The Synthesis of Racemic α-*trans*- and β-*trans*-Bergamotene

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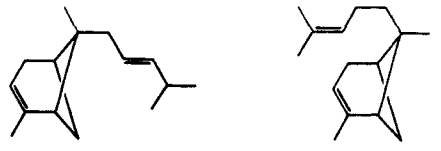
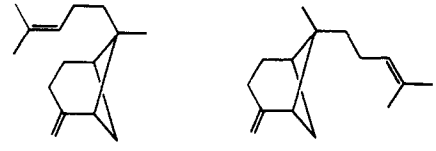
Abstract: A synthesis of racemic α-*trans*- and β-*trans*-bergamotenes (**1** and **4**, respectively) is described in which a key step is the photocyclization of a 2-allyl-1,3-butadiene derivative (**7**) to a methylenebicyclo[2.1.1]hexane structure (**8**). Further transformations of **8** involving pinacolic ring expansion and adjustment of functionality and substitution led to the two *trans*-bergamotenes. One of these, the α isomer **1**, was identical with the naturally occurring sesquiterpene first described by Sorm and assigned this structure. The other synthetic bergamotene, the β isomer **4**, was different from a natural product described previously which had been assigned this structure, and which consequently can no longer be considered as a true bergamotene. All four resulting stereoisomeric bergamotenes have now been obtained as racemates by synthesis, *i.e.*, *cis*- and *trans*-α- and -β-bergamotenes (**1**–**4**).

Since the isolation of α-*trans*-bergamotene (**1**) by Sorm in 1950, this compound has been detected in a number of essential oils,[1,2] at times accompanied by its cis isomer (**2**).[3] The structure of **1** was based entirely on spectroscopic (nmr and ir) evidence and has never been confirmed by synthesis. Bhattacharyya, in the meantime, has reported the isolation of a new bicyclic sesquiterpene hydrocarbon from Indian Valerian root oil and has proposed the β-*cis*-bergamotene structure (**3**) on the basis of chemical and spectroscopic studies.[4] This structure has been revised to the trans isomer **4** by Erman, who synthesized **3** and found it was not identical with natural Valerian root derived sesquiterpene.[5]



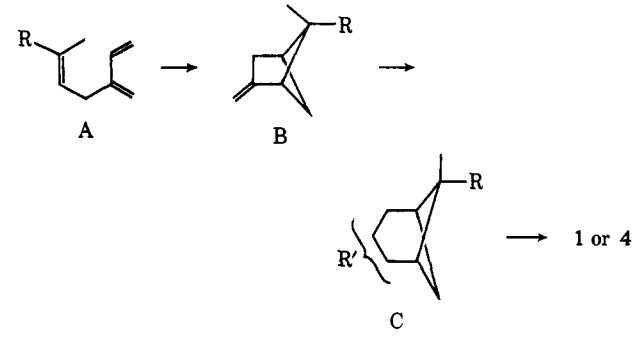
1 **2**



3 **4**

We now report the unambiguous synthesis of both trans isomers, **1** and **4**, with the result that the proposed structure of Sorm's compound (**1**) has been confirmed, whereas structure **4** has been ruled out for Bhattacharyya's sesquiterpene. The pathway of synthesis may be divided into four stages: (1) synthesis of a suitably substituted triene (A); (2) photolytic formation of a methylenebicyclo[2.1.1]hexane (B); (3) ring expansion to the pinane nucleus, bicyclo[3.1.1]heptane (C); and (4) appropriate functional modifications leading to **1** and **4** (Scheme I).

Scheme I



Results

Geranyl acetate was selectively ozonized in methylene chloride–pyridine at −78° to give 6-acetoxy-4-methyl-*trans*-4-hexenal in 42% yield after distillation. This aldehyde acetate was in turn converted to the ethylene acetal, deacetylated, and transformed further to the bromide. The addition of calcium hydride to the latter reaction utilizing phosphorus tribromide prevented cleavage of the acid-labile acetal.

For the conversion to the aldehyde **6**, a series of novel reagents was employed. 2-Bromo-3-dimethylaminopropene could be metalated by lithium–halogen exchange with *n*-butyllithium at −25° in ether.[6] Intermediate formation of the divinylcopper(I) lithium species by reaction of the lithio anion with 0.5 equiv of CuI followed by reaction with the above allylic bromide gave the expected tertiary amine **5** in 80–90% yield. When the amine oxide, formed by reaction of **5** with excess 30% hydrogen peroxide, was treated with 3 equiv of perfluoroacetic anhydride in methylene chloride (1 hr, 0°)[7] and then poured into aqueous potassium bicarbonate, the α-substituted acrolein **6** was obtained in 57% overall yield based on bromide. Treatment

(1) V. Herout, V. Ruzicka, M. Vrany, and F. Sorm, *Collect. Czech. Chem. Commun.*, **15**, 373 (1950).

(2) For example: (a) in lime, E. sz. Kovats, *Helv. Chim. Acta*, **46**, 2705 (1963); (b) in lemon, W. D. MacLeod, W. H. McFadden, and N. M. Buigues, *J. Food Sci.*, **31**, 591 (1966); and (c) in Indian marijuana, M. C. Nigam, K. L. Handa, I. C. Nigam, and L. Levi, *Can. J. Chem.*, **43**, 3372 (1965).

(3) For example: (a) in black pepper, C. J. Muller and W. G. Jennings, *J. Agr. Food. Chem.*, **15**, 762 (1967); and (b) in opopanax, J. A. Wenninger and R. L. Yates, *J. Ass. Offic. Anal. Chem.*, **52**, 1155 (1969).

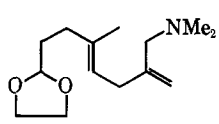
(4) K. S. Kulkarni, S. K. Paknikar, A. S. Vaidya, G. R. Kelkar, R. B. Bates, and S. C. Bhattacharyya, *Tetrahedron Lett.*, 505 (1963); C. S. Narayanan, K. S. Kulkarni, A. S. Vaidya, S. Kanthamani, G. Lakshmi Kumari, B. V. Bapat, S. K. Paknikar, S. N. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 963 (1964).

(5) T. W. Gibson and W. F. Erman, *Tetrahedron Lett.*, 905 (1967); *J. Amer. Chem. Soc.*, **91**, 4771 (1969).

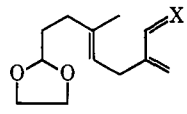
(6) Earlier, Ficini formed the analogous Grignard reagent: J. Ficini, G. Sarrade-Loucheur, and H. Normant, *Bull. Soc. Chim. Fr.*, 1219 (1962). The reagent is unusual in that it contains an anionic center β to a potential leaving group, Me_2N.

(7) For a discussion of this modification of the Polonovski reaction see: A. Cave, C. Kan-Fan, P. Potier, and J. LeMen, *Tetrahedron*, **23**, 4681 (1967).

