The Total Synthesis of (±)-Hinesol

JAMES A. MARSHALL* AND STEPHEN F. BRADY

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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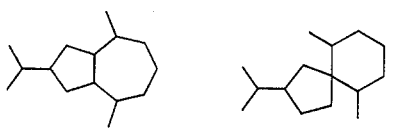
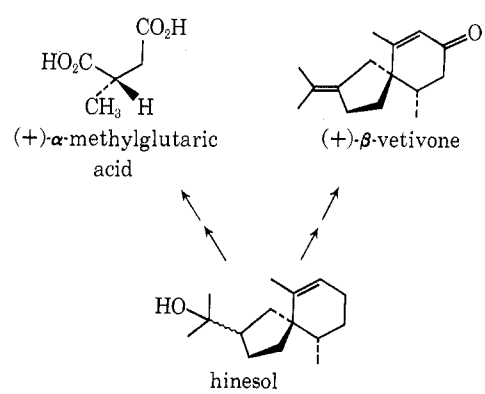
The total synthesis of (±)-hinesol was effected by a route which defines the stereochemistry of that substance. The known 6,10-ethano-1,3-hexal-2-one (**9**) was methylated with lithium dimethylcopper to give a mixture of 4-methyl adducts in which the *cis*-methyl/ethano isomer (**10b**) predominated. The minor *trans*-methyl/ethano isomer (**10a**) was converted to racemic hinesol through transposition of the 1(9)-en-2-one system to the related 8-en-7-one system. The 7,9-diol monomesylate **29** obtained from this enone underwent fragmentation on base treatment to generate the requisite spiro[4.5]decane ring system **30**. Addition of methyllithium, dehydration of the derived tertiary alcohol intermediate **34**, and conversion of the vinylic grouping of the fragmentation product to an isopropyl alcohol moiety completed the synthesis.

The recognition that the class of sesquiterpenes once regarded as derivatives of decahydrovetivazulene (I) actually possess the spiro[4.5]decane skeleton II[1] has stimulated interest in synthetic approaches to the latter carbon framework.[2] Perhaps the most subtle aspect of the synthetic problem posed by a spiro[4.5]decane such as hinesol is the need for unambiguous stereochemical control between substituents in the two carbocyclic rings. It was our interest in this stereochemical problem that prompted the synthetic work described in this report.



I II

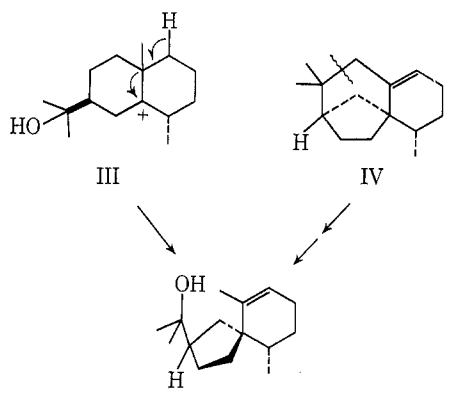
Before synthetic strategy could be developed we had to deduce a probable stereochemical assignment for hinesol. The relative and absolute stereochemistry of the cyclohexane ring substituents could be assigned on the basis of (1) a chemical correlation between hinesol and β-vetivone,[3] and (2) the degradation of hinesol to (+)-α-methylglutaric acid.[4] This left the orientation of the isopropyl alcohol substituent as the only uncertain structural feature.



(+)-α-methylglutaric acid (+)-β-vetivone

hinesol

Consideration of probable biogenetic routes to hinesol involving rearrangement of the eudesmol-related cation III[5] focused our attention on the stereoisomer depicted below wherein the isopropyl chain and the vinylic carbon of the cyclohexene ring are cis related. This proposed relationship suggested a synthetic approach in which these centers would initially be joined through a carbocyclic structure such as IV. Cleavage of the indicated bond would then generate the postulated hinesol framework with substituents appropriate for further elaboration to the natural product itself.



III IV

hinesol

In view of the foregoing considerations we selected the tricyclic dienone **9** as our starting material. This substance had been prepared previously through an ingenious sequence involving, as the key step, base-initiated cyclization of the phenol tosylate **8**.[6] Our route to dienone **9** (Scheme I) differed only in the use of 6-methoxy-1-tetralone (**1**) as the starting point rather than the less available isomeric 6-methoxy-2-tetralone employed by Masamune. Condensation of ketone **1** with glyoxylic acid, generated by *in situ* periodate cleavage of tartaric acid,[7] afforded the keto acid **2**. Clemmensen reduction effected both removal of the keto function and saturation of the ylidine double bond to give the acid **3**. The subsequent steps leading to dienone **9** were effected along the lines described earlier by Masamune.[6]

Methylation of dienone **9** with lithium dimethylcopper in ether[8] proceeded in high yield *via* attack at the less substituted double bond to give a 1:3 mixture of stereoisomers **10a** and **10b** (Scheme II). Direct anal-

* To whom correspondence should be addressed.

(1) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Org. Chem.*, **35**, 186 (1970); J. A. Marshall and P. C. Johnson, *ibid.*, **35**, 192 (1970).

(2) A. P. Johnson, "An Approach to the Total Synthesis of (±)-β-Vetivone," presented at the International Symposium on Synthetic Methods and Rearrangements in Alicyclic Chemistry, Oxford, July 22–24, 1969, Abstracts, p 13. Private communication with P. Deslongchamps (Sherbrooke), G. Stork (Columbia), and W. Reusch (Michigan State).

(3) I. Yosioka and T. Kumura, *Chem. Pharm. Bull. Jap.*, **13**, 1430 (1965).

(4) W. Z. Chow, O. Motl, and F. Šorm, *Collect. Czech. Chem. Commun.*, **27**, 1914 (1962).

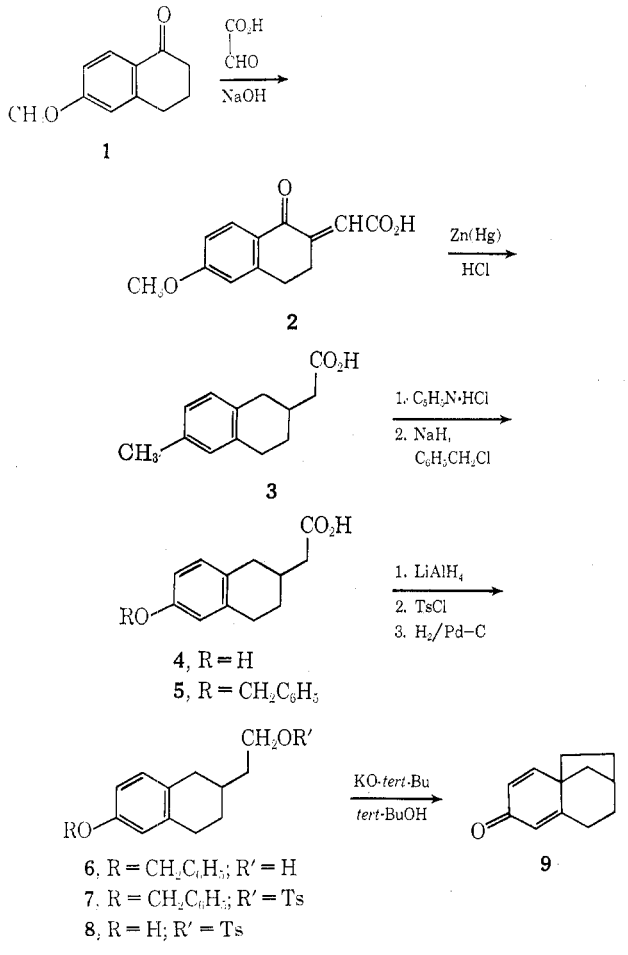
(5) *Cf.* K. R. Varma, M. L. Maheshwari, and S C. Bhattacharyya, *Tetrahedron*, **21**, 115 (1965); D. F. MacSweeney, R. Ramage, and A. Sattar, *Tetrahedron Lett.*, 557 (1970).

(6) S. Masamune, *J. Amer. Chem. Soc.*, **83**, 1009 (1961).

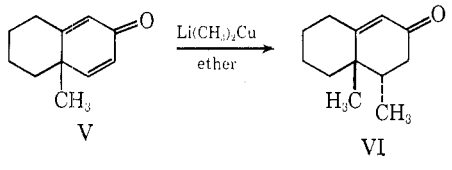
(7) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958).

(8) *Cf.* H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966). For pertinent stereochemical studies, see J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966).

SCHEME I



ysis of this mixture proved difficult but the corresponding enol ether derivatives (**11**) could be readily prepared and separated *via* vapor phase chromatography. Initially we felt that by analogy with the dienone V → methylated enone VI conversion[9] likewise effected with ethereal lithium dimethylcopper, the methylation of die-



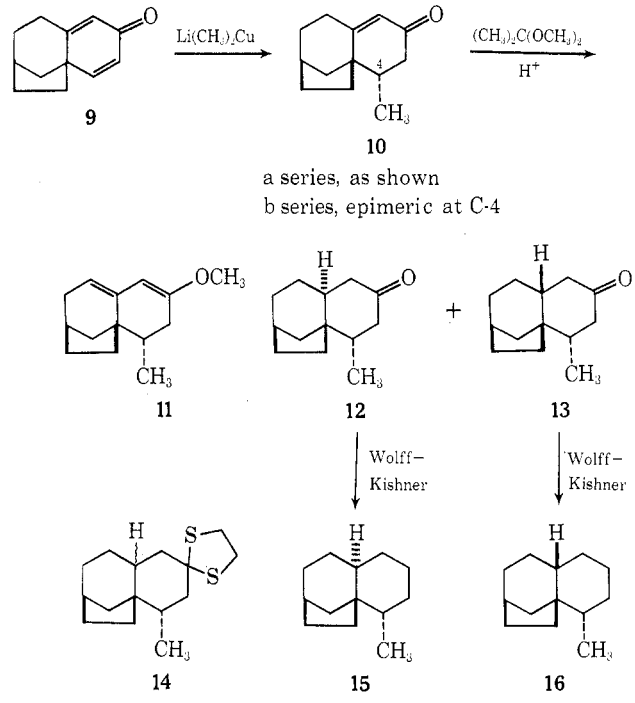
none **9** should lead predominantly to enone **10a**. We subsequently found (see below) that this was not the case. After a number of unsuccessful attempts to enhance the proportion of the desired trans isomer **10a** in this reaction through temperature variation, we discovered that the use of dioxane as a cosolvent led to a 2:3 ratio of adducts **10a** and **10b**. In pure dioxane only 1,2 addition to dienone **9** took place.

