not be expected to result from differences in position of an internal proton relative to the magnetically anisotropic peptide bond adjacent, in any case. Tigelaar and Flygare have reported the magnetic susceptibility anisotropy of formamide, which may be taken as a model for that of a peptide bond.[24] From their value, it can be calculated that the internal proton, which is 2–2.5 Å above the plane of the peptide bond and a similar distance radially from a perpendicular through the carbonyl carbon, will experience shielding only of the order of 0.1 ppm. If the above argument is correct, it should be possible, once a peptide proton has been established as shielded from the solvent, to deduce from its chemical shift something about its internally hydrogen bonded state, *e.g.*, that the valine peptide protons of gramicidin S (7.2 ppm in dimethyl sulfoxide[20]) are involved in a weak hydrogen bond, while those of the leucines (8.35 ppm[20]) are in a good one.

An Additional Possibility for Conformation B. In model building to fit the basic parameters of conformation B, we obtained another that can be constructed with C_2 symmetry, cis xxx-Pro peptide bonds, 150° H–N–C–H angles for the nonproline residues, and standard bond angles and lengths, B-2 in Table III. This is an esthetically satisfying one in which antiparallel pairs of Pro-Phe and Phe-xxx peptide bonds are stacked in roughly parallel planes, with positive and negative centers of the amide functions paired, H closest to O and C closest to N. These transannular electrostatic interactions could make conformation B-2 stable, even though there is little vibrational freedom for the backbone because of very close packing. Interference between the proline ring and the side chain of the preceding residue is absent.

Conformation B-2 could be stabilized by N–H···O–H···O=C bridges involving a molecule of water and does have all four peptide protons exposed to solvent–hydrogen bonding, in distinction to conformation A. However, the relative orientation of the amide groups does not provide a clear reason why B-2 should be more stable in dimethyl sulfoxide than in pyridine. A more serious objection is that the phenylalanine peptide proton is not at all hindered from association with the stable free radical. We are not prepared to rule conformation B-2 out entirely, however, and have optical experiments underway, using hydrogenated derivatives, that may provide information about amide group stacking.

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A Stereoselective Approach to Eremophilane Sesquiterpenes. A Synthesis of (±)-Nootkatone and (±)-α-Vetivone

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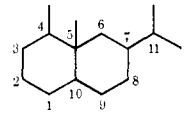
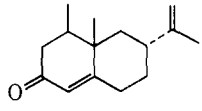
Contribution from the Research School of Chemistry, The Australian National University, Canberra, A.C.T. 2600, Australia. *Received October 25, 1973*

Abstract: A method for the stereoselective construction of the eremophilane sesquiterpene skeleton has been developed. The method's potential is exemplified by a synthesis of (±)-nootkatone and (±)-α-vetivone.

The eremophilane group of sesquiterpenoids possesses the carbon skeleton **1**, which does not conform to the isoprene rule.[1] Two representative members of this group of natural products are nootkatone (**2**) and α-vetivone (**3**). (+)-Nootkatone was originally identified as a heartwood constituent of Alaska yellow cedar (*Chamaecyparis nootkatensis*)[2] and was subsequently shown to be a major bitter principle in grapefruit peel oil (*inter alia*).[3,4] (+)-α-Vetivone is a constituent of vetiver oil[5,6] used extensively in perfumery.



1



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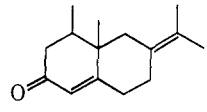

3

The commercial interest in these compounds has already resulted in three total syntheses of (±)-nootkatone[7–9] and two of (±)-α-vetivone[9,10] as well as two partial syntheses of (+)-nootkatone.[11,12]

Most synthetic approaches to construction of the eremophilane skeleton have relied on the Robinson annelation reaction.[8–10,13,14] However, the crucial stereospecific establishment of the cis C(4),(5)-dimethyl moiety, and in the case of nootkatone, the equatorial C(7)-isopropenyl functionality, has presented problems in previous syntheses.[7–9] Mixtures of epimers often resulted, and it would not be unreasonable to suggest that a general scheme inherently giving rise to the

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(2) H. Erdtman and Y. Hirose, *Acta. Chem. Scand.*, **16**, 1311 (1962).
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(13) R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968).
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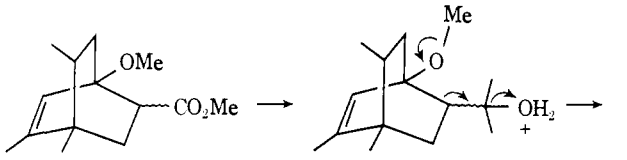
stereochemistry required at the three centers in question was not realized.

