Total Synthesis of Eremophilone

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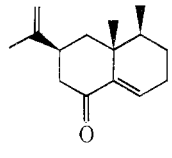
A stereoselective total synthesis of (±)-eremophilone (1) is reported starting from the known 7-epinootkatone. The synthetic sequence involves reductive deconjugation of 7-epinootkatone to homoallylic alcohol **10**. Dehydration of **10** by pyrolysis of its acetate gives triene **18**, which can be selectively epoxidized at the more substituted double bond to give **19**. Mild acid catalyzed rearrangement of this allylic epoxide is effected with lithium perchlorate in refluxing benzene, and, after base-catalyzed equilibration of the enone system, a 1:1 mixture of eremophilone and its β,γ-unsaturated isomer, itself a natural product, is produced.

Eremophilone (1) occupies a prominent place in sesquiterpene chemistry both because of the long and intricate history of its structure elucidation, and because of the considerable challenge it has provided to synthetic organic chemists.[2] Eremophilone was isolated in 1932 from the wood oil of *Eremophila mitchelli,* a shrub indigenous to Australia, by the great terpene chemist J. L. Simonsen.[3] Although they proposed an incorrect structure in their initial paper, Simonsen and his colleagues continued a series of researches through the 1930's.[4] At the suggestion of Robert Robinson, Simonsen proposed the correct structure in 1939,[5] and eremophilone thus became the first sesquiterpene found in nature whose structure does not obey the biogenetic isoprene rule. Further proof of the correctness of the nonisoprenoid structure of eremophilone was added over the next two decades,[6-8] culminating in 1959 with determination of both the relative and the absolute configuration.[9-12]



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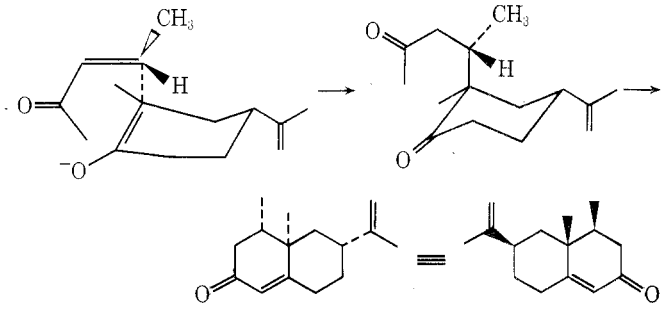
Total synthesis of eremophilone required a further wait of 15 years until Ziegler published his successful, though nonstereoselective, route in early 1974.[13] We wish now to report a second, stereoselective, total synthesis of eremophilone.

General Considerations. The most obvious problems one would expect to encounter in a synthesis of eremophilone are stereochemical.[14] One expected difficulty is in establishing the required cis relationship of the vicinal methyl groups, and another is in establishing the isopropenyl group in the thermodynamically less favorable stereochemistry (axial in the chair–chair conformer). Both of these stereochemical problems can be overcome immediately, however, if one chooses as starting material the Robinson annelation product of 2-penten-3-one with 4-isopropenyl-2-methylcyclohexanone. Van der Gen and his colleagues have studied this reaction in considerable detail, and have demonstrated conclusively that the product dimethylisopropenylhexahydronaphthalenone has the desired all-cis stereochemistry (7-epinootkatone).[15] This result is understandable if the initial Michael addition occurs axially to the methylisopropenylcyclohexanone, and if the pentenone is oriented so as to minimize steric interference (i.e., vinyl methyl away from ring) and to maximize electrostatic attractions (pentenone carbonyl near enolate oxygen).[15-17]

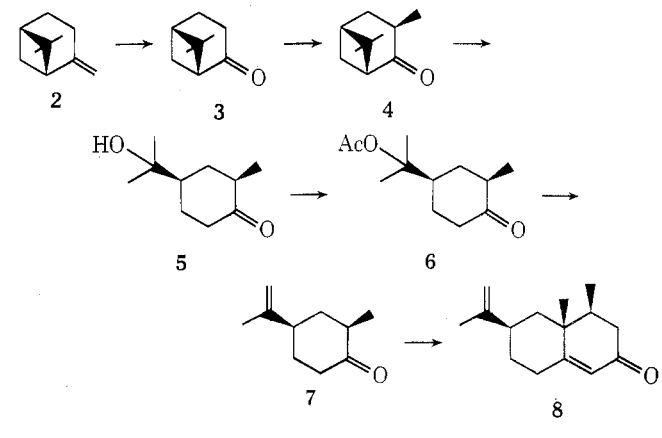
With 7-epinootkatone in hand, the problem of eremophilone synthesis is then reduced to one of functional group interchange.



