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The Total Synthesis of *dl*-Oplopanone[1a-c]

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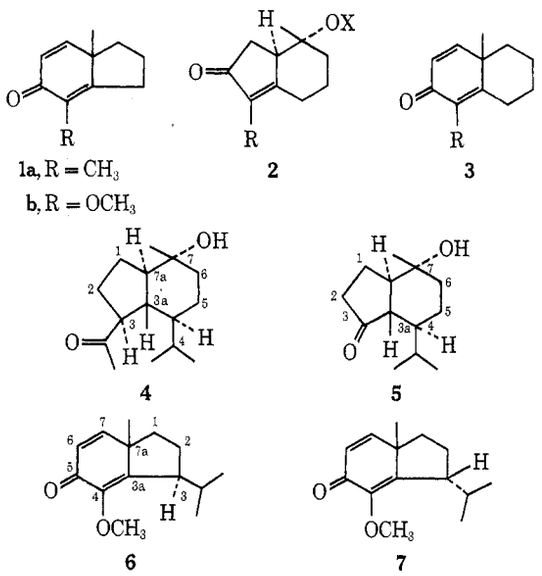
The total synthesis of *dl*-oplopanone (**4**) is described. The acetoxy ketone **12**, having the ring skeleton and three of the asymmetric centers of the natural product intact, was produced by photochemical rearrangement of the 6/5-fused, cross-conjugated cyclohexadienone **6** in glacial acetic acid. The transformation of **12** into *dl*-**4** was accomplished in a straightforward manner.

A number of successful syntheses of hydroazulene sesquiterpenoids have involved photochemical rearrangement of various 6/6-fused cross-conjugated cyclohexadienone derivatives as a means of establishing the 5/7-fused ring system.[2] In studies on the photochemistry of 6/5-fused cross-conjugated cyclohexadienone systems we have found that the 4-methyl dienone **1a** yields exclusively the 5/6-fused hydroxy ketone **2a** (X = H) on irradiation in aqueous acetic acid.[3] This behavior, which is analogous to that of the related 6/6-fused system **3a**,[4,5] suggested that photolysis of 6/5-fused dienones might provide useful intermediates for the synthesis of sesquiterpenes having a six-membered B ring. The sesquiterpene oplopanone (**4**), isolated from *Oplopanax japonicus* by Minato and coworkers,[6] has the same carbon skeleton and stereochemistry at positions 7 and 7a as does the photoproduct **2**. Thus a total synthesis of **4** by a route involving the photochemical rearrangement of an appropriately substituted 6/5-fused dienone appeared easily possible. As a key intermediate we hoped to prepare the hydroxy ketone **5**, which was obtained from oplopanone by Baeyer–Villiger oxidation followed by hydrolysis and oxidation.[6] Compound **5** has four of the five asymmetric centers of oplopanone intact and the addition of an appropriate two-carbon unit to the carbonyl group would provide a means of elaborating the acetyl group of the natural product. It was felt that the 4-methoxy dienone **6** would serve as a useful precursor to **5**. Provided that photochemical rearrangement of this compound occurred in the desired manner, the α-methoxy-α,β-unsaturated ketone system of the photoproduct could be converted into an enol ether which would then serve as a source of the carbonyl group. However, of major concern was the readiness with which the cis relationship of the methyl and isopropyl groups in **6** could be established. Examination of models of **6** and its 3α-isopropyl epimer **7** revealed that $A^{1,3}$ strain[7] involving the methoxyl and isopropyl



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(2) (a) D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *J. Chem. Soc.*, 2518 (1964); (b) G. Buchi, S. M. Kauffman, and H. J. E. Loewenthal, *J. Amer. Chem. Soc.*, **88**, 3403 (1966); (c) E. H. White, S. Eguchi, and J. N. Marx, *Tetrahedron*, **25**, 2099 (1969); (d) J. N. Marx and E. H. White, *ibid.*, **25**, 2117 (1969); (e) E. Piers and K. F. Cheng, *Can. J. Chem.*, **48**, 2234 (1970); (f) D. Caine and P. F. Ingwalson, *J. Org. Chem.*, **37**, 3751 (1972).

(3) D. Caine, W. J. Powers, III, and J. T. Gupton, III, Abstracts of Papers, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 23–27, 1970, No. ORGN 97.

(4) (a) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29**, 3108 (1964); (b) P. J. Kropp, *ibid.*, **29**, 3110 (1964).

(5) For comprehensive reviews on the photochemistry of 6/6-fused dienones see (a) P. J. Kropp, *Org. Photo. Chem.*, **1**, 1 (1967); (b) K. Schaffner, *Advan. Photo. Chem.*, **4**, 81 (1966).

(6) K. Takeda, H. Minato, and M. Ishikawa, *Tetrahedron, Suppl.*, **No. 7**, 219 (1965); *Chem. Commun.*, 79 (1965).

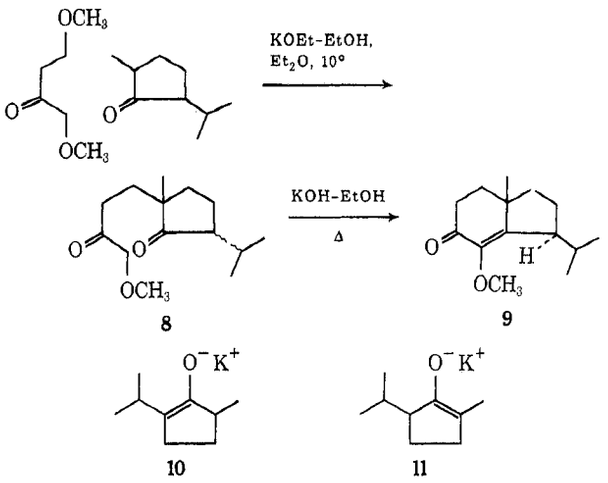
(7) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

groups was more severe when the latter was in the α configuration. It seemed possible that such an interaction in **7** might be sufficiently strong to outweigh the cis methyl–isopropyl interaction which exists in **6** so that the latter isomer might be the more thermodynamically stable of the two. Thus a method of synthesis of **6** which involved equilibration at C-3 appeared to have reasonable likelihood of success.

Before the synthesis of **6** was attempted the photochemical behavior of the model 4-methoxy dienone **1b** was investigated. This dienone was prepared by condensation of 1,4-dimethoxy-2-butanone with 2-methylcyclopentanone using the procedure of Wenkert and Berges[8] followed by oxidation of the resulting 6/5-fused enone with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane.[9] Previous work had shown that the 6/6-fused methoxy ketone **3b** was hydrolyzed to a diosphenol without rearrangement of the skeleton when irradiated in aqueous acetic acid; however, it was smoothly converted into a 5/7-fused acetoxy ketone when glacial acetic acid was employed as the solvent.[10] Thus methoxyl and methyl substituents at the 4 position exert a similar influence on the course of photochemical rearrangements of dienones such as **3** in nucleophilic solvents. This also proved to be the case for the 6/5-fused system. When a *ca.* 2% solution of **1b** in glacial acetic acid was irradiated for 4 hr using a 450-W Hanovia lamp fitted with a Pyrex sleeve, the 5/6-fused acetoxy ketone **2b** (X = Ac) was obtained in 85% yield. The structure and stereochemistry of this compound were assigned on the basis of the similarity of its nmr spectrum to that of **2a** (X = H) and the related 5/7-fused hydroxy and acetoxy ketones derived from **3a**[4] and **3b**,[10] respectively.

