Metalation of Limonene. A Novel Method for the Synthesis of Bisabolane Sesquiterpenes[1]

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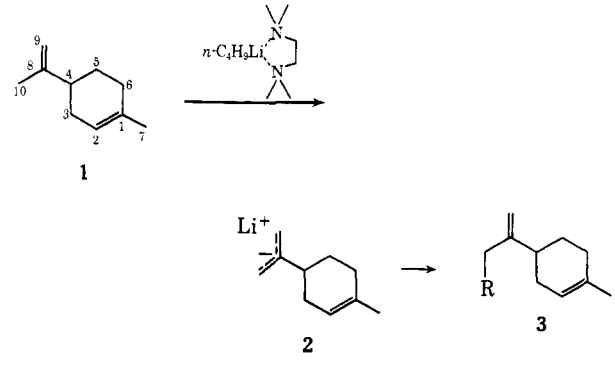
Abstract: The reaction of limonene with the complex of *n*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine results in selective metalation at C-10 of limonene to produce the allyllithium species **2**. This intermediate can be converted by treatment with various reagents to derivatives of limonene, including many of the known bisabolane sesquiterpenes. Both (+)-(*R*)- and (−)-(*S*)-limonene have been metalated and derivatized, and the optical activity of the starting material is retained in the products. Thus, reaction of **2** with carbon dioxide followed by esterification leads to the ester **6**. Derivatization with oxygen affords a one-step synthesis of the naturally occurring monoterpene alcohol **10**. β-Bisabolene (**12**) is produced in one step by reaction of **2** with 1-bromo-3-methyl-2-butene. Ethylene oxide reacts with **2** to give the alcohol **14**, which is converted to the *E* and *Z* isomers of lanceol (**18** and **19**). The reaction of metalated limonene with isovaleraldehyde affords a three-step synthesis of (±)-dihydro-*ar*-turmerone (**22**). Finally, **2** reacts with 3-methyl-2-butenal to provide efficient syntheses of (±)-*ar*-turmerone (**25**) and α-atlantone (**27**). Comparison of synthetic, optically active α-atlantone with the corresponding natural product reveals that the latter occurs in nearly racemic form.

The carbon skeleton of sesquiterpenes in the bisabolane family consists of a *p*-menthane group joined at C-10 to an isopentane unit (*e.g.*, β-bisabolene, **12**). In view of the ready availability of isopentane derivatives and monoterpenes of the *p*-menthane series, a method for direct combination of these fragments would constitute a convenient synthesis of the bisabolane system. Although numerous syntheses of bisabolane sesquiterpenes have been described,[2-14] this approach has not been used. We report here a novel reaction that accomplishes this operation and affords a remarkably facile route to several naturally occurring bisabolane derivatives.

We have found that limonene (**1**), on reaction with the 1:1 complex of *n*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA), undergoes selective metalation at C-10 to afford the 2-substituted allyllithium species represented by **2**. The intermediate **2** is converted by a variety of reagents to products having structure **3**. This process represents a general method for functionalization of limonene at C-10. When the substituent R in **3** is provided by reaction of **2** with a suitable isopentane derivative, the bisabolane system is obtained in a single step. In addition, the metalation-derivatization of optically active limonene occurs without racemization at the asymmetric center C-4. Limonene is readily available from natural sources in both of its enantiomeric forms. Thus it is possible with this process to prepare either enantiomer of **3** in high optical purity and desired absolute configuration.



1 2 3

The rapid metalation of **1** under mild conditions depends on the enhanced reactivity of *n*-butyllithium in the form of its TMEDA complex. Complexes of this type have been shown to have wide utility since they were first described in 1964.[15-19] However, their application in the metalation of simple olefins has received relatively little attention. Eberhardt and Davis metalated butenes with *n*-butyllithium–sparteine to initiate olefin telomerization with ethylene,[20] and one of us described the metalation-derivatization of α olefins using *n*-butyllithium–TMEDA.[21] In subse-

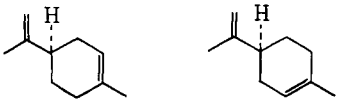
(1) Presented before the Joint Conference of the Chemical Institute of Canada and the American Chemical Society, Toronto, Canada, May 24–29, 1970.
(2) B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Amer. Chem. Soc.*, **92**, 336 (1970).
(3) K. Mori, M. Matsui, I. Yoshimura, and K. Saeki, *Agr. Biol. Chem. (Tokyo)*, **34**, 204 (1970).
(4) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).
(5) A. J. Birch, P. L. MacDonald, and V. H. Powell, *J. Chem. Soc. C*, 1469 (1970).
(6) K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.*, **46**, 1467 (1968).
(7) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968).
(8) C. D. Gutsche, J. R. Maycock, and C. T. Chang, *ibid.*, **24**, 859 (1968).
(9) A. Manjarrez and A. Guzmán, *J. Org. Chem.*, **31**, 348 (1966).
(10) R. Reugg, A. Pfiffner, and M. Montavon, *Recherches*, **No. 15**, 3 (1966).
(11) (a) O. P. Vig, B. Vig, and J. C. Kapur, *J. Indian Chem. Soc.*, **46**, 1078 (1969); (b) O. P. Vig, K. L. Matta, G. Singh, and I. Raj, *ibid.*, **43**, 27 (1966); (c) O. P. Vig, J. P. Salota, B. Vig, and B. Ram, *Indian J. Chem.*, **5**, 475 (1967). (d) Several additional examples have been published in the numbered series of papers by O. P. Vig, *et al.*
(12) G. D. Joshi and S. N. Kulkarni, *Indian J. Chem.*, **6**, 127 (1968); *ibid.*, **3**, 91 (1965).
(13) V. K. Honwad and A. S. Rao, *Tetrahedron*, **21**, 2593 (1965).
(14) For a summary of the literature prior to 1965, see J. M. Mellor and S. Munavalli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).
(15) Numerous references to reactions of organolithium–TMEDA complexes are listed in the review by C. Agami, *Bull. Soc. Chim. Fr.*, 1619 (1970).
(16) D. J. Peterson, *J. Organometal. Chem.*, **21**, 63 (1970); *ibid.*, **9**, 373 (1967); *ibid.*, **8**, 199 (1967); *J. Org. Chem.*, **32**, 1717 (1967).
(17) R. E. Ludt, G. P. Crowther, and C. R. Hauser, *ibid.*, **35**, 1288 (1970).
(18) G. Hallas and D. R. Waring, *Chem. Ind. (London)*, 620 (1969).
(19) E. J. Corey and H. A. Kirst, *Tetrahedron Lett.*, 5041 (1968).
(20) G. G. Eberhardt and W. R. Davis, *J. Polym. Sci., Part A*, **3**, 3753 (1965).

quent papers we will discuss the metalation of olefins other than limonene, and further applications in the synthesis of natural products.

Metalation of Limonene. The metalation is carried out by allowing a mixture of 2 equiv of limonene and 1 equiv of 1:1 *n*-butyllithium–TMEDA complex (*ca.* 1.5 *M* in *n*-hexane) to stand overnight at room temperature. Solutions of **2** are stable for several days when maintained under inert atmosphere. Derivatization of **2** is effected by direct addition of the appropriate reagent, followed by a standard work-up procedure. Excess limonene is readily separated from the product by fractional distillation. The yields of distilled products vary considerably with different derivatizing agents. Although yields reported here were not optimized, in the more favorable examples they range between 55 and 61%.[22]

In every case studied, the distilled product contained a single major fraction resulting from metalation-derivatization at C-10 of limonene. These products were obtained in purities ranging between 87 and 97% (glpc analysis), and were further purified for characterization by preparative glpc. Minor components were present in such small amounts that their identification was not attempted. If metalation processes occur at positions other than C-10 of limonene (*e.g.*, C-7), they must represent very minor pathways. The preferential metalation at C-10 probably reflects the greater stability of the 2-substituted allyllithium species **2** relative to the more highly substituted carbanionic systems that would arise from metalation at alternative sites. The selectivity of the metalation facilitates the purification of products and greatly enhances the synthetic utility of the reaction.

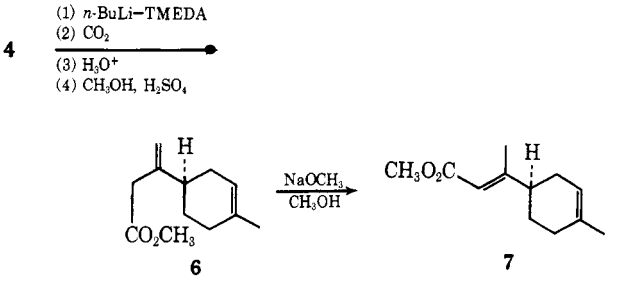
Metalations were conducted using commercially available samples of both (+)-(*R*)-limonene (**4**), $[\alpha]^{22}D$ +112°, and (−)-(*S*)-limonene (**5**), $[\alpha]^{22}D$ −102°. The absence of racemization was demonstrated by addition of water to a solution of metalated **4** that had been aged for 4 days at room temperature; the regenerated (+)-limonene showed no significant change in optical rotation. In addition, the rotations of known, optically active products **3** are in excellent agreement with literature values.



4 **5**

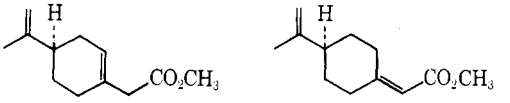
Syntheses of 10-substituted limonene derivatives, including several bisabolane sesquiterpenes, are treated separately under the headings that follow. In these examples, products were identified by their analytical and spectral properties and, in the case of natural products and other known materials, by comparison with literature data. This evidence is detailed in the Experimental Section.

Carbonation. Metalated (+)-limonene was derivatized with carbon dioxide, and the crude product mixture was separated into neutral (recovered limonene) and acidic fractions. Esterification of the latter with methanol–sulfuric acid afforded the β,γ-unsaturated ester **6**, $[\alpha]^{30}D$ +74°, in 19% overall yield.[23] Ester **6** was converted to the conjugated isomer **7**, $[\alpha]^{30}D$ +79°,



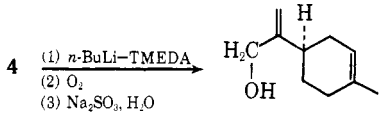
6 **7**

by brief treatment with sodium methoxide in methanol.[24] These experiments provide independent proof that metalation-derivatization occurs at C-10 of limonene. Although the spectral properties of the β,γ-unsaturated ester **6** do not exclude the isomeric product **8** that would result from reaction at C-7 of limonene, this ambiguity is resolved by conversion of the product to its conjugated isomer. Of the α,β-unsaturated esters **7** and **9** obtainable *via* C-10 or C-7 metalation pathways, respectively, only **7** has a structure consistent with the observed spectral data.