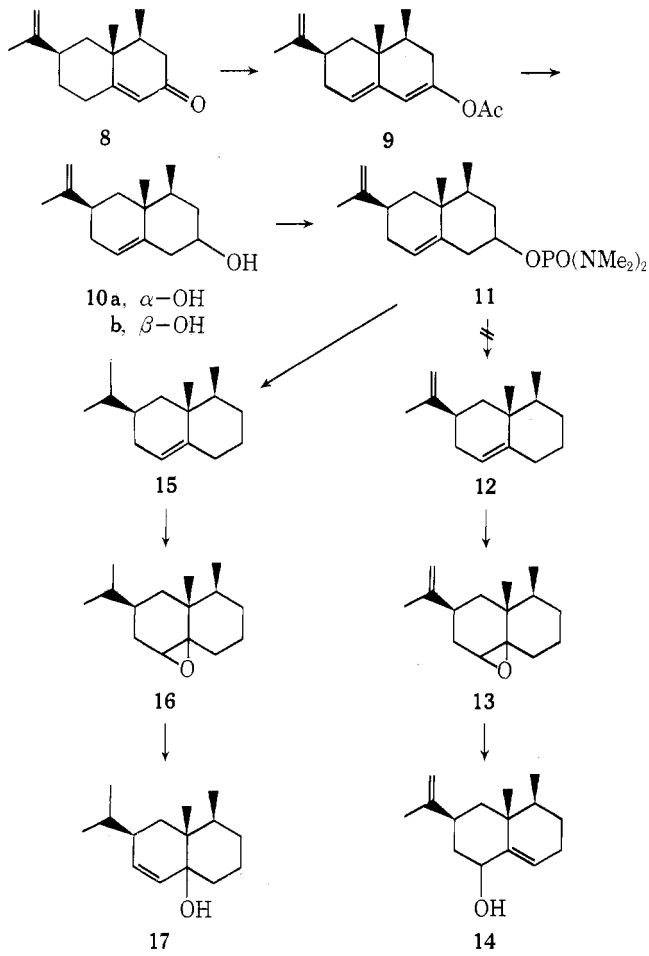
Results and Discussion

7-Epinootkatone (8) was synthesized from (−)-β-pinene by a modification of Van der Gen's procedure as outlined in Scheme I. Thus β-pinene was ozonized to nopinone (**3**, 75%), which was selectively monomethylated in 95% yield by treatment with 1.1 equiv of lithium diisopropylamide in tetrahydrofuran at −78°, followed by quenching of the enolate with methyl iodide. Methylnopinone (**4**) was then opened by treatment with aqueous sulfuric acid to give racemic hydroxy ketone **5** (75%). Although we encountered considerable difficulty in acetylating this tertiary alcohol with acetic anhydride using literature conditions,[15] we found that 4-*N*,*N*-dimethylaminopyridine strongly catalyzed the reaction,[18] and we isolated keto acetate **6** in 95% yield. Pyrolysis of this acetate in a stream of nitrogen at 600° gave 4-isopropenyl-2-methylcyclohexanone (45% overall from β-pinene). Careful reaction of **7** with 2-penten-3-one in the presence of sodium amide in liquid ammonia then gave 7-epinootkatone. In our hands, annelation precisely according to Van der Gen's detailed experimental procedure gave a rather poor yield of product. If, however, we modified the work-up to substitute a chromatographic isolation rather than a distillation, a considerably increased yield of 7-epinootkatone could be isolated (50% based on recovered starting material).