The behavior of **1b** clearly indicated that the photochemical rearrangement of **6** would be expected to take place in the desired manner. Dienone **6** was prepared by way of the diketone **8** and the enone **9**. Condensation of 1,4-dimethoxy-2-butanone[8] with 2-methyl-5-isopropylcyclopentanone[11] gave the diketone **8** in 25% yield as a mixture of cis and trans isomers.[12] It is of interest that none of the alternative diketone derived from alkylation at the α position bearing the isopropyl group was observed. The reaction was carried out under conditions which should allow equilibration between the two potassium enolates **10** and **11** which may be derived from 2-methyl-5-isopropylcyclopentanone. The enolate **11**, having the smaller methyl substituent on the double bond, might be expected to be both more stable thermodynamically and more reactive in the Michael reaction than the isomeric species **10**. Perhaps the combination of these factors accounts for the fact that **8** is formed exclusively.

On heating **8** with alcoholic potassium hydroxide for 1 hr a single aldol product, which was unaffected by prolonged base treatment, was obtained in 68% yield. The spectral properties of this product were consistent



with the enone structure **9** or the corresponding 3α-isopropyl isomer. As in the case of the dienones **6** and **7** discussed earlier, examination of models indicated that the strong A[1,3] interaction involving the methoxyl group and the 3α-isopropyl group might cause the 3β-isopropyl enone to be the more thermodynamically stable isomer. Although it was surprising that only a single isomer was obtained under thermodynamic conditions, the subsequent work provided support for the assignment of the 3β-isopropyl structure **9** to this material.

Oxidation of **9** with selenium dioxide in *tert*-butyl alcohol using a modification of the procedure of Bloom[13] yielded a 5:1 mixture of cross-conjugated dienones.[14] Treatment of this mixture with potassium *tert*-butoxide in *tert*-butyl alcohol left its composition unchanged, indicating that equilibrium was established under the conditions of the oxidation reaction. The subsequent conversion of the major component of this mixture into **5** (and its unstable 3α epimer) indicated that it was the desired 3β-isopropyl dienone **6**. Thus the minor component of the mixture was the 3α-isopropyl compound **7**. Examination of models in the α and β series revealed that the distances between the isopropyl groups and the angular methyl and the methoxyl groups change very little in going from the enones to the corresponding dienones. Therefore, it seemed likely that the 3β-isopropyl isomer would be the more thermodynamically stable one in both cases. However, since two isomeric dienones were isolated, it appears that the difference in energy between the α and β isomers is smaller in the dienone than in the enone systems. It is possible that the increased stability of the α-isopropyl dienone relative to the corresponding enone results from a decrease in the interaction between the isopropyl group and C-7 owing to the change in hybridization from sp^3 to sp^2 at the latter position.

Dienones **6** and **7** were separated by careful chromatography on silica gel. Irradiation of **6** under the same conditions as described for **1b** gave the crystalline acetoxy ketone **12** in 91% yield. The nmr spectrum (CCl_4) of **12** showed a singlet at δ 1.22 for the 7-methyl group, a singlet at δ 1.91 for the acetate group, a singlet

(8) (a) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967). (b) We are grateful to Professor Wenkert for making the details of this procedure available to us prior to publication.

(9) D. Burn, R. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(10) D. Caine and P. F. Ingwalson, unpublished work.

(11) K. Sisido, S. Kurozumi, K. Utimoto, and T. Ishida, *J. Org. Chem.*, **31**, 2795 (1966).

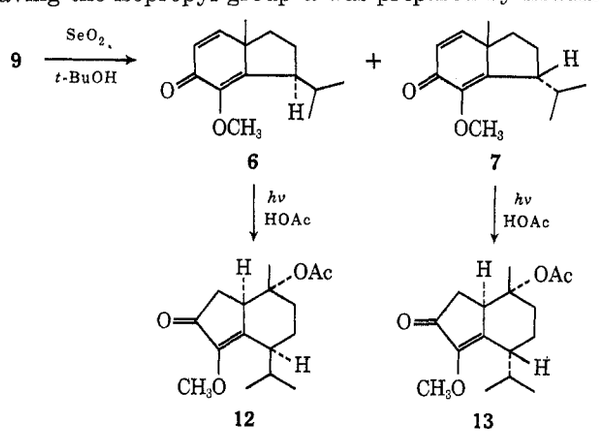
(12) Although this condensation was attempted under a variety of conditions and 1-methoxy-3-buten-2-one was substituted for 1,4-dimethoxy-2-butanone, the yield of **8** could not be significantly improved.

(13) S. M. Bloom, *J. Amer. Chem. Soc.*, **81**, 4728 (1959).

(14) Treatment of **9** with DDQ in dioxane under the same conditions as were employed for the synthesis of **1b** from the corresponding enone gave a mixture of dienones composed mainly of the linearly conjugated system. The reasons for the difference in behavior of these two enones toward DDQ are not clear.

at δ 3.84 for the methoxyl group, and pairs of doublets (J = 6 Hz) at δ 0.88 and 0.97 for the nonequivalent methyls of the isopropyl group. An apparent triplet (J = 4.5 Hz) at δ 3.01 and an apparent doublet (J = 4.5 Hz) at δ 2.18 were assigned to the 7a proton and the 1-methylene protons. This apparent AB_2 pattern for the 7aα and 1 protons as well as the location of the absorption for the 7β-methyl group (which because of shielding by the 3,3a double bond is at higher field than is normally observed for a methyl group attached to a carbon bearing an acetoxy group) is characteristic of enones such as **2** and the related 5/7-fused systems. Thus the spectral properties of **12** were indicative of the cis relationship of the angular hydrogen and the adjacent oxygen function.

For comparison purposes the acetoxy ketone **13** having the isopropyl group α was prepared by irradia-

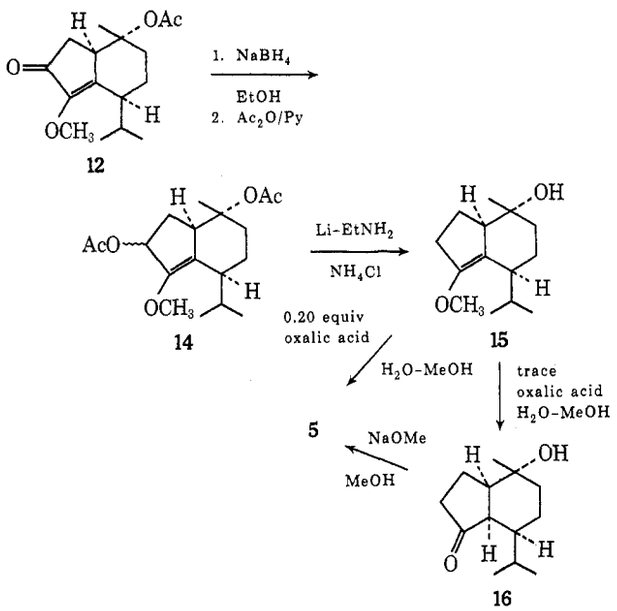


tion of the 5:1 mixture of **6** and **7** followed by fractional crystallization of the photoproducts from ether–hexane. Compound **13** exhibited a similar nmr spectrum (CCl_4) to that of **12** except that the doublets for the methyl absorptions of the isopropyl group were somewhat more separated.