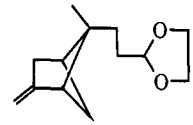
of **6** with methylenetriphenylphosphorane gave the conjugated diene **7** in 50–70% purified yield. This substance in turn in 1% pentane solution was irradiated in the ultraviolet using benzophenone as a sensitizer to produce the desired 5-methyl-5-(3-ethylenedioxypropyl)-2-methylenebicyclo[2.1.1]hexane (**8**) in 80% yield after purification. The photoproduct consisted of a 5:3 mixture of trans to cis isomers as determined by nmr and tlc analysis.[8,9] All of the synthetic products derived from **8** in this work, which are described below,



5



6, X = O
7, X = CH_2



8

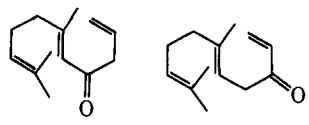
were obtained as racemates, since no effort was made to effect resolution. The cis,trans mixture **8** was used without separation in the next few steps with purification being effected at the stage of **11** as described below.

The diastereomeric mixture was treated with 1.1 equiv of osmium tetroxide (dioxane, 25°, 19 hr) and the resulting osmate ester exposed briefly to hydrogen sulfide gas to afford the vicinal diol **9** in 50% yield. Reaction of the diol thus obtained with *p*-toluenesulfonyl chloride gave the monohydroxy tosylate **10** which was further transformed to the iodohydrin **11** by reaction with excess sodium iodide in refluxing acetone. The latter product was separated into its component epimers by preparative layer chromatography on silica gel. The overall yield of the major isomer, *trans*-**11**, was 16% based on total methylenebicyclo[2.1.1]hexane. The structural assignment was based on the nmr spectrum, which displayed a quaternary methyl resonance at δ 0.92, whereas that of the cis isomer appeared at δ 1.30.[9]

Reaction of the iodohydrin **11** with excess silver nitrate (tetrahydrofuran–water, 25°, 3 hr) gave the bicyclo[3.1.1]heptan-3-one (**12**) in 55% yield after tlc purification. The crude product contained 22% of the position isomeric 2 ketone in addition to the 3 ketone (**12**). The 3 ketone was characterized by two multiplets, of four and two protons each, occurring at δ 2.46 (CH_2COCH_2) and 2.18 (CH), respectively, as well as a quaternary methyl resonance at δ 0.85.

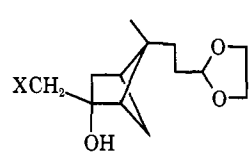
Hydrolysis of the acetal function and subsequent reaction with isopropylidenetriphenylphosphorane gave the ketone **13**, in 35–40% yield after purification.

(8) (a) See J. L. Charlton, P. de Mayo, and L. Skattebol, *Tetrahedron Lett.*, 4679 (1965), for the photocyclization of 3-methylene-1,5-hexadiene to 2-methylenebicyclo[2.1.1]hexane, the prototype reaction. (b) The photocyclization of allyl vinyl ketone to bicyclo[2.1.1]hexan-2-one [F. T. Bond, H. L. Jones, and L. Scerbo, *ibid.*, 4685 (1965)] suggested that irradiation of the ketones i or ii might also produce the bicyclo-[2.1.1]hexanone derivative iii which could be utilized in the synthesis of **1** and **4**. In practice the irradiation of either i or ii under a variety of conditions failed to provide the desired bicyclic product iii.

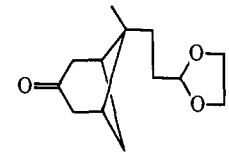


i ii iii

(9) See N. Nakagawa, S. Saito, A. Suzuki, and M. Itoh, *Tetrahedron Lett.*, 1003 (1967), for a discussion of the nmr spectra of compounds containing puckered cyclobutane rings.



9, X = OH
10, X = OTs
11, X = I



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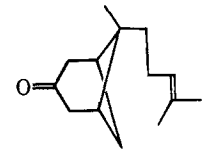

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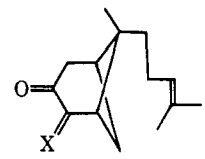
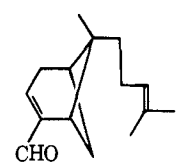
Treatment of **13** with sodium hydride and excess ethyl formate (dimethoxyethane, 25°, 3 hr) afforded the hydroxymethylene derivative **14**, which was converted without purification to the isopropyloxymethylene ketone **15** by alkylation with isopropyl iodide (sodium hydride in tetrahydrofuran–hexamethylphosphoramide, 60°, 2 hr). The keto enol ether was reduced with sodium borohydride (ethanol, 60°, 3 hr) to the vinylogous hemiacetal which underwent hydrolysis to the unsaturated aldehyde **16** upon treatment with aqueous hydrochloric acid. The yield for the three-step process, after tlc purification, was 30–45%.[10]

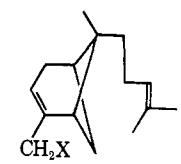
Sodium borohydride reduction (ethanol, 25°, 1 hr) of **16** gave the allylic alcohol **17** in quantitative yield. Application of the recently developed pyridine–sulfur trioxide–lithium aluminum hydride reduction sequence[11] gave α-*trans*-bergamotene (**1**) in 60–70% yield. The nmr (quaternary methyl at δ 0.85) and ir spectral properties of synthetic **1** were identical with those reported for natural α-*trans*-bergamotene.[1,2a] An exact mass determination gave *m/e* 204.1874 (calcd for $C_{15}H_{24}$: 204.1878).



14, X = CHOH
15, X = CHO-*i*-Pr



16



17, X = OH
18, X = Br
19, X = $TsNNH_2$

Alternatively the allylic alcohol **17** was treated with 1.2 equiv of phosphorus tribromide (ether, 0°, 10 hr), and the resulting allylic bromide **18** was allowed to react with the sodium salt of *p*-toluenesulfonylhydrazine, thereby furnishing the allyl tosylhydrazide **19**.[12] Decomposition of this substance in acetic acid buffered with 20% sodium acetate (60°, 1.25 hr) gave, after isolation and tlc purification, a product whose nmr (quaternary methyl at 0.72, exo methylene at 4.55) and ir properties were consistent in all respects with the expected β-pinene-derived structure **4**. An exact mass determination gave *m/e* 204.1874 (calcd for $C_{15}H_{24}$: 204.1878). Comparison of the ir and nmr spectra reported for natural "β-bergamotene" isolated from

(10) *Cf.* P. A. Grieco, *J. Amer. Chem. Soc.*, **91**, 5660 (1969).
(11) E. J. Corey and K. Achiwa, *J. Org. Chem.*, **34**, 3667 (1969).
(12) T. Sato, I. Homma, and S. Nakamura, *Tetrahedron Lett.*, 872 (1969).

Valerian root oil with those of synthetic **4** showed that the two compounds were not identical. The nmr spectrum of the former, for instance, displays a singlet due to quaternary methyl at δ 0.95 and two peaks due to C=CH_2 at 4.57 and 4.76, whereas in contrast the peaks due to the corresponding groups in **4** occur at δ 0.72 (CH_3) and δ 4.55 (2 H, C=CH_2).