8 **9**

Oxygenation. The reaction of metalated (+)-limonene with oxygen, followed by a reductive work-up to destroy hydroperoxide intermediates, gave (+)-(*R*)-*p*-mentha-1,8(10)-dien-9-ol (**10**), $[\alpha]^{30}D$ +104°, in 97% purity and 33% yield after distillation. This alcohol and its acetate ester are naturally occurring minor constituents of various citrus oils.[25] The enantiomer of **10** has been synthesized previously in four steps from (−)-limonene,[10] and the racemic mixture has been prepared by a six-step procedure.[11c] Synthesis of **10** by the limonene metalation reaction thus provides, in one step, a monoterpene alcohol that has hitherto been relatively inaccessible. Compound **10**, as well as the ester **6** described above, are themselves potentially useful intermediates for syntheses of bisabolane sesquiterpenes and other 10-substituted limonene derivatives.



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(21) C. D. Broaddus, Abstracts of the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22–27, 1970, Division of Petroleum Chemistry, No. 91.

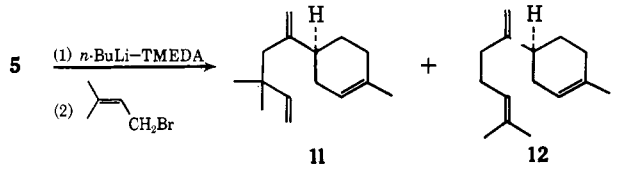
(22) Unless stated otherwise, yields are based on *n*-butyllithium.

(23) The low yield in this experiment was due, in part, to formation of high boiling by-products during the acid-catalyzed esterification. The complexity of the product mixture can be reduced by esterification with diazomethane. However, carbonation remains one of the least favorable methods for derivatization of **2** that we have encountered.

(24) The stereochemical assignment of *E* configuration to the conjugated double bond of **7** is based on nmr evidence. The absorption due to the methyl group on this double bond occurs at τ 7.88, indicating a cis relationship to the carbomethoxy group. In the model compound, methyl 3-methyl-2-butenoate, the methyl groups oriented cis and trans to the carbomethoxy group absorb at τ 7.88 and 8.16, respectively: L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960).

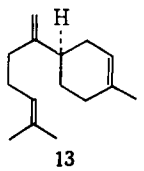
(25) (a) R. L. Coleman, E. D. Lund, and M. G. Moshonas, *J. Food Sci.*, **34**, 610 (1969); (b) G. L. K. Hunter and M. G. Moshonas, *ibid.*, **31**, 167 (1966); *Anal. Chem.*, **37**, 378 (1965); (c) Y. Ohta and Y. Hirose, *Agr. Biol. Chem.*, **30**, 1196 (1966); (d) these reports do not specify which enantiomer of the alcohol occurs in nature.

β-Bisabolene. The reaction of metalated (−)-limonene with 1-bromo-3-methyl-2-butene afforded, in 42% yield, a product mixture consisting of one part hydrocarbon **11**, $[\alpha]^{30}D$ −58°, and four parts (−)-β-bisabolene (**12**), $[\alpha]^{30}D$ −67°.[26] The latter is probably the most widely occurring member of the bisabolane family in essential oils. Hydrocarbons **11** and **12** can be



11 **12**

separated readily by spinning band distillation or by preparative glpc.[27] This one-step synthesis of optically active β-bisabolene offers obvious advantages over the many-step syntheses of the racemic material that have been reported in the literature.[9,11a–c] The control of product stereochemistry that this synthesis affords was illustrated by an identical synthesis of (+)-β-bisabolene (**13**), $[\alpha]^{30}D$ +74°, starting with (+)-limonene. This



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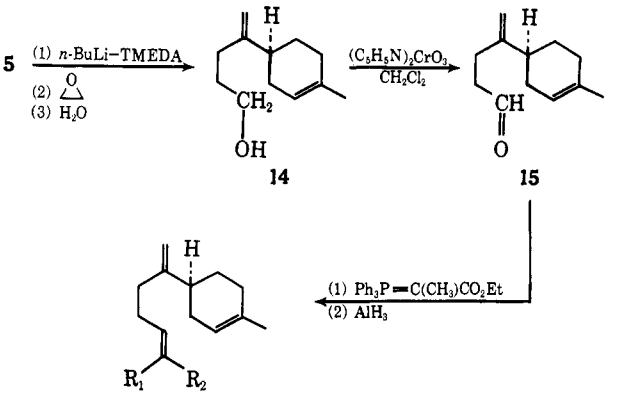
enantiomer also is known to occur naturally.[28]

Lanceol. The synthesis of lanceol stereoisomers **18** and **19** was carried out by a stepwise procedure starting with the reaction of metalated (−)-limonene with ethylene oxide. This reaction afforded the primary alcohol **14**, $[\alpha]^{30}D$ −75°, in 55% yield. Oxidation of **14** with Collins reagent[29] provided the known aldehyde **15**, $[\alpha]^{30}D$ −75°, also in 55% yield. The latter has been employed as a key intermediate in two previous syntheses of lanceol, but its preparation required six[10] or more[11c] steps.

In order to prepare both the *E* and *Z* stereoisomers of lanceol, **15** was first converted by a Wittig reaction with ethyl 2-(triphenylphosphoranylidene)propionate into an 8:1 mixture of (−)-(*E*)-ethyl lanceolate (**16**), $[\alpha]^{30}D$ −50°, and (−)-(*Z*)-ethyl lanceolate (**17**), $[\alpha]^{30}D$ −49°, in 97% yield. Brief ultraviolet irradiation of this mixture in cyclohexane solution altered the ratio[30] of **16**:**17** to 5:3. The esters were then separated by preparative glpc, and each was quantitatively reduced with aluminum hydride in ether[31] to afford (−)-(*E*)-lanceol (**18**), $[\alpha]^{30}D$ −60°, and (−)-(*Z*)-lanceol (**19**), $[\alpha]^{30}D$ −58°.



14 **15**

16, $R_1 = CH_3$; $R_2 = CO_2Et$
17, $R_1 = CO_2Et$; $R_2 = CH_3$
18, $R_1 = CH_3$; $R_2 = CH_2OH$
19, $R_1 = CH_2OH$; $R_2 = CH_3$

The stereochemical assignments for the acyclic, trisubstituted double bond in compounds **16**–**19** are based on well established nmr spectral properties for this system.[32] Comparable nmr data for natural lanceol have not been reported, and its identity with **18** or **19** remains uncertain. The earlier assignment of *E* stereochemistry to natural lanceol reported by Manjarrez, *et al.*,[33] must be held in question. In the process of converting lanceol to methyl lanceolate for spectral analysis, these workers first oxidized the natural alcohol to the corresponding aldehyde with chromium trioxide–pyridine, and purified the aldehyde by chromatography on alumina. It has since been shown that the *Z* isomers of 2-methyl-α,β-unsaturated aldehydes are unstable, and readily isomerize to the *E* form under a variety of conditions[32,34] (including contact with CrO_3–pyridine[35]). Thus, if natural lanceol is identical with **19**, the procedure of Manjarrez, *et al.*, may have caused its isomerization, and consequent identification as the *E* isomer.

(±)-Dihydro-*ar*-turmerone. The efficient derivatization of metalated limonene with aliphatic aldehydes is illustrated by a three-step synthesis of (±)-dihydro-*ar*-turmerone (**22**), and in the following section by a parallel synthesis of (±)-*ar*-turmerone (**25**). Addition of isovaleraldehyde to metalated (+)-limonene afforded the alcohol **20**, $[\alpha]^{30}D$ +68°, in 61% yield. Aromatization of **20** with *N*-lithioethylenediamine in ethylenediamine[36] resulted in smooth conversion to **21** in 82% yield. The aromatic alcohol was obtained as a mixture of two racemic diastereomers in a ratio of 3 to 4. The diastereomers were separated by preparative glpc and individually characterized. Comparisons between ir, nmr, and mass spectra of the isomers showed only minor differences in detail and did not provide a basis for assignment of stereochemical configurations. Both diastereomers afforded (±)-dihydro-*ar*-turmerone (**22**) as the sole product of Jones

(26) A similar distribution of isomeric products has been observed in the reaction of this same bromide with the sodium enolate of ethyl acetoacetate: P. Teisseire and M. Rinaldi, *Recherches*, No. 13, 4 (1963).

(27) Although these isomers should be thermally interconvertible by Cope rearrangement [H. M. Frey and R. K. Solly, *Trans. Faraday Soc.*, **65**, 1372 (1969)], no evidence of this was seen during glpc analysis or distillation. However, **11** and **12** have virtually identical mass spectra, indicating that equilibration may occur on electron impact.

(28) (a) N. H. Andersen and D. O. Syrdal, *Phytochemistry*, **9**, 1325 (1970); (b) V. A. Pentegova, O. Motl, and V. Herout, *Collect. Czech. Chem. Commun.*, **26**, 1362 (1961).

(29) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(30) (a) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967); (b) R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968); (c) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968); (d) M. J. Jorengson and L. Gundel, *ibid.*, 4991 (1968).

(31) M. J. Jorgenson, *ibid.*, 559 (1962).

(32) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968).

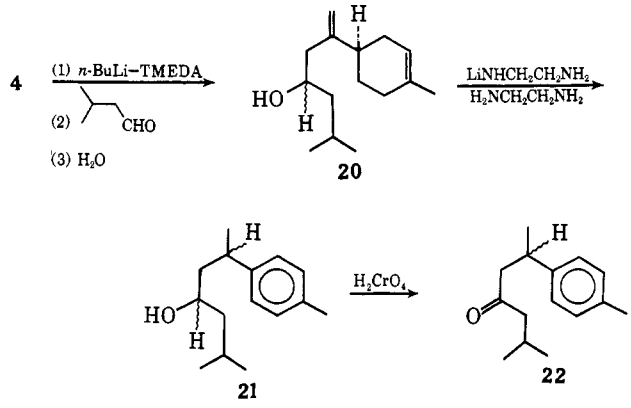
(33) A. Manjarrez, T. Riós, and A. Guzmán, *Tetrahedron*, **20**, 333 (1964).