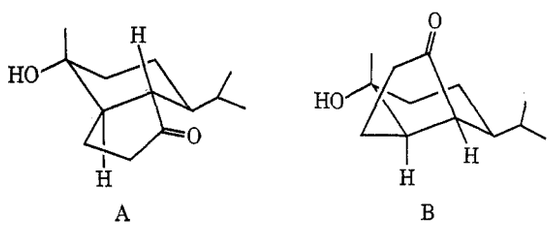
The transformation of **12** into the hydroxy ketone **5** was accomplished *via* a procedure similar to that employed for the conversion of other α-methoxy-α,β-unsaturated ketones into saturated ketones with the carbonyl group at this α position.[15,16] Treatment of **12** with sodium borohydride in ethanol followed by acetic anhydride in pyridine gave a 2:1 mixture of allylic acetates (**14**) in 94% yield. Addition of lithium to a solution of **14** in ethylamine containing 1 equiv of *tert*-butyl alcohol at −78° followed by quenching with ammonium chloride caused cleavage of the allylic acetate group[17] and reduction of the tertiary acetate group to produce the hydroxy enol ether **15**. Hydrolysis of **15** using 0.20 equiv of oxalic acid in aqueous methanol gave a 70% yield of the racemic trans-fused hydroxy ketone **5** which showed identical nmr and ir spectral properties with those reported by Minato and coworkers[6] for the product obtained from degradation of oplopanone. As reported,[6] compound **5** was stable to sodium methoxide in methanol. Alternatively, brief treatment of **15** with a trace of oxalic acid in aqueous methanol produced another hydroxy ketone which was converted into **5** on extended acid treatment

(15) D. Caine and J. B. Dawson, *Chem. Commun.*, 1232 (1970).
(16) R. E. Ireland, D. R. Marshall, and J. W. Tilley, *J. Amer. Chem. Soc.*, **92**, 4754 (1970).
(17) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

or on reflux with sodium methoxide in methanol. Kinetic hydrolysis of **15** should yield the cis-fused hydroxy ketone **16**, since kinetic protonation of the enol

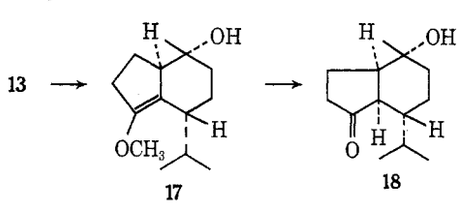


ether function should occur from the side of the molecule opposite the axial 7β-methyl group. Structures A and B represent the most favorable conformation of the

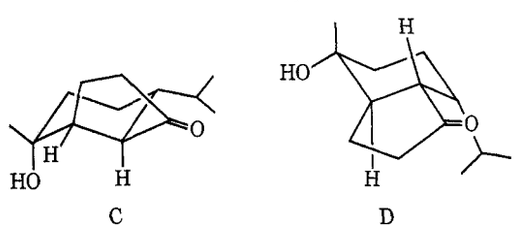


trans- and cis-fused ketones **5** and **16**. Clearly the cis isomer is the less stable of the two because of the unfavorable 1,3 interaction between the carbonyl group and the 7β-methyl group which is absent in the trans compound. Thus acid- or base-catalyzed epimerization of **16** at C-3a should occur readily to give **5**.

The photoproduct **13** was converted into the enol ether **17** by a route similar to that described above.



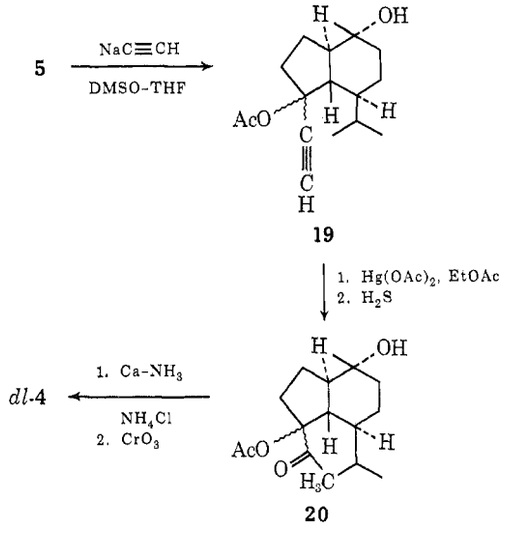
Hydrolysis of **17** with oxalic acid under mild conditions produced a hydroxy ketone which was unchanged after being refluxed with sodium methoxide in methanol. We believe that this compound has the cis-fused ring structure **18**. Structure C represents the most stable



conformation of **18** while the trans isomer in this series would be represented by D. The cis isomer should be the much more stable of the two because in the trans compound both the isopropyl group and the methyl group must be axial to the B ring unless it adopts a boat conformation. Kinetic β protonation of **17** at the 3a position to give a trans ring system would be hindered by the 7-methyl group. Thus it is not surprising that hydrolysis of **17** yielded the thermodynamically more stable cis product.

The nmr absorptions for the 7-methyl groups of hydroxy ketones **16**, **5**, and **18** occurred at δ 0.96, 1.14, and 1.17, respectively. The observed downfield shift in going from **16** to **5** is consistent with the structural assignments, because shielding of the methyl group by the carbonyl group would be removed in going from the cis to the trans ring fusion. It should be noted that, if the configuration of the isopropyl group were α as in **18** or its unstable 3a epimer, no such change in the chemical shift of the 7-methyl group would be expected. The formation of two hydroxy ketones from hydrolysis of **15** and only one from hydrolysis of **17** provides direct chemical evidence for the assignment of the β and α configurations, respectively, for the isopropyl groups in these compounds and in their dienone precusors.

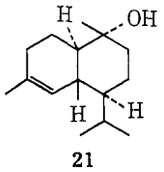
Completion of the synthesis of *dl*-oplopanone from **5** required introduction of the acetyl side chain at the 3 position. This was accomplished *via* intermediates **19** and **20**, which, although not fully characterized, exhibited the expected spectral properties. Treatment of **5** with sodium acetylide in dimethyl sulfoxide (DMSO)–tetrahydrofuran (THF)[18] gave the ethynyl carbinol **19**, which showed a one-proton absorption at δ 2.43 for the ethynyl proton. The crude product was then converted into the α-acetoxy ketone **20** by treatment



with mercuric acetate followed by hydrogen sulfide.[19] The nmr spectrum of **20** exhibited two three-proton singlets at δ 2.09 and 2.16 for the acetyl and acetoxyl groups, respectively. Reductive removal of the α-acetoxyl group with calcium in liquid ammonia[20] followed by oxidation with Jones reagent[21] and chromatography on silica gel afforded *dl*-oplopanone, mp 101.5–102.0°, which exhibited nmr, ir, and glc properties which were identical with those of an authentic sample of the natural product.[22]

The synthetic work provides no new evidence for the stereochemistry of oplopanone at C-3. Steric factors would favor α protonation of the enolate intermediate formed in the reductive removal of the acetoxyl group leading to a β acetyl side chain, but it is probable that equilibration at C-3 would have occurred prior to reduction of the carbonyl group or during the Jones oxidation and subsequent chromatography. Examination of models having the 3-acetyl group α and β does not allow one to say unambiguously which isomer is the more thermodynamically stable. The conditions employed by Minato and coworkers for the isolation of the natural product would very likely have allowed equilibration at C-3.[6] The evidence provided by these authors indicated that the C-3 side chain is β as shown in **4**.[6] Although this assignment is probably correct, further confirmation of this point would be desirable.

The stereochemistry of photoproducts **12** and **13** is the same as is found in α-cadinol (**21**)[23] and T-murrolol (**22**),[24] respectively, at three of the four asymmetric



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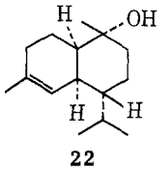

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centers. Approaches to these 6/6-fused natural products by ring expansion of the corresponding 5/6-fused systems are under investigation.

Experimental Section[25]

7,7a-Dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone.—In a 500-ml round-bottom flask equipped with a mechanical stirrer and a dropping funnel was placed 1.47 g (0.9376 g-atom) of potassium, and 11 ml of absolute ethanol was added dropwise with stirring under nitrogen. After the reaction was complete and the flask had cooled to room temperature, 900 ml of anhydrous ether was added, and the mixture was cooled with an ice bath to 10°. To this was added 19.6 g (0.200 mol) of 2-methylcyclopentanone in 20 ml of anhydrous ether. A solution of 13.2 g (0.100 mol) of

(18) J. Kříž, M. J. Beneš, and J. Peška, *Tetrahedron Lett.*, 2881 (1965).

