Syntheses of Natural (+)-Juvabione, Its Enantiomer (−)-Juvabione, and Their Diastereoisomers (+)- and (−)-Epijuvabione

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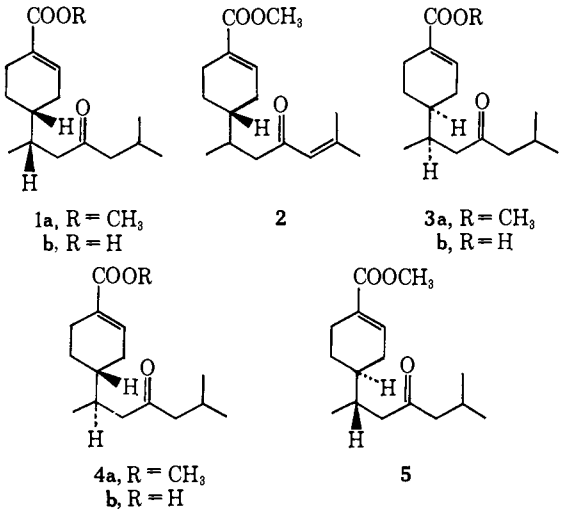
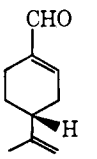
Abstract: The insect juvenile hormone, (+)-juvabione (**1a**), has been synthesized from (+)-(4*R*,8*R*)-*p*-menth-1-en-9-ol, obtained by hydroboration of (*R*)-(+)-limonene, *via* (2*S*)-[4-methyl-3-cyclohexen-(1*R*)-yl]-6-methylheptan-4-one (**10**). Two routes for the oxidation of the allylic methyl group of **10**, photochemical oxygenation and formation and opening of an oxirane *via* β elimination, are described. This work establishes the absolute stereochemistry of **1a** as *R,S* at the two asymmetric centers, in contradiction to the previously deduced *R,R* configuration. Syntheses of (−)-juvabione (**3a**), (+)-epijuvabione (**4a**), and (−)-epijuvabione (**5**) are also reported. The four diastereoisomers were very similar in all physical properties, except optical rotatory dispersion and circular dichroism which showed striking differences. These data are discussed.

In 1965, Slama and Williams[1] reported the juvenile hormone action of a substance found in American paper products on the metamorphosis of the insect *Pyrrhocoris apterus*. Bowers and coworkers[2] isolated the active material, (+)-juvabione (**1a**), from Balsam fir and identified it as the methyl ester of the known (+)-todomatuic acid (**1b**).[3-5] Another compound having insect juvenile hormone activity, (+)-dehydrojuvabione (**2**), was found together with (+)-juvabione in Czechoslovakian balsam fir wood.[6] These reports stimulated research in this area and several syntheses of (±)-juvabione and (±)-dehydrojuvabione have appeared.[7-9] This paper describes the stereospecific syntheses of natural (+)-juvabione (**1a**),[10] its enantiomer **3a**, and the diastereoisomeric (+)- and (−)-epijuvabiones (**4a** and **5**, respectively). Further, the absolute stereochemistry of (+)-juvabione had been established[11] as *R,S* (as shown in **1a**) in contradiction to the *R,R* configuration previously deduced for (+)-todomatuic acids.[12]



Results and Discussion

In considering an appropriate scheme for the synthesis of natural (+)-juvabione, it at first seemed desirable to start with a suitable monoterpene of known absolute stereochemistry containing the desired ester group or precursor thereof. (+)-Perillaldehyde[13] (**6**) seemed to meet all the requirements and a scheme



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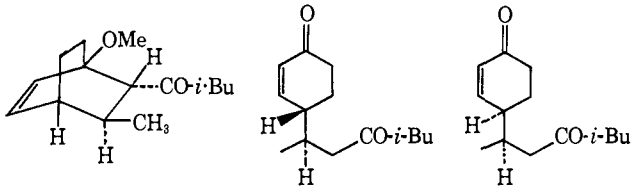
similar to that described below for introduction of the second asymmetric center, elaboration of the aliphatic



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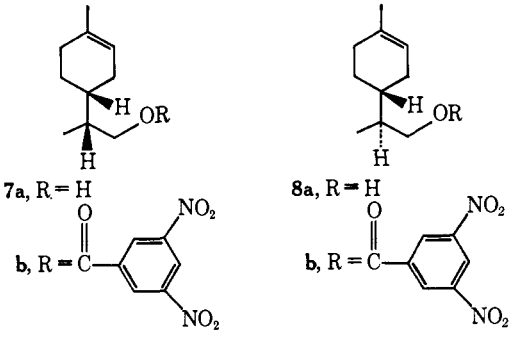
(1) K. Slama and C. M. Williams, *Proc. Nat. Acad. Sci. U. S.*, **54**, 411 (1965).
(2) W. S. Bowers, H. M. Fales, M. J. Thompson, and E. C. Uebel, *Science*, **154**, 1020 (1966).
(3) R. Tutihasi and T. Hanazawa, *J. Chem. Soc. Jap.*, **61**, 1041 (1940); *Chem. Abstr.*, **37**, 258 (1943).
(4) T. Momose, *J. Pharm. Soc. Jap.*, **61**, 288 (1941); *Chem. Abstr.*, **44**, 9383 (1950).
(5) M. Nakazaki and S. Isoe, *Bull. Chem. Soc. Jap.*, **34**, 741 (1961); **36**, 1198 (1963).
(6) V. Cerny, L. Dolejs, L. Labler, F. Sorm, and K. Slama, *Tetrahedron Lett.*, 1053 (1967); *Collect. Czech. Chem. Commun.*, **32**, 3926 (1967).
(7) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968).
(8) K. S. Ayyar and G. S. Krishna Rao, *Can. J. Chem.*, **46**, 1467 (1968).
(9) (a) A. J. Birch, P. L. MacDonald, and V. H. Powell, *Tetrahedron Lett.*, 351 (1969). (b) This stereoselective synthesis does in fact afford (±)-juvabione of the correct stereochemistry (see below) since opening of intermediate i gives ii and not iii as previously reported.[9a] Upon further transformations,[9a] ii leads to (−)-juvabione (**3a**). Similarly, the mirror image of i leads to (+)-juvabione (**1a**): A. J. Birch, The Australian National University, personal communication, 1969.
(10) For a preliminary communication on the synthesis of natural (+)-juvabione, see B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *Chem. Commun.*, 1057 (1968).
(11) J. F. Blount, B. A. Pawson, and G. Saucy, *ibid.*, 715, 1016 (1969).
(12) The absolute stereochemistry of (+)-todomatuic acid had been assigned[5] based upon comparisons of the molecular rotations ([M]D) of the acid and its conversion products with sesquiterpenes of known absolute stereochemistry.
(13) J. L. Simonsen, "The Terpenes," Vol. I, University Press, Cambridge, 1947, p 311.

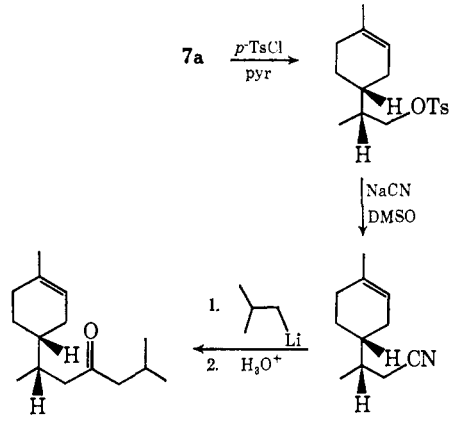
side chain, and conversion to (±)-**1a** indeed proved successful when applied to (±)-perillaldehyde. However, difficulties in obtaining or preparing optically pure (+)-**6** caused us to look for another suitable starting material.