The present approach to construction of the ring system and steric control in this important area depends on the Diels–Alder reaction.[15] Such is the nature of the transformations involved that the various precursors of **2** and **3** are "locked" in the correct configuration. The final step involves "unlocking" of a bicyclo[2.2.2]-octyl derivative to an intermediate which instantly "snaps shut" in a different sense, giving rise to a single eremophilane derivative possessing the correct stereochemistry at C(4),(5), and (7).

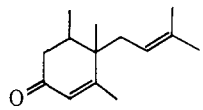
Discussion and Results

Recent reports[16,17] have described the facile production of bicyclo[2.2.2]octyl esters (*e.g.*, **4**) by Diels–Alder reaction of 1-methoxycyclohexa-1,4-dienes with suitable dienophiles. The derived tertiary carbinols (*e.g.*, **5**) have been shown to undergo transformation in aqueous perchloric acid[18] to 4-substituted cyclohexenones (*e.g.*, **6**, Scheme I).

Scheme I

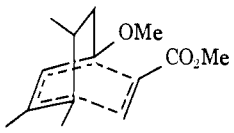


4 5

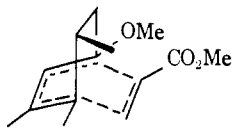


6

The interesting and important feature of Scheme I is that in formation of dienone **6**, the adjacent methyl groups are forced to adopt a cis steric relationship. The reason for this is borne out by a consideration of the two possible transition states between 1-methoxy-3,4,5-trimethylcyclohexa-1,3-diene and methyl acrylate in the Diels–Alder reaction giving rise to ester **4**. Clearly, transition state **7** would be preferred over **8** since it



7

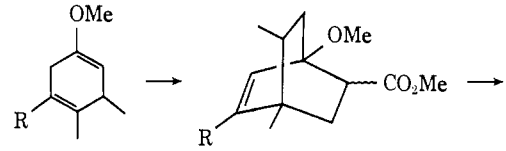


8

involves less steric congestion. As a result, the indicated configuration of the bridge methyl group in ester **4** (Scheme I) would be expected to predominate, and eventually give rise to the *cis*-dimethyl structure of **6**.

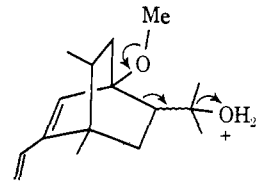
The exciting possibility of projecting the previous transformation to a general synthesis of eremophilane sesquiterpenoids had manifested itself, and it was conceived that the trienone **13**, formally a modification of **6**, might undergo ring closure in formic acid[19] to afford 11-formyloxy-11,12-dihydronootkatone (**14**) (Scheme II). It would be reasonable to expect cyclization to

Scheme II

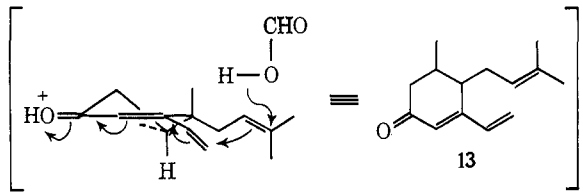


9, R = Me

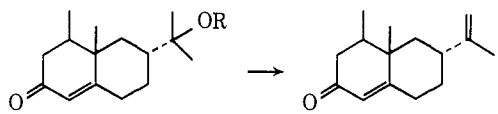
4, R = Me
10, R = CHO
11, R = CH=CH2



12



13

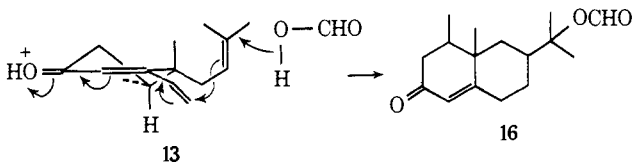


14, R = CHO
15, R = H
17, R = Ac

2 + 3

proceed in the sense shown (Scheme II), giving rise to the required configuration at C(7). The alternative mode of ring closure (Scheme III) would give rise to the

Scheme III



13 16

7-epi isomer **16**. However, as a result of the severe steric interactions brought about between the axial C(5)-methyl group and the isopropylidene functionality, this process would not be expected to occur to any great extent.