(34) A. F. Thomas and M. Ozianne, *J. Chem. Soc. D*, 46 (1969).

(35) T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **38**, 381 (1965).

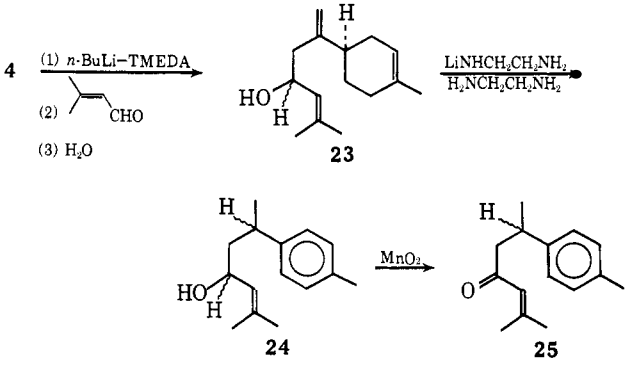
(36) (a) B. N. Joshi, R. Seshadri, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2911 (1964); (b) B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *ibid.*, **19**, 1189 (1963); (c) B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *J. Org. Chem.*, **27**, 1430 (1962); (d) L. Reggel, S. Friedman, and I. Wender, *ibid.*, **23**, 1136 (1958).

oxidation. For preparative purposes, the mixture of diastereomers was converted directly to **22** in 89% yield.



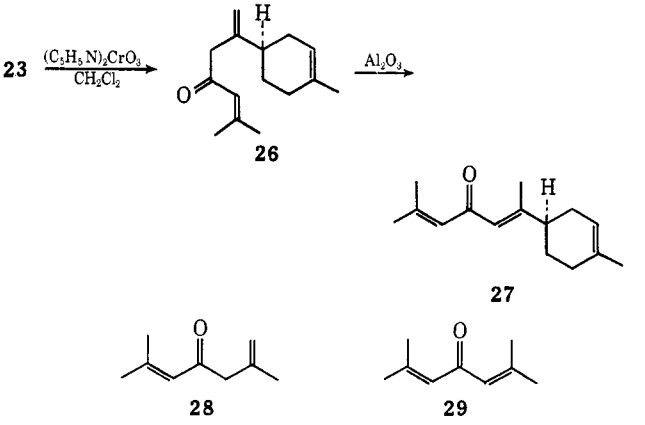
Optically active dihydro-*ar*-turmerone has been obtained from natural sources,[37] and can be prepared by catalytic hydrogenation of natural *ar*-turmerone.[6,13] An alternative synthetic route to the (±) form also has been mentioned,[37] but the number of steps is unspecified.

(±)-*ar*-Turmerone. The reaction of metalated (+)-limonene with 3-methyl-2-butenal gave the alcohol **23**, $[\alpha]^{30}D$ +68°, in 59% yield. Aromatization of **23** by the *N*-lithioethylenediamine technique[36] afforded **24** in 41% yield as a 1:1 mixture of racemic diastereomers. Although the diastereomers could be separated by preparative glpc, they were found to undergo partial decomposition during the separation and could not be isolated in pure form. As in the case of **21**, comparisons between the spectra of these isomers did not lead to stereochemical assignments.



Oxidation of either diastereomer with activated manganese dioxide afforded (±)-*ar*-turmerone (**25**) as the only product. On a preparative scale, MnO_2 oxidation of the crude mixture of diastereomers of **24** provided **25** in 58% yield. This synthesis of (±)-*ar*-turmerone, despite its low overall yield, appears to be shorter and more convenient than previously available routes.[38]

α-Atlantone. The alcohol **23**, obtained from the reaction of metalated (+)-limonene with 3-methyl-2-butenal, was oxidized with Collins reagent[29] to give (+)-β-atlantone (**26**), $[\alpha]^{30}D$ +65°, in 67% yield. The β designation for this compound is based on the usual nomenclature convention for bisabolene isomers. The ir,[39] uv,[39] and nmr[40,41] spectra of the model compound **28** show a marked similarity to the corresponding spectra of **26**.[42] We have found no report in the literature indicating that β-atlantone has been synthesized previously or isolated from nature.



Treatment of (+)-β-atlantone with activity grade I alumina resulted in smooth isomerization to (+)-α-atlantone (**27**), $[\alpha]^{30}D$ +77°, in 76% yield. The structural assignment of **27** is supported by comparison of its ir, uv, and nmr spectra[42] with the corresponding spectra of phorone (**29**).[39,43] The nmr spectrum of **27** shows that it has the *E* configuration at the C-8(10) double bond: the spectrum has absorptions at τ 7.90 due to *two* methyl groups cis to the carbonyl group, and at τ 8.17 due to *one* methyl trans to the carbonyl. The *cis*- and *trans*-methyl groups of phorone absorb at τ 7.86 and 8.14, respectively.[43]

α-Atlantone (along with γ-atlantone, the $\Delta^{4(8)}$ isomer) is reported to be an important odor constituent of the oils of various *Cedrus* species (the "true" cedars).[44] This was confirmed in the present case by isolation of an authentic sample of (+)-α-atlantone from the oil of *Cedrus atlantica*. Analysis of the oil by glpc on an SE-30 column showed a component having a retention time identical with that of **27**; this substance constituted *ca.* 8% of the oil, and was well separated from other components.[45] It was isolated from a high boiling fraction of the oil by preparative glpc on SE-30, and was found to be identical with synthetic (+)-α-atlantone in every respect but optical rotation. The naturally derived sample of **27** had $[\alpha]^{30}D$ +3°, in good agreement with literature values.[44b,46] Comparison of this rotation with that of the synthetic sample reveals that α-atlantone isolated from nature is nearly racemic. This is not surprising because **27** has a labile hydrogen at its asymmetric center C-4.

(37) J. Alexander and G. S. K. Rao, *Chem. Ind. (London)*, 139 (1969), ref 4.

(38) (a) R. P. Gandhi, O. P. Vig, and S. M. Mukherji, *Tetrahedron*, 7, 236 (1959); (b) J. Colonge and J. Chambion, *C. R. Acad. Sci.*, 222, 557 (1946).

(39) E. C. Craven and W. R. Ward, *J. Appl. Chem.*, 10, 18 (1960).

(40) K. J. Crowley, R. A. Schneider, and J. Meinwald, *J. Chem. Soc. C*, 571 (1966).

(41) P. J. Kropp and T. W. Gibson, *ibid.*, 143 (1967).

(42) The unique spectral properties of α,β-unsaturated ketones of this type have been related to the preferred s-cis conformation of the conjugated system: see D. D. Faulk and A. Fry, *J. Org. Chem.*, 35, 364 (1970); R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960); and ref 43.

(43) H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. B*, 75 (1966).

(44) (a) A. S. Pfau, *Helv. Chim. Acta*, 15, 1481 (1932); (b) A. S. Pfau and P. Plattner, *ibid.*, 17, 129 (1934).

(45) The glpc analysis did not indicate the presence of other atlantone isomers in the oil (*cf.* ref 46).

(46) B. S. Pande, S. Krishnappa, S. C. Bisarya, and S. Dev, *Tetrahedron*, 27, 841 (1971).

To our knowledge, this work represents the first confirmation of structure of α-atlantone by synthesis.

Experimental Section

Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates Model HA-100 spectrometer. Chemical shifts are reported in ppm on the τ scale, with tetramethylsilane as internal standard; coupling constants are in hertz (Hz). Nmr data are recorded in the order: chemical shift, multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant, interpretation. Samples were run in 1.5-mm o.d. glass capillary tubes according to the micro nmr technique developed in these laboratories.[47] Signals due to the hydroxyl protons of alcohols were identified by their characteristic upfield shift at increased sample temperature. Optical rotations were measured on a Jasco Model ORD/UV-5 optical rotatory dispersion recorder under the supervision of Dr. R. S. Treptow of these laboratories. Mass spectra were determined under the direction of Drs. J. H. Collins and G. G. Engerholm of these laboratories on Atlas CH-4 and SM-1 spectrometers. Gas chromatographic separations were carried out on a Varian Aerograph Model 202-2B instrument equipped with the following columns: column A, 10 ft × 0.25 in. stainless steel packed with 20% SE-30 on 60–80 mesh AW-DMCS Chromosorb W; column B, 10 ft × 0.25 in. stainless steel packed with 20% FFAP on 60–80 mesh AW-DMCS Chromosorb W; column C, 20 ft × $^3/_8$ in. stainless steel packed with 20% SE-30 on 45–60 mesh AW-DMCS Chromosorb W; column D, 20 ft × $^3/_8$ in. stainless steel packed with 20% Carbowax-20M on 45–60 mesh AW-DMCS Chromosorb W. Helium was used as the carrier gas, and was operated at a flow rate of 60 cc/min on columns A and B, and 150 cc/min on columns C and D. An apparatus of the type described by Johnson and Schneider[48] was used in reactions carried out under inert atmosphere (dry nitrogen or argon). The procedure for isolation of products following solvent extraction consisted of drying the organic solution over anhydrous sodium sulfate and removal of solvent at reduced pressure on a rotary evaporator. Analytical samples collected from preparative glpc were distilled in a bulb-to-bulb molecular distillation apparatus. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, Alfred Bernhard Microanalytisches Laboratorium, Elbach, West Germany, and Spang Microanalytical Laboratory, Ann Arbor, Mich.

Materials. *n*-Butyllithium in hexane was obtained from Foote Mineral Co. The concentration of active butyllithium was checked by the double titration procedure of Gilman and Haubein.[49] *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) was obtained from Matheson Coleman and Bell, and was dried immediately prior to use by distillation from calcium hydride. (+)-Limonene was obtained from Matheson Coleman and Bell, and had $[\alpha]^{22}D$ +112° (*c* 0.50, C_2H_5OH);[50] (−)-limonene was obtained from Glidden Co., Organic Chemicals Division, and had $[\alpha]^{22}D$ −102° (*c* 0.50, C_2H_5OH).[50]

Metalated Limonene. To a stirred solution of 200 ml (0.30 mol) of 1.5 *M* *n*-butyllithium in hexane under a static atmosphere of dry, inert gas (nitrogen or argon) was added dropwise 45 ml (35 g, 0.30 mol) of dry TMEDA; a crystalline precipitate formed during the mildly exothermic reaction, and redissolved when the addition was complete. To the resulting yellow solution was added dropwise 100 ml (84 g, 0.62 mol) of either (+)- or (−)-limonene. Stirring was continued for *ca.* 1 hr, and the solution became dark red in color. The solution was allowed to stand overnight at room temperature prior to further use.