Attempts to ascertain the stereochemistry of the enones **10a** and **10b** through reduction experiments were unsuccessful. Treatment of the 1:3 mixture of enones **10a** and **10b** with lithium in ammonia–ethanol followed by Jones oxidation[10] of the resulting alcoholic product afforded a mixture of ketones. The major product, se-

(9) T. M. Warne, Jr., Ph.D. Thesis, Northwestern University, June 1970 p 40.

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

SCHEME II



cured *via* the crystalline thioketal derivative **14b** (cis-ring fusion), was reduced to a hydrocarbon later shown (see below) to be the cis-fused compound **16b**. A careful product analysis indicated that a 10:1 mixture of the cis- and trans-fused products **13b** and **12b** had been produced in the aforementioned Birch reduction of enone **10b**.

Catalytic hydrogenation of the 1:3 mixture of enones **10a** and **10b** over palladium on carbon afforded a mixture of ketones **12** and **13**. The major isomer **12b** was purified *via* the crystalline thioketal derivative **14b** (trans-ring fusion). The material thereby secured afforded, *via* Wolff–Kishner reduction, a hydrocarbon later shown (see below) to be the trans-fused compound **15b**. Thus the catalytic hydrogenation of enone **10b** affords mainly the trans isomer **12b**, whereas Birch reduction gives rise predominantly to the cis isomer **13b**. This behavior is exactly the opposite of that observed in chemical and catalytic reductions of related bicyclic octalones such as VI.[11,12]

The stereochemistry of enones **10a** and **10b** was deduced unequivocally on the basis of chemical transformations *en route* to hinesol (Scheme III). Deconjugation–reduction of the 1:3 enone mixture either by treatment with sodium hydride followed by acidification with sodium dihydrogen phosphate[13] and reduction of the resulting β,γ-unsaturated ketone with lithium aluminum hydride, or *via* reduction of the related enol acetate mixture with ethanolic sodium borohydride,[14] afforded the homoallylic alcohols **17a** and **17b** (mixture of C-2 and C-4 epimers). The major alcohol **17b** could be isolated by preparative vapor phase chromatography. This alcohol yielded a crystalline *p*-bromophenylurethane derivative **19b** whose single crystal X-ray anal-

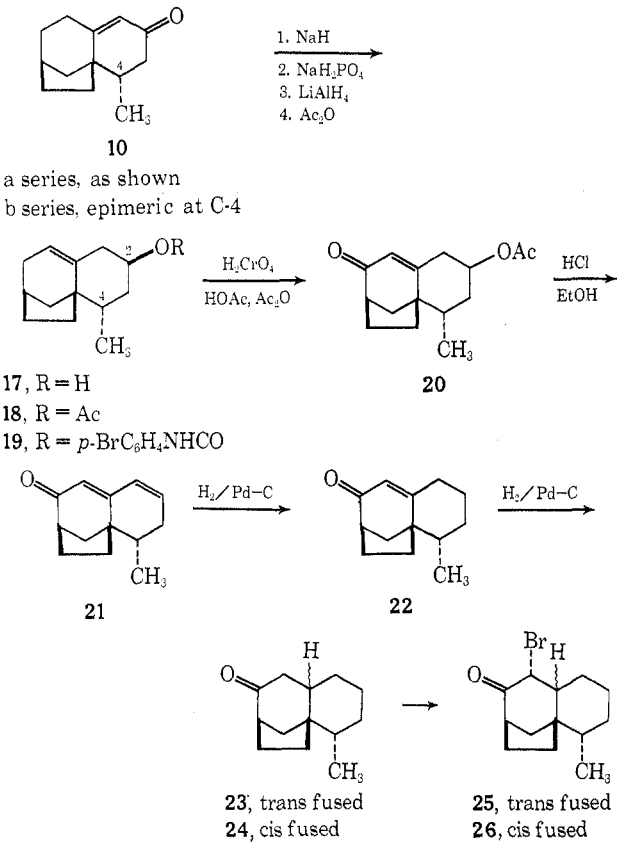
(11) *Cf.* H. J. E. Lowenthal, *Tetrahedron*, **6**, 269 (1959).

(12) *Cf.* G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

(13) A. G. Armour, G. Büchi, A. Eschenmoser, and A. Storm, *Helv. Chim. Acta*, **42**, 2233 (1959).

(14) *Cf.* W. G. Dauben and J. F. Eastham, *J. Amer. Chem. Soc.*, **73**, 4463 (1951).

SCHEME III



ysis[15] confirmed the stereochemical assignment deduced on chemical grounds (see below).

Acetylation of the above-described mixture of homoallylic alcohols followed by allylic oxidation with chromic acid[16] gave the acetoxy enone mixture **20** (mixture of acetoxyl stereoisomers). Dehydroacetylation with ethanolic hydrochloric acid afforded the isomeric dienones **21a** and **21b** as a 28:72 mixture. The composition of this latter mixture closely resembled that of the starting enone mixture (25% **10a**, 75% **10b**).

The dienones **21a** and **21b** could be readily separated *via* preparative vapor phase chromatography. The major epimer (**21b**) afforded essentially one product (**23b**) upon hydrogenation over Pd–C, whereas the minor dienone epimer (**21a**) gave rise to a roughly 70:30 mixture of ring fusion isomers (**23a** and **24a**) under comparable conditions. Molecular models indicate that the bottom face of dienone **21b** is relatively accessible to approach by a catalyst surface. Hence catalytic hydrogenation might reasonably be expected to produce the trans-fused tetrahydro derivative **23b**. Dienone **21a**, on the other hand, has an axially oriented methyl group which could partially block the approach of a catalyst surface to its bottom face. Therefore, this dienone would be more likely to afford a mixture of tetrahydro stereoisomers upon catalytic hydrogenation. In view of the foregoing considerations dienone **21b** might also be expected to hydrogenate at a faster rate than dienone **21a**. This was indeed the case. Partial hydrogenation of a mixture of dienones **21a** and **21b** over palladium–strontium carbonate in benzene yielded a mixture of the tetrahydro derivative **23b** and the dihydro derivative **22a** which could be separated by column elution chromatography. This method was the preferred one for separating the epimeric ketones and obtaining the enone **22a**, a desired intermediate in the hinesol synthesis scheme.

Evidence for the stereochemistry of the ring fusion of ketones **23b**, **23a**, and **24a** was secured through spectral analysis of the α-bromo ketone derivatives. The α-bromo ketone (**25b**) derived from the hydrogenation product (**23b**) of dienone **21b** exhibited an infrared band at 5.79 μ (equatorial α-bromocyclohexanone[17]) and a doublet (J = 11 Hz) at 4.38 ppm in the nmr spectrum indicative of axial–axial α-H,β-H coupling.[18] The mixture of bromo ketones (**25a** and **26a**) derived from the hydrogenation product of dienone **21a** likewise showed an infrared band at 5.79 μ indicative of an equatorial α-bromocyclohexanone.[17] However, in this case two doublets at 4.26 (J = 11 Hz) and 5.12 ppm (J = 7 Hz) in the ratio 3:1 were observed indicating a mixture of the trans- and cis-fused isomers **25a** and **26a**.[18] Dehydrobromination of this mixture afforded the enone **22a**, thus confirming its isomeric nature.

Having established the stereochemistry of ketone **23b** we could now clarify the stereochemical consequences of our reduction experiments on enone **10b** (Scheme II). This was accomplished through Wolff–Kishner reduction of ketone **23b** to the hydrocarbon **15b**. This material was identical with the hydrocarbon derived from the hydrogenation product of enone **10b** and differed from the hydrocarbon **16b** secured from the Birch reduction product of this enone.

We examined a number of short reaction sequences for converting enone **22a** to hinesol (**38**), but none of these appeared sufficiently promising to warrant discussion. The sequence which finally evolved from our studies (Scheme IV) could be effected relatively efficiently despite its length, since all but two of the steps [**29** → **30** (64% yield) and **34** → **35** (*ca.* 70% yield of the β isomer)] could be accomplished in 80–90% yield.

The alcohol **27**, obtained upon reduction of ketone **22a** with lithium tri-*tert*-butoxyaluminohydride, afforded the crystalline diol **28** through reduction of the derived epoxide with lithium aluminum hydride. The stereochemistry of this diol is assigned on the expectation of a cis directing effect by the hydroxyl function in the epoxidation reaction.[19] The hydroxyl stereochemistry, in turn, can be deduced from a consideration of steric approach control in enone **22a**.[20] This point is of major concern with respect to the subsequent ring cleavage reaction (**29** → **30**) since the isomeric cis (diaxial) diol monomethanesulfonate would not be able to attain the proper stereochemical alignment for this reaction.[21] In any case, the methanesulfonate derivative **29** of diol **28** did in fact fragment upon treatment with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, affording the unsaturated ketone **30**. The stereochemistry of the newly formed spiro[4.5]decanone **30** is defined by the

(15) We are indebted to Professor R. E. Ireland and Dr. J. Bordner for carrying out this analysis.

(16) *Cf.* W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

(17) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *ibid.*, **74**, 2828 (1952).

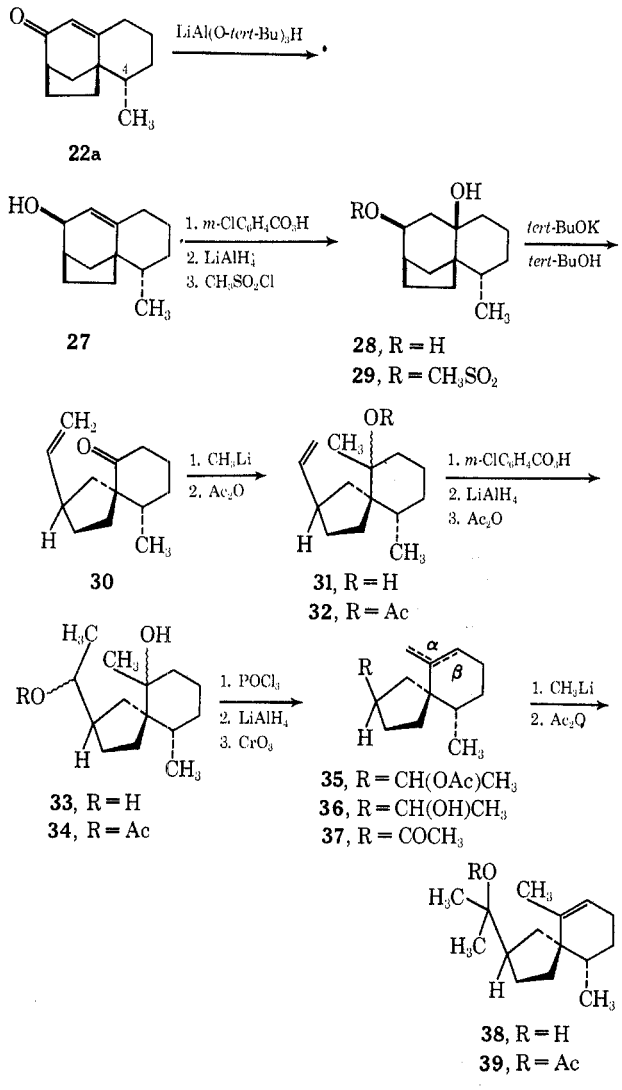
(18) *Cf.* W. S. Johnson and K. L. Williamson, *ibid.*, **83**, 4623 (1961).