Discussion

The foregoing results have conclusively proved the structure of α-*trans*-bergamotene while ruling out β-*trans*-bergamotene as the structure of Bhattacharyya's sesquiterpene. In fact, as a result of the present study taken together with Erman's prior synthetic results, the four possible bergamotenes, **1**, **2**, **3**, and **4**, have now all been synthesized, thereby demonstrating that Bhattacharyya's compound is not even a true member of the bergamotene class of sesquiterpenes.

Based on the close resemblance of the ir and nmr spectra of Bhattacharyya's compound and those of both β- and epi-β-santalene, it seems possible that this compound is a substitution product of the α- or β-fenchene type (**20**, **21**) with a γ,γ-dimethylallyl grouping replacing a methyl hydrogen. Further verification of this hypothesis must await reexamination of Bhattacharyya's compound.[13]

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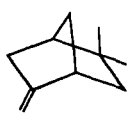

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Experimental Section

Instrumentation. Infrared spectra were taken using a Perkin-Elmer Model 137 Infracord or Model 237 grating spectrophotometer. Nmr data were obtained with a Varian Associates Model A-60 or T-60 spectrometer. Nmr shifts are expressed in parts per million downfield from internal tetramethylsilane (δ = 0). Mass spectra were measured using an AEI MS-9 double focusing mass spectrometer at an ionizing voltage of 70 eV. Vpc analyses were performed on Hewlett-Packard F&M Models 810 or 5750 gas chromatographs, equipped with dual flame detectors and utilizing nitrogen carrier gas (30 cc/min.) A Welsbach Ozonizer (Model T-23) was used to generate ozone from a stream of dry oxygen, using settings (8 psi, 0.01 ft^3/min) which had been previously found to correspond to a flow of 2 mmol/min.

All compounds which were submitted to mass spectrometric molecular weight determination were of high purity as determined by nmr analysis, as well as being homogeneous by vpc and/or tlc. (The single exception was **8**, a mixture of epimers, distinguishable but not separable by vpc.)

Solvents. The following solvents were used: tetrahydrofuran, dimethoxyethane, and *p*-dioxane—freshly distilled from lithium aluminum hydride; diethyl ether—Mallinckrodt AR, freshly opened cans; dimethyl sulfoxide and hexamethylphosphoramide—stirred overnight over calcium hydride, then distilled under vacuum; ethanol—Gold Shield absolute alcohol; ethyl formate—dried over potassium carbonate, then distilled from phosphorus pentoxide; *n*-pentane (for photolysis)—stirred overnight over concentrated sulfuric acid, then decanted and distilled onto 4 Å molecular sieves; pyridine—distilled from barium oxide.

6-Acetoxy-4-methyl-*trans*-4-hexenal. Ozone (2 mmol/min) was bubbled into a solution of 50 g (255 mmol) of geranyl acetate and 20 g (255 mmol) of pyridine in 650 ml of methylene chloride at −78°. After 275 min, vpc analysis indicated less than 5% geranyl acetate was present. The solution was flushed with argon to remove any ozone present, after which 128 g (1.96 mol) of zinc dust followed by 300 ml of glacial acetic acid was added at −78°. After stirring for 2 hr at room temperature, the mixture was filtered through Celite, the Celite pad was rinsed with ether, and the filtrate was extracted with four 600-ml portions of 5% hydrochloric acid at 0°, three 100-ml portions of 3 *N* sodium hydroxide (0°), and saturated sodium chloride. Drying over magnesium sulfate and evaporation of the solvent gave an oil which was fractionally distilled through a 12-in. vacuum-jacketed Vigreux column under reduced pressure. The aldehyde (16 g) was collected as a fraction boiling at 95–100° (1 mm): nmr (CCl_4) δ 1.72 (s, CH_3, 3 H), 1.98 (s, O_2CCH_3, 3 H), 2.1–2.65 (m, CH_2CH_2, 4 H), 4.5 (d, J = 7 Hz, CH_2O, 2 H), 5.33 (t, J = 7 Hz, olefinic, 1 H), 9.75 (t, J = 1.5 Hz, CHO, 1 H); ir $\lambda_{max}^{CCl_4}$ 3.65 (C(O)H), 5.73 μ (CHO, CH_3CO_2).

6-Ethylenedioxy-1-acetoxy-3-methyl-*trans*-2-hexene. The aldehyde acetate (16 g, 106 mmol) plus 16 ml of ethylene glycol and 0.5 g of toluenesulfonic acid monohydrate were refluxed for 2 hr in 500 ml of benzene using a Dean–Stark water separator to remove the water. Ether (250 ml) was then added, and the mixture was extracted with two 40-ml portions of saturated potassium bicarbonate and washed once with water and once with saturated sodium chloride before drying over sodium sulfate and evaporation of the solvent gave 22.1 g of acetal: nmr (CCl_4) δ 1.70 (s, CH_3, and m, CH_2) (total 5 H), 1.97 (s, CH_3CO_2) and 1.85–2.3 (m, allyl) (total 5 H), 3.81 (m, OCH_2CH_2O, 4 H), 4.48 (d, J = 7 Hz, CH_2O, 2 H), 4.75 (t, J = 4 Hz, CH, 1 H), 5.33 (t, J = 7 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.72 μ (CH_3CO_2).

6-Ethylenedioxy-3-methyl-*trans*-2-hexenol. The acetal acetate (31.5 g, 0.147 mol) plus 3.7 g of anhydrous potassium carbonate in 1400 ml of methanol was stirred for 4 hr at room temperature. After evaporation of the methanol, water and ether were added, and the mixture was extracted twice with ether. The combined ether extracts were washed with water and shaken with saturated sodium chloride. Drying over sodium sulfate and solvent evaporation gave 21.0 g (123 mmol) of alcohol: nmr (CCl_4) δ 1.67 (s, CH_3) and 1.67–1.9 (m, CH_2) (total 5 H), 1.9–2.3 (m, allyl, 2 H), 3.05 (s, OH, 1 H), 3.85 (m, OCH_2CH_2O, 4 H), 4.02 (d, J = 7 Hz, CH_2OH, 2 H), 4.78 (t, J = 4 Hz, CH, 1 H), 5.35 (t, J = 7 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.82 (OH), 5.96 μ (C=C). An exact mass determination gave *m/e* 172.1094 (calcd for $C_9H_{16}O_3$: 172.1099).

6-Ethylenedioxy-1-bromo-3-methyl-*trans*-2-hexene. Phosphorus tribromide (4.4 ml, 12.5 g, 46 mmol) in 10 ml of ether was added dropwise under argon to a stirred slurry of 10 g of calcium hydride and 21.0 g (123 mmol) of alcohol in 330 ml of ether at 0°. After addition was complete, the reaction mixture was protected from light and stirred at 0° for 18 hr. Celite was added, the reaction mixture was filtered, and the solvent was evaporated to give 23 g (100 mmol) of bromide: nmr (CCl_4) δ 1.75 (s, CH_3) and 1.5–1.9 (m, CH_2) (total 5 H), 1.9–2.5 (m, allyl, 2 H), 3.83 (m, OCH_2CH_2O, 4 H), 3.98 (d, J = 8 Hz, CH_2Br, 2 H), 4.77 (t, J = 4.5 Hz, CH, 1 H), 5.55 (t, J = 8 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 6.01 μ (C=C).