In order to prove the stereochemical assignment of **1a**, an intermediate of known absolute stereochemistry, which would allow subsequent chemical transformations to **1a** while preserving the stereochemical integrity of the molecule, was required. To this end, the diastereoisomeric (+)-(4*R*)-*p*-menth-1-en-9-ols, obtained by anti-Markovnikov hydration of (*R*)-(+)-limonene with bis-3-methyl-2-butylborane ("disiamylborane")[14] or triisobutylaluminum,[15] appeared to be attractive starting compounds. Separation of the diastereoisomers had been achieved *via* fractional crystallization of their corresponding 3,5-dinitrobenzoates.[16] Further, the less soluble, higher melting diastereoisomer **7b** had been assigned[11,17] the 4*R*,8*R* configuration and the lower melting, more soluble diastereoisomer **8b** had the 4*R*,8*S* configuration.



The alcohol **7a** could be readily transformed according to Scheme I to the ketone **10**. Oxidation of the

Scheme I



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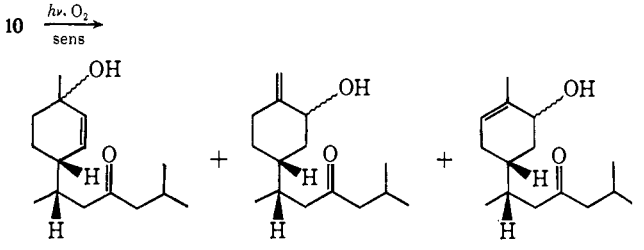
allylic methyl group of **10** with preservation of stereochemistry would give (+)-todomatuic acid (**1b**), which upon esterification would yield the desired natural (+)-juvabione (**1a**).

(14) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 1241 (1961).
(15) K. Ziegler, F. Krupp, and K. Zosel, *Ann. Chem.*, **629**, 241 (1960).
(16) K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **49**, 2150 (1966).
(17) The original assignment[16] for the diastereoisomeric esters **7b** and **8b** had been 4*R*,8*S* and 4*R*,8*R*, respectively. The corrected assignment is based on the single-crystal X-ray structure determination of the *p*-iodobenzoate of **7a**.[11]

Accordingly, hydroboration[14] of (*R*)-(+)-limonene with disiamylborane afforded in 50% yield a 3:2 mixture of (4*R*,8*R*)- and (4*R*,8*S*)-*p*-menth-1-en-9-ols (**7a** and **8a**). Although the alcohols could not be separated by vapor phase chromatography, the ratio of isomers was determined by 100-MHz nmr spectroscopy in which the methyl protons at C-10 in each of the diastereoisomers exhibited slightly different chemical shifts. Thus the methyl group of the 4*R*,8*R* isomer showed a doublet centered at δ 0.87 (J = 6 Hz), and in the 4*R*,8*S* isomer the doublet occurred at 0.90 (J = 6 Hz). Fractional crystallization[16] of the mixture of diastereoisomeric 3,5-dinitrobenzoates from *n*-hexane and hydrolysis of the less soluble, higher melting ester gave (4*R*,8*R*)-*p*-menth-1-en-9-ol (**7a**).

As shown in Scheme I, alcohol **7a** was converted to (+)-(3*S*)-[4-methyl-3-cyclohexen-(1*R*)-yl]butyronitrile (**9**) *via* the tosylate by displacement with sodium cyanide in dimethyl sulfoxide. Reaction[18] of the nitrile **9** with isobutyllithium at 0° afforded the ketone **10** having the desired *R*,*S* configuration at the asymmetric centers. Photooxygenation[19-21] of **10** in pyridine solution with hematoporphyrin as sensitizer afforded a mixture of secondary and tertiary alcohols **11–13** after reduction of the initially formed hydroper-



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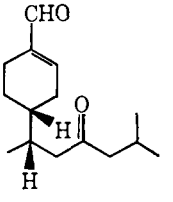
oxides with potassium iodide in acetic acid. It follows from previous studies of the reaction mechanism[19-21] that, in the formation of alcohols **11–13**, the stereochemistry of the asymmetric centers is unaffected.

Oxidation[22,23] of the mixture of secondary alcohols containing **12** in benzene with aqueous sodium dichromate–sulfuric acid–acetic acid afforded a mixture from which the keto aldehyde **14** could be isolated.



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Oxidation of **14** with basic silver oxide[24] afforded (+)-todomatuic acid (**1b**) which was converted directly into

(18) J. Büchi, F. Kracher, and G. Schmidt, *Helv. Chim. Acta*, **45**, 729 (1962).
(19) G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann. Chem.*, **674**, 93 (1964).
(20) J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966), and references cited therein.
(21) C. S. Foote, *Accounts Chem. Res.*, 1, 104 (1968), and references therein.
(22) Y. R. Naves and A. V. Grampoloff, *Bull. Soc. Chim. Fr.*, 37 (1960).
(23) F. Porsch, *Dragoco Rept.*, 11, 149 (1964); *Chem. Abstr.*, **61**, 16099*d* (1964).
(24) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

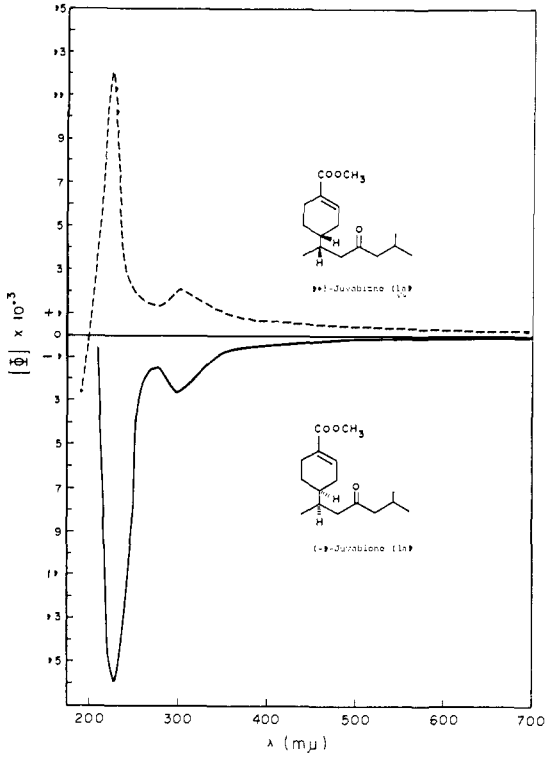


Figure 1. Ord spectra of (+)-juvabione (**1a**) and (−)-juvabione (**3a**) in ethanol.

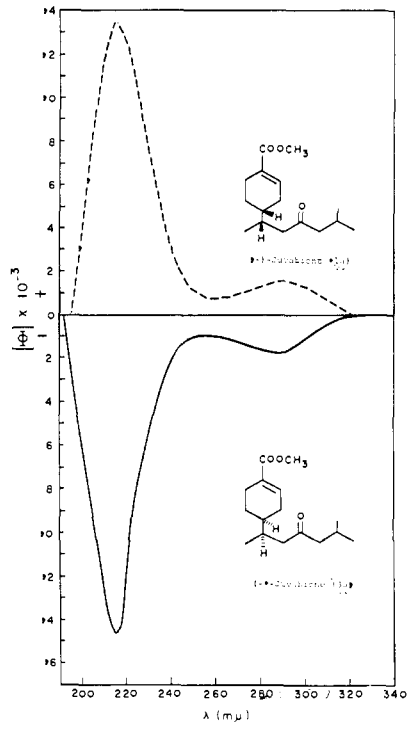
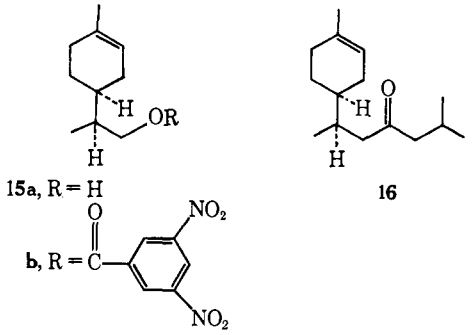


Figure 2. Cd spectra of (+)-juvabione (**1a**) and (−)-juvabione (**3a**) in ethanol.

the ester **1a** with diazomethane. Purification of **1a** by column chromatography on neutral alumina gave material whose spectral properties were identical with those of the natural ester.[25] The optical rotatory dispersion and circular dichroism spectra of the synthetic ester are shown in Figures 1 and 2.