(19) *Cf.* H. B. Henbest and R. A. Wilson, *J. Chem. Soc.*, 1958 (1957).

(20) *Cf.* J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965); J. A. Marshall and R. D. Carroll, *ibid.*, **30**, 2748 (1965); M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968).

(21) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).

SCHEME IV



foregoing synthetic pathway. Thus the only remaining task in our synthesis was to introduce the requisite substituents at the vinylic and ketonic centers of this intermediate.

To that end, addition of methyllithium followed by acetylation afforded the unsaturated acetate **32**. The acetylation step was found necessary to prevent participation of the tertiary alcohol function in the next step, epoxidation of the vinyl grouping. This reaction gave rise to an apparent tetrahydrofuran derivative when carried out on alcohol **31**.[22] The unsaturated acetate, however, was epoxidized smoothly with *m*-chloroperoxybenzoic acid and subsequent reduction with lithium aluminum hydride gave the diol **33**. The monoacetate derivative **34** afforded a 3:1 mixture of the endocyclic (β) and exocyclic (α) olefins **35** upon dehydration with phosphorous oxychloride in pyridine. This mixture was treated directly with lithium aluminum hydride to remove the acetyl grouping, and the resulting alcohol **36** was oxidized with Jones reagent[10] to give the ketone **37**, likewise a mixture of double bond isomers.

Addition of methyllithium to ketone **37** (mixture of α and β double bond isomers) afforded a mixture of hinesol (**38**) and the corresponding exocyclic methylene isomer. These compounds were readily separated *via* chromatography of their acetate derivatives on silver nitrate impregnated silica gel. The major isomer thereby obtained was identical with authentic hinesol acetate. Cleavage of the synthetic acetate **39** with ethereal lithium aluminum hydride yielded racemic hinesol (**38**) identified by spectral and chromatographic comparison with natural hinesol.[23]

(22) *Cf.* J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968), and references therein.

Experimental Section[24]

1-Oxo-6-methoxy-1,2,3,4-tetrahyro-2-naphthylideneacetic Acid (2).—The procedure was adapted from that reported by Newman, *et al.*,[7] for condensation of α-tetralone with ethyl glyoxylate. Accordingly, an ice-cooled solution of 62.2 g of sodium metaperiodate in 340 ml of water was treated with 5.7 ml of concentrated sulfuric acid, followed by a solution of 43.2 g of (−)-tartaric acid in 85 ml of water over a period of 15 min. After the addition the ice bath was removed, and the solution was stirred for 30 min. Then, in order, were added 50.0 g (0.284 mol) of 6-methoxy-1-tetralone, a solution of 43.5 g of NaOH in 770 ml of water, and 170 ml of absolute ethanol. A white precipitate appeared almost immediately. The mixture was stirred for 17 hr at 20–25°, and then heated with a steam bath to 65–70° for 40 min. The cooled mixture was diluted with enough water to dissolve the precipitated salts (*ca.* 1500 ml), and the resulting basic solution was washed once with 800 ml of ether and then acidified with 3 *N* HCl in a beaker. The resulting pale yellow microcrystalline precipitate (45.8 g, 70%)) was isolated by suction filtration and air-dried overnight. A small sample of crude acid from a previous run, mp 177–180° dec, upon recrystallization twice from ethanol–water, afforded pale orange-yellow needles, mp 177° dec.

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.20; H, 5.33.

6-Methoxy-1,2,3,4-tetrahydro-2-naphthylacetic Acid (3).—The procedure of Newman, *et al.*,[7] was followed. A mixture of 38.5 g of mercuric chloride, 570 ml of water, and 19.1 ml of concentrated HCl in a flask equipped with a Hirschberg stirrer was treated portionwise with 380 g of mossy Zn and stirred for 20 min. The aqueous solution was then removed *via* pipet from the resulting Zn amalgam. To this ice-cooled amalgam were added, in order, 115 ml of water, 460 ml of concentrated HCl (*slowly*!), 570 ml of toluene, 38 ml of glacial acetic acid, and finally, 45.7 g (0.197 mol) of naphthylideneacetic acid (**2**). The resulting three-phase mixture was heated under reflux for a total of 45 hr with 120 ml of concentrated HCl being added after 7 hr, 170 ml after 19 hr, and 170 ml after 31 hr. The cooled reaction mixture was diluted with 800 ml of aqueous NaCl and extracted twice with ether. The acidic product was extracted from the combined organic solvent fractions with 5% aqueous NaOH, from which it was isolated as a white solid after acidification. After drying overnight at 25° (0.03 mm), the product, mp 91.5–93.5° (lit.[6] mp 91–92°), amounted to 40.8 g (96% yield). A sample prepared by sublimation at 85–90° (0.03 mm) exhibited mp 93–94°.

6-Hydroxy-1,2,3,4-tetrahydro-2-naphthylacetic Acid (4).—The procedure for methoxyl cleavage was adapted from Sheehan, *et al.*[25] Thus, a sample of 20.8 g (0.095 mol) of the aforementioned naphthylacetic acid **3** (crude dry material) was fused under nitrogen[24a] with 80 g of pyridine hydrochloride [dried at 30° (0.05 mm) overnight]. After stirring (Teflon paddle stirrer) for 1.5 hr at 200–210°, the cooled mixture was treated with the minimum amount of water necessary to effect solution of all salts (*ca.* 120 ml). This light orange solution was poured into a beaker, and the desired product was precipitated by the addition of 800 ml of saturated NaCl followed by storage at 0° overnight. The precipitate was filtered, washed with ice–water, and dried *in vacuo*

(23) We are indebted to Professor Šorm for a sample of (−)-hinesol.

(24) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extraction with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(25) J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Amer. Chem. Soc.*, **79**, 147 (1957).

overnight affording 16.9 g (86%) of off-white crystals, mp 141–142°.

The crude sample obtained from another run was recrystallized from water to give white needles: mp 151.5–152°; λ_{max}^{KBr} 5.89 μ (CO); $\delta_{TMS}^{CCl_4}$ 6.5–7.0 ppm (aromatic H, multiplet), no signals beyond 7.0 ppm. An analytical sample was secured by sublimation at 140° (0.05 mm) as a white microcrystalline solid, mp 152–153°.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.19, H, 6.93.

6-Benzyloxy-1,2,3,4-tetrahydronaphthylacetic Acid (5).—A sample of 44.2 g (0.214 mol) of acid **4** in 950 ml of absolute ethanol under nitrogen was stirred vigorously during the addition of 21.1 g (equivalent to 0.440 mol of hydride) of 50% NaH in mineral oil, portionwise. Then 55 ml of benzyl chloride was added and the mixture was heated under reflux with stirring for 18 hr, during which time a white precipitate appeared. The slightly cooled mixture was treated with 230 ml of 20% aqueous NaOH and the solution was stirred for 2.5 hr at reflux to saponify any benzyl ester which might have formed. The cooled reaction mixture was diluted with 4 l. of water and was extracted three times with ether. Each extract was washed successively with 50% saturated brine, and the basic aqueous layers were combined and acidified with 4 *N* HCl to give a pale orange granular solid weighing 56.5 g (89% crude yield) after drying at 25° (0.05 mm): mp 92–95°; λ_{max}^{KBr} 5.90 (CO), 13.6, 14.35 μ (–$OCH_2C_6H_5$). Recrystallization of a small specimen twice from ethanol–water afforded white needles, mp 93.5–95°.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.18; H, 6.96.

Reduction of 6-Benzyloxy-1,2,3,4-tetrahydro-2-naphthylacetic Acid.—A solution of 33.1 g (0.112 mol) of the aforementioned acid **5** in 135 ml of dimethoxyethane (DME) was added slowly to a stirred mixture of 9.2 g of lithium aluminum hydride and 350 ml of DME under nitrogen. After completion of the addition the mixture was heated under reflux for 15 hr, cooled to 0°, and treated with 700 ml of ether and, slowly, with 40 ml of saturated sodium sulfate. After 1 hr the mixture was dried over anhydrous magnesium sulfate, whereupon filtration and solvent removal afforded 31.0 g (98% crude yield) of alcohol **6** after evacuation at 25° (0.1 mm). After standing overnight the material solidified, mp 54–56° (lit.[6] mp 61–62°). The sample of alcohol was used in subsequent steps without further purification.

Tosylation of Alcohol 6.—An ice-cold solution of 30.9 g (0.108 mol) of alcohol **6**, mp 54–56°, in 300 ml of dry pyridine was treated with a cold solution of 33.5 g of *p*-toluenesulfonyl chloride in 150 ml of pyridine. After 16 hr at 0–10° the reaction mixture was treated with 60 ml of water, stirred for 0.5 hr at 0°, and then processed[24b] after dilution with 1500 ml of water, affording 45.0 g (94% crude yield) of tosylate **7**, λ_{max}^{film} 7.35, 8.48 μ ($OSO_2C_7H_7$), which failed to crystallize upon standing at 0–10° overnight (lit.[6] mp 76–78°). The sample was used without further purification.

Hydrogenolysis of Benzyl Ether 7.—A solution of 45.0 g of the benzyl ether **7** in 600 ml of ethyl acetate was hydrogenated over 23 g of 5% palladium on carbon until the uptake of hydrogen had ceased (*ca.* 8 hr). The time required for complete uptake of hydrogen varied markedly from run to run, up to a maximum of about 24 hr. The solution was filtered through Supercel Hyflo, the solvent was removed at reduced pressure, and residual ethyl acetate was removed by addition of benzene and further evacuation at reduced pressure to give the phenol **8**, λ_{max}^{film} 2.90 μ (OH), which was used directly in the next step without further purification.