2-Bromo-3-(*N*,*N*-dimethylamino)propene. 2,3-Dibromopropene (88.2 g, 0.44 mmol) was added over 0.5 hr to 100 g (2.2 mol) of dimethylamine and 25 ml of ether at 0°. Additional ether was added, and the reaction mixture was stirred for 2 hr at 0° and overnight at room temperature. After filtration and evaporation of the solvent, the residue was distilled to give 41.7 g (58%) of 2-bromo-3-(*N*,*N*-dimethylamino)propene: bp 49.5–51° (38 mm); nmr (CCl_4) δ 2.25 (s, CH_3, 6 H), 3.05 (s, NCH_2, 2 H), 5.53 (m, olefinic, 1 H), 5.83 (m, olefinic, 1 H).

8-Ethylenedioxy-2-(*N*,*N*-dimethylaminomethyl)-5-methyl-*trans*-1,4-octadiene (5). A 2-l., three-necked flask, fitted with a septum, a mechanical stirrer, and an addition funnel equipped with a three-way stopcock, was flushed with argon, then charged with 33.5 g (204 mmol) of 2-bromo-3-(*N*,*N*-dimethylamino)propene in 300 ml of ether and cooled to −78°. *n*-Butyllithium (1.3 *M*, 168 ml, 218 mmol) was added, the solution was stirred for 10 min at −78° and 15 min at −25°, after which 21.2 g (111 mmol) of copper(I) iodide, degassed and flushed with argon, was added under a stream of argon. The copper salt dissolved upon warming to 0° for 15 min, giving a deep red solution which was recooled to −30°. The allylic bromide (23 g, 100 mmol) in 30 ml of ether was added *via* the addition funnel, and the resulting mixture was stirred for 6 hr at −30°. Degassed methanol (75 ml) was added, the solution was warmed to room temperature, and 400 ml of 4 *N* ammonium hydroxide was added to the vigorously stirred solution. After filtration through a pad of Supercel, the mixture was extracted with ether. The red ether phase was extracted repeatedly with 100-ml portions of 4 *N* ammonium hydroxide, each aqueous portion being back-extracted with a single 150-ml volume of ether, until the aque-

(13) Compound **4** may already have been isolated in its own right from a natural source. The ir spectrum of **4** is completely identical with that of a hitherto unidentified minor constituent of the α-bergamotene-rich opopanax oil.[3b]

ous extracts were no longer blue. After washing with two 100-ml portions of water, the ether fractions were combined and shaken with saturated sodium chloride solution, then dried over sodium sulfate and evaporated to give 26 g of amine **5**. A small sample was purified by preparative layer chromatography (plc) (alumina; hexane–ether, 5:1): nmr (CCl_4) δ 1.62 (s, CH_3) and 1.55–1.90 (m, CH_2) (total 5 H), 2.10 (s, NCH_3) and 1.9–2.3 (m, allyl) (total 8 H), 2.70 (m, NCH_2, $=CCH_2C=$, 4 H), 3.78 (m, OCH_2CH_2O, 4 H), 4.72 (t, J = 4 Hz, CH, 1 H), 5.17 (t, J = 7 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 6.02 (C=C), 11.1 μ (CH_2=C). An exact mass determination gave m/e 239.1879 (calcd for $C_{14}H_{25}NO_2$: 239.1885).

8-Ethylenedioxy-2-(*N*-oxy-*N*,*N*-dimethylaminomethyl)-5-methyl-*trans*-1,4-octadiene. Hydrogen peroxide (30%, 40 ml, 12 g, 350 mmol) was added to 26 g (100 mmol) of **5** in 200 ml of methanol. Additional peroxide (40 ml) was added after 24 and 60 hr. At the end of 84 hr, platinum oxide (*ca.* 0.2 g) was added, and stirring was continued until evolution of oxygen had ceased. The reaction mixture was then filtered, and the solvent was evaporated at room temperature under reduced pressure (12–50 mm). Benzene was repeatedly added to the residue and reevaporated until all the water had been azeotroped, leaving *ca.* 26 g of crude amine oxide: nmr ($CDCl_3$) δ 1.62 (s, CH_3) and 1.5–2.4 (m, CH_2CH_2) (total 7 H), 3.08 (d, J = 7.5 Hz, $=CCH_2C=$) and 3.32 (s, NCH_3) (total 8 H), 3.9 (m, NCH_2 and OCH_2CH_2O, 6 H), 4.87 (t, J = 4.5 Hz, CH, 1 H), 5.05–5.5 (m, olefinic, 3 H).

8-Ethylenedioxy-2-methylene-5-methyl-*trans*-4-octenal (6). Amine oxide (26 g, 100 mmol) in 300 ml of dry methylene chloride was added over 0.5 hr to 73 g (350 mmol) of trifluoroacetic anhydride in 400 ml of methylene chloride at 0°. The solution was stirred at 25° for 0.5 hr, then recooled to 0° and added dropwise to a vigorously stirred mixture of 1 l. of ether, 300 g of potassium bicarbonate, and 1 l. of water at 0°. The organic layer was separated, and the aqueous phase was extracted with two 100-ml portions of ether, after which the combined ether extracts were in turn washed with two 50-ml volumes of half-saturated potassium bicarbonate, 50 ml of water, and 50 ml of saturated sodium chloride. The ether solution was concentrated to *ca.* 500 ml, cooled to 0°, and extracted rapidly with 500 ml of 0.05 *N* hydrochloric acid, 100 ml of water, and 100 ml of saturated potassium bicarbonate, all at 0°. Each aqueous wash was back-extracted with a single 100-ml portion of ether. The ether phases were combined, shaken with saturated sodium chloride, dried over sodium sulfate, and evaporated to yield 12 g of unsaturated aldehyde (**6**). A small sample was purified by plc (silica gel, pH 7; ether–hexane, 3:2): nmr (CCl_4) δ 1.62 (s, CH_3) and 1.45—1.9 (m, CH_2) (total 5 H), 1.9–2.28 (m, allyl, 2 H), 2.86 (d, J = 7 Hz, $=CCH_2C=$, 2 H), 3.78 (m, OCH_2CH_2O, 4 H), 4.73 (t, J = 4 Hz, CH, 1 H), 5.17 (t, J = 7 Hz, olefinic, 1 H), 5.93 (m, olefinic, 1 H), 6.17 (m, olefinic, 1 H), 9.55 (s, CHO, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.87 μ (C=O). An exact mass determination gave m/e 210.1243 (calcd for $C_{12}H_{18}O_3$: 210.1256).