Samples of synthetic and natural (+)-juvabione (**1a**) were hydrolyzed to the corresponding (+)-todomatuic acids (**1b**) which were recrystallized from pentane. The melting points of the acid samples were the same and did not depress on admixture. The optical rotatory dispersion and circular dichroism spectra of the acids were also identical.

The synthesis of the enantiomeric (−)-juvabione (**3a**) was carried through similarly starting from *S*-(−)-limonene ($[\alpha]_D$ −106.5°). After fractional crystallization, the less soluble isomer **15b** afforded (4*S*,8*S*)-*p*-menth-1-en-9-ol (**15a**) upon hydrolysis. The ketone **16**,



prepared as described above, was subjected to photooxygenation and reduction of the initially formed hydroperoxides. Without further purification, the mixture of allylic alcohols was carried through as described to (−)-juvabione (**3a**), which was purified by column chromatography. The uv, ir, nmr, tlc, vpc, and mass spectral properties of (−)-juvabione were identical with those of the (+) ester **1a**. The ord and cd spectra of this ester showed negative Cotton effects equal and opposite to that of the ester **1a** (Figures 1 and 2).

(+)-(4*R*,8*S*)-*p*-Menth-1-en-9-ol (**8a**), the minor diastereoisomeric alcohol formed in the hydroboration of *R*-(+)-limonene with disiamylborane,[14] served as the starting material for the synthesis of (+)-epijuvabione (**4a**). The pure diastereoisomer was obtained by hydrolysis of the more soluble, lower melting 3,5-dinitrobenzoate **8b** from repeated fractional crystallization of the mother liquor residues from hexane, after removal of less soluble 4*R*,8*R* diastereoisomer **7b**.[16,17] The alcohol **8a** was converted to **4a** by the synthetic steps described previously. The pure ester **4a** could not be distinguished from its diastereoisomer **1a** by vpc, tlc, ir, uv, nmr, or mass spectral comparison. The ord and cd spectra (Figures 3 and 4) of **4a** were dramatically different from those of **1a** (Figures 1 and 2). The cd spectrum of **4a** showed a negative maximum at λ 291 mμ, whereas the cd spectrum of (+)-juvabione (**1a**) had a positive maximum at this wavelength.

For the synthesis of (−)-epijuvabione (**5**), (−)-(4*S*-8*R*)-*p*-menth-1-en-9-ol (**17a**), the minor diastereoisomeric alcohol formed in the hydroboration of (*S*)-(−)-limonene with disiamylborane,[14] was obtained by hydrolysis of the more soluble, lower melting 3,5-dinitrobenzoate, obtained by repeated fractional crystallization of the mother liquor residues from hexane after removal of the less soluble ester **15b**. The alcohol **17a** was converted into (−)-epijuvabione (**5**) as described above. Again, only the ord and cd spectra (Figures 3 and 4) reflected the stereochemical differences between **5** and its enantiomer **4a** and diastereoisomers **1a** and **3a**.

(25) We are grateful to Professor Cerny for kindly providing a sample of natural (+)-juvabione.

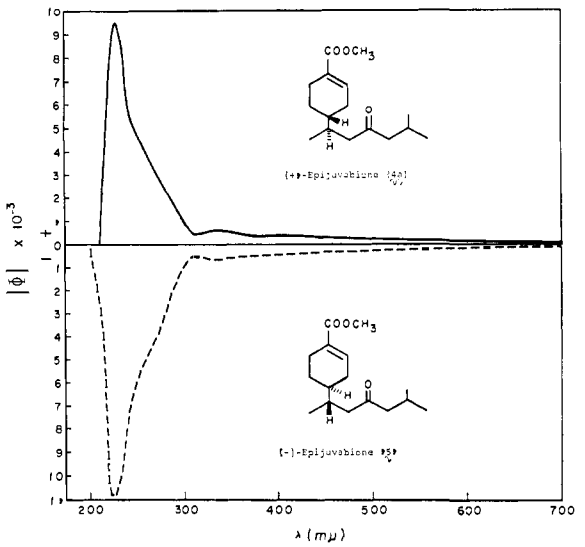
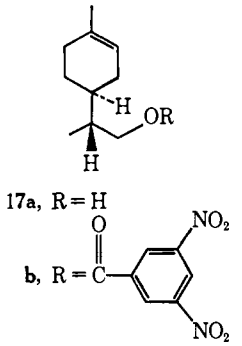
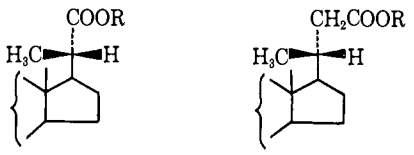


Figure 3. Ord spectra of (+)-epijuvabione (**4a**) and (−)-epijuvabione (**5**) in ethanol.

The ord and cd data for these four isomers (Figures 1–4) correlate well with data obtained earlier for dinor- and norcholanic acid derivatives.[26] The dinorcholanic



acids had been correlated[26] with monosubstituted alkylsuccinic acids.[27] (*S*)-Dinorcholanic acid derivatives (partial formula **18**) showed a negative Cotton effect as did (*R*)-norcholanic acid derivatives (**19**) in which the



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configuration remains the same but the sequence rule designation[28] is changed. In analogy with the (*R*)-norcholanic acid derivatives (**19**), (+)-epijuvabione (**4a**) and (−)-juvabione (**3a**), which also have the *R* configuration *β* to the carbonyl group, showed a negative Cotton effect in their ord spectra and a negative maximum in their cd spectra in the carbonyl region. (+)-Juvabione (**1a**) and (−)-epijuvabione (**5**), having the *S* configuration *β* to the carbonyl group, had positive ord Cotton effects and positive cd maxima. It is clear from these data that the asymmetric center at the cyclohexene ring has little effect on the Cotton effect associated with

(26) G. Gottarelli and P. M. Scopes, *J. Chem. Soc., C*, 1370 (1967).
(27) A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjoberg, and S. Sjoberg, *ibid.*, 3298 (1965).
(28) (a) R. S. Cahn and C. K. Ingold, *ibid.*, 612 (1951); (b) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

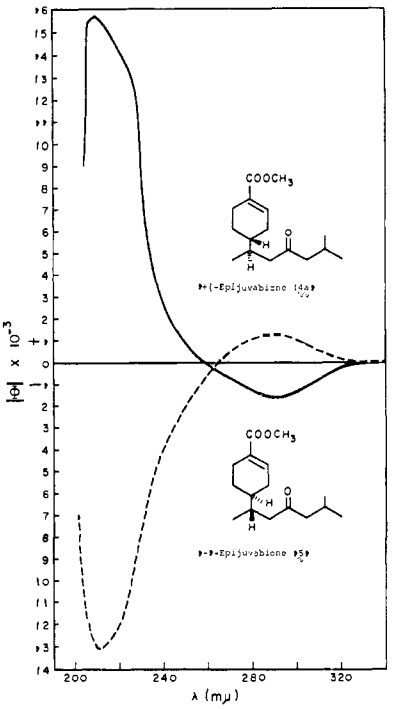
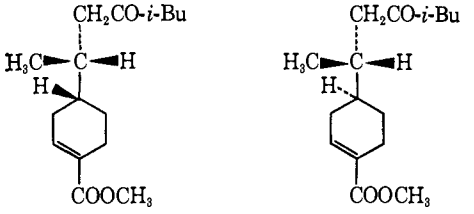


Figure 4. Cd spectra of (+)-epijuvabione (**4a**) and (−)-epijuvabione (**5**) in ethanol.

the carbonyl group. Thus, in these cases, the sign of the carbonyl Cotton effect is determined solely by the configuration at the *β* carbon atom.