4a,6-Ethano-5,6,7,8-tetrahydro-2(4a)-naphthalenone (9).—The procedure described by Masamune[6] was employed. A solution of the crude phenol tosylate **8** (see previous experiment) in 4 l. of dry *tert*-butyl alcohol (*ca.* 0.025 *M*) was degassed under nitrogen and treated with 100 ml of 1.00 *N* KO-*tert*-Bu in *tert*-BuOH. The solution was vigorously stirred and heated under reflux for 8 hr, the reaction flask was then equipped for downward distillation, the *tert*-butyl alcohol was distilled until about 1 l. remained. The rest of the *tert*-BuOH was removed under aspiration pressure, and the product was isolated from the residue by addition of water and extraction with ether.[24b] A 2% aqueous sodium hydroxide wash was used to rid the crude product of any phenolic impurities. The orange liquid isolated upon removal of solvent was distilled to give a major fraction boiling at 100–103° (0.06 mm). The total material recovered amounted to 10.0 g (56% yield based on tosylate **8**) of dienone **9**, which solidified upon cooling, mp 33–35°.

Redistillation of a small sample at 90° at 0.03 mm (bulb-to-bulb) afforded an almost colorless oil, $n^{23}D$ 1.5764 (lit.[6] $n^{26}D$ 1.5738), which gave a crystalline semicarbazone, mp 222.5–224° (lit.[6] mp 222–224°).

Conjugate Methylation of Dienone 9. A. Reaction in Ether.—According to the procedure of House, *et al.*,[8] a solution of lithium dimethylcopper was prepared under nitrogen by the addition of 7.0 ml of 1.6 *M* ethereal methyllithium to an ice-cold suspension of 1.06 g of cuprous iodide in 25 ml of ether. A yellow precipitate of polymeric methylcopper formed immediately and dissolved as the addition was completed. After 10 min of stirring at 0°, the ether solution was treated with a solution of 0.49 g (2.8 mmol) of dienone **9** in 25 ml of dry ether. After 1 hr at 0°, the reddish-yellow reaction mixture was poured into 35 ml of saturated ammonium chloride, and enough concentrated ammonium hydroxide was added to dissolve the precipitated copper salts. The product was isolated by ether extraction **24b** and distilled (short path) at 110° (0.09 mm) to give 0.51 g (95% yield) of colorless liquid: λ_{max}^{film} 5.98 (CO), 6.15 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.95 (doublet, CH_3, J = 6.4 Hz), 5.50 ppm (broad singlet, vinyl H). Vpc on a 15 ft × 1/8 in., 3% FFAP column at 179° showed a single peak (90–95%), retention time (RT) 12.4 min, with a shoulder, RT 13.8 min (*ca.* 5%). It is worth noting that in previous runs this contaminant varied from anywhere between 10 and 30% of the distilled sample, as determined by vpc. It is unlikely that it arises in the conjugate addition step, since the ir spectrum exhibited no peak for a saturated carbonyl (due to addition of two methyl groups) and the nmr spectrum provided no evidence in the vinyl proton region for addition to the trisubstituted double bond. Thus, it probably was present to varying degrees in certain samples of the starting dienone.

In a subsequent run using 9.05 g of the dienone **9** with appropriate scaling up, 9.50 g (96% yield) of enone **10** was obtained after distillation.

The ratio of epimers **10a**:**10b** was obtained *via* vpc analysis of the enol ethers **11a** and **11b** prepared as follows. A solution of 198 mg (1.04 mmol) of the aforementioned enones in 4.0 ml of 1:1 2,2-dimethoxypropane and dimethylformamide was treated with 0.08 ml of dry methanol and 21 mg of *p*-toluenesulfonic acid monohydrate. The solution was degassed and heated to reflux under nitrogen for 3.5 hr.[24a] The cooled solution was treated with solid sodium bicarbonate, diluted with 15 ml of water, and extracted with pentane.[24b] Short-path distillation at 80–85° (0.03 mm) gave 223 mg (*ca.* 100% yield) of pale orange liquid which darkened slowly upon exposure to air: λ_{max}^{film} 6.06, 6.18 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.90 (doublet, J = 6.8 Hz) overlapping with 0.93 ppm (doublet, J = 6.0 Hz) (ratio *ca.* 2:1 in favor of low-field signal), 4.97 (2 H, singlet, vinyl H), 3.45 ppm (3 H, singlet, CH_3O). Accurate analysis was obtained by vpc on a 22 ft × 1/8 in., 1% Carbowax column at 151°. Two sharp peaks were observed, RT 12.4 min (26%), and 15.8 min (74%). Further experiments (see below) permitted assignment of structure **10a** to the minor component, and structure **10b** to the major component.

B. Reaction in Dioxane–Ether.—A suspension of 1.36 g of cuprous iodide in 12 ml of dry dioxane, cooled to 10° under nitrogen, was treated with 8.0 ml of 1.75 *M* ethereal methyllithium. During addition of the first 4 ml, the reaction mixture became yellow and methylcopper precipitated. As the second 4 ml of methyllithium solution was added, the mixture became orange-yellow and first thickened considerably so that stirring became difficult and then became slightly less viscous toward the end of the addition. After 20 min, a solution of 0.53 g of dienone **9** in 24 ml of dioxane was introduced, and the mixture was stirred at 15–20° for 6.0 hr. The reaction mixture was poured into 120 ml of saturated ammonium chloride and processed as above to give 0.56 g of crude product. A 59-mg sample afforded, following the procedure outlined above, a mixture of enol ethers found by vpc analysis to consist of 40% **11a** and 60% **11b**.

In a subsequent large scale experiment the crude material from three combined runs was distilled (short path) at 90–95° (0.04 mm) to give a 2:3 mixture of enones **10a** and **10b** in 69% yield.

The Semicarbazone of Enone 10b.—A sample of 186 mg (0.91 mmol) of an approximately 1:3 mixture of enol ethers **11a** and **11b** (see above) in 5 ml of methanol and 0.5 ml of water was treated with 2 drops of concentrated HCl and stirred for 0.5 hr. Processing[24b] gave a yellow liquid, which in turn afforded 98 mg (44% yield) of white semicarbazone, mp 193–196° dec. Recrystallization twice from methanol gave a white microcrystalline solid, mp 198–200° dec.

Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.24; H, 8.76; N, 17.03.

Birch Reduction of Enone Mixture 10.—A solution of 3.15 g of a 1:3 mixture of **10a** and **10b** (*ca.* 70% by vpc) in 80 ml of ether was added over a period of 10 min to a solution of 1.58 g of Li wire in 400 ml of liquid ammonia. After 40 min, the mixture was treated dropwise over a period of 2 hr with a mixture of 50 ml of absolute ethanol and 85 ml of ether. The blue color was discharged after 80 ml had been added. After treatment with 14.6 g of ammonium chloride the ammonia was allowed to evaporate and replaced with ether. Work-up[24b] afforded 3.27 g of a pale yellow liquid, λ_{max}^{film} 3.0 μ (OH).

A solution of this crude alcohol in 100 ml of acetone was cooled to 0° and treated with 4.5 ml of Jones reagent[10] dropwise over a period of 5 min. After stirring for 8 min, the reaction mixture was treated with 0.5 ml of 2-propanol, and, after an additional 5 min, 0.5 ml of saturated sodium bicarbonate was added. Most of the acetone was removed at reduced pressure (bath temperature 30–35°), and the product was isolated by ether extraction,[24b] affording 3.12 g, λ_{max}^{film} 5.82 μ (C=O). Vpc on a 15 ft × 1/8 in. 3% FFAP column showed two peaks, RT 23.6 min and 25.2 min (ratio *ca.* 2:1).

The foregoing sequence was repeated using a sample of the enone mixture **10a** and **10b** freed of the longer retention time contaminant by preparative vpc on a 15 ft × 1/2 in., 8% FFAP column. The product thus obtained exhibited a single peak, RT 24.2 min, on a 15 ft × 1/8 in., 3% FFAP column at 150°. It was then subjected to further purification as described below.

Purification of Ketone 13b *via* the Thioketal 14b (Cis Fused).—An ice-cold solution of 514 mg (3.74 mmol) of the above ketone secured by preparative vpc in 3.1 ml of ethanedithiol was treated dropwise with 2.0 ml of distilled boron trifluoride etherate, then warmed to 20–25° and stirred for 0.5 hr. The ice-cooled solution was treated dropwise with 10 ml of 10% sodium hydroxide, and the product was isolated by ether extraction.[24b] The 1.03 g of colorless oil thus obtained deposited a white solid upon cooling to −70° in 10 ml of pentane. One recrystallization from pentane at −40° gave 377 mg (52% yield) of white needles, mp 76–79°. Two more recrystallizations afforded the analytical sample, mp 81.5–82°, $\delta_{TMS}^{CCl_4}$ 3.18 ppm (4 H, $-SCH_2CH_2S-$).

Anal. Calcd for $C_{15}H_{24}S_2$: C, 67.11; H, 9.01. Found: C, 67.10; H, 9.14.

The procedure of Corey and Crouse[26] was utilized for the hydrolysis. A solution of 236 mg (0.88 mmol) of the thioketal in a mixture of 9.5 ml of acetonitrile and 0.5 ml of water was added to a mixture of 0.50 g of mercuric chloride and 0.33 g of cadmium carbonate under nitrogen, and the reaction mixture was stirred for 8 hr at 50–55° and 10 hr at 20–25°. The excess acetonitrile was removed under reduced pressure, and the residual powder was suspended in benzene and filtered through Supercel Hyflo. Removal of the solvent at reduced pressure left a yellow residue, which was extracted with hexane. Short-path distillation of the crude ketone at 95–100° (0.06 mm) gave a 141-mg (79%) yield of ketone **13b**, which became crystalline, mp 37–38.5° (softens at 35°), upon storage at 0–10°. The liquid exhibited λ_{max}^{film} 5.85 μ, $\delta_{TMS}^{CCl_4}$ 0.86 ppm (3 H, doublet, J = 7.0 Hz, axial CH_3).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.27; H, 10.59.