9-Ethylenedioxy-3-methylene-6-methyl-*trans*-1,5-nonadiene (7). *n*-Butyllithium (1.3 *M*, 51 ml, 67 mmol) was added to 25.4 g (71 mmol) of methyltriphenylphosphonium bromide in 250 ml of tetrahydrofuran at 0°. After 1.5 hr the mixture was cooled to −78°, 12 g (57 mmol) of **6** in 50 ml of tetrahydrofuran was added, and the solution was stirred for 4 hr at room temperature. Water (50 ml) was then added, the tetrahydrofuran was evaporated, and the residue was dissolved in 500 ml of 40% aqueous methanol and extracted with four 100-ml portions of pentane. The combined pentane extracts were shaken with three 25-ml portions of water and 25 ml of saturated sodium chloride, following which the solution was dried over sodium sulfate and the solvent was evaporated. Redissolving in pentane, filtration, and reevaporation gave 9.7 g of oil containing a small amount of triphenylphosphine oxide. A small sample was further purified by plc (silica gel, pH 7; hexane–ether, 3:1): nmr (CCl_4) δ 1.64 (s, CH_3) and 1.5–1.9 (m, CH_2) (total 5 H), 1.9–2.4 (m, allyl, 2 H), 2.95 (d, J = 7 Hz, $=CCH_2C=$, 2 H), 3.8 (m, OCH_2CH_2O, 4 H), 4.88 (t, J = 4 Hz, CH, 1 H), 4.96–5.2 (m, olefinic, 5 H), 6.16 (d of d, $J_{H_aH_x}$ = 5 Hz, $J_{H_bH_x}$ = 9 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 6.10, 6.25 μ (C=CC=C). An exact mass determination gave m/e 208.1465 (calcd for $C_{13}H_{20}O_2$: 208.1463).

An alternate procedure was also used which provided diene free of triphenylphosphine oxide. *n*-Butyllithium (1.3 *M*, 9.0 ml, 11.7 mmol) was added to a slurry of 4.44 g (12.4 mmol) of methyltriphenylphosphonium bromide in 50 ml of dry tetrahydrofuran at 0°. After 1 hr, the solution was cooled to −78°, 2.04 g (9.8 mmol) of **6** was added, and the mixture was stirred for 2.5 hr at room temperature. After addition of water and evaporation of the tetrahydrofuran, the residue was extracted three times with ether, whereupon the ether was shaken with saturated sodium chloride, dried, and evaporated, leaving 1.87 g of oil. This oil was further purified by chromatography on basic alumina (II) (Woelm) using cyclohexane as eluent, followed by plc on the early fractions, to yield a combined 1.05 g of diene **7**.

5-Methyl-5-(3-ethylenedioxypropyl)-2-methylenebicyclo[2.1.1]-hexane (8). Benzophenone (2.5 g) and 4.8 g of **7** were dissolved in 750 ml of olefin-free, distilled *n*-pentane. The solution was deoxygenated and irradiated for 1.5 hr under argon using a 450-W Hanovia Model 679A36 mercury lamp and a Pyrex filter. This process was then repeated on a second 4.8-g batch of diene. The irradiation mixtures were then combined and evaporated, and the residue was dissolved in 200 ml of ethanol and stirred with 2 g of sodium borohydride at room temperature for 1.5 hr (in order to convert the benzophenone to more easily separable benzhydrol). Water was added, the ethanol was evaporated, and the aqueous residue was extracted with three 100-ml portions of pentane. The combined pentane extracts were shaken with water and saturated sodium chloride, then dried over sodium sulfate. Evaporation of the solvent and chromatography of the residual oil on 100 g of basic alumina (II) (Woelm) using 5:1 pentane–ether as eluent gave 5.3 g of **8**, shown by vpc (8 ft × 0.125 in., Carbowax 20M + 2% KOH on 80–100 Chrom WAW DMCS, 190°; R_t 8.1 min (cis), 9.2 min (trans)) to be a 5:3 mixture of the two C-5 epimers. A small sample was further purified by plc (silica gel, pH 7; hexane–ether, 3:1): nmr (CCl_4) δ 0.88 (s, *cis*-CH_3), 1.26 (s, *trans*-CH_3), 0.9–1.3 (m, CH_2), and 1.67 (m, CH_2) (total 9 H), 2.0–2.4 (m, allyl and bridgehead CH, 3 H), 2.5 (m, allylic bridgehead CH, 1 H), 3.82 (m, OCH_2CH_2O, 4 H), 4.55–5.0 (m, olefinic and CH, 3 H); ir $\lambda_{max}^{CCl_4}$ 5.95 (C=C), 11.4 μ (CH_2=C). An exact mass determination gave m/e 208.1467 (calcd for $C_{13}H_{20}O_2$: 208.1463).

2α-Hydroxy-2β-hydroxymethyl-5-methyl-5-(3-ethylenedioxypropyl)bicyclo[2.1.1]hexane (9). Osmium tetroxide (6.8 g, 27 mmol) was added to 5.06 g (24 mmol) of **8** in 90 ml of dry dioxane, and the resulting solution was stirred in the dark for 19 hr at room temperature. The reaction mixture was then diluted with methylene chloride, and hydrogen sulfide gas was bubbled in for 15 min, after which the mixture was filtered through Supercel and the filtrate was evaporated, leaving 3.06 g of diol **9**: nmr (CCl_4) δ 0.9, 1.3, 1.7, 2.15 (m, 12 H), 3.5–4.4 (m, CH_2OH, OCH_2CH_2O, OH, 8 H), 4.75 (m, CH, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.95 μ (O–H); mass spectrum m/e 242 (calcd for $C_{13}H_{24}O_4$: 242).

2α-Hydroxy-2β-tosyloxymethyl-5-methyl-5-(3-ethylenedioxypropyl)bicyclo[2.1.1]hexane (10). *p*-Toluenesulfonyl chloride (3.7 g, 19.4 mmol) was added at 0° to 3.06 g (12.5 mmol) of **9** in 75 ml of dry pyridine. The solution was stirred for 20 hr at 0°, then poured into water, and extracted with several portions of ether. The combined organic extracts were in turn shaken with several portions of water, each aqueous wash being back-extracted with a single 50-ml volume of ether. After shaking of the ether extracts with saturated sodium chloride and drying over sodium sulfate, the solvent was evaporated, first at 12 and then at 0.1 mm, to yield 4.15 g of hydroxy tosylate **10** containing some residual pyridine: nmr (CCl_4) δ 0.70 (s, CH_3), 1.25 (s, CH_3), 1.0–2.35 (m), and 2.43 (s, CH_3) (total 16 H), 2.7 (m, OH, 1 H), 3.9 (m, OCH_2CH_2O, 4 H), 4.3 (m, CH_2O, 2 H), 4.82 (m, CH, 1 H), 7.34 (d, J = 8 Hz, aromatic, 2 H), 7.82 (d, J = 8 Hz, aromatic, 2 H); ir $\lambda_{max}^{CCl_4}$ 2.74 (O–H), 6.23 μ (aromatic).