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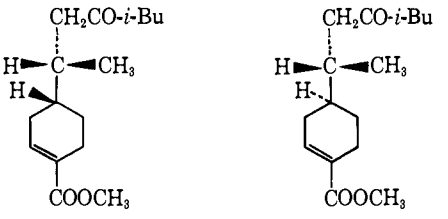

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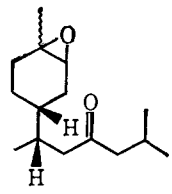
As an alternative to photooxygenation, a chemical approach to oxidation of the allylic methyl group with preservation of stereochemistry involves ring opening of an epoxide *via* *β* elimination to form a mixture of allylic alcohols, which can then be oxidized further as described above. This *β* elimination can be accomplished with various reagents (N-lithiodiethylamide,[29] active alumina,[30] aluminum isopropoxide,[31] and diisobutylaluminum hydride[32]). Thus, treatment of ep-

(29) J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968), and references therein.
(30) (a) I. C. Nigam and L. Levi, *Can. J. Chem.*, **46**, 1944 (1968); and (b) V. S. Joshi, N. P. Damodaran, and Sukh Dev, *Tetrahedron*, **24**, 5817 (1968).
(31) E. H. Eschinasi, *Israel J. Chem*, **6**, 713 (1968).
(32) (a) W. Kirchhof, *Chem. Ber.*, **93**, 2712 (1960); and (b) P. Teisseire, A. Galfré, M. Plattier, and B. Corbier, *Recherches* (Paris), No. 15, 52 (1966); *Chem. Abstr.*, **65**, 15430*a* (1966).



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oxide mixture **20**, obtained by the action of *m*-chloroperbenzoic acid on ketone **10**, with N-lithiodiethylamide in refluxing tetrahydrofuran[33] afforded a mixture of allylic alcohols containing **12**. Oxidation and treatment of the resulting acid **1b** with diazomethane gave (+)-juvabione (**1a**), identical with a sample of natural material.

It is interesting to note that the hydroboration of (*R*)-(+)-limonene with disiamylborane at 0° afforded a 20% excess of the 4*R*,8*R* diastereoisomer **7a**. Hydroboration at lower temperatures (−15 and −30°) did not affect the product ratio. Although this reaction had been reported previously,[14] it had not been possible to determine the degree of asymmetric induction at that time. Few, if any, cases of asymmetric induction in the hydroboration of an acyclic optically active olefin with disiamylborane appear to have been reported, although there are many examples[34] of the formation of optically active alcohols from hydroboration of *cis*- and *trans*-olefins, terminal methylenes, and ketones with diisopinocampheylborane. In these latter cases, several models[34,35] have been proposed to predict or rationalize the absolute configuration of the newly formed asymmetric center. In the hydroboration of terminal methylenes with (−)-diisopinocampheylborane, the models[34b,35c] predict the predominance of the *S* alcohol, in accordance with experimental results. From a consideration of molecular models, the steric requirements for the four-center transition state with disiamylborane appear to be considerably less than those with diisopinocampheylborane, and it is difficult to predict *a priori* the predominant formation of the 4*R*,8*R* alcohol as observed.

Experimental Section

General. Melting points were taken on a Kofler hot stage and are uncorrected; boiling points are uncorrected. Infrared spectra were recorded on Beckman Model IR-9 and Perkin-Elmer Models 221 or 237B spectrophotometers; ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Nmr spectra were measured on a Varian Associates HA-100 or A-60 spectrometer or a Jeolco C 60H instrument using tetramethylsilane as internal standard. Ord and cd spectra were recorded on a Jasco Model ord, uv, cd 5. Mass spectra were measured on CEC Model 21-110 or Jeolco Model 01SG spectrometers. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Spectra and analyses were determined by our Physical Chemistry Department.

Materials. Disiamylborane was obtained as a 1 *M* solution in tetrahydrofuran from Alfa Inorganics, Inc. Isobutyllithium in heptane solution was supplied by Lithium Corporation of America. *n*-Butyllithium (1.6 *M* in hexane) was purchased from Foote Mineral Co. (*S*)-(−)-Limonene was obtained from the Glidden Co.

(4*R*,8*R*)-*p*-Menth-1-en-9-ol (7a). Hydroboration of *R*-(+)-limonene ([α]D +116°, neat) with disiamylborane according to the procedure of Brown and Zweifel[14] afforded in 50% yield a mixture of (4*R*,8*R*)- and (4*R*,8*S*)-*p*-menth-1-en-9-ols in a 3:2 ratio, determined by nmr spectroscopy (see Discussion). Conversion of the mixture of diastereoisomeric alcohols to their 3,5-dinitrobenzoates and fractional crystallization from *n*-hexane afforded in 44% yield the less soluble 4*R*,8*R* diastereoisomer: mp 94–95°; [α]^{25}D +36.7° (*c* 0.77, $CHCl_3$) (lit.[16] mp 98°, [α]^{25}D +32°[36] ($CHCl_3$)); nmr ($CDCl_3$) δ 1.03 (3 H, doublet, *J* = 6.5 Hz).

Hydrolysis of this crystalline material gave pure **7a** [bp 64–69° (0.2 mm); [α]^{25}D +104° (neat, d_{20} 0.9420[16]) (lit.[16] α^{25}D +98°)] in 75% yield; nmr ($CDCl_3$) δ 0.89 (3 H, doublet, *J* = 6 Hz).

(+)-(3*S*)-[4-Methyl-3-cyclohexene-(1*R*)-yl]butyronitrile (9). (+)-(4*R*,8*R*)-*p*-Menth-1-en-9-ol (**7a**) (30.0 g, 0.2 mole) and 74.0 g (0.39 mole) of *p*-toluenesulfonyl chloride in 650 ml of dry pyridine were stirred at room temperature for 18 hr. The reaction mixture was poured into ice water and the organic material was extracted with benzene. The benzene solution was washed with 1 *N* hydrochloric acid and then with water, dried, and evaporated to give 60.0 g of tosylate: [α]^{25}D +39.01° (*c* 1.32, benzene); $\nu_{max}^{CHCl_3}$ 1600 and 1180 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, doublet, *J* = 7.0 Hz), 1.60 (3 H, singlet), 1.4–2.0 (8 H), 2.44 (3 H, singlet), 3.94 (2 H, eight lines, AB pattern), 5.28 (1 H, broad singlet), and 7.33 and 7.79 (4 H, AB pattern); mass spectrum *m/e* 308 (M^+), 266, 173, 155, 136, 121, 107, and 94.

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.21; H, 7.85; S, 10.38. Found: C, 66.02; H, 7.65; S, 10.25.

The tosylate (60.0 g, 0.2 mole) was dissolved in 650 ml of anhydrous dimethyl sulfoxide. Sodium cyanide (14.3 g, 0.3 mole) was added to the solution and the mixture was stirred at 90° for 5 hr in an atmosphere of nitrogen. The reaction mixture was poured into water containing ammonium chloride and extracted with methylene chloride. The methylene chloride extracts were washed well with water, dried, and evaporated to give 34.9 g of crude nitrile **9**. Distillation at 74–78° (0.25 mm) afforded 28.5 g (86% over-all yield) of pure **9**: [α]^{25}D +76.66° (*c* 1.6, benzene); $\nu_{max}^{CHCl_3}$ 2250 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, doublet, *J* = 8 Hz), 1.63 (3 H, singlet), 1.20–2.20 (8 H), 2.32 (2 H, multiplet), and 5.35 (1 H, broad singlet).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.83; H, 10.38; N, 8.74.

(2*S*)-[4-Methyl-3-cyclohexene-(1*R*)-yl]-6-methylheptan-4-one (10). Isobutyllithium (172 ml of a 2 *M* solution in heptane, 0.344 mole) and 70 ml of anhydrous ether were placed in a 1-l. flask fitted with a condenser, thermometer, dropping funnel, and magnetic stirrer, which had been carefully dried and allowed to cool in an atmosphere of nitrogen. The flask and contents were cooled to 0–2° in an ice bath and a solution of the nitrile **9** (27.5 g, 0.169 mole) in 30 ml of anhydrous ether was added over a period of 2 hr at this temperature. The reaction mixture was stirred at 0° for 3 hr and 1 hr at room temperature. A solution of 175 ml of 6 *N* sulfuric acid in 350 ml of dioxane was added and the mixture was heated to 50–60° for 2 hr. The organic phase was separated and the aqueous phase was neutralized with an aqueous solution containing 10% by weight of sodium hydroxide. Extraction with ether gave the crude ketone **10** which was purified by column chromatography on activity III neutral alumina followed by distillation at 90–93° (0.15 mm) to give 28.6 g (76.5% yield) of pure **10**: [α]^{27}D +80.48° (*c* 0.81, benzene); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.83–0.97 (9 H), 1.60 (3 H, singlet), 1.0–2.5 (13 H), and 5.32 (1 H, broad singlet).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.63.