In an experiment designed to test for racemization of limonene, a solution of metalated (+)-limonene was stored under argon at room temperature for 4 days. The solution was quenched with water and extracted with ether. Regenerated (+)-limonene was obtained in 90% yield after distillation, glpc purity > 98% (column A, 175°), $[\alpha]^{25}D$ +110° (*c* 0.50, C_2H_5OH).[50]

(+)-(*R*)-Methyl 3-(4-Methyl-3-cyclohexen-1-yl)-3-butenoate (6). A solution of metalated limonene was prepared from 40 ml (0.064 mol) of 1.6 *M* *n*-butyllithium in hexane, 9.6 ml (7.5 g, 0.065 mol) of TMEDA, and 21.2 ml (17.8 g, 0.13 mol) of (+)-limonene. A 60-ml portion of this solution was added rapidly by syringe to a slurry of Dry Ice in ether. When the resulting mixture had warmed to room temperature, water was added, the layers were separated, and the aqueous layer was extracted with two additional portions of ether. The combined ether solutions were dried and evaporated to give 10.2 g of recovered limonene. The aqueous solution was acidified with dilute hydrochloric acid and extracted three times with ether, and the combined ether solutions were dried and evaporated to give 6.0 g of liquid acid. A solution of this material in 100 ml of methanol containing 1 ml of concentrated sulfuric acid was heated to reflux for 2.5 hr, cooled, and poured into water. The resulting mixture was extracted with three portions of ether, and the combined ether solutions were washed successively with sodium bicarbonate solution and water, and were dried and evaporated. Distillation of the residue (5.3 g) through a short Vigreux column gave 1.98 g (19% based on *n*-butyllithium, 28% based on limonene consumed) of **6** as a colorless oil, bp 67–91° (0.2 mm), glpc purity 87% (column A, 200°). The analytical sample was obtained by preparative glpc on column C at 200°: bp (bath) <75° (0.05 mm); $[\alpha]^{30}D$ +74° (*c* 0.35, C_2H_5OH); ir (film) 3090 (>C=CH$_2$), 3010 (>C=CH–), 1745 (–CO_2CH_3), 1646 (>C=CH$_2$), 903 (>C=CH$_2$), and 804 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.70 (m, 1 H, >C=C*H*–), 5.16 (m, 2 H, >C=C*H*$_2$), 6.42 (s, 3 H, –CO_2CH_3), 6.99 [s, 2 H, $CH_3O_2CCH_2C$(=CH_2)–], and 7.7–8.7 ppm [m, 10 H, including τ 8.39 ppm (m, –CH=C(C*H*$_3$)–)]; mass spectrum (70 eV) *m/e* (rel intensity) 194 (24), 162 (28), 147 (15), 135 (26), 121 (58), 120 (72), 119 (37), 105 (64), 102 (39), 93 (73), 87 (26), 79 (39), 74 (14), 68 (100), 59 (20).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.40; H, 9.30.

(+)-(*E*)-Methyl 3-[4-Methyl-3-cyclohexen-1-(*R*)-yl]-2-butenoate (7). A solution of 0.30 g (1.54 mmol) of **6** (purity 90%) in 6 ml of methanol containing 0.25 g (4.7 mmol) of sodium methoxide was stirred and heated to reflux for 20 min, and then was allowed to stand at room temperature for 1 hr. The reaction mixture was diluted with 50 ml of water and extracted with three portions of ether. The combined ether solutions were washed with sodium chloride solution, and were dried and evaporated to afford 0.28 g (93%) of **7** as a pale yellow oil, glpc purity 80% (column A, 200°). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column C at 225° followed by molecular distillation: bp (bath) 75° (0.05 mm); $[\alpha]^{30}D$ +79° (*c* 0.35, C_2H_5OH); ir (film) 3015 (>C=CH–), 1725 (>C=O), 1646 (conjugated >C=CH–), and 802 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.40 (m, 1 H, >C=C*H*CO_2–), 4.68 (m, 1 H, >C=C*H*CH_2–), 6.42 (s, 3 H, –CO_2CH_3), and 7.7–8.5 ppm [m, 13 H, including τ 7.88 (s, –C(C*H*$_3$)=$CHCO_2$–) and 8.38 ppm (broadened s, –C(C*H*$_3$)=$CHCH_2$–)]; mass spectrum (70 eV) *m/e* (rel intensity) 194 (10), 163 (10), 162 (8), 147 (8), 135 (15), 125 (23), 121 (9), 120 (11), 119 (15), 111 (24), 107 (14), 105 (15), 101 (42), 94 (54), 79 (24), 68 (100), 67 (48).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.37; H, 9.25.

(+)-(*R*)-*p*-Mentha-1,8(10)-dien-9-ol (10). A solution of metalated limonene was prepared from 50 ml (0.075 mol) of 1.5 *M* *n*-butyllithium in hexane, 11.25 ml (8.77 g, 0.075 mole) of TMEDA, and 25.0 ml (21.0 g, 0.154 mol) of (+)-limonene. The solution was stirred, cooled to −35°, and a stream of dry air was introduced beneath the surface of the liquid. The rate of addition of air was regulated so that the solution temperature did not exceed −20°. When the exothermic reaction had ceased, the solution was allowed to warm to room temperature and 15 ml of water was added, followed by 70 ml of 25% sodium sulfite solution. The resulting two-phase mixture was stirred vigorously for 17 hr, the layers were separated, and the aqueous solution was extracted with three portions of ether. The combined organic solutions were washed successively with 5% sulfuric acid containing 5% potassium iodide, 5% sulfuric acid, and water, and were dried and evaporated. Distillation of the residue afforded 10.8 g of recovered limonene and 3.74 g (33%, based on *n*-butyllithium) of **10** as a faintly yellow oil, bp 66–71° (0.1 mm), glpc purity 97% (column A, 225°). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column D at 225° followed by molecular distillation: bp (bath) 64–71° (0.10 mm); $[\alpha]^{30}D$ +104° (*c* 0.33,

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(50) Measured on an optical polarimeter (error ±2%).

C_2H_5OH); the infrared spectrum was identical in all respects with the published spectrum of **10**;[51] nmr ($CDCl_3$) τ 4.64 (m, 1 H, >C=C*H*–), 5.00 and 5.17 (two broadened s, 2 H, >C=CH_2), 5.95 (s, 2 H, –CH_2OH), 7.08 (s, 1 H, –O*H*), and 7.7–8.7 ppm [m, 10 H, including τ 8.37 ppm (broadened s, –CH=C(CH_3)–)] (*cf.* lit.[52] nmr); mass spectrum (70 eV) *m/e* (rel intensity) 152 (30), 134 (71), 121 (18), 119 (100), 106 (84), 105 (30), 93 (53), 91 (63), 84 (49), 79 (54), 68 (78), 67 (69).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.07; H, 10.55.

(–)-β-Bisabolene (12) and (–)-(*S*)-4,4-Dimethyl-2-(4-methyl-3-cyclohexen-1-yl)-1,5-hexadiene (11). A solution of metalated limonene was prepared from 67 ml (0.10 mol) of 1.5 *M* *n*-butyllithium in hexane, 15 ml (11.7 g, 0.10 mol) of TMEDA, and 33 ml (27.7 g, 0.20 mol) of (–)-limonene. The solution was stirred, cooled to −60°, and 15.2 g (0.10 mol) of 1-bromo-3-methyl-2-butene[53] was added dropwise. The rate of addition was adjusted so that the solution temperature did not exceed −40°. The reaction mixture was allowed to warm to room temperature and 50 ml of water was added. The layers were separated, the aqueous solution was extracted with three portions of ether, and the combined organic solutions were washed successively with sodium chloride, 3 *M* hydrochloric acid, sodium bicarbonate, and sodium chloride solutions, and were dried and evaporated. Distillation of the residue afforded 16.8 g of recovered limonene and 8.64 g (42%, based on *n*-butyllithium, 53% based on limonene consumed) of colorless oil, bp 60–80° (0.10 mm). Glpc analysis of the latter on column B at 200° showed that 94% of this material consisted of a *ca.* 1:4 mixture of **11** (retention time 5.7 min) and (–)-β-bisabolene (**12**) (retention time 8.3 min). These were separated and purified by preparative glpc on column D at 225° followed by molecular distillation.

Hydrocarbon 11 was obtained as a colorless oil, bp (bath) 65° (0.05 mm), $[\alpha]^{30}D$ −58° (*c* 0.37, C_2H_5OH); ir (film) 3085 (>C=CH_2 and –CH=CH_2), 3002 (>C=CH–), 1641 (>C=CH_2 and –CH=CH_2), 1380 and 1365 (>C(CH_3)$_2$), 1006 and 916 (–CH=CH_2), 900 (>C=CH_2), and 803 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.25 (d of d, 1 H, J_1 = 18 Hz, J_2 = 10 Hz, –C*H*=CH_2), 4.71 (m, 1 H, >C=C*H*–), 5.1–5.5 (m, 4 H, –CH=CH_2 and >C=CH_2), 7.7–8.5 [m, 12 H, including 7.97 (s, –C(CH_3)$_2$CH_2C(=CH_2)–) and 8.40 (broadened s, –CH=C(CH_3)–)], and 9.02 ppm (s, 6 H, >C(CH_3)$_2$); mass spectrum (70 eV) *m/e* (rel intensity) 204 (22), 189 (8), 161 (21), 147 (5), 135 (16), 134 (15), 121 (15), 119 (18), 109 (15), 107 (19), 105 (15), 93 (50), 79 (24), 69 (100), 68 (13), 67 (20), 55 (14).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.27; H, 11.80.