(19) H. B. Kagen, A. Marquet, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1079 (1960).

(20) J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

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

(22) We wish to express our deep appreciation to Dr. H. Minato for supplying us with an authentic sample of oplopanone.

(23) (a) V. Herout and V. Sykora, *Tetrahedron*, **4**, 246 (1958); (b) Y. T. Lin, Y. S. Cheng, and Y. H. Kuo, *Tetrahedron Lett.*, 3881 (1968).

(24) (a) Y. S. Cheng, Y. H. Kuo, and Y. T. Lin, *Chem. Commun.*, 565 (1967); (b) Y. H. Kuo, Y. S. Cheng, and Y. T. Lin, *Tetrahedron Lett.*, 2375 (1969).

(25) Melting points and boiling points are uncorrected. Infrared spectra were taken on Perkin-Elmer Model 457 or 137 infrared spectrophotometers. Ultraviolet spectra were taken on a Cary Model 14 or a Beckman DBGT recording spectrophotometer using 1-cm matched quartz cells. Nmr spectra were determined at 60 MHz with a Varian A-60 spectrometer and at 100 MHz with a Jeolco 4H-100 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. The abbreviations s, d, d of d, t, and m refer to singlet, doublet, doublet of doublets, triplet, and multiplet, respectively. Mass spectra were obtained using a Varian M-66 spectrometer. Gas–liquid chromatography was carried out with a Perkin-Elmer Model 881 or Aerograph A-90-P3 gas chromatograph. The following columns were used: A (6 ft × 0.125 in. stainless steel, 10% Carbowax K-20M on 60/80 Chromosorb W HMDS); B (10 ft × 0.25 in. stainless steel, 12% tris(2-cyanoethoxy)propane on 80/100 Diataport silanized with dichlrodimethylsilane). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Atlantic Microlab, Inc., Atlanta, Ga.

1,4-dimethoxy-2-butanone[26] in 120 ml of anhydrous ether was added dropwise with rapid stirring over about 2 hr, while the temperature was maintained at 8–10° with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being warmed to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. The ether layer was decanted from the solid, washed with 50 ml each of water and saturated brine, dried (Na_2SO_4), concentrated, and distilled, giving 11.13 g (62%) of 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone as a colorless liquid, bp 85–88° (0.51 mm). Redistillation of a small portion afforded an analytical sample: bp 73° (0.04 mm); uv max (95% EtOH) 254 nm (ϵ 8260); ir (film) 1673 (α,β-unsaturated C=O), 1647 (conjugated C=C), 1210, 1110, and 1089 cm^{-1}; nmr (CCl_4) δ 1.18 (s, 3 H, 7a-CH_3), 1.62–2.02 (m, 6 H, 1, 2, and 7-CH_2), 2.24–2.78 (m, 4 H, 3- and 6-CH_2), and 3.54 ppm (s, 3 H, 4-OCH_3); mass spectrum (70 eV) *m/e* 180.11490 (M^+) (calcd, 180.11494) and 165 ($M^+ - CH_3$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 9.05.

4-Methoxy-7a-methyl-5(7a*H*)-indanone (1b).—A 1000-ml round-bottom flask equipped with a magnetic stirrer and reflux condenser and having a nitrogen atmosphere was charged with 400 ml of dioxane (freshly distilled over sodium), 5.4 g (0.03 mol) of 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone, and 7.02 g (0.31 mol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The mixture was stirred until homogeneous and then stirred at reflux for 36 hr. After it cooled to room temperature, the dioxane was removed *in vacuo* and the residue was dissolved in 100 ml of benzene and filtered to remove 2,3-dichloro-5,6-dicyano-*p*-hydroquinone (DDHQ). The filter cake was washed with 50 ml of benzene and the combined filtrates were concentrated. The residue was placed on a column of 50 g of neutral alumina and rapidly eluted with 500 ml of benzene. Evaporation of the benzene gave 3.86 g of a pale yellow oil which by glc analysis (column A) was shown to contain about equal amounts of **1b** and the starting material. Chromatography on 100 g of silica gel using hexane–ether as eluent afforded 1.85 g of the starting enone (20% ether in hexane) and 1.80 g (51%) of the dienone **1b** (40% ether in hexane). Distillation of a small portion of the latter afforded an analytical sample: bp 75° (0.03 mm); uv max (95% EtOH) 242 nm (ϵ 5430) and 276 (1371);[27] ir (film) 1649 (α,β-unsaturated C=O), 1608 (conjugated C=C), 1452, 1208, 1152, 1081, and 840 cm^{-1}; nmr (CCl_4) δ 1.22 (s, 3 H, 7a-CH_3), 3.68 (s, 3 H, 4-OCH_3), and 6.01 and 6.99) ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 5,7-H); mass spectrum (70 eV) *m/e* 178.09907 (M^+) (calcd, 178.09930) and 163 ($M^+ - CH_3$).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.01.

Irradiation of 4-Methoxy-7a-methyl-5(7a*H*)-indanone (1b).—A solution of 2.0 g of **1b** in 250 ml of gacial acetic acid (dried over 5A molecular sieves and distilled) was irradiated with a 450-W high-pressure mercury lamp for 4 hr using a Pyrex probe. A slow stream of dry nitrogen was bubbled through the solution for 10 min prior to and during the entire irradiation period. The solution was washed into a 500-ml round-bottom flask with benzene and frozen quickly in a Dry Ice–acetone bath, and the solvents were removed by lyophilization to afford a yellow oil which on distillation gave 2.27 g (85%) of **2b**: bp 102–105° (0.05 mm); mp 54.5–55°; uv max (95% EtOH) 252 nm (ϵ 11,300); ir (film) 1732 (ester C=O), 1710 (α,β-unsaturated C=O), 1650 (conjugated C=C), 1450, 1370, 1257, 1237, and 1098 cm^{-1}; nmr (CCl_4) δ 1.28 (s, 3 H, 7-CH_3), 1.97 (s, 3 H, 7-OAc), 2.27 (d, J = 4 Hz, 2 H, 1-CH_2), 3.08 (t, J = 4 Hz, 1 H, 7a-CH), and 3.90 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) *m/e* 178 ($M^+ - HOAc$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.26; H, 7.75.

2-Methyl-5-isopropylcyclopentanone.—A 3000-ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer, and an addition funnel, was flame dried and established with a dry nitrogen atmosphere. Potassium (30.1 g, 0.771 g-atom) was introduced and 340 ml of anhydrous ethanol was added dropwise at a rate that allowed gentle reflux. After the reaction was complete, 136.4 g (0.675 mol) of diethyl adipate was added slowly with stirring, and the mixture was stirred at reflux for 7 hr. The ethanol (200 ml) was removed by distillation and 1000 ml of dry toluene was added. Distillation was continued until the temperature of the vapor was 110°. Often the addition of about 200–500 ml more of dry toluene was necessary during the distillation to sufficiently reduce the viscosity of the enolate sludge to allow efficient agitation. The mixture was allowed to cool slightly, and 131 g (0.77 mol) of 2-iodopropane was added. Stirring at reflux was continued for 12 hr, 30 g more of 2-iodopropane was added, and stirring at reflux was continued for 12 hr. After the reaction mixture had been cooled to room temperature, 200 ml of water was added with stirring, the layers were separated, and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with saturated brine, concentrated, and distilled to give 110 g (82%) of 2-carbethoxy-2-isopropylcyclopentanone, bp 90° (1.5 mm) [lit.[28] bp 112° (11 mm)].