Photooxygenation of 10. A 24.0-g sample of **10** in 250 ml of dry pyridine was placed in a gas-washing bottle and 350 mg of hematoporphyrin was added. The mixture was irradiated with 3000-Å light in a Rayonet photochemical reactor while a stream of dry oxygen was passed through the solution. After irradiation for 115 hr, the mixture was diluted with ether and filtered. Evaporation of the solvent afforded a mixture of hydroperoxides (29.2 g), which was diluted with 300 ml of methanol and 250 ml of anhydrous ether. A solution of 73.0 g of potassium iodide in 466 ml of acetic acid and 165 ml of water was added and the resulting mixture was stirred at

(33) The reaction of **20** could not be effected in refluxing ether, conditions reported[29] to give the best yield of 2-methylenecyclohexanol from 1-methylcyclohexene oxide.

(34) (a) D. R. Boyd and M. A. McKervey, *Quart. Rev.* (London), **22**, 95 (1968), and references therein; (b) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964); and (c) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *ibid.*, **86**, 1076 (1964).

(35) (a) D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 667 (1967); (b) A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967); and (c) K. R. Varma and E. Caspi, *Tetrahedron*, **24**, 6365 (1968).

(36) Dr. G. Ohloff, Firmenich & Cie, personal communication, 1968.

room temperature for 4 hr. The mixture was poured slowly into 1.6 l. of water and extracted with benzene. The organic phase was washed with saturated sodium bicarbonate, saturated sodium thiosulfate, and saturated sodium chloride solutions and dried with anhydrous sodium sulfate.

Evaporation of the solvent gave 28.3 g of a mixture of secondary and tertiary alcohols **11–13**. Separation of the secondary alcohols was achieved by formation of their acetates followed by column chromatography. Hydrolysis of the acetate mixture and purification of the resulting secondary alcohols by column chromatography gave 5.8 g of a mixture of compounds **12** and **13**.

(4*R*)-[1(*S*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxaldehyde (14). The mixture of secondary alcohols **12** and **13** (5.8 g) in 10 ml of benzene was placed in a 100-ml round-bottomed flask fitted with a magnetic stirrer and a reflux condenser. A solution of 5.5 g of sodium dichromate dihydrate in 14.5 ml of water and 6.1 ml of acetic acid were added. The mixture was stirred at 70° and a solution of 4.35 g of sulfuric acid in 5 ml of water was added slowly over a period of 2 hr. The mixture was allowed to stir at this temperature for another 2 hr and then was cooled and poured into ice water. Extraction with ether produced 5.2 g of crude **14** which was purified by column chromatography on activity III neutral alumina to give 1.80 g of pure aldehyde: bp 140–150° (0.25 mm); $\nu_{max}^{CCl_4}$ 2700, 1710, 1680, and 1650 cm^{-1}; λ_{max}^{EtOH} mμ (ϵ) 232 (14,240); nmr ($CDCl_3$) δ 0.85–0.91 (9 H), 1.00–2.60 (13 H), 6.76 (1 H, broad multiplet), and 9.43 (1 H, singlet); mass spectrum *m/e* 136 (base peak), 127, 109, and 85; ord (*c* 0.228, ethanol, 23°) $[\phi]_{700}$ +153°, $[\phi]_{589}$ +1262°, $[\phi]_{338}$ +1138°, $[\phi]_{328}$ +993°, $[\phi]_{295}$ +1339°, $[\phi]_{268}$ +978°, $[\phi]_{239}$ +6695°, $[\phi]_{222}$ 0°, and $[\phi]_{193}$ (last) −10,815°; cd (*c* 0.00967 *M*, ethanol, 23°) $[\theta]_{360}$ 0, $[\theta]_{348}$ +545, $[\theta]_{315}$ +272, $[\theta]_{292}$ +1159, $[\theta]_{260}$ +204, $[\theta]_{230}$ +10,912, $[\theta]_{214}$ +7502, $[\theta]_{204}$ +9548, and $[\theta]_{195}$ 0.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.02; H, 10.22.

(4*R*)-[1(*S*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic Acid Methyl Ester. [(+)-Juvabione (1a)]. The keto aldehyde (1.8 g, 7.65 mmoles) was dissolved in 27 ml of ethanol in a 250-ml flask and a solution of 3.6 g of silver nitrate in 7.2 ml of water was added. Aqueous sodium hydroxide (3.6 g in 63 ml of water) was added dropwise to the stirred reaction mixture. Stirring was continued for 3 hr at room temperature. The mixture was filtered and the filtrate was concentrated and extracted once with ether. The aqueous phase was then made acidic with 5 *N* hydrochloric acid and extracted three times with ether. The latter ether extracts were combined, washed with water, and dried with anhydrous magnesium sulfate. Evaporation of the solvent afforded 0.6 g of crude (+)-todomatuic acid (**1b**).

A solution of 0.6 g of **1b** in 10 ml of anhydrous ether was treated with 12 ml of a 10% solution of diazomethane in ether. The reaction mixture was allowed to stir for 1 hr; 1 ml of dilute acetic acid was added. The layers were separated and the aqueous phase was extracted with three 20-ml portions of ether. The combined organic phase was washed with saturated sodium bicarbonate solution and dried with anhydrous sodium sulfate. Evaporation of the solvent afforded 0.55 g of crude product which was purified by column chromatography on activity III neutral alumina to give 146 mg of (+)-juvabione (**1a**). Distillation at 150–160° (bath temperature) and 0.33 mm afforded 94 mg of pure ester **1a**: $\nu_{max}^{CCl_4}$ 1715, 1650, 1250, and 1080 cm^{-1}; λ_{max}^{EtOH} mμ (ϵ) 218 (11,030); nmr ($CDCl_3$) δ 0.80–0.90 (9 H), 3.64 (3 H, singlet) and 6.83 (1 H, broad singlet); mass spectrum *m/e* 266 (M^+), 234, 167, and 134 (base peak). The ord and cd spectra are shown in Figures 1 and 2.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.18; H, 9.83.

(+)-Todomatuic Acid (1b). A 27-mg sample of synthetic (+)-juvabione (**1a**) was dissolved in 1 ml of methanol and 0.8 ml of 1*N* potassium hydroxide solution was added. The mixture was heated to reflux for 2 hr and then concentrated. The oily residue was diluted with water and made acidic to pH 1 with 6 *N* sulfuric acid. The aqueous acid solution was extracted with ether and the ether extracts were washed with saturated sodium chloride solution and then dried with anhydrous sodium sulfate. Evaporation of the solvent afforded a solid which after recrystallization from pentane had mp 64.0–65.5°. The mixture melting point of the above product and (+)-todomatuic acid (**1b**) (mp 64.0–65.5°), obtained from natural (+)-juvabione, was 63.5–65°. The ord spectrum of synthetic (+)-todomatuic acid was (*c* 0.273, ethanol, 23°) $[\phi]_{700}$ +179°, $[\phi]_{589}$ +249°, $[\phi]_{303}$ +2473°, $[\phi]_{277}$ +1439°, $[\phi]_{224}$ +9230°, $[\phi]_{212}$ 0°, and $[\phi]_{192}$ −15,229°; cd (*c* 0.108 *M*, ethanol, 23°) $[\theta]_{324}$ 0, $[\theta]_{286}$ +1799, $[\theta]_{260}$ +1189, $[\theta]_{212}$ +17,080, and $[\theta]_{192}$ +10,980.

(−)-(4*S*,8*S*)-*p*-Menth-1-en-9-ol (15a). Hydroboration[14] of (*S*)-(−)-limonene ($[\alpha]_D$ −106.5°, neat, d_4^{20} 0.8422) with disiamylborane afforded in 40–45% yield a mixture of the diastereoisomeric (4*S*,8*S*)- and (4*S*,8*R*)-*p*-menth-1-en-9-ols in a ratio of 2:1 as determined by nmr spectroscopy (see above).