Birch reduction[20] of 3,4,5-trimethylanisole gave the expected reduction product **9**. *In situ* Diels–Alder reaction of this compound with methyl acrylate in the presence of dichloromaleic anhydride[16,17] afforded the ester **4**. Selective oxidation of the olefinic methyl group of **4** to give **10** was accomplished with selenium

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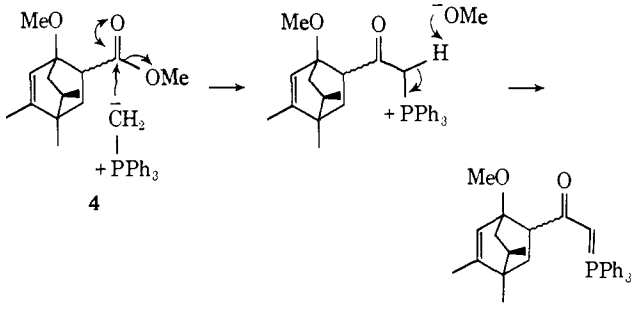
(20) A. J. Birch and G. Subba Rao, *Advan. Org. Chem.*, **8**, 1 (1972).

dioxide,[21] owing to the absence of any other allylic position.

Wittig reaction of **10** with methylenetriphenylphosphorane in the usual way[22] gave rise to a mixture of diene **11** and unchanged starting material. This seemed strange since a slight excess of the Wittig ylide was employed. Clearly, the vicinity of the carbaldehyde functionality of **10** was sterically congested and α,β-unsaturation further decreased its reactivity. Nevertheless, these considerations did not seem to provide an adequate explanation for this result, and it was felt that ester participation was involved. While it was generally believed that phosphonium ylides were inert to such functionalities, a literature survey revealed instances where methylenetriphenylphosphorane was observed to react with the carbonyl group of esters.[23,24] In order to establish that this type of process was occurring in the present case, ester **4** was added to 2 equiv of methylenetriphenylphosphorane, followed by 2 equiv of benzaldehyde. As expected, the product contained a 1:1 ratio of unchanged benzaldehyde and styrene (glc), showing that **4** had reacted with 1 equiv of the ylide (Scheme IV).

Scheme IV



A simple solution for overcoming the inconvenience caused by this side reaction was based on a consideration of the reaction course itself. The usual procedure (and that carried out on **10**) involved addition of the carbonyl compound to the ylide.[22] Obviously, at any time during addition, an excess of methylenetriphenylphosphorane prevailed so that both the carbaldehyde and ester functionalities of **10** were open to attack. Since only 1 equiv of ylide was present, it is hardly surprising that the reaction product was significantly contaminated with starting material. In view of this, it was felt that slow inverse addition (ylide to **10**) would enhance selectivity of ylide attack, hopefully, in favor of the carbaldehyde group. This alteration affords **11** in reasonable yield (50%), and the small proportion of unchanged aldehyde **10** that remained was easily removed by chromatography.

Reaction of **11** with ethereal methyllithium at room temperature afforded the required bicyclodiene **12**.

Stirring of **12** with excess formic acid gave rise to 11-formyloxy-11,12-dihydronootkatone (**14**), as expected. Saponification of **14** afforded the alcohol **15** whose spectral properties were identical with those reported for 11-hydroxy-11,12-dihydronootkatone.[9]

In *trans*-C(4),(5)-dimethyleremophilanes the nmr signal of the C(5)-methyl group is shifted up to 30 Hz upfield with respect to the corresponding cis isomers.[9] Since no such signal could be detected in the nmr spectrum of **15**, the Diels–Alder reaction giving rise to ester **4** was stereoselective as pointed out previously.

Boelens, *et al.*,[9] had reported a method for conversion of **15** into nootkatone (**2**), which involved prolonged refluxing of the former compound with excess acetic anhydride in pyridine. This method did not prove fruitful in the author's hands, even when the recommended reflux periods were doubled. The only recoverable product was the corresponding acetate **17**. This suggested that the temperature required for elimination of acetic acid to give **2** was higher than the boiling point of pyridine (115°). Furthermore, since the initial rearrangement product of **12** was, in fact, the formate ester **14**, it seemed desirable to effect direct elimination of this compound rather than go through the rigmarole of hydrolysis and esterification to the acetate.