A 3000-ml three-neck flask, equipped with a variable takeoff distilling head, a mechanical stirrer, and an addition funnel, was flame dried and charged with 750 ml of anhydrous ethanol under nitrogen. Sodium, 50 g (2.3 g-atoms), was added in small pieces at a sufficient rate to maintain slow reflux. After the sodium had reacted, 396 g (2.00 mol) of 2-carbethoxy-2-isopropylcyclopentanone was added slowly and the mixture was refluxed with rapid stirring for 7 hr. The ethanol (500 ml) was distilled, 1500 ml of dry toluene was added, and distillation was continued until the temperature of the vapor was 110°. The mixture was cooled to room temperature, 142 g (2.0 mol) of methyl iodide was added, and stirring was continued for 8 hr at room temperature; additional methyl iodide (40 g) was added and the mixture was stirred at reflux for 6 hr. After the reaction mixture cooled to room temperature, 200 ml of water was added, the layers were separated, and the aqueous layer was extracted with 100 ml of benzene. The combined organic layers were washed with brine, concentrated, and returned to the 3000-ml three-neck flask along with 1200 ml of water and 600 ml of concentrated sulfuric acid. The mixture was refluxed with vigorous stirring for 24 hr and cooled to room temperature, and the layers were separated. The aqueous layer was extracted with 3 × 100 ml of benzene, and the combined organic extracts were washed with 100 ml of water, 150 ml saturated sodium bicarbonate solution, and 50 ml of water, dried (Na_2SO_4), concentrated, and distilled to give 186 g (67%) of 2-methyl-5-isopropylcyclopentanone, bp 185° (760 mm) [lit.[11] bp 181–186° (740 mm)].

2-(1-Methoxy-2-butanon-4-yl)-2-methyl-5-isopropylcyclopentanone (8).—In a 5000-ml round-bottom flask equipped with a mechanical stirrer, dropping funnel, a thermometer, and a condenser was placed potassium (13.2 g, 0.1128 g-atom), and 100 ml of anhydrous ethanol was added slowly. After the potassium had reacted and the solution was cooled to room temperature, 900 ml of anhydrous ether was added. The mixture was cooled to 10° and 252 g (1.8 mol) of 2-methyl-5-isopropylcyclopentanone in 120 ml of anhydrous ether was added. Then a solution of 132.0 g (1.0 mol) of 1,4-dimethoxy-2-butanone[26] in 1000 ml of anhydrous ether was added dropwise with rapid stirring over about 4 hr, while the temperature was maintained at 10–13° with an ice bath. After the addition was complete, the reaction mixture was stirred for 3 hr longer while being allowed to warm to room temperature. An ethereal solution of glacial acetic acid (10% by volume) was added dropwise until the red color of the reaction mixture changed to yellow. Saturated sodium bicarbonate solution (200 ml) was added with stirring, the layers were separated, and the aqueous layer was extracted with 100 ml of ether. The combined ethereal extracts were washed with water and dried (Na_2SO_4). The ether was removed *in vacuo* at room temperature and the unreacted 2-methyl-5-isopropylcyclopentanone (170 g) was removed by distillation at reduced pressure, bp 30–40° (20 mm), while the pot temperature was maintained at 75° or below. The residue was further distilled to yield 35 g (25%) of **8**, bp 140–150° (0.75 mm). A small portion was redistilled to afford an analytical sample: bp 113° (0.25 mm); ir (film) 1729 (C=O), 1460, 1370, 1200, and 1108 cm^{-1}; nmr (CCl_4) δ 0.90 and 0.98 (2 s, 3 H, 2-CH_3), 0.71–1.08 (m, 6 H, 5-*i*-Pr), 3.35 (s, 3 H, OCH_3),

(26) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, **18**, 1601 (1953).

(27) The short and the less intense long wavelength uv absorption bands exhibited by dienones **1b**, **6**, and **7** are apparently characteristic of α-methoxy cross-conjugated dienone systems. For example, the 6/6-fused dienone related to **1b** exhibits similar bands. Also, for a somewhat related case, hydroxyeremophilone methyl ether, see L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 6354 (1960).

(28) A. Kotz and P. Schuler, *Justus Liebigs Ann. Chem.*, **350**, 221 (1906).

and 3.86 ppm (s, 2 H, $COCH_2O$); mass spectrum (70 eV) *m/e* 240.17243 (M^+) (calcd, 240.17241) and 195 ($M^+ - CH_2OCH_3$).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.09; H, 10.16.

7,7a-Dihydro-4-methoxy-7a-methyl-3-isopropyl-5(6*H*)-indanone (9).—To a 500-ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer containing 20.0 g of potassium hydroxide in 200 ml of absolute ethanol was added 20.0 g (0.083 mol) of **8**. After stirring at reflux for 1 hr under nitrogen, the reaction mixture was cooled and glacial acetic acid was added dropwise with stirring until the red color of the solution had turned yellow (usually about 20 ml). The ethanol was removed *in vacuo* and the residue was mixed with ether and water. The layers were separated, the aqueous layer was extracted with ether, and the combined ethereal solutions were washed with 50 ml each of saturated sodium bicarbonate and water, dried (Na_2SO_4), concentrated, and distilled to yield 12.5 g (68%) of **9**, bp 100–105° (0.45 mm). Redistillation of a small portion afforded an analytical sample: bp 89–90° (0.04 mm); uv max (95% EtOH) 259 nm (ϵ 7969); ir (film) 1675 (α,β-unsaturated C=O), 1631 (C=C), 1461, 1295, 1209, 1112, and 1085 cm^{-1}; nmr (CCl_4) δ 0.83 and 0.95 (pair of d's, J = 7 Hz, 6 H, 3-CH_3CHCH_3), 1.19 (s, 3 H, 7a-CH_3), and 3.61 ppm (s, 3 H, 4-OCH_3); mass spectrum (70 eV) *m/e* 222.16196 (M^+) (calcd, 222.16186), 207 ($M^+ - CH_3$), and 179 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.44; H, 9.71.

Oxidation of 9 with Selenium Dioxide.—A 5000-ml three-neck flask fitted with a mechanical stirrer and variable takeoff distilling head was flame dried and charged with 22.2 g (0.200 mol) of freshly sublimed selenium dioxide, 3000 ml of *tert*-butyl alcohol (freshly distilled over sodium *tert*-butoxide), and 10 ml of glacial acetic acid. The mixture was stirred under nitrogen with warming until the selenium dioxide had dissolved and a solution of 11.1 g (0.05 mol) of **9** in 500 ml of *tert*-butyl alcohol was added. After the reaction mixture had been stirred at reflux for 4 days, 3000 ml of *tert*-butyl alcohol was removed by distillation. The remaining suspension was cooled and filtered through a fritted glass funnel to remove metallic selenium. The filtrate was concentrated *in vacuo* and the residue was dissolved in 500 ml of ether and filtered again to remove unreacted selenium dioxide. The ethereal filtrate was stirred with 200 ml of saturated sodium carbonate solution, and solid sodium carbonate was added slowly until the evolution of carbon dioxide ceased. The ether–water mixture was filtered with suction and the filter cake was washed with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was triturated with 3 × 75 ml of hot hexane, and the hexane extracts were concentrated and distilled to give 8 g of a yellow oil, bp 90–100° (0.3 mm), which by glc analysis (column A) was shown to be a 3:1 mixture of dienone products and the enone **9**. Chromatography on 200 g of neutal alumina using hexane–ether as the eluent afforded 1.95 g of **9** (10% ether in hexane) and 5.92 g (65%) of a mixture of dienones (25% ether in hexane). Analysis by glc (column B) and nmr showed that this mixture was composed of dienones **6** and **7** in a 5:1 ratio. Careful chromatography on silica gel permitted the isolation of the pure components of this mixture. The physical properties of the 3β-isopropyl compound **6** were bp 94–97° (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 4145) and 283 (1113);[27] ir (film) 1659 (α,β-unsaturated C=O), 1608 (C=C), 1462, 1370, 1330, 1213, 1148, 1077, and 840 cm^{-1}; nmr (CCl_4) δ 0.92 and 0.97 (pair of d's J = 7 Hz, 6 H, 3β-CH_3CHCH_3), 1.21 (s, 3 H, 7a-CH_3), 3.79 (s, 3 H, 4-OCH_3), and 5.99 and 6.88 ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 6,7-H); mass spectrum (70 eV) *m/e* 220.14607 (M^+) (calcd, 220.14622), 205 ($M^+ - CH_3$), and 177 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.26.