Analysis of the Birch Reduction of Enone 10b.—A 52-mg sample of ketone mixture **12** and **13** from preparative vpc (see above) was heated under nitrogen with 1.2 ml of triethylene glycol, 0.35 ml of hydrazine hydrate, and 41 mg of hydrazine dihydrochloride for 4 hr at 130°. Then a pellet of potassium hydroxide (*ca.* 0.17 g) was added and the temperature was slowly raised to 225° while the volatile materials distilled through an 8-in. Vigreux column. After 3 hr at 220–225°, the cooled mixture was diluted with water and treated with pentane,[24b] whereby 45 mg of crude colorless product was obtained. Upon vpc on a 50 ft × 1/8 in., 2% LP-118 silicone gum rubber (SE-30) column at 162° this sample exhibited three peaks, RT 30.0 min (22%), 31.0 min (10%), and 32.0 min (68%). Coinjection of an authentic specimen of the pure trans-fused hydrocarbon **15b**, obtained *via* independent synthesis, confirmed the identity of the 22% component. Thus, the major product derived from Birch reduction of enone **10b** could be assigned the cis-fused structure **13b**. The question of the ratio of cis to trans isomers (**13b**:**12b**) was resolved by first assuming the 10% component of the above sample to be derived from one of the epimers of the ketone mixture **12a** or **13a** derived in turn from enone **10a**. Then, according to previous analysis (see above) of the ratio of enone epimers **10a**:**10b** (26:74), about 16 percentage units of either the 22% peak or the 68% peak might be contributed to by the other epimer in the a series. The choice of the 22% peak is favored by the high yield (52%) of crystalline **14** (cis ring fusion). If the contaminant were part of the 68% peak, this yield would represent a highly unlikely quantitative (68% − 16% = 52%) recovery of thioketal **14b** from a mixture of *four* ketones. Thus, the mixture is calculated to contain about 6% hydrocarbon **12b** and 68% **13b**, or about a 1:11 ratio of isomers, reflecting a corresponding degree of stereoselectivity in the Birch reduction of enone **10b**.

A 41-mg sample of pure ketone **13b**, was reduced to give the hydrocarbon **16b**, as described above. Vpc as above exhibited two peaks, RT 33.0 min (6%) and 33.8 min (94%). Both were shown to differ from an authentic sample of hydrocarbon **15b** by coinjection but were identical with the 10 and 68% components, respectively, described above.

An analytical sample was prepared by filtration through Woelm neutral alumina (grade I) with pentane, and by short-path distillation at 75–80° (14 mm) to give a colorless liquid.

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.57; H, 12.27.

Catalytic Hydrogenation of Enone Mixture 10.—A solution of 400 mg (2.10 mmol) of enone mixture **10** (1:3 **a**:**b**) in 20 ml of ethyl acetate was hydrogenated over 157 mg of 5% palladium on carbon for 2.0 hr. Filtration and removal of the solvent afforded 368 mg (92% crude yield) of saturated ketone. Vpc showed two peaks, a major component, RT 17.2 min (*ca.* 75–80%) and a minor, RT 18.4 min (shoulder).

According to the previously described procedure (see above), 310 mg (1.61 mmol) of the crude ketone mixture from the above catalytic hydrogenation was thioketalized to give 260 mg (60% crude yield) of white solid, mp 75–79°. One recrystallization gave 210 mg of white crystals, mp 79.5–81.5°. Two further recrystallizations (pentane at −40°) afforded the analytical sample, as white cubic crystals, mp 81–82°.

Anal. Calcd for $C_{15}H_{24}S_2$: C, 67.11; H, 9.01. Found: C, 67.33; H, 9.16.

According to the previously described procedure (see above), a sample of 138 mg of thioketal **14b** (trans ring fusion), was converted to the liquid ketone **12b**, λ_{max}^{film} 5.82 μ, in 87% yield after short-path distillation at 85–90° (0.07 mm).

A sample was purified for analysis by chromatography on silica gel and short-path distillation at 70–75° (0.03 mm) to give a colorless liquid, $\delta_{TMS}^{CCl_4}$ 0.92 (3 H, doublet, J = 5.8 Hz).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.00; H, 10.32.

Wolff–Kishner Reduction of Samples Containing Ketone 12b.—A 58-mg sample of the crude mixture of ketones obtained from catalytic hydrogenation (see above) was mixed with 1.3 ml of triethylene glycol, 0.38 ml of 85% hydrazine hydrate, and 46 mg of hydrazine dihydrochloride. After heating to 130° under nitrogen for 3 hr, the reaction mixture was treated with a pellet of potassium hydroxide and processed as above to give a colorless liquid. Vpc on a 50 ft × 1/8 in., 1% LP-118 silicone gum rubber (SE-30) column at 160° exhibited two peaks, RT 31.6 mm (*ca.* 70%) and 32.4 min (*ca.* 30%), in addition to a trace peak at 33.2 min. The first peak was identified as the hydrocarbon **15b** by coninjection with an authentic specimen; the trace peak at 33.2 min stems from the other isomeric hydrocarbon **16b**.

A 36-mg sample of ketone **12b** obtained by hydrolysis of the thioketal **14b** was subjected to Wolff–Kishner reduction as above to give a colorless product. Vpc (see above) showed a single peak, RT 32.6 min. The infrared spectrum was identical with that of an authentic specimen of hydrocarbon **15b** prepared in an unambiguous manner (see below).

Deconjugation of Tricyclic Enone 10.—The procedure of Armour, *et al.*,[13] was adapted. A sample of 3.84 g (20.1 mmol) of enone mixture **10a** and **10b**, about 80% pure by vpc, in 80 ml of dry tetrahydrofuran was added to 0.95 g of 56% sodium hydride in mineral oil (freed of oil by washing with pentane three times), along with 0.07 ml of absolute ethanol. The mixture was then heated at reflux under nitrogen for 2.0 hr;[24a] hydrogen was given off during the first 1.5 hr. The cooled mixture was transferred to an addition funnel under nitrogen and then added dropwise to 400 ml of rapidly stirred 0.5 *M* sodium dihydrogen phosphate. The crude product, λ_{max}^{film} 5.81 (C=O), 5.97 μ (C=O),

(26) E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).

was isolated by extraction with ether[24b] and used immediately for the next step.

To a suspension of 1.8 g of lithium aluminum hydride in 220 ml of ether, cooled to 0°, was added dropwise a solution of the above crude ketone mixture in 90 ml of ether. After 3 hr the reaction was quenched by the addition of 10 ml of saturated sodium sulfate. After 1 hr, the mixture was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed to give a pale yellow oil, which was then heated at reflux under nitrogen with 50 ml of acetic anhydride and 4.0 g of sodium acetate for 2 hr.[27] The reaction mixture was processed by removal of excess acetic anhydride at reduced pressure (bath temperature 50°) and addition of water and ether.[24b] The ether solution thus obtained was treated portionwise with 3.6 g of lithium aluminum hydride, stirred at 25° overnight, and quenched by the addition of 20 ml of saturated sodium sulfate.[24b] The crude material thus secured was chromatographed on 140 g of Fisher alumina. The alcoholic components (2.32 g, 60% crude yield) were obtained by elution with ether. Vpc on a 15 ft × 1/8 in., 3% FFAP column at 172° showed three components, RT 12.4 min (plus shoulder 12.8 min) (total *ca.* 1/3), 16.0 min (*ca.* 2/3).

Reproducibility of this sequence was variable, perhaps as a reflection of the purity of the starting material, overall yields of 50–70% being obtained.

An analytical sample of the major alcoholic component was isolated by preparative vpc on a 15 ft × 0.5 in., 8% FFAP column at 210°. Short-path distillation at 120–125° (0.05 mm) afforded a colorless, rather viscous oil: λ_{max}^{film} 3.01 (–OH), 6.02 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.93 (3 H, doublet, J = 5.9 Hz, $CHCH_3$), 5.06 ppm (1 H, broad singlet, vinyl H).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.94; H, 10.51.

Conversion of Alcohol 17 to the *p*-Bromophenylurethane (19).—A solution of 119 mg (0.62 mmol) of alcohol purified by preparative vpc in 1.0 ml of benzene was treated with 163 mg of *p*-bromophenyl isocyanate. After heating under reflux for 15 min, the mixture was filtered through glass wool to remove insoluble di-*p*-bromophenylurea. The benzene was then blown off with nitrogen, and 2–3 ml of hexane was added to induce crystallization, which began almost immediately without cooling. The white crystals, isolated by suction filtration after cooling the hexane to 0°, were washed with cold hexane. One recrystallization from hexane afforded 116 mg (47% yield) of white prisms: mp 143–144.5°; λ_{max}^{KBr} 3.00 (–NHCO–), 5.70, 5.78 (C=O), and 6.27 μ (aromatic). Two more recrystallizations fron hexane gave the analytical sample, mp 144–145°.

Anal. Calcd for $C_{20}H_{24}BrNO_2$: C, 61.53; H, 6.20; N, 3.59; Br, 20.47. Found: C, 61.75; H, 6.13; N, 3.63; Br, 20.22.

Deconjugation of Tricyclic Enones 10a and 10b.—The procedure of Edwards and Rao[28] was employed. A solution of 8.03 g of enone mixture **10a** and **10b** (1:3, *ca.* 90% purity) in 160 ml of dry ethyl acetate was treated with a solution made from 0.16 ml of 70% perchloric acid, 160 ml of ethyl acetate, and 77 ml of acetic anhydride, diluted to 640 ml with ethyl acetate (reagent "A"). After stirring for 10 min the reaction mixture was treated with 100 ml of ether, and slowly, in portions, with 500 ml of saturated sodium bicarbonate. After 3 hr of stirring the crude enol acetate was isolated *via* ether extraction[24b] as an orange liquid, λ_{max}^{film} 5.78 (C=O), 6.01, 6.14 μ, which slowly darkened upon exposure to air. This material was used immediately in the next step.

A solution of the aforementioned enol acetate in 260 ml of absolute ethanol was added dropwise over 2.5 hr to an ice-cooled solution of 32 g of sodium borohydride in 1300 ml of absolute ethanol and 200 ml of water. After the addition the reaction mixture was stored at 0–10°[24a] for 24 hr and then treated with 200 ml of 10% sodium hydroxide and poured into 5 l. of water. The product was isolated by extraction with ether[24b] as a pale yellow oil. This material was acetylated directly through treatment with 130 ml of acetic anhydride and 10.4 g of sodium acetate at reflux under nitrogen for 3 hr. Work-up described previously (see above) gave 9.68 g of crude orange-red acetate mixture, which was chromatographed on 260 g of silica gel. The major fraction, eluted with benzene, amounted to 8.40 g of pale yellow liquid, λ_{max}^{film} 5.76 μ (C=O). Vpc on a 15 ft × 1/8 in., 3% FFAP column at 187° exhibited three peaks, RT 14.8 min (14%), 16.0 min (24%), and 17.6 min (62%). The major component is the acetate **18b**. Assignment of structure **18a** (possibly a mixture of C-2 epimers) to the 24% component is consistent with the analysis of the enol ethers **11** (see above). By implication the 14% component may be assigned structure **18b** (C-2 epimer). Short path distillation at 95–100° (0.1 mm) afforded 7.99 g (90% overall yield corrected for purity of enone mixture **10**) of colorless liquid.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.81; H, 9.54.