In view of this, **14** was stirred with alumina in refluxing collidine (bp 172°). The alumina was incorporated in order to facilitate elimination since previous work had shown that it assisted dehydration of alcohols, presumably by a surface binding effect.[25] As expected, refluxing of **14** in this manner caused complete elimination to a mixture of nootkatone (**2**) (75%) and α-vetivone (**3**) (25%). The relative proportions of **2** and **3** present were deduced from the nmr spectrum of the product mixture since the isopropenyl group of **2** showed a singlet at δ 4.68 (two olefinic protons) whereas the isopropylidene group of **3** gave no such signal. When **14** was heated with alumina in the absence of collidine, the major product was α-vetivone (75%) possessing spectral properties identical with those reported.[26]

The above results suggest that the initial elimination product on alumina was nootkatone. In the presence of collidine most of the formic acid generated *in situ* would have been removed by salt formation so that little acid catalyzed isomerization of **2** to **3** could have occurred.[9] However, in the absence of collidine, the formic acid produced presumably remained bound to the alumina, thereby effecting conversion of nootkatone into α-vetivone. Since **2** and **3** were noted to be stable during high temperature glc analysis, their thermal interconversion did not occur. No 7-*epi*-nootkatone could be detected by careful nmr analysis[27] of the elimination product, showing that the final ring closure step of Scheme II was stereospecific, as earlier suggested.

A pure sample of (±)-nootkatone (**2**), obtained from the elimination product by preparative glc, was shown to be spectrally identical and superimposible on glc with an authentic sample.[28] Furthermore, when both the synthetic and authentic materials were tasted by the author and Professor A. J. Birch, they could not be differentiated.

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(22) C. Wittig and U. Schoellkopf, *Org. Syn.*, **40**, 66 (1960).
(23) G. Wittig and U. Schoellkopf, *Chem. Ber.*, **87**, 1318 (1954).
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(25) E. von Rudolf, *Can. J. Chem.*, **39**, 1860 (1961).
(26) J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1611 (1967).
(27) The nmr signal of the C(5)-methyl group is shifted 3 Hz downfield going from nootkatone to 7-*epi*-nootkatone. No signal corresponding to the latter compound could be detected at optimum resolution on a JEOL 100-MHz nmr spectrometer. Similar analysis has been employed previously.[9]
(28) The author is indebted to Dr. M. Pesaro, Givaudan-Esrolko, Zurich, for a gift sample of nootkatone.

Experimental Section

Ir spectra were run for liquid films with a Perkin-Elmer 257 spectrometer; mass spectra were determined using an AEI MS 902 spectrometer, and nmr spectra were attained with a JEOL MINIMAR 100 spectrometer unless otherwise stated. Glc measurements were recorded with a Varian Aerograph 1700 machine. Helium was employed as carrier gas, the flow rate being 35–45 ml/min. All solvent removals and distillations were carried out under reduced pressure. Drying of organic phases prior to distillation or solvent removal was attained with anhydrous sodium sulfate. Merck Kieselgel 60 silica was employed as adsorbent for all column chromatography.

1-Methoxy-3,4,5-trimethylcyclohexa-1,4-diene (9). A mixture of dry tetrahydrofuran (100 ml), anhydrous *tert*-butyl alcohol (100 ml), and 3,4,5-trimethylanisole (31 g) was added to liquid ammonia (1 l., freshly distilled from sodium) with stirring. Lithium (13 g) was then introduced over 30 min and the mixture was allowed to reflux under a CO_2–acetone condensor for 6 hr. Excess methanol was subsequently squirted in (reaction mixture rendered white) and the ammonia evaporated off under nitrogen. The solid residue was digested in water (300 ml) and thoroughly ether extracted (3 × 200 ml). The aqueous layer was saturated with sodium chloride and further extracted (2 × 100 ml). Drying of the combined extract followed by solvent removal and distillation afforded 1-methoxy-3,4,5-trimethylcyclohexa-1,4-diene (**9**) (28.3 g, 90%): bp 65–68° (17 mm); ir 1690 and 1660 cm^{-1}; nmr ($CDCl_3$) δ 4.55 (d, 1, J = 3 Hz, olefinic proton), 3.55 (s, 3, MeO), 1.65 (bs, 6, 2 × olefinic Me), and 1.05 (d, 3, J = 6 Hz, Me).