Fractional crystallization of the mixture of 3,5-dinitrobenzoates from *n*-hexane afforded as the least soluble isomer the 4*S*,8*S* ester, mp 94–96°, $[\alpha]^{25}D$ −34.0° (*c* 3.27, $CHCl_3$), in 35% yield.

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.93; H, 5.93; N, 8.01.

Hydrolysis of this diastereoisomeric ester gave (−)-(4*S*,8*S*)-*p*-menth-1-en-9-ol (**15a**): bp 70–78° (0.15 mm); $[\alpha]^{25}D$ −103.1° (*c* 4.79, benzene); $\nu_{max}^{CHCl_3}$ 3600 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, doublet, J = 6 Hz), 1.61 (3 H, singlet), 2.04 (1 H, singlet, hydroxyl proton), 3.3–3.7 (2 H, multiplet), and 5.36 (1 H, broad singlet); mass spectrum *m/e* 154 (M^+), 136, 121, 107, 94 (base peak), 79, and 68.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.68; H, 11.58.

(−)-(3*R*)-[4-Methyl-3-cyclohexen-(1*S*)-yl]butyronitrile. In the manner described above, the alcohol (43.3 g, 0.28 mole) afforded 83.8 g of tosylate: $\nu_{max}^{CHCl_3}$ 1600 and 1180 cm^{-1}; nmr ($CDCl_3$) δ 0.84 (3 H, doublet, J = 7 Hz), 1.58 (3 H, singlet), 2.41 (3 H, singlet), 3.90 (2 H, eight lines, AB pattern), 5.30 (1 H, broad singlet), and 7.31 and 7.77 (4 H, AB pattern); mass spectrum *m/e* 308 (M^+), 266, 173, 155, 136, 121, 107, and 94.

Anal. Calcd for $C_{17}H_{24}SO_3$: C, 66.21; H, 7.85; S, 10.38. Found: C, 66.29; H, 7.87; S, 9.76.

The tosylate (83.8 g, 0.272 mole) was converted to the nitrile as described for the preparation of **9**. Distillation afforded 38.0 g (83% yield based on alcohol **15a**) of pure nitrile: bp 76–84° (0.4 mm); $[\alpha]^{25}D$ −71.72° (*c* 0.83, benzene); $\nu_{max}^{CHCl_3}$ 2250 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, doublet, J = 7 Hz), 1.62 (3 H, singlet), 2.31 (2 H, multiplet), and 5.34 (1 H, broad singlet); and mass spectrum *m/e* 163 (M^+), 148, 131, 123, 105, 95 (base peak), 81, and 68.

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.98; H, 10.60; N, 8.70.

(2*R*)-[4-Methyl-3-cyclohexen-(1*S*)-yl]-6-methylheptan-4-one (16). The nitrile (38.0 g, 0.235 mole) was converted to the ketone **16** by treatment with isobutyllithium as described above for **10**. Distillation gave 39.3 g (76% yield) of pure **16**: bp 80–92° (0.15 mm); $[\alpha]^{25}D$ −80.34° (*c* 1.06, benzene); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.78–0.90 (9 H), 1.60 (3 H, singlet), and 5.33 (1 H, broad singlet); mass spectrum *m/e* 222 (M^+), 205, 189, 165, 147, 127 (base peak), 122, 119, 105, and 93.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.75; H, 11.44.

(−)-(4*S*)-[1(*R*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic Acid Methyl Ester [(−)-Juvabione (3a)]. An 18.0-g sample of (−)-ketone **16** in 360 ml of dry pyridine containing 270 mg of hematoporphyrin was irradiated as described above. Reduction of the crude mixture of hydroperoxides gave 20.1 g of a mixture of secondary and tertiary alcohols, which was oxidized without further purification as described for **11–13**. After the work-up, the crude keto aldehyde was separated from the other oxidation products by shaking overnight with 11.6 g of sodium bicarbonate, 16.3 g of sodium sulfite, and 100 ml of ice water. The mixture was diluted with water and extracted with ether. The aqueous phase was made basic with 10% sodium hydroxide and then extracted with ether. These latter extracts were washed with water and dried with anhydrous sodium sulfate. Evaporation of the solvent afforded 4.1 g of a crude mixture which contained approximately 25% of the desired keto aldehyde according to vpc. The mixture was converted to (−)-juvabione (**3a**) without further purification, as follows.

The crude keto aldehyde (4.1 g) was dissolved in 15 ml of ethanol and solutions of 2.0 g of silver nitrate in 4 ml of water and 2.0 g of sodium hydroxide in 35 ml of water were added. The procedure was the same as that described above. The crude (−)-todomatuic acid (1.2 g) obtained was dissolved in 20 ml of anhydrous ether and was treated with 24 ml of a 10% solution of diazomethane in ether. Following the usual work-up, the product was purified by column chromatography on activity III neutral alumina to give 675 mg of ester which was distilled at 130–140° (bath temperature) and 0.1 mm. The resulting pure (−)-juvabione (**3a**) (420 mg, 2% over-all yield from the ketone **16**) had $[\alpha]^{25}D$ −94.14° (*c* 0.64, benzene); $\nu_{max}^{CHCl_3}$ 1710, 1655, 1260, and 1085 cm^{-1}; nmr ($CDCl_3$) δ 0.86–0.90 (9 H), 3.69 (3 H, singlet), and 6.94 (1 H, broad singlet); mass spectrum *m/e* 266 (M^+), 234, 167, and 134 (base peak).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.92; H, 9.89.

(−)-**Todomatuic Acid (3b).** A 100-mg sample of (−)-juvabione (**3a**) was hydrolyzed to (−)-todomatuic acid according to the procedure and conditions used in the preparation of (+)-todomatuic acid (see above). After recrystallization from pentane, the product (40 mg) had mp 64–66°. The ord spectrum of this material was (*c* 0.220, ethanol, 23°) $[\phi]_{700}$ −165°, $[\phi]_{589}$ −229°, $[\phi]_{299}$ −2347°, $[\phi]_{274}$ −1259°, $[\phi]_{228}$ −15,457°, $[\phi]_{207}$ 0°, and $[\phi]_{200}$ +3435°; cd (*c* 0.00873 *M*, ethanol, 23°) $[\theta]_{324}$ 0, $[\theta]_{286}$ −2192, $[\theta]_{260}$ −1209, $[\theta]_{214}$ −18,900, and $[\theta]_{192}$ 0.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.67; H, 9.57.

The *S*-benzylisothiuronium salt[37] of (−)-todomatuic acid had mp 168–171° (lit.[8] mp 162°) after two recrystallizations from ethanol. On admixture with the salt of (+)-epitodomatuic acid (see below), the melting point (164–167°) was depressed.

(4*R*,8*S*)-*p*-Menth-1-en-9-ol (8a). After removal of the less soluble (4*R*,8*R*)-3,5-dinitrobenzoate (see above), the mother liquors yielded the pure more soluble 4*R*,8*S* diastereoisomer in 4% yield upon repeated crystallization from hexane. The progress of the separation was monitored by 100-MHz nmr spectroscopy; the chemical shift of the methyl doublet due to the protons at C-10 occurred at δ 1.05 (*J* = 6.5 Hz) for the 4*R*,8*S* compound **8b**. Fractions enriched in the lower field doublet were recrystallized from hexane until less than 10% of the higher field doublet was present. The pure 4*R*,8*S* diastereoisomer **8b** had mp 70–71°, $[\alpha]^{25}D$ +41.85° (*c* 0.965, chloroform) (lit.[16] mp 70–71°, $[\alpha]^{20}D$ +28° ($CHCl_3$)).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.79; H, 5.89; N, 7.99.