Conversion of the Acetate Mixture 18 to Dienones 21a and 21b.—A solution of 7.72 g (33.0 mmol) of the aforementioned acetate mixture in 44 ml of acetic anhydride and 74 ml of glacial acetic acid, was cooled to 0° under nitrogen and treated portionwise with 21.3 g of sodium chromate. The mixture was allowed to warm to 25–30° and stirred for 22 hr. It was then poured slowly into 500 ml of rapidly stirred saturated sodium bicarbonate overlaid with 300 ml of ether and stirred for 3 hr. Work-up gave 6.21 g of keto ester **20**, λ_{max}^{film} 5.85, 5.96 μ (C=O). The sample was used without further purification.

Dehydroacetoxylation of the above acetate was effected *via* a procedure based on that of Nickon and Bagli.[29] The foregoing sample of keto acetate in 200 ml of absolute ethanol was treated with 1.7 ml of concentrated hydrochloric acid and then heated at reflux under nitrogen for 3 hr. The cooled mixture was diluted with 600 ml of water and extracted with ether,[24b] thereby affording 4.51 g of dienones **21**. Distillation through a short-path micro apparatus gave 3.07 g (*ca.* 50% overall yield) of pale yellow liquid, λ_{max}^{film} 6.01 (C=O), 6.20, 6.33 μ (C=C). Vpc on a 15 ft × 1/8 in., 3% FFAP column at 210° exhibited two major peaks, RT 20.8 min (28%), and 23.4 min (72%), roughly consistent with the ratio of enones **10a** and **10b** in the starting mixture.

In one run the dienone mixture was secured in comparable yield by short-path distillation at 125–130° (0.03 mm). The two components were readily separated by preparative vpc on a 13.5 ft × 0.5 in., 9% FFAP column at 245° and purified *via* short-path distillation. Both had very similar infrared and nmr spectra: minor component **21a** [$\delta_{TMS}^{CCl_4}$ 0.97 (3 H, doublet, J = 6.2 Hz, CH_3CH–), 2.77 (1 H broad triplet, $J \sim 5$ Hz, bridgehead H), 5.50 (1 H, broad singlet, vinyl H α to C=O), 6.10, 6.14 ppm (2 H, vinyl H γ and δ to C=O)]; major component **21b** [$\delta_{TMS}^{CCl_4}$ 1.02 (3 H, doublet, J = 5.5 Hz, CH_3CH–), 2.75 (1 H, broad triplet, $J \sim 5$ Hz, brigehead H), 5.50 (as above), 6.15, 6.23 ppm (as above)].

The major isomer **21b** secured *via* preparative vpc from another run afforded a crystalline pale yellow semicarbazone, mp 208–209° dec.

Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.72; H, 7.77; N, 16.97.

The above samples of dienones were used in studies of the stereochemistry of the methyl group.

Catalytic Hydrogenation of Dienone 21b.—A solution of 122 mg (0.65 mmol) of dienone **21b** in 9.0 ml of ethyl acetate was hydrogenated at 25° and 1 atm over 80 mg of 5% palladium on carbon for 4 hr. Filtration and removal of the solvent at reduced pressure afforded a pale yellow liquid, which was distilled at 85–90° (0.04 mm) to give 103 mg (84% yield) of saturated ketone **23b**: λ_{max}^{film} 5.83 μ (C=O); $\delta_{TMS}^{CCl_4}$ 2.64 (1 H, triplet, J = 5 Hz, bridgehead H), 1.02 ppm (3 H, doublet, J = 6.0 Hz, CH_3CH–). Vpc on a 15 ft × 1/8 in., 3% FFAP column at 150° exhibited a single peak, RT 22.4 min.

An analytical sample was prepared by chromatography on silica gel and two short-path distillations at 70–75° (0.03 mm) to give almost colorless material, mp 38–42°.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.12; H, 10.38.

This ketone could also be secured by selective reduction of the aforementioned mixture of dienones **21a** and **21b** (see below). The sample thus obtained was identical with the above specimen.

Bromination of Ketone 23b.—A solution of 1.076 g (5.65 mmol) of ketone **23b** in 20 ml of glacial acetic acid was treated dropwise with stirring at 20°, with 1.71 ml of 3.30 *M* bromine in acetic acid. After the addition (5 min), the mixture was transferred to 100 ml of water in a separatory funnel and extracted with hexane[24b] (the bromo ketone at this point precipitated from the hexane solution, so enough ether was added to effect solution. A dilute bisulfate wash was included in the work-up). Removal

(27) The acetic anhydride treatment serves to remove allylic alcohols through elimination to the corresponding dienes under these conditions. The homoallylic alcohols survive this treatment.

(28) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(29) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961).

of the solvent at reduced pressure afforded 1.58 g of crystalline ketone **25**. Similar material obtained from a previous run exhibited λ_{max}^{KBr} 5.79 μ (C=O); $\delta_{TMS}^{CCl_4}$ 4.38 (1 H, doublet, J = 11 Hz, -CHBr), 3.02 (1 H, triplet, J = 4 Hz, bridgehead H), 0.95 ppm (3 H, doublet, J = 6 Hz, CH_3CH-). One crystallization from hexane afforded 1.20 g (79% yield) of colorless prisms, mp 136.5–137.5°. A second recrystallization gave the analytical sample, mp 137–138.5°.

Anal. Calcd for $C_{13}H_{19}BrO$: C, 57.57; H, 7.06; Br, 29.47. Found: C, 57.52; H, 6.97; Br, 29.40.

Wolff–Kishner Reduction of Ketone 23b.—A sample of 55 mg (0.29 mmol) of ketone **23b** was heated with 1.3 ml of triethylene glycol, 0.38 ml of 85% hydrazine hydrate, and 44 mg of hydrazine dihydrochloride under nitrogen for 4 hr at 130°.[24a] Then a pellet (0.16 g) of potassium hydroxide was introduced and the mixture was heated at 220–225° for 3 hr. The product, isolated by extraction with pentane,[24b] amounted to 45 mg of colorless liquid, which upon vpc on a 50 ft × 1/8 in., 1% LP-118 silicone gum rubber (SE-30) column at 162°, exhibited a single peak, RT 29.6 min (98%). This compound could be unambiguously assigned structure **15b** based upon its derivation from ketone **23b** of proven stereochemistry. Short-path distillation at 90° (15 mm) gave 19 mg (37% yield) of colorless liquid, which was filtered through Woelm neutral alumina (grade I) and again distilled at 80° (13 mm) to give the analytical sample.

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.84; H, 12.48.

Hydrogenation of Dienone 21a.—A sample of 207 mg (1.10 mmol) of dienone **21a** (95% one epimer), in 14.5 ml of ethyl acetate, was hydrogenated at 1 atm over 141 mg of 5% palladium on carbon for 3.5 hr at 25°. Filtration and removal of the solvent at reduced pressure gave a pale yellow liquid which was distilled at 90–120° (0.02 mm) to give 196 mg of colorless liquid, λ_{max}^{film} 5.82 μ (C=O). The nmr spectrum in carbon tetrachloride solution clearly indicated the presence of two isomeric ketones **23a** and **24a** [$\delta_{TMS}^{CCl_4}$ 0.98 (doublet, $J \simeq 6.8$ Hz, axial CH_3), 0.90 (doublet, $J \simeq 6.0$ Hz, equatorial CH_3)], in about a 7:3 ratio, although vpc analysis of the sample on a 15 ft × 1/8 in., 3% FFAP column at 150° exhibited a single broad peak, RT 22.6 min (*ca.* 90%), as well as a low RT (2.4 min) component corresponding probably to hydrocarbon arising from hydrogenolysis. The sample was used in the next step without further purification.

In a later experiment, a sample of 25 mg of dienone **21a** was hydrogenated in 5 ml of benzene over 34 mg of 2% palladium on strontium carbonate, and the uptake of hydrogen was followed by vpc on a 15 ft × 1/8 in., 3% FFAP column at 210°. After 2.5 hr the vpc indicated *ca.* 20% reduction to two saturated ketones, RT 10.4 min and 11.0 min (shoulder), in a ratio of about 3:1. This analysis is consistent with the nmr results (see above).

Bromination of Ketone Mixture 23a and 24a.—A solution of 196 mg of the aforementioned ketone mixture obtained from hydrogenation of the dienone **21a** in 3.6 ml of acetic acid was treated with 0.31 ml of 3.30 *M* bromine in acetic acid. After 5 min the reaction mixture was worked up as in the case of the methyl epimer to give 248 mg of ketones **25a** and **26a**: λ_{max}^{film} 5.79 μ (C=O); $\delta_{TMS}^{CCl_4}$ 4.26 (doublet, J = 11 Hz, -CHBr), 5.12 (doublet, $J \simeq 7$ Hz, -CHBr), 1.00 (doublet, $J \simeq 7$ Hz, axial CH_3CH-), 0.94 ppm (doublet, $J \simeq 6$ Hz, equatorial CH_3CH-). The ratios of the 4.26–5.12-ppm and 1.00–0.94-ppm signals were both about 3:1, thereby confirming the results of the nmr analysis on ketone mixture **23a** and **24a**.

Preparation of Enone 22a.—According to a previously described procedure,[30] a solution of the above crude mixture of bromo ketones in 6.3 ml of dimethylacetamide along with 0.32 g of calcium carbonate was degassed, flushed with nitrogen, and heated at reflux for 0.5 hr. After cooling, the mixture was transferred to 30 ml of 0.2 *N* hydrochloric acid and 15 ml of hexane in a separatory funnel and extracted in the usual manner[24b] to give 170 mg of yellow liquid, λ_{max}^{film} 5.97 (C=O), ~5.8 μ (C=O). Chromatography on silica gel afforded upon elution with 2% ether–benzene the enone **22a**, which upon short-path distillation at 105–110° (0.03 mm) gave 70 mg (36% yield based on the ketone mixture **23a** and **24a**) of colorless liquid: λ_{max}^{film} 5.97 (C=O), 6.11 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.96 (3 H, doublet, J = 6.8 Hz, CH_3CH-), 2.76 (1 H, triplet, J = 5.5 Hz, bridgehead H), 5.58 ppm (1 H, doublet, J = 1 Hz, C=CH).