Scheme I



Scheme II

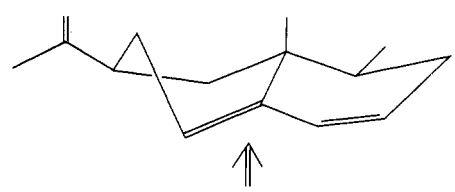


Our original plan for effecting the enone transposition necessary to convert 7-epinootkatone into eremophilone was to first deconjugate and then remove the carbonyl group to generate diene **12.** Selective epoxidation of the trisubstituted double bond should lead to epoxy olefin **13,** which we hoped to be able to rearrange to allylic alcohol **14** on treatment with strong base. Oxidation would then give eremophilone. Both Rickborn[19] and Crandall[20] have studied the base-induced rearrangement of epoxides and have found that the reaction proceeds by syn elimination. In our case, however, two different syn eliminations are possible, and no suitable examples have been reported to allow us to predict one path or the other. Presumably, the epoxide bond which breaks is the one which has the better overlap with a neighboring syn proton. Models of epoxide **13,** however, do not allow a clear prediction to be made in this case. We were hopeful, nonetheless, that epoxide **13** might rearrange by breaking the weaker, tertiary, C–O bond rather than the secondary bond. Our plan is summarized in Scheme II.

7-Epinootkatone was therefore enol acetylated and reduced with sodium borohydride according to the usual conditions[21] to give diene alcohol **10** (88%) as a 1:2 mixture of **10a** and **10b.** Although separation of these alcohols could be accomplished by high-pressure liquid chromatography on Porosil A,[22] we normally used the mixture for our further reactions. Alcohol **10** was then converted to its *N,N,N',N'*-tetramethylphosphoroamidate, which we attempted to hydrogenolyze with lithium in ethylamine according to Ireland's procedure.[23] The sole reaction product, however, was monoolefin **15.** Evidently reduction of the isolated isopropenyl double bond occurs at a rate similar to that of phosphorodiamidate hydrogenolysis. Rather than immediately turn our attention to solving this problem, we decided to epoxidize olefin **15** and use it as a near-perfect model to study the projected base-induced epoxide opening. When epoxide **16** was prepared and treated with lithium di-*n*-propylamide in THF, however, epoxide opening occurred exclusively in the wrong sense to give tertiary alcohol **17** rather than the desired secondary alcohol. Spectral identification of the product was unequivocal (absence of OCH protons, presence of two vinyl protons in the NMR). We experimented briefly with the use of other bases (e.g., magnesium diisopropylamide) hoping that the reaction might take a different course in the presence of a Lewis acid cation, since the transition state might now be expected to have considerable carbonium ion character, thus favoring breakage of the tertiary C–O bond. These experiments were unsuccessful, however.

An alternate method of enone transposition was therefore necessary, and the homoallylic alcohol **10** which we had already obtained seemed a useful starting material, since the annular double bond is correctly disposed to allow functionalization of the proper positions. We therefore dehydrated **10** by pyrolysis of the corresponding acetate (760°, 51%) and isolated the sensitive triene **18.** The conjugated nature of the two annular double bonds follows from the uv spectrum [λ_{max} 237 nm (ϵ 14,200)]. It was our intention to selectively epoxidize the trisubstituted double bond. Acid-catalyzed rearrangement should then generate a β,γ-unsaturated ketone, which would isomerize to eremophilone.

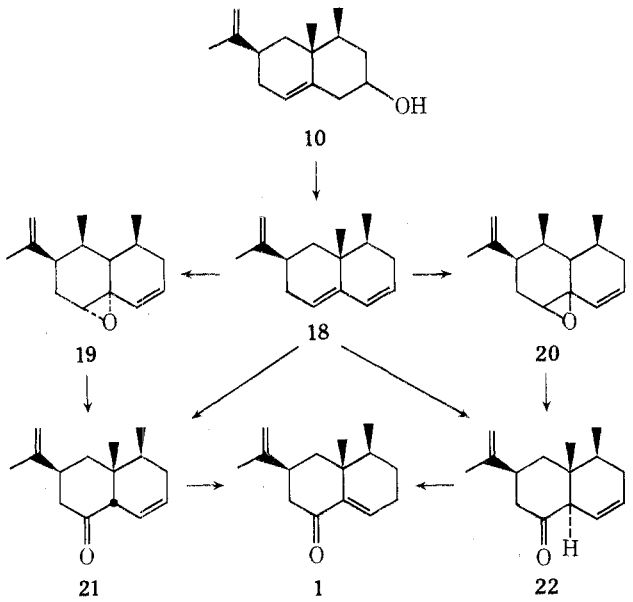
In practice, epoxidation of triene **18** with 1 equiv of *m*-chloroperbenzoic acid at 0° in a methylene chloride–0.5 *M* sodium bicarbonate two-phase system gave a complex mixture of products along with recovered starting material. High-pressure liquid chromatography on Porosil A[22] separated the product mixture into its components, among which we could identify the two epoxides **19** (21%) and **20** (7%) and the two β,γ-unsaturated ketones **21** (16%) and **22** (5%). Fortunately, all four (49% total yield) are useful for the synthesis of eremophilone. Evidently the desired epoxides are partially rearranged even under the mild conditions used in their formation. From Dreiding models of triene **18,** it is clear that peracid should approach the triene preferentially from the less hindered α face, leading to **19** as the major product.