(–)-β-Bisabolene (12) was obtained as a colorless oil, bp (bath) 65° (0.05 mm) [lit. bp 85° (0.5 mm);[9] 112–114° (5 mm);[11a] 110–111° (3 mm)[54]]; $[\alpha]^{30}D$ −68° (*c* 0.33, C_2H_5OH) (lit. $[\alpha]D$ −66.8°;[54] $[\alpha]^{20}D$ −84.4°;[55] $[\alpha]D$ −62.92°;[56] $[\alpha]^{15}D$ −67°[57]); the infrared spectrum was identical in all respects with published ir spectra[54,57,58] of (–)-β-bisabolene; nmr ($CDCl_3$) τ 4.67 (m, 1 H, –C*H*=C(CH$_3$)CH$_2$–), 4.93 (m, 1 H, –C*H*=C(CH$_3$)$_2$), 5.32 (broadened s, 2 H, >C=CH_2), 7.7–8.3 (m, 11 H), and 8.3–8.45 ppm (m, 9 H, –CH=C(CH_3)$_2$ and –CH=C(CH_3)CH$_2$–) (*cf.* lit.[59] nmr); mass spectrum (70 eV) *m/e* (rel intensity) 204 (21), 189 (8), 161 (17), 147 (4), 135 (10), 134 (8), 121 (14), 119 (20), 109 (20), 107 (18), 105 (13), 93 (66), 79 (27), 69 (100), 68 (10), 67 (33), 55 (27) (*cf.* lit.[60] mass spectrum).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.38; H, 11.81.

A similar experiment was carried out starting with (+)-limonene, and yielded (+)-β-bisabolene (**13**), $[\alpha]^{30}D$ +74° (*c* 0.36, C_2H_5OH) (lit. $[\alpha]D$ +52 ± 20°;[28a] $[\alpha]^{20}D$ +75°[28b]), which had spectral properties identical with those of the (–)-enantiomer.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.34; H, 11.71.

(–)-(*S*)-4-(4-Methyl-3-cyclohexen-1-yl)-4-penten-1-ol (14). A solution of metalated limonene was prepared from 200 ml (0.29 mol) of 1.45 *M* *n*-butyllithium in hexane, 45 ml (35 g, 0.30 mol) of TMEDA, and 100 ml (84 g, 0.62 mol) of (–)-limonene. The solution was stirred, cooled to −60°, and a stream of dry ethylene oxide gas was introduced through a gas inlet tube at a point just above the surface of the liquid. The rate of addition of ethylene oxide was regulated so that the solution temperature did not exceed −40°. When the exothermic reaction had ceased, the ethylene oxide flow was continued and the solution was allowed to warm to room temperature. Water was added, the layers were separated, and the aqueous solution was extracted with three portions of ether. The combined organic solutions were washed successively with sodium chloride, 3 *M* hydrochloric acid, and sodium chloride solutions, and were dried and evaporated. Distillation of the residue yielded 33 g of recovered limonene and 28.8 g (55%, based on *n*-butyllithium) of **14** as a colorless oil, bp 92–97° (0.20 mm), glpc purity 94% (column A, 225°). The analytical sample was purified by preparative glpc on column D at 240°, followed by molecular distillation: bp (bath) 80° (0.10 mm); $[\alpha]^{30}D$ −75° (*c* 0.35, C_2H_5OH); ir (film) 3330 broad (OH), 3075 (>C=CH_2), 3005 (>C=CH–), 1647 (>C=CH_2), 1060, 891 (>C=CH_2), and 800 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.60 (m, 1 H, >C=C*H*–), 5.25 (broadened s, 2 H, >C=CH_2), 6.40 (t, 2 H, J = 6 Hz, –CH_2OH), 6.94 (s, 1 H, –O*H*), and 7.7–8.5 ppm [m, 14 H, including τ 8.36 ppm (broadened s, –CH=C(CH_3)–)]; mass spectrum (70 eV) *m/e* (rel intensity) 180 (39), 162 (8), 149 (6), 147 (8), 136 (19), 121 (63), 105 (19), 93 (78), 79 (63), 68 (100).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.12.

(–)-(*S*)-4-(4-Methyl-3-cyclohexen-1-yl)-4-pentenal (15). To a stirred solution of 2.00 g (0.011 mol) of **14** (purity 94%) in 22 ml of anhydrous dichloromethane (freshly distilled from phosphorus pentoxide) under argon was added rapidly a solution of 18.6 g (0.072 mol) of dipyridine–chromium(VI) oxide in 350 ml of anhydrous dichloromethane (Collins reagent).[29] The resulting mixture was stirred for 15 min and was filtered under suction through a cake of Celite. The filter cake was washed with ether, and the combined filtrate and washings were washed successively with sodium chloride, 2 *M* hydrochloric acid, sodium bicarbonate, and sodium chloride solutions and were dried and evaporated. Distillation of the residue (1.88 g) through a short-path apparatus yielded 1.08 g (55%) of **15** as a pale yellow liquid, bp 70–76° (0.2 mm), glpc purity 89% (column B, 225°). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column D at 240° followed by molecular distillation: bp (bath) 59° (0.10 mm); $[\alpha]^{30}D$ −75° (*c* 0.33, C_2H_5OH) [lit.[10] $[\alpha]^{25}D$ −77.8° (*c* 0.64, C_2H_5OH)]; ir (film) 3080 (>C=CH_2), 3005 (>C=CH–), 2715 (–CHO), 1735 (–CH=O), 1648 (>C=CH_2), 895 (>C=CH_2), and 800 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 0.23 (t, 1 H, J = 1.5 Hz, –C*H*O), 4.60 (m, 1 H, >C=C*H*–), 5.19 and 5.29 (two broadened s, 2 H, >C=CH_2), and 7.3–8.4 ppm [m, 14 H, including τ 8.35 ppm (broadened s, –CH=C(CH_3)–)] (*cf.* lit.[10] nmr); mass spectrum (70 eV) *m/e* (rel intensity) 178 (12), 160 (10), 145 (15), 135 (9), 134 (64), 121(15), 119 (42), 105 (38), 93 (56), 85 (6), 79 (46), 68 (100).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.54; H, 10.12.

(–)-(*E*)-Ethyl Lanceolate (16) and (–)-(*Z*)-Ethyl Lanceolate (17). A solution of 0.915 g (5.14 mmol) of **15** (purity 100%) and 2.06 g (5.69 mmol) of ethyl 2-(triphenylphosphoranylidene)propionate in 25 ml of absolute ethanol was allowed to stand at room temperature for 3.5 hr. The solvent was removed by evaporation, and the residue, a mixture of liquid and solid materials, was triturated with 25 ml of hexane. The solid was separated by filtration, and the filtrate was evaporated; this process was repeated several times until nearly all of the solid had been separated. Molecular distillation of the liquid fraction at 0.1 mm gave 1.31 g (97%) of colorless oil. Glpc analysis on column A at 240° showed that the product consisted entirely of a mixture of **17** (retention time 19.1 min) and **16** (retention time 24.6 min) with relative peak areas of 1 and 8, respectively. A solution of the entire product mixture in 185 ml of deoxygenated cyclohexane was bubbled with nitrogen and irradiated with a 200-W Hanovia high-pressure ultraviolet lamp housed in a water-cooled Vycor immersion well. The progress of the photolysis was followed by periodic removal of small aliquots from the solution for glpc analysis. The irradiation was stopped after 16.5 min when the proportion of minor constituents in the

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mixture (*e.g.*, deconjugated isomers) had increased to *ca.* 5%; at this point the peak area ratio of **17**:**16** was 3:5 (column A, 240°). The isomers were separated and purified by preparative glpc on column D at 250° followed by molecular distillation.

16 was obtained as a colorless oil, bp (bath) <120° (0.1 mm); $[\alpha]^{30}D$ −50° (*c* 0.38, C_2H_5OH); ir (film) 3080 (>C=CH_2), 1719 (>C=O), 1653 (conjugated >C=CH–), 1275, 1120, 893 (>C=CH_2), and 802 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 3.27 (m, 1 H, –C*H*=C(CH_3)CO_2Et), 4.64 (m, 1 H, –C*H*=C(CH_3)CH_2–), 5.23 and 5.28 (two broadened s, 2 H, >C=CH_2), 5.86 (q, 2 H, *J* = 7 Hz, –$CO_2CH_2CH_3$), 7.5–8.6 [m, 17 H, including 8.18 (broadened s, –CH=C(CH_3)CO_2Et), and 8.37 (broadened s, –CH=C(CH_3)-CH_2–)], and 8.73 ppm (t, 3 H, *J* = 7 Hz, –$CO_2CH_2CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 262.1906 (43) (calcd for $C_{17}H_{26}O_2$, 262.1933), 233 (5), 216 (14), 189 (18), 188 (20), 173 (9), 167 (9), 161 (10), 160 (17), 145 (7), 135 (16), 128 (20), 121 (52), 119 (81), 107 (18), 105 (21), 102 (12), 100 (11), 93 (100), 79 (64), 67 (45).

17 was obtained as a colorless oil, bp (bath) <110° (0.1 mm); $[\alpha]^{30}D$ −49° (*c* 0.35, C_2H_5OH); ir (film) 3080 (>C=CH_2), 1723 (>C=O), 1650 (conjugated >C=CH–), 1187, 1128, 893 (>C=CH_2), and 802 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.07 (m, 1 H, –C*H*=C(CH_3)CO_2Et), 4.61 (m, 1 H, –C*H*=C(CH_3)CH_2–), 5.23 (m, 2 H, >C=CH_2), 5.81 (q, 2 H, *J* = 7 Hz, –$CO_2CH_2CH_3$), 7.2–8.6 [m, 17 H, including 8.11 (broadened s, –CH=C(CH_3)CO_2Et) and 8.36 (broadened s, –CH=C(CH_3)CH_2–)], and 8.71 ppm (t, 3 H, *J* = 7 Hz, –$CO_2CH_2CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 262.1927 (14) (calcd for $C_{17}H_{26}O_2$, 262.1933), 233 (5), 216 (13), 189 (13), 188 (12), 173 (7), 167 (6), 161 (10), 160 (14), 145 (9), 135 (18), 128 (14), 121 (65), 119 (100), 107 (18), 105 (21), 102 (11), 100 (11), 93 (99), 79 (62), 67 (17).