The physical properties of the 3α-isopropyl isomer **7** were bp 94–97° (0.07 mm); uv max (95% EtOH) 243 nm (ϵ 6700) and 283 (3600);[27] ir (film) 1661 (α,β-unsaturated C=O), 1609 (C=C), 1460, 1370, 1211, 1150, 1073 and 840 cm^{-1}; nmr (CCl_4) δ 0.68 and 0.97 (pair of d's, J = 7 Hz, 6 H, 3α-CH_3CHCH_3), 1.22 (s, 3 H, 7a-CH_3), 3.69 (s, 3 H, 4-OCH_3), and 5.99 and 6.94 ppm (AB quartet, J_{AB} = 10 Hz, 2 H, 6,7-H); mass spectrum (70 eV) *m/e* 220.14632 (M^+) (calcd, 220.14622), 205 ($M^+ - CH_3$), and 177 ($M^+ - CH_3CHCH_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 9.34.

Attempted Equilibration of a 5:1 Mixture of 6 and 7.—In a 25-ml three-neck flask fitted with a reflux condenser, a mechanical stirrer, and an addition funnel and maintained under a nitrogen atmosphere was placed 0.012 g (0.00033 g-atom) of potassium and 10 ml of dry *tert*-butyl alcohol. After the potassium had reacted, 0.67 g (0.0033 mol) of the 5:1 mixture of **6** and **7** in 10 ml of dry *tert*-butyl alcohol was added and the mixture was stirred at reflux overnight. After cooling and addition of 0.018 g (0.0003 mol) of glacial acetic acid in 10 ml of *tert*-butyl alcohol, the mixture was concentrated by lyophilization and the residue was dissolved in ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give a brown oil, which by glc (column B) and nmr analysis could not be distinguished from the starting material.

Irradiation of 4-Methoxy-7a-methyl-3β-isopropyl-5(7a*H*)-indanone (6).—A solution of 0.90 g of **6** in 250 ml of glacial acetic acid (dried over 5A molecular sieves and freshly distilled) was irradiated for 4 hr using a 450-W high-pressure mercury lamp fitted with a Pyrex probe. A slow stream of dry nitrogen was bubbled through the solution for 10 min prior to and during the entire irradiation period. Removal of the solvent by lyophilization and recrystallization of the residue from ether–hexane gave 1.04 g (91%) of 3-methoxy-4β-isopropyl-7α-acetoxy-7β-methyl-5,6,7,7aα-tetrahydro-2(4*H*)-indanone (**12**): mp 73–74.5°; uv max (95% EtOH) 252 nm (ϵ 9800); ir (CCl_4) 1738 (OAc), 1714 (α,β-unsaturated C=O), 1630 (C=C), 1444, 1383, 1370, 1250, 1237, and 1102 cm^{-1}; nmr (CCl_4) δ 0.88 and 0.97 (pair of d's, J = 6 Hz, 6 H, 4β-CH_3CHCH_3), 1.22 (s, 3 H, 7-CH_3), 1.91 (s, 3 H, 7-OAc), 2.18 (d, J = 4.5 Hz, 2 H, 1-CH_2), 3.01 (t, J = 4.5 Hz, 1 H, 7a-CH), and 3.84 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) *m/e* 220 ($M^+ - HOAc$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.33; H, 8.79.

Irradiation of a 5:1 Mixture of 6 and 7.—A solution of 2.0 g of a 5:1 mixture of **6** and **7** in 250 ml of glacial acetic acid was irradiated as described above. Removal of the solvent by lyophilization afforded 2.20 g (86%) of a yellow solid. This material was fractionally crystalized from ether–hexane to yield 1.80 g of **12**, mp 73–75°, and 0.36 g of 3-methoxy-4α-isopropyl-7α-acetoxy-7β-methyl-5,6,7,7aα-tetrahydro-2(4*H*)-indenone (**13**): mp 98–99°; uv max (95% EtOH) 254 nm (ϵ 10,900); ir (CCl_4) 1733 (OAc), 1709 (α,β-unsaturated C=O), 1643 (C=C), 1448, 1371, 1249, 1232, and 1098 cm^{-1}; nmr (CCl_4) δ 0.84 and 1.02 (pair of d's, J = 6 Hz, 6 H, 4α-CH_3CHCH_3), 1.28 (s, 3 H, 7-CH_3), 1.97 (s, 3 H, 7-OAc), 2.30 (d, J = 4 Hz, 2 H, 1-CH_2), 3.21 (t, J = 4 Hz, 1 H, 7a-CH), and 3.90 ppm (s, 3 H, 3-OCH_3); mass spectrum (70 eV) *m/e* 220 ($M^+ - HOAc$).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.47.

2,7α-Diacetoxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,-7aα-hexahydroindene (14).—In a 10-ml round-bottom flask a mixture of 0.526 g (0.0188 mol) of **12**, 0.0720 g (0.00188 mol) of sodium borohydride, and 8 ml of absolute ethanol was stirred at room temperature under nitrogen for 48 hr. Acetone (1 ml) was added, and, after the mixture was stirred for 2 hr, the volatile material was removed *in vacuo* with warming. The residue was dissolved in a mixture of 10 ml of ether and 10 ml of water; the layers were separated; and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4), and concentrated to give 0.635 g of a pale yellow oil, which exhibited the nmr and ir spectral properties expected for a 2:1 mixture of the 2 epimers of 7α-acetoxy-2-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene. The crude reaction product was placed in a 25-ml round-bottom flask along with 1.5 g of acetic anhydride and 8 ml of dry pyridine and the mixture was stirred under nitrogen for 20 hr at room temperature. After the reaction mixture was cooled to 0° with an ice bath, 2 g of ice was added and the mixture was stirred for 2 hr while being allowed to warm to room temperature. The mixture was poured into 50 ml of ether and washed with water. The aqueous layer was extracted with 20 ml of ether and the combined ether extracts were washed with 5-ml portions of 10% aqueous sulfuric acid until the washing remained acidic. The ether layer was washed with saturated sodium bicarbonate, dried (Na_2SO_4), and concentrated to give 0.572 g (94%) of **14** as a viscous oil. Crystallization from hexane at −78° afforded a solid which melted upon warming to room temperature: ir (film) 1720 (ester C=O), 1668 (C=C), 1448, 1369, 1243, 1090, and 1018 cm^{-1}; nmr (CCl_4) δ 0.89 and 0.93 (pair of d's, J = 6 Hz, 6 H, 4β-CH_3CHCH_3), 1.27 and 1.33 (s, 3 H, 7-CH_3 of two

isomers), 1.89 (s, 3 H, 7-OAc), 2.01 (s, 3 H, 2-OAc), 3.51 (s, 3 H, 3-OCH_3) and 5.63–5.92 ppm (m, 1 H, 2-H); mass spectrum (70 eV) *m/e* 264 (M^+ − HOAc).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 68.06; H, 9.28. Found: C, 68.32; H, 9.37.