Acid rearrangement would then occur with a 1,2-proton migration across the β face leading to β,γ-unsaturated ketone **21.** When we treated the two isolated epoxides **19** and **20** with lithium perchlorate in refluxing benzene,[24] rearrangement occurred in near-quantitative yield to give the two β,γ-unsaturated ketones **21** and **22,** respectively. From a preparative standpoint, it was simplest to treat the crude epoxidation product with lithium perchlorate directly. After so doing, a 3:1 mixture of ketones **21** and **22** could be isolated in 45% yield. Ketone **21,** the major epoxidation–rearrangement product, is itself a natural product isolation in 1969 from *Eremophila mitchelli.*[25] Our synthetic sequence, which presumably results in a cis ring fusion for the major isomer, thus further defines the ring junction stereochemistry of this minor sesquiterpene.

The total synthesis of eremophilone was completed by

Scheme III



conjugation of ketones **21** and **22** with dilute sodium methoxide in methanol at room temperature. Our synthetic eremophilone was identical with the natural product in all respects, including ir, NMR, and mass spectra. Transformations leading to eremophilone are summarized in Scheme III. Although one might expect a priori that this synthesis would result in optically active product, since (+)-β-pinene was used as starting material, this was not the case. Van der Gen has shown[15] that the acid-catalyzed opening of methylnopinone occurs with complete racemization; thus (±)-eremophilone results.

Experimental Section

(+) 3-Methylnopinone (4). To a solution of lithium diisopropylamide, prepared by treating 15 ml of freshly distilled diisopropylamine in 100 ml of dry tetrahydrofuran (THF) with *n*-BuLi (40 ml of 1.98 *M* solution) at −78°, was added a solution of (+)-nopinone[15] (10.0 g, 0.072 mol) in 10 ml of THF. After 30 min of stirring to form the enolate, the solution was warmed to 0° and 14 ml of methyl iodide was added. After stirring for an additional 2 hr, the reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with dilute HCl and with saturated brine, then filtered, dried (Na_2SO_4), and concentrated to give a pale yellow oil [10.4 g, 95%, bp 50° (2 mm)] whose physical properties correspond to those reported.[15]

4-(1′-Acetoxyisopropyl)-2-methylcyclohexanone (6). 3-Methylnopinone was treated with aqueous sulfuric acid exactly as reported[15] to give 4-(1′-hydroxyisopropyl)-2-methylcyclohexanone (**5**) in 75% yield. Hydroxy ketone **5** (4.6 g, 0.027 mol), 4-*N*,*N*-dimethylaminopyridine (0.8 g), and acetic anhydride (8 ml) were dissolved in 25 ml of freshly distilled triethylamine, and the solution was stirred at room temperature for 7 hr. Methanol (10 ml) was then added to remove excess anhydride, and the mixture was then concentrated at the rotary evaporator. The residue was taken up in ether, then washed with water, dilute HCl, dilute sodium bicarbonate, and saturated brine. The ethereal solution was then dried (Na_2SO_4), filtered, and concentrated to give keto acetate **6** as a pale yellow oil with physical properties identical with those reported[15] (5.4 g, 95%).