(−)-(*E*)-Lanceol (18). A solution of *ca.* 1 *M* aluminum hydride in ether was prepared by adding 0.60 g (4.5 mmol) of aluminum chloride to a slurry of 0.58 g (15 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether (freshly distilled from calcium hydride) at 0°. To a stirred solution of 0.20 g (0.76 mmol) of **16** (purity 100%) in 1 ml of anhydrous ether at 0° under nitrogen was added dropwise *via* syringe 3.7 ml of aluminum hydride solution. The resulting mixture was stirred at room temperature for 0.5 hr, and was cooled to 0° while 30 ml of water was added. The solution was acidified to pH 3–4 with hydrochloric acid and extracted with three portions of ether. The combined ether solutions were washed successively with sodium bicarbonate solution and water, and were dried and evaporated to give 0.17 g (100%) of **18** as a light yellow oil, glpc purity >99% (column B, 240°). The product was obtained as a colorless oil after molecular distillation: bp (bath) 103° (0.05 mm) [lit.[10] bp 106–107° (0.06 mm)]; $[\alpha]^{30}D$ −60° (*c* 0.29, C_2H_5OH) [lit.[10] $[\alpha]^{25}D$ −61.6° (*c* 0.56, C_2H_5OH)]; ir (film) 3320 broad (OH), 3075 (>C=CH_2), 3000 (>C=CH–), 1648 (>C=CH_2), 1068, 1010, 891 (>C=CH_2), and 801 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.67 (m, 2 H, –C*H*=C(CH_3)CH_2– and –C*H*=C-(CH_3)CH_2OH), 5.30 (broadened s, 2 H, >C=CH_2), 6.12 (broadened s, 2 H, –CH_2OH), 6.95 (s, 1 H, –O*H*), and 7.7–8.5 ppm [m, 17 H, including τ 8.37 ppm (broadened s, –CH=C(CH_3)CH_2– and –CH=C(CH_3)CH_2OH)] (*cf.* lit.[10] ir and nmr); mass spectrum (70 eV) *m/e* (rel intensity) 220.1810 (3) (calcd for $C_{15}H_{24}O$: 220.1827), 202 (27), 189 (8), 187 (11), 174 (5), 159 (38), 145 (14), 134 (45), 123 (18), 121 (26), 119 (53), 107 (34), 105 (35), 93 (100), 79 (61), 68 (40), 67 (63).

(−)-(*Z*)-Lanceol (19). This alcohol was prepared in quantitative yield by aluminum hydride reduction of 0.10 g of **17** by a procedure identical with that used to prepare (−)-(*E*)-lanceol. The product was obtained as a faintly yellow oil after molecular distillation: bp (bath) 100–105° (0.05 mm); $[\alpha]^{30}D$ −58° (*c* 0.31, C_2H_5OH) [lit.[10] $[\alpha]D$ −60° (*c* 0.95, C_2H_5OH)]; ir (film) 3320 broad (OH), 3075 (>C=CH_2), 3000 (>C=CH–), 1648 (>C=CH_2), 1038, 1010, 890 (>C=CH_2), and 800 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.69 (m, 1 H, –C*H*=C(CH_3)CH_2–), 4.80 (m, 1 H, –C*H*=C(CH_3)-CH_2OH), 5.31 and 5.35 (two broadened s, >C=CH_2), 5.98 (s, 2 H, –CH_2OH), 7.34 (s, 1 H, –O*H*), and 7.7–8.6 ppm [m, 17 H, including τ 8.26 (broadened s, –CH=C(CH_3)CH_2OH), and 8.39 ppm (broadened s, –CH=C(CH_3)CH_2–)] (*cf.* lit.[10] ir and nmr); mass spectrum (70 eV) *m/e* (rel intensity) 220.1832 (7) (calcd for $C_{15}H_{24}O$: 220.1827), 202 (34), 189 (11), 187 (15), 174 (10), 161 (15), 159 (50), 145 (12), 134 (60), 123 (23), 121 (21), 119 (57), 107 (40), 105 (40), 93 (100), 84 (39), 79 (73), 68 (30), 67 (62).

(+)-6-Methyl-2-[4-methyl-3-cyclohexen-1-(*R*)-yl]-1-hepten-4-(*RS*)-ol (20). A solution of metalated limonene was prepared from 50 ml (0.075 mol) of 1.5 *M* *n*-butyllithium in hexane, 11.3 ml (8.8 g, 0.076 mol) of TMEDA, and 25.0 ml (21.0 g, 0.154 mol) of (+)-limonene. The solution was stirred, cooled to −50°, and 10.0 ml (8.0 g, 0.093 mol) of freshly distilled isovaleraldehyde was added dropwise. The rate of addition was adjusted so that the solution temperature did not exceed −20°. The reaction mixture was allowed to warm to room temperature and 50 ml of water was added. The layers were separated, the aqueous solution was extracted with three portions of ether, and the combined organic solutions were washed successively with sodium chloride, 0.5 *M* hydrochloric acid, and sodium chloride solutions, and were dried and evaporated. Distillation of the residue afforded 9.6 g of recovered limonene and 10.14 g (61%, based on *n*-butyllithium) of **20** as a colorless oil, bp 79–101° (0.10 mm), glpc purity 88% (column A, 225°). The analytical sample was purified by preparative glpc on column D at 225° followed by molecular distillation: bp (bath) <90° (0.05 mm); $[\alpha]^{30}D$ +68° (*c* 0.35, C_2H_5OH); ir (film) 3370 broad (OH), 3085 (>C=CH_2), 3015 (>C=CH–), 1642 (>C=CH_2), 1386 and 1370 (–$CH(CH_3)_2$), 898 (>C=CH_2), and 802 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.68 (m, 1 H, >C=C*H*–), 5.17 and 5.23 (two broadened s, 2 H, >C=CH_2), 6.29 (m, 1 H, >C*H*OH), 7.6–8.9 [m, 16 H, including 7.92 (s, –O*H*), and 8.38 (broadened s, –CH=C(CH_3)–)], and 9.09 ppm (d, 6 H, *J* = 7 Hz, –$CH(CH_3)_2$); mass spectrum (70 eV) *m/e* (rel intensity) 222 (0.5), 204 (3), 189 (1), 165 (1), 161 (4), 147 (12), 136 (13), 127 (1), 121 (26), 119 (18), 107 (23), 105 (18), 93 (74), 85 (7), 79 (31), 69 (47), 68 (100), 57 (29).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.03; H, 11.70.

(±)-2-Methyl-6-*p*-tolyl-4-heptanol (21). To 225 ml of vigorously stirred, anhydrous ethylenediamine (freshly distilled from calcium hydride) at 100–110° under argon was added 3.15 g (0.45 g-atom) of lithium wire in small pieces (1–2-cm length) over a period of 0.5 hr. When the blue color of the solution had disappeared, the mixture was heated to reflux, and 10.0 g (0.045 mol) of **20** (purity 88%) was added dropwise over a period of 10 min. The solution was refluxed for 90 min, and then was cooled in an ice bath while 275 ml of water was added. The resulting mixture was extracted with four portions of ether, the combined ether solutions were dried and evaporated, and the residue was distilled through a short-path apparatus to give 8.1 g (82%) of faintly yellow oil, bp 65–100° (0.1–0.05 mm). Glpc analysis on column B at 240° showed clean separation of the two stereoisomers of the product, and these were labeled diastereomer A (retention time 11.1 min) and diastereomer B (retention time 12.8 min); the peak area ratio for A:B was *ca.* 3:4. The analytical samples were obtained as colorless oils after purification by preparative glpc on column C at 225° followed by molecular distillation: **21-A** bp (bath) <110° (0.05 mm); $[\alpha]^{30}_{700-250}$ 0° (*c* 0.37, C_2H_5OH); ir (film) 3350 broad (OH), 3052 and 3025 (–C_6H_4–), 1518 (–C_6H_4–), 1388 and 1370 (–$CH(CH_3)_2$), 1024, and 823 cm^{-1} (*p*-C_6H_4–); nmr ($CDCl_3$) τ 3.03 (s, 4 H, *p*-$CH_3C_6H_4$–), 6.67 (m, 1 H, >C*H*OH), 7.10 (m, 1 H, $C_7H_7CH(CH_3)$–), 7.53 (s, 1 H, –O*H*), 7.79 (s, 3 H, *p*-$CH_3C_6H_4$–), 8.1–8.9 [m, 8 H, including 8.80 (d, *J* = 6.5 Hz, $C_7H_7CH(CH_3)$–)], and 9.23 ppm (d, 6 H, *J* = 6 Hz, –$CH(CH_3)_2$); mass spectrum (70 eV) *m/e* (rel intensity) 220 (9), 218 (1), 202 (15), 187 (4), 163 (3), 159 (4), 145 (30), 131 (43), 120 (47), 119 (100), 105 (24), 91 (11).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.72; H, 10.96.

21-B had: bp (bath) <110° (0.05 mm); $[\alpha]^{30}_{700-250}$ 0° (*c* 0.37, C_2H_5OH); ir (film) 3350 broad (OH), 3052 and 3021 (–C_6H_4–), 1517 (–C_6H_4–), 1388 and 1370 (–$CH(CH_3)_2$), 1060, and 823 cm^{-1} (*p*-C_6H_4–); nmr ($CDCl_3$) τ 3.04 (s, 4 H, *p*-$CH_3C_6H_4$–), 6.46 (m, 1 H, >C*H*OH), 7.20 (m, 1 H, $C_7H_7CH(CH_3)$–), 7.63 (s, 1 H, –O*H*), 7.79 (s, 3 H, *p*-$CH_3C_6H_4$–), 8.1–8.9 [m, 8 H, including 8.81 (d, *J* = 6.5 Hz, $C_7H_7CH(CH_3)$–)], and 9.17 ppm [t (overlapping doublets), 6 H, *J* = 6 Hz, –$CH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 220 (1), 218 (2), 202 (9), 187 (1), 161 (1), 159 (1), 145 (16), 132 (24), 131 (14), 120 (21), 119 (100), 105 (14), 91 (11).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.95.