Selective Catalytic Hydrogenation of Dienone Mixture 21.—A solution of 1.89 g (10.0 mmol) of a mixture of 38% dienone **21a** and 62% dienone **21b** in 120 ml of benzene was stirred under an atmosphere of hydrogen with 1.42 g of 2% palladium on strontium carbonate. The uptake of hydrogen was followed by vpc (see above). Analysis of the system was particularly difficult because of the nature and vpc behavior of the products formed. Thus, within about 1.5 hr both dienones were reduced to give the enone **22a** and its corresponding epimer **22b** which, in turn, were further reduced at significantly different rates. However, these two enones were inseparable by vpc, so that the only way the reaction could be monitored was by observing the peaks for the saturated components in the reaction mixture. Since the two saturated isomers **23a** and **23b** (though appearing at the same RT) were known to be separable from **24a**, the reaction could be run until the appearance of a small low retention time shoulder on the major peak. The crude product mixture obtained after filtration and removal of solvent at reduced pressure was chromatographed on silica gel, whereby 0.87 g of the saturated component (ketone **23b**) was eluted with 1% ether–benzene and 0.44 g of the unsaturated component (enone **22a**) was eluted with 4% ether–benzene. Short-path distillation of the crude unsaturated material at 95–100° (0.03 mm) gave 408 mg (84% yield based upon dienone mixture) of pale yellow liquid: λ_{max}^{film} 5.97 (C=O), 6.24 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.95 (3 H, doublet, $J \simeq 7$ Hz, axial CH_3-), 2.72 (1 H, triplet, $J \simeq 5.5$ Hz, bridgehead H), 5.54 ppm (1 H, doublet, $J \simeq 1$ Hz, vinyl H). Both spectra were nearly identical with the corresponding spectra of the specimen of enone **22a** obtained as described above.

The ketone afforded a deep red microcrystalline 2,4-dinitrophenylhydrazone, mp 156.5–158° (ethanol).

Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.41; H, 5.95; N, 15.05.

Conversion of Enone 22a to Diol 28.—A solution of 375 mg (1.97 mmol) of enone **22a** (*ca.* 90% one epimer) in 7.0 ml of dry tetrahydrofuran was added to an ice-cooled solution of 1.05 g of lithium tri-*tert*-butoxyaluminum hydride in 10.4 ml of tetrahydrofuran. After stirring for 22 hr at 20–25°, the mixture was treated dropwise at 0° with 0.75 ml of saturated sodium sulfate and then dried over anhydrous magnesium sulfate and filtered to give, after removal of the solvent and evacuation at 25° (0.03 mm), 0.41 g of alcohol **27**: λ_{max}^{film} 2.99 (-OH), 6.03, 11.85 μ (C=C); $\delta_{TMS}^{CDCl_3}$ 5.02 (1 H, singlet, vinyl H), 0.91 ppm (3 H, doublet, J = 6.2 Hz, CH_3CH-).

A sample of 0.29 g of the above crude allylic alcohol in 2.5 ml of chloroform cooled to 0° under nitrogen[24a] was treated with a solution of 360 mg of *m*-chloroperoxybenzoic acid in 2.4 ml of chloroform, allowed to warm to 20–25°, and stirred for 3 hr. The reaction mixture was processed by addition of 5.0 ml of water and 1.3 ml of 10% sodium hydroxide, followed by dilution with ether. The remainder of the sample of allylic alcohol **27** was converted to the epoxide in an analogous manner, $\delta_{TMS}^{CDCl_3}$ 3.88 (1 H, doublet, J = 5.0 Hz, -CHOH), 3.07 ppm (1 H, broad singlet, epoxide H). The combined crude epoxide sample in 10 ml of ether was added dropwise to a suspension of 0.50 g of lithium aluminum hydride in 10 ml of ether, at 0°. After stirring overnight at 20–25°, the reaction mixture was cooled to 0° and treated dropwise with 1.0 ml each of water and 10% sodium hydroxide, then stirred for 8 hr at 25°, dried over anhydrous magnesium sulfate, and filtered. Solvent removal afforded 366 mg (88% overall yield based on enone **22a**) of crystalline diol (mainly **28**). An additional 11 mg was obtained upon further ether washing of the inorganic salts, thus totaling 377 mg (91% yield).

A small sample of the diol, upon crystallization from 3:1 pentane–ether at −30°, afforded fluffy, fine needles, mp 159–163°. Two recrystallizations from 3:1 pentane–ether afforded the analytical sample, mp 164–165°.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.26; H, 10.43.

Conversion of Diol 28 to Methanesulfonate 29.—A sample of 361 mg (1.72 mmol) of the aforementioned crude diol **28** in 2.0 ml of dry pyridine was cooled to 0°, treated dropwise with 0.16 ml of methanesulfonyl chloride and stirred for 3.25 hr at 0°. The reaction mixture was first treated with 0.5 ml of water and then an additional 10 ml of water and extracted with ether[24b] to give 467 mg (92% yield) of a white solid. A small sample (16 mg) recrystallized from 2:1 pentane–ether at −30° gave colorless microcrystals (12 mg): mp 95.5–96.5°; λ_{max}^{KBr} 2.85 (-OH), 7.59, 8.59 μ ($-OSO_2CH_3$).

Anal. Calcd for $C_{14}H_{24}O_4S$: C, 58.30; H, 8.39; S, 11.12. Found: C, 58.46; H, 8.36; S, 11.25.

(30) G. Greene and A. Long, *J. Chem. Soc.*, 2532 (1961).

Fragmentation of Hydroxy Mesylate 29. Spiro Ketone 30.—A solution of 448 mg (1.55 mmol) of the aforementioned crude crystalline hydroxy mesylate **29** in 30 ml of dry *tert*-butyl alcohol was degassed and flushed with nitrogen and then treated with 3.0 ml of 0.98 *M* potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction mixture was heated under reflux for 8 hr, cooled to 25°, and transferred to 120 ml of 50% saturated brine overlaid with 75 ml of ether. The product, λ_{max}^{film} 5.86 μ (C=O), was isolated by extraction with ether.[24b] Chromatography on silica gel afforded the ketone **30** upon benzene elution. Short-path distillation at 70° (0.03 mm) gave 191 mg (64% yield) of colorless liquid: λ_{max}^{film} 5.87 (C=O), 3.25 (C=CH), 6.08, 10.01, 10.96 μ; $\delta_{TMS}^{CCl_4}$ 5.5–6.0 (1 H, multiplet, $-CH=CH_2$), 4.8–5.0 (2 H, multiplet, $-CH=CH_2$), 0.95 (3 H, doublet, J = 6.0 Hz, CH_3-), 0.91 ppm (shoulder, *ca.* 10%, J = 6.8 Hz, epimeric CH_3-).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.38; H, 10.39.

Conversion of Spiro Ketone 30 to Acetate 32.—A solution of 4.4 ml of 1.5 *M* ethereal methyllithium was diluted under nitrogen with 4.5 ml of ether. Then a solution of 175 mg (0.91 mmol) of spiro ketone **30** in 6.0 ml of ether was added, followed by stirring at 20–25° overnight. The reaction mixture was cooled to 0° and treated with 0.9 ml of saturated brine, and then water to dissolve the inorganic salts, and alcohol **31**, 207 mg of colorless oil, was isolated by extraction with ether.[24b]

This crude sample was heated at reflux under nitrogen with 4.0 ml of acetic anhydride, and 0.32 g of sodium acetate for 3 hr. The cooled mixture was treated with 25 ml of saturated sodium carbonate and ether, stirred for 1.5 hr and the product was isolated by extraction with ether.[24b] Short-path distillation at 80–85° (0.03 mm) gave 214 mg (94% overall yield) of the colorless acetate **32**: λ_{max}^{film} 5.75 (C=O), 6.08 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.90 (3 H, doublet, $J \simeq 6$ Hz, CH_3CH-), 1.58 (singlet, $CH_3\overset{|}{C}-O$), 1.95 (singlet, CH_3COO-). The sample was used in the next step without further purification.

Conversion of Acetate 32 to Hydroxy Acetate 34.—A solution of 204 mg (0.82 mmol) of the above acetate in 1.5 ml of dry chloroform, cooled to 0° under nitrogen, was treated with a solution of 224 mg of *m*-chloroperoxybenzoic acid (80%) in 2.0 ml of chloroform. The mixture was stirred for 0.5 hr at 0°, and then at 20–25° for 3.0 hr (a white precipitate of *m*-chlorobenzoic acid slowly deposited). The reaction mixture was then transferred to a separatory funnel containing 20 ml of 50% saturated brine, 20 ml of ether, and 1 drop of phenolphthalein, and the acid was neutralized by the dropwise addition of 10% sodium hydroxide. The organic layer was washed twice with 50% saturated brine and once with saturated brine.[24b] The epoxy acetate was isolated as a colorless oil, λ_{max}^{film} 5.79 μ (C=O).

The crude material was dissolved in 5 ml of ether and added dropwise to an ice-cooled suspension of 0.50 g of lithium aluminum hydride in 10 ml of ether. After stirring at 20–25° overnight, the reaction mixture was treated at 0° with 1.1 ml each of water and 10% sodium hydroxide and then stirred for 8 hr and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent afforded 187 mg of diol **33**, which without further treatment was dissolved in 4 ml of dry pyridine, cooled to 0°, and treated with 2 ml of acetic anhydride. After 19.5 hr at 0–10°, the mixture was diluted with 30 ml of water and extracted with ether[24b] to give 210 mg (96% overall yield based on acetate **28**) of crude oily hydroxy acetate, λ_{max}^{film} 5.78, 5.82 (C=O), 2.88 μ (-OH). This material, a mixture of epimers, was used in the next step without further purification.

Conversion of Hydroxy Acetate 34 to Ketone Mixture 37.—A solution of 191 mg (0.71 mmol) of the above crude hydroxy acetate mixture in 3.2 ml of dry pyridine, under nitrogen, was treated with 0.36 ml of phosphorus oxychloride and heated to 80–85° for 3.5 hr. The cooled mixture was transferred to ice-cold water and ether, and the product was isolated by ether extraction[24b] to give 199 mg of acetate **35**, λ_{max}^{film} 5.77 (C=O), 6.04, 12.5 (C=C), 6.12, 11.2 μ ($C=CH_2$), a mixture of double bond isomers.