7-Epinootkatone (8). Keto acetate **6** was pyrolyzed at 575° as reported[15] to give 2-methyl-4-isopropenylcyclohexanone (**7**, 80%), and this material was treated with 2-penten-3-one using van der Gen's conditions. Thus a solution of **7** (4.0 g, 0.026 mol) in 10 ml of dry dimethoxyethane containing 10 mg of triphenylmethane indicator was added over 30 min to a solution of sodium amide in 150 ml of dry liquid ammonia (0.7 g of sodium, 0.030 mol). After 30 min of stirring, an additional 30 ml of dry dimethoxyethane was added, and the ammonia was allowed to evaporate. A solution of 2-penten-3-one (2.6 g, 0.030 mol) in 20 ml of dry dimethoxyethane was slowly added, and the solution was stirred overnight at ice temperature. The reaction mixture was then diluted with water and extracted with ether. The ethereal extracts were dried (Na_2SO_4), filtered, and concentrated to a residue which was dissolved in 50 ml of methanolic sodium hydroxide and refluxed for 7 hr. After dilution with water, this solution was extracted with ether. These extracts were washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. High-pressure liquid chromatography (HPLC) on Porasil A[22] (16 ft × 0.25 in.) gave 2.8 g (50%) of 7-epinootkatone whose physical properties correspond to those reported.[15]

Enol Acetate 9. A solution of 7-epinootkatone (**8**, 6.47 g, 29.7 mmol) in 50 ml of dry THF was added to a degreased suspension of sodium hydride (2.43 g of 57% dispersion in mineral oil, 38.0 mmol) in 100 ml of dry THF. Hexamethylphosphoramide (100 ml) was added, and the reaction mixture was stirred for 4 hr under nitrogen at room temperature. Acetic anhydride (6.05 g, 0.059 mol) in 50 ml of THF was added, and the mixture was stirred for an additional 30 min, then diluted with water and extracted with ether. The ether extracts were combined, washed with saturated brine, dried (Na_2SO_4), filtered, and concentrated to yield enol acetate **9** (7.72 g, 100%): ir (neat) 1765 cm^{-1}; NMR (CCl_4) δ 0.92 (d, 3 H, J = 6 Hz), 0.97 (s, 3 H), 1.76 (s, 3 H), 2.13 (s, 3 H), 4.74 (s, 2 H), 5.70 (broad s, 2 H). This material was used without further purification.

Homoallylic Alcohol 10. Enol acetate **9** (7.72 g, 0.0297 mol) was dissolved in 100 ml of ethanol and, after cooling to 0°, was added to a solution of sodium borohydride (3.84 g, 0.081 mol) in 200 ml of ethanol. The solution was stirred overnight at 0°, then heated to reflux, and 100 ml of 5% aqueous sodium hydroxide was added. After concentration at the rotary evaporator, the residue was acidified with dilute HCl and extracted with ether. The ether extracts were combined, washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue on 350 g of silica gel gave alcohol **10** (6.95 g, 88%) as a 1:2 mixture of **10a** and **10b** after elution with 20:1 hexane–ethyl acetate. Alcohol **10b** had the following properties: ir (neat) 3380 cm^{-1}; NMR (CCl_4) δ 0.88 (d, 3 H, J = 6 Hz), 0.93 (s, 3 H), 1.73 (s, 3 H), 4.67 (s, 2 H), 5.42 broad s, 1 H); mass spectrum *m/e* (rel intensity) 220 (P^+, 7.6).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.81; H, 11.16.

Triene 18. Homoallylic alcohol **10** (4.16 g, 0.0189 mol), acetic anhydride (5.74 g, 0.054 mol), and 4-*N*,*N*-dimethylaminopyridine (5 mg) were dissolved in 30 ml of triethylamine, and the resulting solution was stirred for 2 days at room temperature. Methanol (10 ml) was then added, and, after 30 min of stirring, the reaction mixture was concentrated at the rotary evaporator. The residue was taken up in ether, and the ether solution was washed with dilute HCl, with dilute bicarbonate, and with brine, then dried (Na_2SO_4) and concentrated. The residue was chromatographed on 200 g of silica gel to give the desired acetate (2.69 g, 60%) along with recovered starting material (1.83 g, 45%). The desired acetate had the following spectral properties: ir (neat) 1730 cm^{-1}; NMR (CCl_4) δ 0.87 (d, 3 H, J = 6 Hz), 0.96 (s, 3 H), 1.75 (s, 3 H), 1.98 (s, 3 H), 4.75 (s, 2 H), 5.55 (m, 1 H).