(±)-Dihydro-*ar*-turmerone (22). To a stirred solution of 4.00 g (0.018 mol) of the mixture of diastereomers of **21** in 100 ml of acetone at 0° was added dropwise 5 ml of Jones reagent (2.67 *M* CrO_3 in 8.6 *N* H_2SO_4)[61] over a period of 10 min. The mixture was stirred for an additional 3 min and was poured into 100 ml of water. The resulting mixture was extracted with three portions of ether, and the combined ether solutions were washed successively with sodium bicarbonate and sodium chloride solutions, and were dried and evaporated. Distillation of the residue gave 3.53 g (89%)

(61) (a) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); (b) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

of **22** as a pale yellow oil, bp 77–90° (0.08 mm) [lit. bp 115° (1 mm)[6]; 100–102° (1 mm)[13]], glpc purity 90% (column B, 235°). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column D at 240° followed by molecular distillation: bp (bath) 80–90° (0.05 mm); $[\alpha]^{30}_{700-250}$ 0° (*c* 0.4, C_2H_5OH); ir (film) 3053 and 3025 ($-C_6H_4-$), 1715 (>C=O), 1518 ($-C_6H_4-$), 1410 ($-CH_2CO-$), 1370 ($-CH(CH_3)_2$), and 821 cm^{-1} (*p*-C_6H_4-); uv max (CH_3OH) mμ (ε) 253 sh (248), 259 (350), 265 (440), 267 sh (424), 273 (450); nmr ($CDCl_3$) τ 3.03 (s, 4 H, *p*-$CH_3C_6H_4-$), 6.78 (m, 1 H, $C_7H_7CH(CH_3)-$), 7.46 (m, 2 H, $-CH_2-COCH_2CH(CH_3)_2$), 7.79 (s, 3 H, *p*-$CH_3C_6H_4-$), 7.8–8.2 (m, 3 H, $-COCH_2CH(CH_3)_2$), 8.82 (d, 3 H, *J* = 6.5 Hz, $C_7H_7CH(CH_3)-$), and 9.19 ppm (d, 6 H, *J* = 6 Hz, $-CH(CH_3)_2$) (*cf.* lit.[13] ir, uv, and nmr); mass spectrum (70 eV) *m/e* (rel intensity) 218 (26), 203 (18), 161 (17), 133 (10), 119 (100), 105 (8), 91 (6), 85 (17), 57 (22).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.62; H, 10.27.

In separate experiments, the individual diastereomers **21-A** and **21-B** were oxidized separately according to the procedure described above. Both isomers gave **22** as the sole product, which was identified by its ir spectrum and glpc retention time.

(+)-6-Methyl-2-[4-methyl-3-cyclohexen-1-(*R*)-yl]-1,5-heptadien-4-(*RS*)-ol (23). A solution of metalated limonene was prepared from 160 ml (0.24 mol) of 1.5 *M* *n*-butyllithium in hexane, 36 ml (28 g, 0.24 mol) of TMEDA, and 80 ml (67 g, 0.49 mol) of (+)-limonene. The solution was stirred, cooled to −27°, and 21.5 g (0.26 mol) of 3-methyl-2-butenal[62] was added dropwise. The addition was carried out over a period of 10 min, and the solution temperature did not exceed −6°. Stirring was continued for 20 min while the temperature increased to 2°, and 100 ml of water was added. The layers were separated, the aqueous solution was extracted with three portions of ether, and the combined organic solutions were washed twice with sodium chloride solution, and were dried and evaporated. Distillation of the residue yielded recovered limonene, and 31.2 g (59%, based on *n*-butyllithium) of **23** as a yellow oil, bp 79–115° (0.15–0.25 mm), glpc purity undetermined (partial decomposition during analysis). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column C at 240° followed by molecular distillation: bp (bath) <100° (0.05 mm); $[\alpha]^{30}D$ +68° (*c* 0.35, C_2H_5OH); ir (film) 3360 broad (OH), 3080 (>C=CH_2), 3010 (>C=CH–), 1678 (>C=CH–), 1642 (>C=CH_2), 895 (>C=CH_2), and 803 cm^{-1} (>C=CH–); nmr ($CDCl_3$) τ 4.68 (m, 1 H, $-CH=C(CH_3)-CH_2-$), 4.91 (m, 1 H, $-CH=C(CH_3)_2$), 5.23 (broadened s, 2 H, >C=CH_2), 5.63 (m, 1 H, >C*H*OH), 7.59 (s, 1 H, –O*H*), and 7.7–8.7 ppm [m, 18 H, including τ 8.35 ppm (m, $-CH=C(CH_3)_2$ and $-CH=C(CH_3)CH_2-$)]; mass spectrum (70 eV) *m/e* (rel intensity) 220 (0.5), 202 (5), 187 (3), 159 (5), 145 (3), 136 (7), 134 (6), 121 (3), 119 (9), 107 (7), 105 (8), 93 (12), 91 (11), 85 (100), 79 (12), 68 (7), 67 (9), 55 (10).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.92; H, 10.92.

(±)-2-Methyl-6-*p*-tolyl-2-hepten-4-ol (24). The reaction of **23** with *N*-lithioethylenediamine was carried out by a procedure identical with that used for the conversion of **20** to **21**. Distillation of the crude product (8.8 g) through a short-path apparatus gave, after removal of a low boiling forerun, 4.1 g (41%) of yellow oil, bp 78–104° (0.1–0.2 mm). Glpc analysis on column B at 240° showed the presence of several minor components, and a clean separation of the two diastereoisomers of the major product; these were labeled **24-A** (retention time 15.1 min) and **24-B** (retention time 16.8 min). A preliminary purification of the mixture of **24-A** and **24-B** (peak area ratio 1:1) was carried out by preparative glpc on column C at 240°. The diastereomers were then obtained as colorless oils after separation by preparative glpc on column D at 240° followed by molecular distillation (because these substances undergo partial decomposition during glpc separation, they were not obtained free of minor impurities): **24-A**, bp (bath) <100° (0.05 mm); $[\alpha]^{30}_{700-250}$ 0° (*c* 0.33, C_2H_5OH); ir (film) 3350 broad (OH), 3050 and 3025 ($-C_6H_4-$), 1517 ($-C_6H_4-$), 1082, 1020, and 822 cm^{-1} (*p*-C_6H_4-); nmr[63] ($CDCl_3$) τ 3.04 (s, *p*-$CH_3C_6H_4-$), 4.94 (m, $-CH=C(CH_3)_2$), 5.95 (m, >C*H*OH), 7.18 (m, $C_7H_7CH(CH_3)-$), 7.67 (s, O*H*), 7.79 (s, *p*-$CH_3C_6H_4-$), and 8.0–8.9 ppm [m, including τ 8.41 and 8.57 (two broadened s, $-CH=C(CH_3)_2$), and 8.82 ppm (d, *J* = 6.5 Hz, $C_7H_7CH(CH_3)-$)]; mass spectrum (70 eV) *m/e* (rel intensity) 218 (0.2), 200 (3), 185 (1), 157 (3), 119 (100), 105 (3), 95 (6), 91 (10), 85 (1), 77 (4).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 83.22; H, 10.13.

24-B had: bp (bath) <100° (0.05 mm); $[\alpha]^{30}_{700-250}$ 0° (*c*, 0.34, C_2H_5OH); ir (film) 3340 broad (OH), 3050 and 3025 ($-C_6H_4-$), 1518 ($-C_6H_4-$), 1060, 1006, and 823 cm^{-1} (*p*-C_6H_4-); nmr ($CDCl_3$) τ 3.06 (s, 4 H, *p*-$CH_3C_6H_4-$), 4.97 (m, 1 H, $-CH=C(CH_3)_2$), 5.93 (m, 1 H, >C*H*OH), 7.35 (m, 1 H, $C_7H_7CH(CH_3)-$), 7.74 (s, 1 H, –O*H*), 7.79 (s, 3 H, *p*-$CH_3C_6H_4-$), 7.9–8.7 [m, 8 H, including 8.36 and 8.56 (two broadened s, $-CH=C(CH_3)_2$)], and 8.82 ppm (d, 3 H, *J* = 6.5 Hz, $C_7H_7CH(CH_3)-$); mass spectrum (70 eV) *m/e* (rel intensity) 218 (16), 203 (3), 200 (20), 185 (11), 157 (18), 119 (100), 105 (34), 91 (35), 85 (96), 77 (17).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 83.05; H, 10.23.

(±)-*ar*-Turmerone (25). A solution of 2.00 g (9.2 mmol) of the mixture of diastereomers of **24** in 80 ml of petroleum ether was stirred with 20.0 g (0.23 mol) of activated manganese dioxide for 3.75 hr at room temperature. The manganese dioxide was separated by suction filtration through a cake of Celite, and the filter cake was washed with several portions of ether. The combined filtrate and washings were dried and evaporated, and the residue (1.6 g) was distilled through a short-path apparatus to give 1.14 g (58%) of **25** as a pale yellow oil, bp 85° (0.05 mm) [lit. bp 115° (1 mm);[6] 156–158° (7 mm);[38a] 120–130° (2 mm)[64]], glpc purity *ca.* 79% (column B, 240°). The analytical sample was obtained as a colorless oil after purification by preparative glpc on column C at 240° followed by molecular distillation: bp (bath) <100° (0.04 mm); $[\alpha]^{30}_{700-350}$ 0° (*c* 0.36, C_2H_5OH); ir (film) 3050 and 3025 ($-C_6H_4-$), 1688 (>C=O), 1622 (>C=CH–), 1517 ($-C_6H_4-$), and 821 cm^{-1} (*p*-C_6H_4-) (lit.[64] ir 1689, 1618 cm^{-1}); uv_{max} (CH_3OH) 238 mμ (ε 11,900) [lit.[64] uv_{max} 239 mμ (ε 11,750)]; nmr ($CDCl_3$) τ 3.03 (s, 4 H, *p*-$CH_3C_6H_4-$), 4.09 (m, 1 H, $-CH=C(CH_3)_2$), 6.77 (m, 1 H, $C_7H_7CH(CH_3)-$), 7.43 (m, 2 H, $-CH_2CO-$), 7.79 (s, 3 H, *p*-$CH_3C_6H_4-$), 7.96 (s, 3 H, $-COCH=C(CH_3)_2$, methyl cis to carbonyl), 8.25 (s, 3 H, $-COCH=C(CH_3)_2$, methyl trans to carbonyl), and 8.80 ppm (d, 3 H, *J* = 6.5 Hz, $C_7H_7CH(CH_3)-$); mass spectrum (70 eV) *m/e* (rel intensity) 216 (20), 201 (7), 132 (15), 119 (100), 105 (8), 98 (3), 91 (10), 83 (98), 77 (3), 55 (17).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.14; H, 9.17.

