 (3 H each, s), 2.36 (1 H, s), 3.05 (2 H, m), 5.88 (1 H, s, H), 6.39 (1 H, s, 1H), 7.73 (1 H, s).

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