2α-Hydroxy-2β-iodomethyl-5-methyl-5-(3-ethylenedioxypropyl)-bicyclo[2.1.1]hexane (11). Acetone (65 ml), dried over calcium sulfate, was distilled into a flask containing 4.15 g (10.5 mmol) of hydroxy tosylate **10**. Sodium iodide (15 g, 0.1 mol) was added, and the reaction mixture was refluxed under argon for 17 hr in the dark. The resulting mixture was poured into water and extracted several times with ether. The combined ether extracts were in turn shaken with two portions of water, saturated sodium thiosulfate, water, and saturated sodium chloride. Each aqueous wash was back-extracted with a single 100-ml volume of ether. Drying over sodium sulfate and evaporation of the solvent gave 3.0 g of crude iodohydrin, which was separated into its component epimers by plc (silica gel, pH 7; ether–hexane, 3:2). Excision of the two ultraviolet–visible bands gave 1.30 g of *trans*-**11** (R_f 0.35) and 0.72 g of *cis*-**11** (R_f 0.45): nmr (*trans*-**11**) (CCl_4) δ 0.92 (s, CH_3, 3 H), 1.45–2.1 (m, CH_2, 6 H), 2.15–2.5 (m, CH_2 and CH, 4 H), 2.6 (s, OH, 1 H), 3.68 (s, CH_2I, 2 H), 3.83 (m, OCH_2CH_2O, 4 H), 4.75 (t, J = 3.5 Hz, CH, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.74 μ (O–H). An exact mass determination gave m/e 352.0511 (calcd for $C_{13}H_{21}O_3I$: 352.0537). Nmr (*cis*-**11**) (CCl_4) δ 1.30 (s, CH_3, CH_2) and 1.2–2.4 (m) (total 14 H), 3.82 (m, OCH_2CH_2O and CH_2I, 6 H), 4.76 (t, J = 3 Hz, CHO, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.75 μ (O–H). An exact mass determination gave m/e 352.0511 (calcd for $C_{13}H_{21}O_3I$: 352.0537).

trans-**6-Methyl-6-(3-ethylenedioxypropyl)bicyclo[3.1.1]heptan-3-one (12).** A solution of 6.3 g (37 mmol) of silver nitrate in 20 ml of water was added to 1.30 g (3.70 mmol) of **11** in 20 ml of tetrahydrofuran, followed by 1.1 g (11 mmol) of potassium bicarbonate. After 3 hr at room temperature, the resulting mixture was filtered through Supercel and extracted with ether. The ether was washed with water and saturated sodium chloride, then dried over sodium sulfate and evaporated to give 0.72 g of crude oil, shown by vpc (3 ft × 0.125 in. LAC 446 on 80–100 Chrom W, 190°) to be a 3.5:1 mixture of **12** and the 2 ketone. The crude product was separated into its component ketones by plc (silica gel, pH 7; ether–hexane, 3:2; two developments; hot-wire visualization), yielding thereby 0.437 g of **12** (R_f 0.4) and 0.24 g of a 2:1 mixture of 2-ketone (R_f 0.3) to **12**. In a small-scale experiment, tlc of 0.124 g of the crude ketones gave 0.078 g of **12** and 0.024 g of 2-ketone. Nmr (**12**) (CCl_4) δ 0.85 (s, CH_3, 3 H), 1.18 (d, J = 9 Hz, CH_2, 1 H), 1.68 (m, CH_2, 5 H), 2.18 (m, CH, 2 H), 2.46 (m, CH_2COCH_2, 4 H), 3.85 (m, OCH_2CH_2O, 4 H), 4.78 (t, J = 3.5 Hz, CH, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.80 μ (C=O). An exact mass determination gave *m/e* 224.1408 (calcd for $C_{13}H_{20}O_3$: 224.1412). Nmr (2 ketone) (CCl_4) δ 0.82 (s, CH_3, 3 H), 1.68 (m, CH_2) and 1.5–2.7 (m) (total 12 H), 3.84 (m, OCH_2CH_2O, 4 H), 4.75 (m, CH, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.80 μ (C=O). An exact mass determination gave *m/e* 224.1408 (calcd for $C_{13}H_{20}O_3$: 224.1412).

trans-**6-Methyl-6-(3-oxopropyl)bicyclo[3.1.1]heptan-3-one. 12** (0.420 g, 1.87 mmol) was stirred in a mixture of 20 ml of 50% aqueous acetic acid and 2 ml of methanol for 2 hr at 55°. After cooling, the reaction mixture was poured into 50 ml of water and extracted with four 50-ml volumes of ether. The combined ether extracts were shaken with two 50-ml portions of water, three 50-ml portions of saturated potassium bicarbonate, and 50 ml of water. Each aqueous extract was in turn back-extracted with a single 50-ml volume of ether. The ether extracts were combined, shaken with saturated sodium chloride, and dried over sodium sulfate. Evaporation of the solvent yielded 0.30 g of aldehyde: nmr (CCl_4) δ 0.87 (s, CH_3, 3 H), 1.24 (d, J = 10 Hz, CH_2) and 1.5–2.8 (m) (total 12 H), 9.95 (t, J = 2 Hz, CHO, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.86 μ (C=O).

trans-**6-Methyl-6-(4-methyl-3-pentenyl)bicyclo[3.1.1]heptan-3-one (13).** *n*-Butyllithium (1.3 *M*, 2.76 ml, 3.60 mmol) was added to a stirred suspension of isopropyltriphenylphosphonium iodide in 25 ml of tetrahydrofuran at 0° under argon. The mixture was stirred for 1.25 hr at room temperature, after which 16 ml (2.0 mmol) of the deep red ylide solution was removed by syringe and added dropwise to a rapidly stirred solution of 0.30 g (1.67 mmol) of aldehyde in 25 ml of tetrahydrofuran at −78° under argon. After 10 min at −78°, the solution was warmed to room temperature and stirred an additional 2 hr, then poured into 200 ml of water. The resulting mixture was extracted with four 50-ml volumes of ether, and the combined ether extracts were shaken once with water and once with saturated sodium chloride, then dried over sodium sulfate and evaporated. The oily residue was rinsed with pentane which was reevaporated to yield 0.33 g of crude ketone. Purification of this oil by plc (silica gel, pH 7; hexane–ether, 1:1; hot-wire visualization) gave 0.115 g of ketone **13** (R_f 0.6): nmr (CCl_4) δ 0.87 (s, CH_3, 3 H), 1.20 (d, J = 10 Hz, CH_2, 1 H), 1.60 (s, CH_3), 1.69 (s, CH_3) and 1.5–2.6 (m) (total 17 H), 5.15 (t, J = 6 Hz, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.79 μ (C=O). An exact mass determination gave *m/e* 206.1674 (calcd for $C_{14}H_{22}O$: 206.1671).

trans-**2-Hydroxymethylene-6-methyl-6-(4-methyl-3-pentenyl)bicyclo[3.1.1]heptan-3-one (14). 13** (0.115 g, 0.56 mmol) in 2 ml of dry dimethoxyethane was added to a slurry of 2.3 mmol of sodium hydride (0.100 g of 55% mineral oil dispersion, three times washed with petroleum ether) in 3 ml of dry ethyl formate. Ethanol (10 μl) was added, and the mixture was stirred at room temperature for 3 hr, then poured into half-saturated ammonium chloride. The aqueous phase was extracted with three portions of ether which were combined and shaken with saturated sodium chloride, dried over sodium sulfate, and concentrated to yield 0.139 g of formyl ketone **14**: nmr (CCl_4) δ 0.80 (s, CH_3, 3 H), 1.2–2.8 (m) and 1.60, 1.67 (s, CH_3) (total 16 H), 5.1 (m, olefinic, 1 H), 6.85 (s, $CHOH$, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.98, 6.15, 6.25 μ (O=CC=CHOH).