Methyl 1-Methoxy-4,5,7-trimethylbicyclo[2.2.2]oct-5-ene-2-carboxylate (4). The 1,4-diene **9** (27.5 g) was refluxed with methyl acrylate (35 g) and dichloromaleic anhydride (25 mg) for 16 hr. Distillation afforded a forerun of unchanged **9** (9.25 g) and the bicyclo ester **4** (24.8 g, 85% based on recovered starting material) (glc 2 m 3% SE-30, 205°, t_R 1.6 min) (Found: M^+, 238.156800; $C_{14}H_{22}O_3$ requires M^+, 238.156899): bp 85–100° (1 mm); ir 1730 cm^{-1}; nmr ($CDCl_3$) δ 5.8 (bs, 1, olefinic proton), 3.6 (s, CO_2Me), 3.3 (s, 3, MeO), 1.75 (d, 3, J = 2 Hz, olefinic Me), 1.05 (s, 3, Me), and 0.7 (d, 3, J = 6 Hz, Me).

Methyl 1-Methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-ene-5-carbaldehyde-2-carboxylate (10). Ester **4** (10 g) was dissolved in 1,4-dioxane (130 ml) and refluxed for 16 hr with selenium dioxide (5 g). After cooling, the reaction mixture was filtered and the solvent removed. The dark red product was taken up in ether (150 ml) and refiltered. Solvent removal followed by slow distillation through a short Vigreux column afforded the bicyclo aldehyde **10** (7.7 g, 70%) as a viscous oil (glc 2 m 3% SE-30, 205°, t_R 2.6 min) (Found: M^+, 252.136195; $C_{14}H_{20}O_4$ requires M^+, 252.136164): bp 110–130° (1 mm); ir 2710 and 1730 cm^{-1}; nmr ($CDCl_3$) δ 9.6 (s, 1, CHO), 7.3 (s, 1, olefinic proton), 3.6 (s, 3, CO_2Me), 3.4 (s, 3, MeO), 1.4 (s, 3, Me), and 0.7 (d, 3, J = 6 Hz, Me). Shorter refluxing periods led to incomplete oxidation of the initially formed alcohol.

Methyl 5-Vinyl-1-methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-ene-2-carboxylate (11). Triphenylmethylphosphonium bromide (8 g) was added in 2 g portions to *n*-butyllithium (1 equiv) in ether (100 ml) with stirring under nitrogen. After 1 hr the orange solution of the ylide was sucked rapidly into a syringe and injected over 15 min onto a well-stirred solution of aldehyde **10** (4.5 g) in ether (130 ml) at room temperature under nitrogen; 1 hr later, the reaction mixture was filtered and the residual solid washed thoroughly with ether (3 × 100 ml). Drying, solvent removal, and column chromatography on silica with chloroform as eluent afforded the bicyclodiene **11** (2.2 g, 50%) as a colorless oil (glc 2 m 3% SE-30, 200°, t_R 1.8 min) (Found: M^+, 250.15692; $C_{15}H_{22}O_3$ requires M^+, 250.15690): ir 1730 cm^{-1}; nmr ($CDCl_3$) δ 6.6–4.8 (complex m, 4, olefinic protons of ABCX system), 3.6 (s, 3, CO_2Me), 3.4 (s, 3, MeO), 1.15 (s, 3, Me), and 0.75 (d, 3, J = 6 Hz, Me).

5-Vinyl-2-(1-hydroxy-1-methylethyl)-1-methoxy-4,7-dimethylbicyclo[2.2.2]oct-5-ene (12). Diene **11** (3.1 g) was stirred in ether (40 ml) under nitrogen at room temperature, and ethereal methyllithium (2.5 equiv) was added dropwise. After 1 hr, the mixture was poured onto saturated sodium chloride solution (30 ml) and ether extracted (3 × 50 ml). Drying, solvent removal, and column chromatography on silica with chloroform as eluent afforded the bicyclodiene **12** (2.82 g, 90%) (glc 2 m 3% SE-30, 207°, t_R 2.7 min) (Found: M^+, 250.19320; $C_{16}H_{26}O_2$ requires M^+, 250.19329): ir 3500 cm^{-1}; nmr ($CDCl_3$) δ 6.6–4.8 (complex m, 4, olefinic protons of ABCX system), 4.5 (s, 1, OH), 3.4 (s, 3, MeO), 1.1 (s, 3, Me), 1.0 (s, 6, 2 × Me), and 0.75 (d, 3, J = 6 Hz, Me).