This acetate, corresponding to **10** (0.84 g, 0.0032 mol), was dissolved in 6 ml of benzene and slowly passed into a quartz pyrolysis tube which was heated to 760° and swept by a stream of nitrogen as carrier gas (150 ml/min). Upon cooling, the column was rinsed with ether, and the ethereal pyrolysate solution was washed with dilute bicarbonate and with brine, then dried (Na_2SO_4), and concentrated. The residue was then subjected to HPLC on Porasil A[22] (16 ft × 0.25 in.). After elution of triene **18** (300 mg), a small amount of recovered starting material was eluted (70 mg). Triene **18** had the following properties: ir (neat) 882 cm^{-1}; uv λ_{max} 229 nm (ϵ 15,200), 237 (14,200), 243 (10,000); NMR (CCl_4) δ 0.85 (d, 3 H, J = 6 Hz), 0.90 (s, 3 H), 1.76 (s, 3 H), 4.78 (s, 2 H), 5.44 (m, 1 H), 5.57 (m, 2 H); mass spectrum *m/e* (rel intensity) 202 (P^+, 22), 119 (100).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.16; H, 10.85.

Epoxide 19. Triene **18** (350 mg, 1.73 mmol) was dissolved in 10 ml of methylene chloride and added to 10 ml of 0.5 *M* sodium bicarbonate at 0°. *m*-Chloroperbenzoic acid (350 mg, 1.75 mmol) in 25 ml of methylene chloride was slowly added and the reaction mixture was stirred for 2 hr at 0°. The organic phase was then separated, washed with dilute bicarbonate and with brine, then dried (Na_2SO_4), filtered, and concentrated. HPLC on Porasil A[22] then gave, in order of elution, recovered triene **18** (80 mg, 0.40 mmol); epoxide **19** (60 mg, 21% based on recovered material); epoxide **20** (20 mg, 7%); ketone **21** (47 mg, 16%); ketone **22** (15 mg, 5%). Epox-

ide **19** had the following spectral properties: ir (neat) 880 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 6 Hz), 1.27 (s, 3 H), 1.72 (s, 3 H), 4.70 (s, 2 H), 5.60 (m, 2 H); mass spectrum m/e (rel intensity) 218 (P^+, 6), 91 (100).

β,γ-Unsaturated Ketone 21. Epoxide **19** (140 mg, 0.64 mmol) was dissolved in 30 ml of dry benzene and refluxed with 70 mg of dry, powdered $LiClO_4$ under nitrogen for 1 hr. After cooling, the reaction mixture was diluted with ether, and the solution was washed with water and with brine, then dried (Na_2SO_4), filtered, and concentrated. HPLC on Porasil A[22] gave recovered epoxide **19** (23 mg, 0.11 mmol) and β,γ-unsaturated ketone **21** (112 mg, 96% based on recovered epoxide): ir (neat) 1710, 885 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3 H, J = 6 Hz), 0.98 (s, 3 H), 1.78 (s, 3 H), 4.80 (s, 2 H), 5.70 (m, 2 H); mass spectrum m/e (rel intensity) 218 (P^+, 16), 93 (100).

The infrared and NMR spectra of this synthetic material were identical with those of the natural product.[26]

Eremophilone (1). A 3:1 mixture of the unsaturated ketones **21** and **22** (110 mg, 0.50 mmol) was dissolved in 20 ml of methanol to which a trace of sodium had been added, and the reaction mixture was refluxed for 30 min to isomerize the double bond. Ether was added, and the solutioniwasiwashed with dilute HCl and with brine, then dried ($MgSO_4$), filtered, and concentrated. HPLC of the residue on Porosil A gave **21** (43 mg, 39%) and eremophilone (**1**, 45 mg, 41%). Synthetic eremophilone had the following physical properties: ir (CCl_4) 1685, 1620, 885 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 6 Hz), 0.97 (s, 3 H), 1.75 (s, 3 H), 4.75 (s, 2 H), 6.48 (t, 1 H); mass spectrum m/e (rel intensity) 218 (P^+, 71), 108 (100). The infrared and NMR spectra of this synthetic material are identical with those of the natural product.[26]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.46; H, 10.37.

Registry No.—**1,** 53797-64-1; **4,** 27040-88-6; **5,** 34182-10-0; **6,** 34181-38-9; **8,** 38906-83-1; **9,** 54798-77-5; **10a,** 54798-78-6; **10a** acetate, 54798-79-7; **10b,** 54798-80-0; **10b** acetate, 54798-81-1; **18,** 54868-33-6; **19,** 54798-82-2; **20,** 54831-49-1; **21,** 54831-50-4; **22,** 54868-34-7; lithium diisopropylamide, 4111-54-0; (+)-nopinone, 473-60-9.

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