2,7α-Diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,-7aα-hexahydroindene.—Following the same procedure described above, a 10-ml round-bottom flask was charged with 0.526 g (0.0019 mol) of **13**, 0.072 g (0.0019 mol) of sodium borohydride, and 8 ml of absolute ethanol; the reaction mixture was stirred for 48 hr. The work-up gave 0.547 g of the expected alcohol as a pale yellow oil which was acetylated using 1.5 g of acetic anhydride and 8 ml of dry pyridine as described above to yield 0.521 g (86%) of a mixture of the 2 epimers of 2,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene. Crystallization from ether–hexane at −20° afforded an analytical sample: ir (film) 1728 (ester C=O), 1688 (C=C), 1458, 1368, 1238, 1072, and 1020 cm^{-1}; nmr (CCl_4) δ 0.78 and 0.94 (pair of d's, J = 6 Hz, 6 H, 4αCH_3CHCH_3), 1.35 (s, 3 H, 7-CH_3), 1.88 (s, 3 H, 7-OAc), 1.98 (s, 3 H, 2-OAc), 2.79 and 2.92 (d of d, J = 3 Hz, 1 H, 7a-H), 3.53 (s, 3 H, 3-OCH_3), and 5.70 and 5.83 ppm (d of d, J = 2 Hz, 1 H, 2 H); mass spectrum (70 eV) *m/e* 264 (M^+ − HOAc).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 68.06; H, 9.28. Found: C, 67.85; H, 9.14.

3aα-Hydro-4α-hydroxy-4β-methyl-7β-isopropyl-*trans*-perhydroindan-1-one (5).—Ethylamine (30 ml, distilled from lithium wire) was introduced under nitrogen into a 50-ml three-neck flask equipped with a glass stirrer, a Dewar condenser, and a dropping funnel. The liquid was cooled to −78° in a Dry Ice–isopropyl alcohol bath. A solution of 0.696 g (0.00215 mol) of **14** and 0.159 g (0.00215 mol) of dry *tert*-butyl alcohol in 15 ml of anhydrous ether was added, followed by about 0.05 g of freshly cut pieces of lithium wire. The reaction mixture was stirred vigorously at −78° until the blue color persisted throughout the solution and then for 1 hr longer. The reaction mixture was rapidly filtered through glass wool into a flask containing about 0.1 g of solid ammonium chloride and swirled to destroy the excess lithium. The supernate was decanted and concentrated *in vacuo*, and the residue was dissolved in a mixture of ether and water. The layers were separated and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 0.415 g of a yellow oil which upon distillation in a Hickman microstill yielded 0.321 g (67%) of the enol ether **15**: bp 100–105° (0.05 mm); nmr (CCl_4) δ 0.82 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7β-CH_3CHCH_3), 0.99 (s, 3 H, 4-CH_3), and 3.48 ppm (s, 3 H, OCH_3).

A solution of 0.309 g (0.00140 mol) of **15**, 6 ml of methanol, and 2 ml of water containing 0.027 g (0.00030 mol) of oxalic acid was stirred at room temperature for 2 hr, and 0.5 ml of saturated sodium bicarbonate solution was added. The solvents were removed *in vacuo*, and the residue was dissolved in ether and water. The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil which yielded 0.2108 g (73%) of **5**: bp 102–108° (bath temperature, 0.07 mm); mp 79–80°; ir (CCl_4) 3520 (OH), 1730 (C=O), 1466, 1381, 1158, 1120, and 1056 cm^{-1}; nmr (CCl_4) δ 0.77 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7β-CH_3CHCH_3) and 1.14 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16201 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.00; H, 10.36.

3aα-Hydro-4α-hydroxy-4β-methyl-7β-isopropyl-*cis*-perhydroindan-1-one (16).—A 5-ml round-bottom flask fitted with a magnetic stirrer and containing a nitrogen atmosphere was charged with a solution of 0.045 g (0.00020 mol) of **15**, 2 ml of methanol, and 0.5 ml of water with 0.002 g of oxalic acid. The mixture was stirred for 0.5 hr at room temperature and 5 drops of saturated sodium bicarbonate solution were added. The solvents were removed *in vacuo*, and the residue was dissolved in ether and water (10 ml each). The layers were separated, and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow oil which on distillation yielded 0.0320 g (76%) of **16**: bp 100–105° (bath temperature, 0.05 mm); ir (film) 3490 (OH), 1734 (C=O), 1470, 1390, 1160, and 1120 cm^{-1}; nmr (CCl_4) δ 0.88 and 0.90 (pair of d's, J = 7 Hz, 6 H, 7β-CH_3CHCH_3) and 0.96 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16192 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.36; H, 10.60.

In a 5-ml round-bottom flask fitted with a reflux condenser and a magnetic stirrer a solution of 0.050 g of **16** in 3 ml of 0.5% methanolic sodium methoxide was refluxed under nitrogen with stirring for 1 hr and was then cooled to room temperature. One drop of acetic acid was added, and the solvent was removed *in vacuo*. The residue was dissolved in ether and water, and the ether layer was isolated, dried (Na_2SO_4), and concentrated to yield 0.048 g (96%) of **5**.

3aα-Hydro-4α-hydroxy-4β-methyl-7α-isopropyl-*cis*-perhydroindan-1-one (18).—In a procedure similar to that described for the preparation of **15**, 30 ml of ethylamine was cooled to −78° with a Dry Ice–isopropyl alcohol bath and a solution of 0.389 g (0.00120 mol) of 2,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene and 0.0889 g (0.00120 mol) of dry *tert*-butyl alcohol in 15 ml of anhydrous ether was added. About 0.05 g of freshly cut lithium wire was added and the reaction mixture was stirred vigorously at −78° until the blue color persisted throughout the solution and then for 1 hr longer. The work-up procedure described earlier gave 0.2318 g (86%) of **17**: bp 100–105° (bath temperature, 0.05 mm); nmr (CCl_4) δ 0.79 and 0.92 (pair of d's, J = 6 Hz, 6 H, 7α-CH_3CHCH_3), 1.01 (s, 3 H, CH_3), and 3.51 ppm (s, 3 H, OCH_3).

In a 5-ml round-bottom flask a solution prepared from 0.141 g (0.00063 mol) of **17**, 3 ml of methanol, 1 ml of water, and 0.01 g of oxalic acid was stirred at room temperature under nitrogen for 2 hr and 0.25 ml of a saturated sodium bicarbonate solution was added. After the solvents were removed *in vacuo* and the residue was dissolved in ether and water (10 ml each), the organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 10 ml of ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give an oil which upon distillation yielded 0.1163 g (88%) of **18**: bp 103–105° (bath temperature, 0.08 mm); ir (film) 3420 (OH), 1733 (C=O), 1458, 1363, 1158, and 1073 cm^{-1}; nmr (CCl_4) δ 0.83 and 0.88 (pair of d's, J = 7 Hz, 6 H, 7α-CH_3CHCH_3) and 1.17 ppm (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* 210.16188 (M^+) (calcd, 210.16186).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.47. Found: C, 74.01; H, 10.65.

When **18** was treated with sodium methoxide in methanol under the same conditions as described for the isomerization of **16** into **5**, the starting material was recovered unchanged. Similarly, treatment of **18** with potassium *tert*-butoxide in *tert*-butyl alcohol–THF left it unchanged.