In separate experiments, the individual diastereomers **24-A** and **24-B** were oxidized separately according to the procedure described above. Both isomers gave **25** as the sole product, which was identified by its ir spectrum and glpc retention time.

(+)-β-Atlantone (26). To a stirred solution of 3.00 g (13.6 mmol) of **23** in 18 ml of anhydrous dichloromethane (freshly distilled from phosphorus pentoxide) under argon was added rapidly a solution of 22.95 g (89.0 mmol) of dipyridine-chromium(VI) oxide in 440 ml of anhydrous dichloromethane (Collins reagent).[29] The resulting mixture was stirred for 15 min and was filtered under suction through a cake of Celite. The filter cake was washed with ether, and the combined filtrate and washings were washed successively with sodium chloride, 2 *N* hydrochloric acid, sodium bicarbonate, and sodium chloride solutions, and were dried and evaporated. Molecular distillation of the residue gave 2.00 g (67%) of **26** as a yellow oil, bp (bath) 85–125° (0.1 mm), glpc purity *ca.* 50% (column A, 225°). The analytical sample was obtained as a faintly yellow oil after purification by preparative glpc on column C at 235° followed by molecular distillation: bp (bath) 85–90° (0.05 mm); $[\alpha]^{30}D$ +65° (*c* 0.39, C_2H_5OH); ir (film) 3080 (>C=CH_2), 3010 (>C=CH–), 1688 (>C=O), 1620 (conjugated >C=CH–), 898 (>C=CH_2), and 802 cm^{-1} (>C=CH–); uv_{max} (CH_3OH) 241 mμ (ε 12,000); nmr ($CDCl_3$) τ 3.94 (m, 1 H, $-CH=C(CH_3)_2$), 4.70 (m, 1 H, $-CH=C(CH_3)CH_2-$), 5.12 and 5.23 (two broadened s, 2 H, >C=CH_2), 6.93 (s, 2 H, $-CH_2CO-$), and 7.7–8.5 ppm [m, 16 H, including τ 7.90 (broadened s, $-COCH=C-(CH_3)_2$, methyl cis to carbonyl), 8.16 (broadened s, $-COCH=C-(CH_3)_2$, methyl trans to carbonyl), and 8.39 ppm (broadened s, $-CH=C(CH_3)CH_2-$)]; mass spectrum (70 eV) *m/e* (rel intensity) 218 (1), 203 (1), 163 (3), 135 (3), 120 (5), 119 (6), 107 (3), 105 (4), 93 (4), 91 (5), 83 (100), 79 (6), 69 (8), 67 (7), 55 (40).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.24; H, 10.08.

(+)-α-Atlantone (27). A solution of 1.00 g (4.6 mmol) of **26** (purity *ca.* 50%) in 30 ml of ether was stirred with 20.0 g of activity grade I alumina (Woelm) for 1.5 hr. The alumina was separated

(62) M. Julia, S. Julia, and M. Langlois, *Bull. Soc. Chim. Fr.*, 1007 (1965).

(63) Signals due to impurities prevented satisfactory integration of this spectrum.

(64) V. K. Honwad and A. S. Rao, *Tetrahedron*, **20**, 2921 (1964).

by suction filtration and was washed with several portions of ether and methanol, and the combined filtrate and washings were evaporated. Molecular distillation of the residue gave 0.76 g (76%) of yellow oil; glpc analysis of this material on column A at 225° showed the β-atlantone (retention time 14.8 min) had been converted to a product with retention time 20.3 min. Purification of the product by preparative glpc on column C at 225° followed by molecular distillation yielded (+)-α-atlantone (**27**) as a yellow oil, bp (bath) <110° (0.05 mm); $[\alpha]^{30}D$ +77° (*c* 0.37, C_2H_5OH); ir (film) 3010 (>C=CH–), 1675 (>C=O), 1625 (conjugated >C=CH–), 1113, 1060, and 878 cm^{-1}; uv_{max} (CH_3OH) 269 mμ (ε 21,000 ± 1100); nmr ($CDCl_3$) τ 4.04 (broadened s, 2 H, >C=C*H*CO-C*H*=C<), 4.69 (m, 1 H, –C*H*=C(CH_3)CH_2–), and 7.7–8.5 ppm [m, 19 H, including τ 7.90 (broadened s, –C(C*H*$_3$)=CHCOCH=C(C*H*$_3$)$_2$, two methyls cis to carbonyl), 8.17 (broadened s, –CO-CH=C(C*H*$_3$)$_2$, methyl trans to carbonyl), and 8.39 ppm (broadened s, –CH=C(C*H*$_3$)CH_2–)]; mass spectrum (70 eV) *m/e* (rel intensity) 218 (9), 203 (6), 163 (9), 150 (5), 135 (18), 123 (17), 121 (7), 120 (11), 119 (12), 109 (6), 107 (10), 105 (13), 95 (14), 93 (10), 91 (10), 83 (100), 79 (10), 69 (19), 55 (31).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.19; H, 10.25.

A sample of naturally occurring α-atlantone was isolated from the oil of *Cedrus atlantica*. Glpc analysis of the oil on column A at 225° showed that the component with longest retention time could be separated from other components, and had a retention time identical with that of synthetic α-atlantone; the area of this peak constituted *ca.* 8% of the sum of peak areas for the entire oil. The oil was separated by distillation into a low boiling fraction, bp 63–65° (0.10–0.05 mm) and a high boiling fraction, bp (bath) 100–130° (0.05 mm). The α-atlantone in the latter fraction was obtained as a yellow oil after purification by preparative glpc on column C at 230° followed by molecular distillation: bp (bath) 100–110° (0.05 mm) [lit. bp 121–123° (1 mm)[44b]; 142–145° (1 mm)[46]]; $[\alpha]^{30}D$ +3° (*c* 0.38, C_2H_5OH) (lit. $[\alpha]D$ +2° 48′[44b]; $[\alpha]D$ +1.2° [46]); uv_{max} (CH_3OH) 269 mμ (ε 19,600 ± 1200). The ir, nmr, and mass spectra were identical in all respects with the corresponding spectra described above for synthetic α-atlantone (*cf.* lit.[46] ir uv, nmr, and mass spectrum).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.56; H, 10.15.

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Polyene Antibiotics. IV. Structure of Chainin[1,2]

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Abstract: The antifungal pentaene antibiotic chainin has been shown to have the structure 2-(*n*-butyl)-16-methyl-3,5,7,9,11,13,15,26,27-nonahydroxyoctacosa-16,18,20,22,24-pentaenoic acid, 27-lactone (**1**). Mass spectra of the octaacetate of **1**, of the octaacetate of its decahydro derivative, and of its hydrocarbon and methyl ester reduction products were instrumental in the structural investigation. Structural studies on norchainin, homochainin, and filipins II and IV are also described.

Recently, Thirumalachar reported the isolation of a new antibiotic from a *Chainia* species.[3] The new antibiotic, which was named chainin, belongs to the pentaene subgroup of the polyene antibiotics,[4] and like most of the polyenes it has antifungal rather than antibacterial activity. In the present report we assign structure **1** to chainin (Figure 1).

Molecular Formula

Previous studies of pentaene antibiotics have employed trimethylsilyl derivatives for volatilization and mass spectral studies.[5] We have developed an alternative procedure, involving exhaustive acetylation with acetic anhydride in pyridine.[6] We regard this method as somewhat superior, since the acetate derivatives are stable and can be isolated; they give good molecular ions at low electron energy. In the present study chainin (**1**) and its decahydro derivative **3**, obtained upon hydrogenation of chainin in acetic acid over platinum oxide, were acetylated to give polyacetates lacking hydroxyl absorption in their infrared spectra. Mass spectra of both polyacetates **2** and **4** gave molecular ions (Table I). The derivative of chainin (**2**) gave a parent ion at *m/e* 946; decahydrochainin octaacetate (**4**) gave a parent ion at *m/e* 956. The high-resolution mass spectrum of **4** indicates its molecular formula to be $C_{49}H_{80}O_{18}$. Both spectra showed ions for losses of one–eight acetic acid units. These correspond to a molecular weight for chainin of 610 (946 − 8 × 42) and a molecular formula $C_{33}H_{54}O_{10}$.[7] A second series of ions 18 amu higher is also found, corresponding to the loss of 1 mol of ketene (to give ion k, Table I), plus the loss of 1–7 mol of acetic acid.

Carbon Skeleton

A modification of the procedure of Cope, *et al.*,[8] was employed to reduce the antibiotic to a saturated hydrocarbon, **5**, as shown in Figure 2. The hydrocarbon had an infrared spectrum characteristic of a saturated hy-

(1) Presented in part at the 7th International Symposium on the Chemistry of Natural Products, IUPAC, Riga, USSR, June 1970, paper E-157.

(2) Paper III in this series: K. L. Rinehart, Jr., W. P. Tucker, and R. C. Pandey, *J. Amer. Chem. Soc.*, **93**, 3747 (1971).

(3) K. S. Gopalkrishnan, N. Narasimhachari, V. B. Joshi, and M. J. Thirumalachar, *Nature (London)*, **218**, 597 (1968).

(4) A review of polyene antibiotics: W. Oroshnik and A. D. Mebane, *Fortsch. Chem. Org. Naturst.*, **21**, 17 (1963).

(5) B. T. Golding, R. W. Rickards, and M. Barker, *Tetrahedron Lett.*, 2615 (1964).

(6) R. C. Pandey and K. L. Rinehart, Jr., *J. Antibiot.*, **23**, 414 (1970).

(7) Microanalyses reported[3] for chainin do not agree well with the molecular formula assigned, but would for a hydrate. *Anal.* Calcd for $C_{33}H_{54}O_{10}$: C, 64.89; H, 8.91. Calcd for $C_{33}H_{54}O_{10}\cdot H_2O$: C, 63.03; H, 8.97. Found:[3] C, 63.25; H, 8.62.

(8) A. C. Cope, R. K. Bly, E. P. Burrows, O. J. Ceder, E. Ciganek, B. T. Gillis, R. F. Porter, and H. E. Johnson, *J. Amer. Chem. Soc.*, **84**, 2170 (1962).