Hydrolysis of the pure ester afforded in 93% yield (4*R*,8*S*)-*p*-menth-1-en-9-ol (**8a**): bp 75–82° (0.25 mm); $[\alpha]^{25}D$ +97.27° (*c* 1.033, chloroform), $[\alpha]^{25}D$ +98° (neat, d_{20} 0.9420[16]) (lit.[16] $\alpha^{20}D$ +82°); nmr ($CDCl_3$) δ 0.91 (3 H, doublet, *J* = 6 Hz), 1.63 (3 H, singlet), 3.53 (2 H, multiplet), and 5.35 (1 H, broad singlet).

(+)-(3*R*)-[4-Methyl-3-cyclohexen-(1*R*)-yl]butyronitrile. (+)-(4*R*,8*S*)-*p*-Menth-1-en-9-ol (**8a**) (7.0 g, 0.0455 mole, $[\alpha]^{25}D$ +98°) was treated with 17.3 g (0.091 mole) of *p*-toluenesulfonyl chloride as described above to give 14.5 g of tosylate: $[\alpha]^{25}D$ +35.42° (*c* 0.514, benzene); $\nu_{max}^{CHCl_3}$ 1600 and 1180 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, doublet, *J* = 6.5 Hz), 1.60 (3 H, singlet), 1.4–2.0 (8 H), 2.40 (3 H, singlet), 3.90 (2 H, seven lines), 5.28 (1 H, broad singlet), and 7.33 and 7.80 (4 H, A_2B_2 pattern).

The tosylate was converted to the nitrile with sodium cyanide in anhydrous dimethyl sulfoxide according to the above procedure. Distillation at 74–82° (0.2 mm) afforded 7.5 g (97% over-all yield) of pure nitrile: $[\alpha]^{25}D$ +76.37° (*c* 1.0345, benzene); $\nu_{max}^{CHCl_3}$ 2250 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (3 H, doublet, *J* = 7.0 Hz), 1.62 (3 H, singlet), 1.20–2.20 (8 H), 2.32 (2 H, multiplet), and 5.32 (1 H, broad singlet).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.95; H, 10.47; N, 8.42.

(+)-(2*R*)-[4-Methyl-3-cyclohexen-(1*R*)-yl]-6-methylheptan-4-one. The above nitrile (7.5 g, 0.046 mole) in 10 ml of anhydrous ether was added over a period of 1 hr at 0–2° to a solution of isobutyllithium (46.5 ml of 1.55 *M* solution in heptane, 0.072 mole) in 15 ml of anhydrous ether in the manner previously described. The work-up procedure afforded crude ketone which was purified by column chromatography on activity III neutral alumina and elution with hexane. Distillation at 92–95° (0.2 mm) afforded 5.0 g (50% yield) of pure ketone: $[\alpha]^{25}D$ +62.72° (*c* 1.017, benzene); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.86–0.89 (9 H), 1.61 (3 H, singlet), and 5.34 (1 H, broad singlet).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.95; H, 11.75.

(+)-(4*R*)-[1(*R*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic Acid Methyl Ester [(+)-Epijuvabione] (4a). A 5.0-g sample of the ketone described above in 120 ml of dry pyridine containing 85 mg of hematoporphyrin was irradiated for 46 hr with 3500-Å light in a Rayonet photochemical reactor while a stream of dry oxygen was passed through the solution. The resulting mixture of allylic hydroperoxides (7.0 g) was reduced to the mixture of allylic alcohols as described above. Without further purification this alcohol mixture was oxidized as described above for **11–13**. Separation of the oxidation mixture *via* the bisulfite adduct gave 1.2 g of crude (+)-(4*R*)-[1(*R*)-5-dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxaldehyde.

The crude keto aldehyde was further oxidized with basic silver oxide (as described above) to give 0.3 g of crude (+)-(4*R*)-[1(*R*)-5-dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic acid [(+)-epitodomatuic acid] (**4b**).

The crude acid in 5 ml of anhydrous ether was treated with 10 ml of a 10% solution of diazomethane in ether to give 0.3 g of crude ester which was purified by column chromatography on activity III neutral alumina and elution with 2:1 hexane–benzene. Distillation at 0.3 mm (bath temperature 150–160°) gave 110 mg of (+)-(4*R*)-[1-(*R*)-5-dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic acid methyl ester [(+)-epijuvabione] (**4a**): $[\alpha]^{25}D$ +65.09° (*c* 0.89, benzene); ν_{max} 1715, 1650, 1250, and 1080 cm^{-1}; λ_{max}^{EtOH} mμ (ε) 218 (10,270); nmr ($CDCl_3$) δ 0.78–0.88 (9 H), 3.70 (3 H, singlet), and 6.90 (1 H, broad singlet); mass spectrum *m/e* 266 (M^+), 234, 206, 177, 167, and 134 (base peak). The ord and cd spectra are shown in Figures 3 and 4.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.78; H, 9.55.

(+)-(4*R*)-[1(*R*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic Acid [(+)-Epitodomatuic Acid] S-Benzylisothiouronium Salt. A 24-mg sample of (+)-epijuvabione (**4a**) was hydrolyzed with 10% aqueous KOH to give (+)-epitodomatuic acid (**4b**) as a waxlike solid, which could not be obtained in well crystalline form. The acid **4b** was converted to the S-benzylisothiuronium salt,[37] which had mp 168.5–170° (lit.[8] mp 162°) after two recrystallizations from ethanol. On admixture with the S-benzylisothiuronium salt of (−)-todomatuic acid (**3b**) (see above), the melting point (164–167°) was depressed.

(−)-(4*S*,8*R*)-*p*-Menth-1-en-9-ol (17a). After removal of the less soluble (4*S*,8*S*) 3,5-dinitrobenzoate **15b** by fractional crystallization, the more soluble 4*S*,8*R* diastereoisomer **17b** (15.8 g, 3%) was obtained in the manner described above after repeated crystallization from *n*-hexane. This ester had mp 72–73°; $[\alpha]^{25}D$ −39.91° (*c* 1.152, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.51; H, 5.91; N, 8.04.

Hydrolysis of the above ester afforded 5.8 g (84%) of (−)-(4*S*,8*R*)-*p*-menth-1-en-9-ol (**17a**): bp 75–80° (0.2 mm); $[\alpha]^{25}D$ −94.0° (*c* 0.92, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3625 and 3450 cm^{-1}; nmr ($CDCl_3$) δ 0.92 (3 H, doublet, *J* = 6 Hz), 1.63 (3 H, singlet), 3.52 (2 H, eight lines), and 5.35 (1 H, broad singlet).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 78.11; H, 11.98.

(−)-(3*S*)-[4-Methyl-3-cyclohexene-(1*S*)-yl]butyronitrile. The alcohol **17a** (5.5 g, 0.036 mole) was converted into the tosylate: $[\alpha]^{25}D$ −41.13° (*c* 1.29, benzene); $\nu_{max}^{CHCl_3}$ 1600, 1360, and 1180 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3 H, doublet, *J* = 6.5 Hz), 1.59 (3 H, singlet), 2.42 (3 H, singlet), 3.90 (2 H, eight lines), 5.28 (1 H, broad singlet), and 7.32 and 7.67 (4 H, A_2B_2 pattern).

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.21; H, 7.85; S, 10.40. Found: C, 66.52; H, 7.93; S, 10.19.

The tosylate (11.0 g, 0.036 mole) was stirred with 2.65 g (0.053 mole) of sodium cyanide in 110 ml of anhydrous dimethyl sulfoxide as described above. Distillation afforded 5.5 g (93% over-all yield) of the nitrile: $[\alpha]^{25}D$ −75.70° (*c* 0.997, benzene); $\nu_{max}^{CHCl_3}$ 2250 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (3 H, doublet, *J* = 6.5 Hz), 1.63 (3 H, singlet), 2.30 (2 H, multiplet), and 5.34 (1 H, broad singlet).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.64; H, 10.43; N, 8.71.

(−)-(2*S*)-[4-Methyl-3-cyclohexen-(1*S*)-yl]-6-methylheptan-4-one. The above nitrile (5.5 g, 0.034 mole) in 7.5 ml of anhydrous ether was added to 32.2 ml of a 1.55 *M* solution of isobutyllithium in heptane at 0°. Work-up as described above furnished 5.2 g (70% yield) of the ketone: bp 85–95° (0.25 mm); $[\alpha]^{25}D$ −61.89° (*c* 0.724, benzene); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.78–0.90 (9 H), 1.63 (3 H, singlet), and 5.35 (1 H, broad singlet).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.95; H, 11.91.