trans-**2-Isopropyloxymethylene-6-methyl-6-(4-methyl-3-pentenyl)-bicyclo[3.1.1]heptan-3-one (15).** Formyl ketone **13** (0.139 g, 0.56 mmol) in 4 ml of tetrahydrofuran was added to 0.67 mmol of sodium hydride (0.030 g of 55% mineral oil dispersion, three times washed with petroleum ether), and the mixture was stirred for 15 min under argon. Isopropyl iodide (0.6 ml) and hexamethylphosphoramide (0.6 ml) were added, and the reaction mixture was refluxed for 2 hr, then stirred an additional hour at room temperature. The solution was poured into half-saturated potassium bicarbonate and extracted three times with ether. The combined ether extracts were shaken twice with water and once with saturated sodium chloride, then dried over sodium sulfate. Evaporation of the solvent gave 0.165 g of isopropyl enol ether **15**: nmr (CCl_4) δ 0.80 (s, CH_3, 3 H), 1.29 (d, J = 7 Hz) and 1.32 (d, J = 7 Hz) ($CHCH_3$), 1.63, 1.68 (s, CH_3) and 1.15–3.2 (m) (total 22 H), 4.10 (sept, J = 7 Hz, CH, 1 H), 5.18 (m, olefinic, 1 H), 6.02 (s, $CHOiPr$, 0.33 H), 7.20 (s, $CHOiPr$, 0.67 H); ir $\lambda_{max}^{CCl_4}$ 5.87 (C=O), 6.17 μ (C=C).

trans-**6-Methyl-6-(4-methyl-3-pentenyl)bicyclo[3.1.1]hept-2-ene-2-carboxaldehyde (16).** Sodium borohydride (0.095 g, 2.5 mmol) was added to 0.165 g (0.56 mmol) of **15** in 5 ml of ethanol, and the mixture was stirred for 3 hr at 60°, then poured into water and extracted three times with ether. The ether extracts were washed twice with water and once with saturated sodium chloride, then concentrated under vacuum. The residue was redissolved in 5 ml of tetrahydrofuran containing 5 ml of 1 *N* hydrochloric acid, and the resulting solution was stirred for 3.5 hr at room temperature. This mixture was poured into water and extracted four times with ether. Washing of the ether extracts successively with water, half-saturated potassium bicarbonate, water, and saturated sodium chloride, followed by drying over sodium sulfate and evaporation of the solvent, produced 0.130 g of oil. This material was purified by plc (silica gel, pH 7; hexane–ether, 3:1; two developments) to give 0.031 g of unsaturated aldehyde **16**: nmr (CCl_4) δ 0.74 (s, CH_3, 3 H), 1.00, 1.15, 1.26, 1.45 (s, CH_2, 2 H), 1.63, 1.67 (s, CH_3) and 1.5–3.0 (m) (total 14 H), 5.15 (m, olefinic, 1 H), 6.61 (m, olefinic, 1 H), 9.50 (s, CHO, 1 H); ir $\lambda_{max}^{CCl_4}$ 5.92 (C=O), 6.15 μ (C=C). An exact mass determination gave *m/e* 218.1670 (calcd for $C_{15}H_{22}O$: 218.1671).

trans-**2-Hydroxymethyl-6-methyl-6-(4-methyl-3-pentenyl)bicyclo-[3.1.1]hept-2-ene (17).** Sodium borohydride (0.040 g, 1.1 mmol) was added to 0.031 g (0.14 mmol) of **16** in 1 ml of ethanol, and the mixture was stirred for 1 hr at room temperature. Water was added, and the solution was extracted four times with ether–pentane. The organic extracts were combined and washed twice with water and once with saturated sodium chloride. After drying over sodium sulfate, the solvent was evaporated, yielding 0.032 g of alcohol **17**: nmr (CCl_4) δ 0.87 (s, CH_3, 3 H), 1.67, 1.73 (s, CH_3), 1.2–2.8 (m) (total 16 H), 3.7 (m, OH, 1 H), 4.0 (m, CH_2OH, 1 H), 5.2 (m, olefinic, 1 H), 5.5 (m, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.70 μ (O–H).

α-*trans*-**Bergamotene (1).** Pyridine–sulfur trioxide complex (0.017 g, 0.11 mmol) was added to 0.010 g (0.045 mmol) of **17** in 1 ml of tetrahydrofuran at −25°. The suspension was stirred for 13 hr at 0° under argon, after which time tlc analysis showed no more starting alcohol. Addition of 0.14 ml (0.35 mmol) of 2.6 *M* lithium aluminum hydride in tetrahydrofuran at −25° was followed by stirring at 0° for 1 hr and at room temperature for 4 hr. Addition of 0.013 ml of water, 0.013 ml of 15% aqueous sodium hydroxide, and 0.039 ml of water precipitated the aluminum salts which were removed by filtration. The filtrate was evaporated, and the residue was redissolved in pentane and passed through 3 g of basic alumina (II) (Woelm). Evaporation of the solvent and purification of the resultant 0.009 g of oil by plc (silica gel; pentane) yielded 0.005 g of α-*trans*-bergamotene (**1**), homogeneous by tlc (R_f 0.5, pentane) and vpc (6-ft × 0.125-in. Carbowax 20M on 80–100 H.P. Chrom W; 180°; R_t 10.8 min): nmr (CCl_4) δ 0.85 (s, CH_3, 3 H), 1.63, 1.67, 1.70 (s, CH_3) and 1.15–2.4 (m) (total 19 H), 5.2 (m, olefinic 2 H); ir $\lambda_{max}^{CCl_4}$ 3.4 (C–H), 6.92, 7.27 μ. An exact mass determination gave *m/e* 204.1874 (calcd for $C_{15}H_{24}$: 204.1878).

trans-**2-Bromomethyl-6-methyl-6-(4-methyl-3-pentenyl)bicyclo-[3.1.1]hept-2-ene (18).** Phosphorus tribromide (0.0038 ml, 10.8 mg, 0.04 mmol) was added to 0.022 g (0.10 mmol) of **17** in 1 ml of ether at 0°. The solution was stirred for 10 hr at 0° in the dark, then poured into water and extracted four times with ether. The ether extracts were shaken with water, half-saturated potassium bicarbonate, and saturated sodium chloride, then dried over sodium sulfate and evaporated to yield 0.19 g of allylic bromide **18**: nmr (CCl_4) δ 0.83 (s, CH_3, 3 H), 1.61, 1.68 (s, CH_3) and 1.2–2.8 (m) (total 16 H), 3.88 (s, CH_2Br, 2 H), 5.1 (m, olefinic, 1 H), 5.68 (m, olefinic, 1 H).