***dl*-Oplopanone (4).**—A 25-ml three-neck flask equipped with a mechanical stirrer, a gas dispersion tube, and an addition funnel was charged with 0.095 g of a 53% sodium hydride–oil dispersion under nitrogen. The dispersion was washed with 2 × 10 ml of anhydrous hexane to remove the oil, leaving 0.0540 g (0.00225 mol) of sodium hydride. Anhydrous DMSO (5 ml) was added and the suspension was warmed with vigorous stirring to 70° for 30 min, during which time a clear solution containing sodium methylsulfinylmethide was formed. The reaction mixture was cooled to room temperature and a steady stream of acetylene was bubbled through it for 30 min to form a clear, black solution of sodium acetylide in DMSO.[18] While a slow stream of acetylene was maintained through the reaction mixture, a solution of 0.158 g (0.00075 mol) of **5** in 5 ml of anhydrous THF was added dropwise over 30 min, and the mixture was stirred at room temperature overnight. The acetylene flow was discontinued and about 0.1 g of solid ammonium chloride was added. The reaction mixture was filtered and the solvents were removed by lyophilization. The residue was dissolved in a mixture of ether and water, and the aqueous layer was isolated and extracted with fresh ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 0.1512 g of a viscous yellow oil whose nmr spectrum (CCl_4) displayed a one-proton absorption at δ 2.43 ppm, characteristic of an ethynyl proton, and a two-proton absorption at δ 3.83 ppm, for the OH protons, which was consistent with the expected ethynyl carbinol structure **19**.

The oil (0.1512 g) obtained above was dissolved in 15 ml of ethyl acetate containing 0.30 g of mercuric acetate and stirred at room temperature for 24 hr under nitrogen. With vigorous stirring, hydrogen sulfide was bubbled through the reaction mixture for about 10 min until a black precipitate had completely formed. After filtration through Celite, the solvent was removed *in vacuo* to leave 0.090 g of a yellow oil whose nmr spectrum (CCl_4) displayed two three-proton absorptions at δ 2.09 and 2.16 ppm,

characteritic of acetyl groups, and a one-proton absorption at δ 3.28 ppm for the OH proton, which was consistent with the expected α-acetoxy methyl ketone **20**.

In a 25-ml three-neck flask equipped with a Dewar condenser and mechanical stirrer was collected 10 ml of liquid ammonia (freshly distilled from dissolved sodium), and a solution of 0.090 g of **20** in 5 ml of anhydrous dioxane was added. To this solution was added 0.065 g of freshly cut calcium. After stirring for 1 hr, the blue solution was filtered into a flask containing about 0.1 g of solid ammonium chloride and swirled until the blue color disappeared. The solvent was removed *in vacuo*, and the residue was dissolved in ether and water. The ether layer was separated, dried (Na_2SO_4), and concentrated to give 0.0561 g of a light yellow oil which was dissolved in 5 ml of acetone and titrated with Jones reagent[21] until the color of the reagent persisted. One drop of isopropyl alcohol was added, and the reaction mixture was filtered. Removal of the solvent *in vacuo* left a yellow oil (0.050 g) which was chromatographed on 5 g of silica gel. Elution with 40% ether in hexane gave 0.015 g of *dl*-oplopanone (**4**): mp 101.5–102°; nmr ($CDCl_3$) δ 0.69 and 0.89 (pair of d's, J = 6 Hz, 6 H, CH_3CHCH_3), 1.19 (s, 3 H, CH_3), and 2.18 ppm (s, 3 H, Ac); ir (CCl_4) 3583 (OH), 1711 (C=O), 1466, 1385, 1370, and 1359 cm^{-1}.

The synthetic material exhibited nmr, ir, and glc properties identical with those of authentic oplopanone.[6,22]

Registry No.—**1b**, 35049-20-8; **2b** (X = Ac), 35049-21-9; **4**, 35049-27-5; **5**, 35049-26-4; **6**, 35049-23-1; **7**, 35106-10-6; **8**, 41263-23-4; **9**, 35049-22-0; **12**, 35049-25-3; **13**, 41263-25-6; 2α-**14**, 35049-37-7; 2β-**14**, 35049-36-6; **15**, 41263-27-8; **16**, 41263-28-9; **17**, 41263-29-0; **18**, 41263-30-3; **19**, 35049-28-6; **20**, 35049-29-7; 7,7a-dihydro-4-methoxy-7a-methyl-5(6*H*)-indanone, 41263-33-6; 2-methylcyclopentanone, 1120-72-5; 1,4-dimethoxy-2-butanone, 25680-86-8; 2-methyl-5-isopropylcyclopentanone, 6784-18-5; 7α-acetoxy-2α-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-36-9; 7α-acetoxy-2β-hydroxy-3-methoxy-7β-methyl-4β-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-37-0; 2α,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41312-35-0; 2β,7α-diacetoxy-3-methoxy-7β-methyl-4α-isopropyl-2,4,5,6,7,7aα-hexahydroindene, 41263-38-1.

The Synthesis of 7α-Trifluoromethyltestosterone Acetate[1]

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Attempted hydrolysis of 7α-cyanotestosterone acetate *via* an imino ether has given the novel bicyclic ring system of 5α-amino-7α-carboxy-17β-hydroxyandrostan-3-one lactam. Decomposition of the *N*-nitroso derivative of the lactam with hydroxide, ethoxide, and *tert*-butoxide has given 7-carboxyandrostanes with a varying amount of substitution at the 5 position. Reaction of 7α-carboxytestosterone acetate with sulfur tetrafluoride under mild conditions has given 7α-trifluoromethyltestosterone acetate.

The increased anabolic and androgenic activity associated with incorporation of certain 7α substituents into steroidal androgens, particularly the high activity of the 7α-methyl derivatives,[2] has led us to attempt the synthesis of 7α-trifluoromethyltestosterone acetate (**2e**). The trifluoromethyl group is about the same size as a methyl group[3] and would be expected to be compatible with biological activity. The metabolic stability as well as the high electron-withdrawing feature of this group gave us reason to anticipate that some unique change in biological activity might result with its incorporation into androgenic steroids.[4]

The most direct method of introduction of substituents into the 7α position of steroids is the conjugate addition of appropriate nucleophiles to the 3-keto-$\Delta^{4,6}$ system.[2d,5] Since the trifluoromethyl anion, because of its instability and difficulty of preparation,[6] would not be suitable for the direct preparation of the 7α-trifluoromethyl group, we sought to derive the desired compound from a 7α-cyano steroid obtained by conjugate addition of cyanide to the dienone system. The hydrolysis of the nitrile to a carboxyl function followed by its reaction with sulfur tetrafluoride appeared to be a suitable means of obtaining our objective.

Reaction of the dienone **1** with a mixture of excess anhydrous hydrogen cyanide and triethylaluminum[7] in tetrahydrofuran afforded a good yield of 7α-cyanotestosterone acetate (**2a**). This method of preparation of **2a** is vastly superior to that reported[8] in that it gives a much higher yield of cleaner product. No products of diaddition were encountered as is found when excess aqueous cyanide is condensed with dienones.[8] There was also no indication of the presence of the epimeric 7β-cyano compound showing that the reaction was also highly stereospecific.

It was hoped that the cyano group of **2a** could be converted to a carbomethoxy function by hydrolysis of its corresponding imino ether hydrochloride. However, when a solution of **2a** in methanol was treated with hydrogen chloride, a product hydrochloride having only weak absorption in the carbonyl region of its ir spectrum was obtained. Aqueous hydrolysis of this material afforded, in addition to traces of the ester **2b**, a material containing ir absorption at 5.88 and 5.94 μm and no uv absorption characteristic of an α,β-unsaturated ketone. The product, $C_{20}H_{29}NO_3$, is the steroidal

(1) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, ORGN 125.

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(8) R. G. Christiansen and W. S. Johnson, *Steroids*, **1**, 620 (1963).