A solution of this crude acetate mixture in 12 ml of dry ether was cooled to 0° and treated portionwise with 0.45 g of lithium aluminum hydride and then stirred overnight at 25° under nitrogen. The ice-cooled mixture was treated dropwise with 0.8 ml each of water and 10% sodium hydroxide, stirred 1 hr, and then dried over anhydrous magnesium sulfate. Filtration and solvent removal under reduced pressure afforded the crude alcohol **36**, which was dissolved in 10 ml of dry acetone, cooled to 0°, and treated dropwise with 0.23 ml of Jones reagent.[10] After 5 min, 15 drops of 2-propanol was added, followed after 5 min by 15 drops of saturated sodium bicarbonate. Then 30 ml each of water and ether were added, and the aqueous layer was extracted with ether[24b] to give 154 mg of pale yellow ketone mixture **37**, λ_{max}^{film} 5.84 (C=O).

Conversion of Ketone Mixture 37 to Racemic Hinesol Acetate 39.—A solution of 6.0 ml of 1.5 *M* ethereal methyllithium was diluted with 8 ml of ether. Then a solution of the above crude ketone mixture **37** in 8 ml of ether was added, and the mixture was stirred overnight under nitrogen.[24a] The excess methyllithium was destroyed by dropwise addition at 0° of 4.0 ml of saturated brine; water was added to dissolve the salts and the product was isolated by ether extraction[24b] to give 165 mg (95% yield based upon hydroxy acetate) of colorless oil, λ_{max}^{film} 2.9 μ (-OH). Vpc analysis on a 15 ft × 1/8 in., 3% FFAP column at 172° showed two peaks, RT 18.4 min (30%) and 20.9 min (70%), identified as the exocyclic and endocyclic olefin isomers, respectively, of racemic hinesol (**38**).

A sample of 139 mg of this crude mixture and 0.27 g of sodium acetate was dissolved in 3.3 ml of acetic anhydride, and the mixture was heated at reflux for 3.25 hr under nitrogen. The cooled mixture was poured into 25 ml of dilute sodium bicarbonate and 20 ml of ether, and stirred for 1 hr. The product, isolated by ether extraction,[24b] amounted to 162 mg of pale yellow liquid. Vpc analysis at 169° showed two peaks, RT 18.6 min (*ca.* 30%) and 21.6 min (*ca.* 70%). The desired endocyclic olefin isomer was secured by chromatography on silica gel impregnated with 10% silver nitrate. This component, λ_{max}^{film} 6.02, 12.51 μ (C=C), was eluted first with 40% benzene–hexane, the exocyclic isomer, λ_{max}^{film} 6.10, 11.22 μ ($C=CH_2$), with 60% benzene–hexane. Vpc analysis of the former component showed two peaks, RT 19.4 min (91%) and 21.2 min (9%), most likely arising from incomplete separation of dienone epimers **21a** and **21b**. Coinjection with a sample of the acetate derived from authentic hinesol (see below) confirmed its identity with the major component. Under these conditions a 60:40 mixture of acetate **39** and its isopropylacetoxyl epimer, prepared by independent synthesis, exhibited two peaks. Short-path distillation at 75–80° (0.03 mm) gave 51 mg of a colorless liquid (24% overall yield based on acetate **34**: λ_{max}^{film} 5.77 μ (C=O); $\delta_{TMS}^{CCl_4}$ 0.93 (3 H, doublet, J = 6.0 Hz), 1.42 [6 H, singlet, $(CH_3)_2CO-$], 1.90 (3 H, singlet, CH_3COO-), 5.16 ppm (1 H, triplet, $J \sim 3$ Hz, vinyl H). Both spectra were virtually superimposable with those of the naturally derived material.

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.02; H, 10.67.

Hinesol Acetate.—A solution of 95 mg (0.43 mmol) of impure (−)-hinesol, mp 47–52°, in 2.4 ml of acetic anhydride was treated with 0.19 g of sodium acetate, and the mixture was heated under reflux for 3 hr.[24a] Processing as with the synthetic sample (see above) afforded the crude product, which was distilled at 90–95° (0.04 mm) to give 90 mg (77% yield) of virtually colorless liquid, λ_{max}^{film} 5.77 μ (C=O). Vpc analysis indicated a purity of about 90% so the specimen was purified by chromatography on silica gel. The material eluted with 40% benzene–hexene was distilled at 85–90° (0.08 mm) to yield 55 mg of colorless liquid whose nmr and infrared spectra were virtually superimposable with those of synthetically derived material. Vpc analysis (see above) showed a single peak, RT 18.6 min (96%).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.46; H, 10.65.

Conversion of Hinesol Acetate to Hinesol. A. Natural.—The sample of hinesol acetate prepared from (−)-hinesol was dissolved in ether, and this solution was treated portionwise with excess lithium aluminum hydride. After stirring overnight, the reaction mixture was quenched with excess saturated sodium sulfate. Filtration and solvent removal gave crude authentic hinesol, mp 51.5–55°, after evacuation at 25° (0.03 mm) (lit.[31] mp 56–58°): λ_{max}^{film} 2.93 (-OH), 6.02, 12.15 μ (C=C); $\delta_{TMS}^{CCl_4}$ 0.90 (3 H, doublet, J = 6.2 Hz, CH_3CH-), 1.13 [6 H, singlet, $(CH_3)_2CO-$], 5.27 ppm (1 H, triplet, $J \sim 3$ Hz, vinyl H). Vpc analysis showed a single peak at 16.8 min. Upon coinjection with synthetic hinesol a single enhanced peak was observed (see below).

B. Synthetic.—To a solution of 43 mg (0.16 mmol) of racemic hinesol acetate (**39**) in 10 ml of ether was added portionwise, as above, 0.26 g of lithium aluminum hydride. After stirring

(31) O. Motl, W. Z. Chow, and F. Šorm, *Chem. Ind. (London)*, 207, (1961).

overnight the mixture was quenched with 0.55 ml each of water and 10% sodium hydroxide, followed by processing as in the natural series to give a colorless, sweet-smelling oil, which failed to crystallize upon trituration with pentane and cooling to −50°, or upon storage for several hours at −30°. The nmr spectrum of the synthetic specimen was virtually identical with that of authentic (−)-hinesol, and the spectra were virtually superimposable. Short-path distillation at 75–80° (0.03 mm) afforded 34 mg (92% yield) of racemic hinesol (**38**).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.74; H, 11.66.

Registry No.—**2**, 13587-70-7; **3**, 26315-70-8; **5**, 26315-71-9; **9**, 26315-72-0; **10a**, 26310-73-6; **10a** dihydro thioketal, 26310-75-8; **10b**, 26310-74-7; **10b** dihydro thioketal, 26310-76-9; **10b** semicarbazone, 26310-77-0; **12b**, 26310-78-1; **13b**, 26310-79-2; **13b** thioketal, 26310-80-5; **15b**, 26310-81-6; **16b**, 26310-82-7; **17b**, 26310-83-8; **18a**, 26358-43-0; **18b**, 26310-84-9; **18b** C-2 epimer, 26310-95-2; **19b**, 26310-85-0; **21b** semicarbazone, 26310-86-1; **22a** 2,4-DNP, 26310-94-1; **23b**, 26310-87-2; **25b**, 26310-88-3; **28**, 26310-89-4; **29**, 26310-90-7; **30**, 26310-91-8; **32**, 26310-92-9; **38**, 22196-40-3; **39**, 22196-41-4.

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Charge Migration in Odd- and Even-Electron Fragment Ions. The Mass Spectrum of a Bisaziridinone

ISTVÁN LENGYEL,* DAVID B. ULISS, AND ROBERT V. MARK

Department of Chemistry, St. John's University, Jamaica, New York 11432

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The synthesis and spectra of a bisaziridinone, *viz.*, 3,3′-(1,3-adamantylene)bis(1-*tert*-butyl-2-aziridinone) (**2**), are described. The 50- and 12-eV mass spectra exhibit an abundant ion at M − 56. The major component of this peak, identified by high resolution mass measurement, is due to the expulsion of two molecules of CO from the two α-lactam rings. Alternatively, part of the molecular ions undergoes two successive McLafferty rearrangements with elimination of two C_4H_8 fragments. Even-electron ions, *m/e* 287 $(M - 2CO - CH_3)^+$ and *m/e* 273 $(M - CO - C_4H_9)^+$, eject C_4H_8 to give *m/e* 231 and 217, respectively. These processes require migration of the positive charge through σ bonds as transfer through space is precluded by the rigidity of the adamantane nucleus. Some ions in the mass spectra originate from skeletal rearrangement.

One of the basic and widely accepted conventions[1] of mass spectrometry is that the unimolecular decomposition of ions occurs at the site of the positive charge. The charge is believed to be localized at the place of lowest ionization potential. Recent work from a number of laboratories[2–5] yielded further experimental confirmation of the concept of charge localization.

However, Mandelbaum and Biemann presented evidence[6] for charge migration within fragment ions. Their model compounds were para,para′-disubstituted 1,3-diphenylcyclopentanes of unknown stereochemistry. Subsequently, Kinstle and Oliver also found[7] a similar example of charge migration: loss of two molecules of propylene in successive steps (McLafferty rearrangements) from *p,p′*-bis(valerylphenyl) ether. Both these reports describe cases in which the charge migrates within an odd-electron fragment ion.

If charge migration in ions can occur, the next as yet unanswered questions are *when* and *how* does it occur? Does the charge migrate through space or through chemical bonds, and, if the latter, can it be transmitted by σ bonds alone?

The present report is an inquiry into these questions, *i.e.*, the "mechanism" of charge migration. It was felt that a suitable model compound would have to satisfy the following prerequisites. (1) It should contain two (or more) functional groups known to trigger facile eliminations to yield *major ions* in the mass spectrum. (2) The functionalities should be joined by σ bonds only, in order to exclude π systems as possible transmittors. (3) The *first* major loss should be that of a neutral fragment, as odd-electron fragment ions are more likely to undergo charge migration than even-electron ions.[6] (4) Interaction of the (two) functionalities through space should be precluded on a stereochemical basis. (5) The difference in ionization potential between the two likely fragmentation sites should be small. (6) To avoid ambiguities, the thermal decomposition pathway of a good model compound should be different from the electron-impact induced decomposition path.

Results

Bisaziridinone **2**, a representative of a hitherto unreported class of compounds, appeared to be a promising model substrate, as it meets all the above conditions. The most favored primary fragmentation mode of monofunctional α lactams (aziridinones) upon electron impact is the loss of CO.[8,9] This process appears to

* To whom correspondence should be addressed.

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