trans-**2-(1-*N*-Tosylhydrazido)-6-methyl-6-(4-methyl-3-pentenyl)-bicyclo[3.1.1]hept-2-ene (19).** *p*-Toluenesulfonylhydrazine (0.017 g, 0.09 mmol) in 0.4 ml of dry dimethyl sulfoxide was added to a slurry of 0.09 mmol of sodium hydride (0.004 g of 55% mineral oil dispersion, three times washed with petroleum ether) in 0.2 ml of tetrahydrofuran. The mixture was stirred 15 min at room temperature, 15 min at 50°, and 15 min at room temperature, after which 0.019 g (0.067 mmol) of **18** in 0.4 ml of tetrahydrofuran was added. The reaction mixture was stirred an additional 0.5 hr at room temperature, then poured into water and extracted four times

with ether. The combined ether extracts were shaken with three portions of water, each aqueous wash being in turn back-extracted with a single 20-ml volume of ether. Shaking of the ethereal solution with saturated sodium chloride followed by drying over sodium sulfate and evaporation of the solvent gave 0.027 g of allyl tosylhydrazide **19**: nmr (CCl_4) δ 0.80 (s, CH_3, 3 H), 1.60, 1.63 (s, CH_3), 2.40 (s, aromatic CH_3) and 1.2–2.6 (m) (total 19 H), 3.5 (m, CH_2N, 2 H), 5.1 (m, olefinic, 1 H), 5.35 (m, olefinic, 1 H), 7.20 (d, J = 8 Hz, aromatic, 2 H), 7.65 (d, J = 8 Hz, aromatic, 2 H); ir $\lambda_{max}^{CCl_4}$ 6.23 μ (aromatic).

β-trans-**Bergamotene (4).** Allyl tosylhydrazide **19** (0.027 g, 0.07 mmol) and 0.2 g of sodium acetate trihydrate in 1 ml of acetic acid were stirred for 1.25 hr at 60°. The solution was diluted with 25 ml of water and extracted with four 10-ml volumes of pentane. The combined pentane extracts were shaken with saturated potassium bicarbonate and saturated sodium chloride, then dried over sodium sulfate and concentrated to *ca.* 5 ml. This solution was passed through 2 g of basic alumina (II) (Woelm), and the eluent was concentrated under vacuum to yield 0.010 g of oil which was further purified by tlc (silica gel; pentane) to afford 0.007 g of *β-trans*-bergamotene (**4**), homogeneous by tlc (R_f 0.5, pentane) and vpc (6 ft × 0.125 in., Carbowax 20M on 80–100 H.P. Chrom W; 180°; R_t 15.6 min): nmr (CCl_4) δ 0.72 (s, CH_3, 3 H), 1.60, 1.68 (s, CH_3) and 1.1–1.27 (m) (total 18 H), 4.55 (m, exo methylene, 2 H), 5.1 (m, olefinic, 1 H); ir $\lambda_{max}^{CCl_4}$ 3.4 (C–H), 6.06 (C=C), 6.9, 7.28, 11.32 μ (CH_2=C). An exact mass determination gave *m/e* 204.1874 (calcd for $C_{15}H_{24}$: 204.1878).

Acknowledgment. This research was assisted financially by the National Science Foundation and the National Institutes of Health.

Aberrant Alkaloid Biosynthesis. Formation of Nicotine Analogs from Unnatural Precursors in *Nicotiana glutinosa*[1]

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Received January 15, 1971

Abstract: Several methyl derivatives of nicotine have been biosynthesized using *Nicotiana glutinosa* plants and the corresponding substituted pyrrolinium precursors. The syntheses of the ^{14}C-labeled pyrrolinium precursors, which were utilized in the biosynthetic experiments, are also described. For chromatographic and spectral comparisons, authentic samples of some of the substituted nicotines were also synthesized. The stereochemistry and absolute configuration of the biosynthesized nicotine analogs have been determined. Incorporation results with 2- and 3-methyl-substituted pyrrolinium precursors allow some speculation on the specificity and steric requirements of the enzyme(s) involved in the latter stages of nicotine biosynthesis.

The biosynthetic pathway of formation of nicotine (**1**) in *Nicotiana* has been subject to a great deal of study. A multitude of experiments have been carried out by means of precursor feedings and short-term biosyntheses with CO_2-^{14}C; however, the precise biosynthetic pathway has yet to be completely elucidated.[2] In conjunction with other biosynthetic experiments with *Nicotiana glutinosa*, we became interested in the possibility of biosynthesizing unnatural nicotine analogs by using substituted precursors instead of the normal, natural precursor.

The possibility of biosynthesizing unnatural nicotine analogs using substituted natural precursors was interesting for several reasons. First, the incorporation of an unnatural precursor (*i.e.*, a substituted natural precursor) into an unnatural product (*i.e.*, nicotine analog) had not been previously reported in plants. Second, experiments with a series of substituted precursors might define the specificity of the enzyme system which catalyzes the biosynthesis of nicotine from a 1-methyl-1-pyrrolinium salt **2** and a nicotinic acid derivative. Third, the formation of unnatural alkaloids *in vivo* should be useful in the preparation of analogs of biologically active natural products. Finally, since the unnatural products possess a structural label in addition to the usual radioactivity label, they should also be of great utility in the study of metabolism and interrelationships among the various alkaloids and other natural products in a given plant.

In a preliminary communication,[3] we have reported the incorporation of 1,3-dimethyl-1-pyrrolinium-*3-methyl*-^{14}C chloride (**4**), into the nicotine analog, 3′-methylnicotine (**3**). We now report the full details for this preliminary communication and additional related experiments concerning the formation of the nicotine analogs **6** and **7** from **9b** and **10b**, respectively.

Precursor Synthesis. In the present work, only derivatives of the natural pyrrolidine ring precursor, 1-methyl-1-pyrrolinium salt (**2**), have been examined as potential unnatural precursors for analogs of nicotine. This choice was based on the fact that **2** has been reported to be a highly efficient precursor of the pyrrolidine ring of nicotine.[4,5] *A priori*, derivatives of the pyridine ring precursor, nicotinic acid, could also have been examined; however, nicotinic acid is a less efficient precursor, probably due to its more wide-

(1) This investigation was supported in part by Grant No. MH 12797 from the National Institute of Mental Health, U. S. Public Health Service, and the U. S. Atomic Energy Commission.

(2) For complete reviews of the present status of nicotine biosynthesis see: M. L. Rueppel, B. P. Mundy, and H. Rapoport, submitted for publication; E. Leete, *Advan. Enzymol.*, **32**, 373 (1969).

(3) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 5528 (1970).

(4) T. Kisaki, S. Mizusaki, and E. Tamaki, *Arch. Biochem. Biophys.*, **117**, 667 (1966); S. Mizusaki, T. Kisaki, and E. Tamaki, *Plant. Physiol.*, **43**, 93 (1968).

(5) E. Leete, *J. Amer. Chem. Soc.*, **89**, 7081 (1967).