(−)-(4*S*)-[1(*S*)-5-Dimethyl-3-oxohexyl]-1-cyclohexene-1-carboxylic Acid Methyl Ester [(−)-Epijuvabione] (5). The above ketone (5.2 g) was irradiated as described above and the resulting hydroperoxides were reduced with potassium iodide in methanol–ether–acetic acid. The mixture of secondary and tertiary alcohols obtained (5.5 g) was oxidized to the aldehyde in the manner described and the resulting crude ketoaldehyde was purified *via* the bisulfite adduct.

Further oxidation of the aldehyde with basic silver oxide afforded 0.25 g of crude (−)-epitodomatuic acid, which was dissolved in 5 ml of anhydrous diethyl ether and treated with 5 ml of a 10% solution of diazomethane in ether. After work-up as described above, the crude product was distilled at 150–160° (bath temperature) and 0.25 mm to give 90 mg of pure (−)-epijuvabione (**5**),

(37) J. J. Donleavy, *J. Amer. Chem. Soc.*, **58**, 1004 (1936).

$[\alpha]^{25}D$ −64.45° (*c* 0.568, benzene), $\nu_{max}^{CCl_4}$ 1710, 1650, 1250, and 1080 cm^{-1}; λ_{max}^{EtOH} mμ (ε) 218 (10,630); nmr ($CDCl_3$) δ 0.83–0.93 (9 H), 3.70 (3 H, singlet), and 6.93 (1 H, broad singlet); mass spectrum *m/e* 266 (M^+), 234, 167, and 134 (base peak). The ord and cd spectra are shown in Figures 3 and 4.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.21; H, 10.13.

(2*R*)-[1-Methyl-7-oxabicyclo[4.1.0]heptan-(4*R*)-yl]-6-methyl-4-heptanone (20). (2*R*)-[4-Methyl-3-cyclohexen-(1*R*)-yl]-6-methylheptan-4-one (**10**, 6.65 g, 0.03 mole) in 45 ml of dichloromethane was placed in a 500-ml flask, fitted with magnetic stirrer, thermometer, condenser, and dropping funnel. *m*-Chloroperbenzoic acid (6.4 g, 0.033 mole) in 90 ml of dichloromethane was added dropwise at 23–25° over a 30-min period. The reaction mixture was allowed to stir at this temperature for 2 hr. The excess *m*-chloroperbenzoic acid was destroyed with 35 ml of 10% sodium sulfite solution until a negative test was obtained with starch–iodide paper. The mixture was extracted with three 50-ml portions of dichloromethane and the extracts were washed with 5% sodium bicarbonate and water, and dried with anhydrous sodium sulfate. Evaporation of the solvent and distillation at 104–106° (0.2 mm) gave 5.1 g of epoxide **20**: $[\alpha]^{25}D$ +47.85° (*c* 1.30, benzene); $\nu_{max}^{CHCl_3}$ 1710 and 840 cm^{-1}; nmr ($CDCl_3$) δ 0.80–0.95 (9 H), 1.30 (3 H, singlet), 2.96 and 3.05 (broad singlets, ratio 1:2, 1 H); and mass spectrum *m/e* 238 (M^+), 138 (base peak), 127, 111, 95, 85, and 57.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.23; H, 11.26.

(+)-Juvabione from Epoxide 20. To an ice-cold solution of diethylamine (4.9 g, 0.067 mole) in 75 ml of dry tetrahydrofuran was added 45.0 ml of a 1.48 *M* solution of *n*-butyllithium in hexane. The entire reaction was carried out in an atmosphere of nitrogen. The reaction mixture was stirred for 30 min and then a solution of 4.1 g (0.0167 mole) of epoxide **20** in 35 ml of dry tetrahydrofuran was added. The mixture was heated to reflux for 3 hr, cooled, and poured into 100 ml of ice water. The mixture was saturated with sodium chloride and the layers were separated. The aqueous layer was extracted with ether and the ether extracts were washed with saturated sodium chloride solution and dried with anhydrous sodium sulfate. Evaporation of the solvent gave 3.9 g of an alcohol mixture containing the desired product **12**.

The alcohol mixture was oxidized with sodium dichromate as described previously. The crude keto aldehyde **14** so obtained was further oxidized to (+)-todomatuic acid with basic silver oxide. The crude (+)-todomatuic acid (0.15 g) was converted to the ester by treatment with an ethereal solution of diazomethane. Column chromatography and distillation at 150–160° (bath temperature) and 0.25 mm gave 20 mg of (+)-juvabione, $[\alpha]^{25}D$ +80° (*c* 1.0, benzene). The ord and cd spectra were identical with those of the natural material.

Acknowledgment. We thank the Physical Chemistry Department, Hoffmann-La Roche Inc., directed by Dr. P. Bommer, for spectral measurements and microanalyses. We are grateful to Professor M. Matsui, University of Tokyo, for samples of (±)-juvabione and (±)-todomatuic acid.

Cyclization of Tryptophan and Tryptamine Derivatives to 2,3-Dihydropyrrolo[2,3-*b*]indoles

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Received July 7, 1969

Abstract: N-Acetylated derivatives of tryptophan and tryptamine (**1–4**) in phosphate buffer at pH 9 with N-bromosuccinimide (NBS) or in methylene chloride containing triethylamine with *t*-butyl hypochlorite give acid-labile tricyclic dihydropyrrolo[2,3-*b*]indoles (**5–8**) characterized by λ_{max} 308 mμ. These cyclizations presumably occur *via* β-haloindolenines, which ring close to β-haloindolines. On standing, the products arise by spontaneous or base-catalyzed dehydrohalogenation. Excess *t*-butyl hypochlorite converts the 2,3-dihydropyrroloindoles to *methyl* and *ethyl* 1-*acetyl*-3*a*-*chloro*-2,3,3*a*,8*a*-*tetrahydropyrrolo*[3,2-*b*]*indolenine*-2-*carboxylate* which on refluxing in aqueous methanol (or ethanol) gave *methyl* (and *ethyl*) *pyrrolo*[2,3-*b*]*indole*-2-*carboxylates* ($\lambda\lambda_{max}$ 332, 272 mμ) as the first synthetic representatives of "anhydrodethiosporidesmin," the dehydration and desulfurization product from sporidesmin. The tetracyclic system present in the sporidesmins was synthetically approached by *t*-BuOCl oxidation of N-methyl-L-alanyl-L-tryptophan diketopiperazine.

N-Acetyl-L-tryptophan ethyl ester (**1**) or N-acetyl-L-tryptophanamide (**3**) with 1 equiv of NBS in aqueous buffers at pH 8–9 yields a product with strong absorption at 308 mμ which is stable above pH 7, but below this pH[2] rapidly changes to that of an oxindole (λ_{max} 250 mμ). The new chromophore was not observed with skatole, indole-3-propionic acid, or N-acetyltryptophan, indicating some participation reaction of the indole side chain. The present work clarifies the structure and transformations of the products with the unusual absorption at 308 mμ.[3]

The minimum requirement for the formation of products possessing the new chromophore was a 3-(2-acetamidoethyl) side chain or, in the case of tryptophan derivatives, a carboxyl-blocked, N_α-acetylated derivative. N-Benzyloxycarbonyltryptophan, N-trifluoroacetyltryptophan, tryptophan methyl ester, N-acetylhomotryptamine, and tryptamine all failed to produce the chromophore with the addition of 1 equiv of NBS. N-Acetyltryptamine (**4**) was found to produce the chromophore, but at a rate much slower than **1** or **2**; about 15 min were required for the development of maximum intensity.

(1) Associate in the visiting program of the U.S. Public Health Service, 1967–1968.

(2) N. M. Green and B. Witkop, *Trans. N. Y. Acad. Sci., Ser. II*, **26**, 659 (1964).

(3) *Cf.* M. Ohno, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 6521 (1968).