11-Formyloxy-11,12-dihydronootkatone (14). The bicyclodiene **12** (2.5 g) was stirred in formic acid (250 ml) for 1 hr at room temperature. Ice-cold saturated sodium hydroxide solution was then cautiously added, the reaction flask being frequently cooled in CO_2–acetone to prevent boiling caused by the exothermic reaction. Addition was stopped when the mixture had reached about pH 9. Rapid ether extraction (4 × 200 ml) followed by drying, solvent removal, and column chromatography on silica with chloroform as eluent afforded 11-formyloxy-11,12-dihydronootkatone (**14**) (1.2 g, 50%): ir 1720, 1660, and 1615 cm^{-1}; nmr ($CDCl_3$) δ 8.0 (s, 1, OCHO), 5.75 (s, 1, olefinic proton), 1.5 (s, 3, Me), 1.48 (s, 3, Me), 1.1 (s, 3, Me), and 1.0 (d, 3, J = 6 Hz, Me). The yield quoted is based on 180 mg of recovered 11-hydroxy-11,12-dihydronootkatone (**15**), presumably formed by hydrolysis during work-up.

11-Hydroxy-11,12-dihydronootkatone (15). 11-Formyloxy-11,12-dihydronootkatone (**14**) (1 g) was stirred at room temperature with *tert*-butyl alcohol (30 ml) and 0.5 *N* sodium hydroxide (20 ml) for 16 hr. The solvent was removed and water (30 ml) was added to the residue. The aqueous layer was saturated with sodium chloride and ether extracted (3 × 50 ml). Drying of the extract followed by solvent removal and column chromatography on silica with chloroform as eluent afforded 11-hydroxy-11,12-dihydronootkatone (**15**) (810 mg, 90%) as viscous gel: ir 3420, 1660, and 1615 cm^{-1}; nmr[9] (CCl_4) δ 5.65 (s, 1, olefinic proton), 1.14 (s, 3, Me), 1.11 (s, 3, Me), 1.07 (s, 3, Me), and 0.97 (d, 3, J = 6 Hz, Me). The nmr spectrum was run on a Varian Associates HA-100 spectrometer.

(±)-Nootkatone (2). 11-Formyloxy-11,12-dihydronootkatone (**14**) (75 mg) was stirred in refluxing collidine (8 ml) with neutral alumina (30 mg) for 16 hr. After cooling, the reaction mixture was shaken with 5 *N* hydrochloric acid (25 ml) and ether extracted (3 × 50 ml). Drying, solvent removal, and column chromatography on silica with chloroform as eluent afforded an oil (48 mg, 79%). A sample of the major component (75%) was obtained by preparative glc with a 3 m 20% SE-30 column at 180° on a Varian Aerograph Model 90-P machine. This sample was observed to be spectrally identical and superimposible on glc with authentic nootkatone (glc 2 m 3% SE-30, 192°, t_R 4.5 min): nmr (CCl_4) δ 5.62 (s, 1, olefinic proton), 4.68 (s, 2, olefinic protons), 1.72 (s, 3, olefinic Me), 1.11 (s, 3, Me), and 0.95 (d, 3, J = 6 Hz, Me). The nmr spectrum was run on a Varian Associates HA-100 spectrometer.

(±)-α-Vetivone (3). 11-Formyloxy-11,12-dihydronootkatone (**14**) (200 mg) was heated to 240° with neutral alumina (500 mg) in a Pyrex tube for 1 hr. After cooling, the alumina was vigorously shaken with methanol (2 × 50 ml). Filtering, drying, solvent removal, and column chromatography on silica with chloroform as eluent afforded an oil (110 mg, 68%). The nmr signals due to the oil's major component (75%) were identical with those reported for α-vetivone.[26] The remaining 25% consisted mainly of nootkatone (nmr).

Acknowledgments. The author is indebted to Professor A. J. Birch for suggesting that the Diels–Alder reaction should give the correct configuration of the methyl groups. Thanks are also due to Messrs. C. Henman, K. Kinealy, and K. Goggin for technical assistance. The award of a Research Scholarship from the Australian National University is gratefully acknowledged.