9b sulfite, 31579-61-0; **9c**, 31579-62-1, **10b**, 31579-63-2; **10c**, 31579-64-3; **11b**, 31579-44-9; **13**, 31579-65-4; **14a**, 31579-66-5; **14b**, 31579-67-6; **15b**, 31579-45-0; **15c**, 31579-46-1; **15** 2,4-DNPH, 31579-47-2; **16**, 31579-48-3; **17b**, 31579-49-4; **20**, 31579-50-7; **20b**, 31579-51-8; **22a**, 31579-52-9; **22b**, 31579-53-0; **23**, 31579-54-1; **24**, 31579-55-2; **25**, 31579-56-3; **26**, 31579-68-7.

Steroids with Abnormal Internal Configuration. A Stereospecific Synthesis of 8α-Methyl Steroids[1]

WILLIAM G. DAUBEN* AND DWIGHT S. FULLERTON

Department of Chemistry, University of California, Berkeley, California 94720

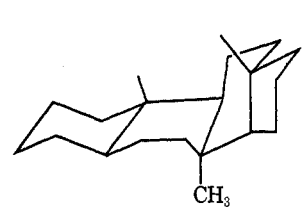
Received February 5, 1971

Stereospecific syntheses of 8α-methylcholestan-3β-ol-6-one acetate and 17-ethynyl-8α-methyltestosterone were accomplished. The synthetic scheme included a series of four reactions starting with steroid 5,7-dienes: hydroboration to the Δ^7-6α-ol, Simmons–Smith addition to form the 7α,8α-methano-6α-ol, Jones oxidation, and lithium in ammonia reductive ring opening to form the 8α-methyl-6-one. The configuration and conformation of the 8α-methyl compounds are discussed with the aid of spectral data. The 8α-methyl group was found to eliminate essentially all the androgenic and anabolic activities in standard biological tests.

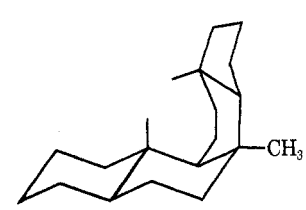
It has been well established that slight changes of the configuration of a biologically active molecule can vastly change its activity.[2] This characteristic has been studied in detail with steroids, where the effects upon biological activity of changing the configuration of substituents attached to carbon atoms on the periphery of the steroid nucleus are well documented.[3] However, the greatest changes in the overall shape of a steroid nucleus result from modification of the stereochemistry of the backbone of the molecule; of the backbone atoms, C-8 and C-9 cause the largest changes in molecular shape.

Several syntheses of 8-iso[4] and 9-iso steroids[5a] have been reported but less has been done with regard to the placement of a substituent at these centers.[5b] Continuing investigations of 8α-methyl steroid type antibiotics[6] have added interest in backbone substituted steroids. The preparation of an 8α-methyl steroid with other backbone carbon atoms possessing the natural configuration has been the basis of two studies.[7] The direct methylation of a 7-keto-9(11)-ene steroid has been reported to yield an 8α-methyl derivative;[8] the stereochemical assignment (first given as 8β)[9] is most likely correct but it is based upon tenuous spectroscopic interpretation. Recently an 8α-methylestrane derivative was prepared by hydrogenolysis of a bicyclobutane estrane precursor.[10] This synthetic route involved a nonstereospecific addition of dibromocarbene to a 6-ene, easily available only with ring-A aromatic steroids. The purpose of this present study was to develop a general, stereospecific synthesis of 8α-methyl steroids and then to evaluate such structural change upon hormonal activity.

The introduction of an 8α hydrogen or 8α substituent makes the B/C ring juncture cis, greatly changing the shape of the steroid nucleus. With the A/B and C/D ring junctures remaining trans, either ring B or ring C must be in a boat or twist conformation in these 8α steroids. In the C-boat or twist conformers, there is extreme steric hindrance because of the C-18 and C-19 angular methyl groups while the B-boat or twist conformers suffer only relatively minor hydrogen–angular methyl interactions. Thus, the B-boat or twist conformations would be preferred.



8α-methyl B boat



8α-methyl C boat

The B-boat conformers have a shape quite different from normal 8β steroids, but the distance between C-3 and C-17 remains approximately the same; for testosterone, 8-isotestosterone, and 8α-methyltestosterone, this distance on Dreiding models is virtually identical. If the C-3 to C-17 distance is important for biological activity, one would predict that 8α steroid hormones

(1) This work was supported, in part, by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) For example, see A. Burger, "Medicinal Chemistry," 3rd ed, Wiley-Interscience, New York, N. Y., 1970.

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959; N. Applezweig, "Steroid Drugs," McGraw-Hill, New York, N. Y. 1962.

(4) W. G. Dauben and L. Ahramjian, *J. Amer. Chem. Soc.*, **78**, 633 (1956); C. Djerassi, H. Bendas, and A. Segaloff, *J. Org. Chem.*, **21**, 1056 (1956); C, Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362, 6377 (1956); W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. I. Jones, *ibid.*, **80**, 661 (1958); G. C. Buzby, Jr., *et al.*, *J. Med. Chem.*, **9**, 338 (1966); K. Kuriyama, M. Moriyama, T. Iwata, and K. Tori, *Tetrahedron Lett.*, 1661 (1968); D. K. Banerjee, B. Sugavanam, and G. Nadamuni, *ibid.*, 2771 (1968); R. Bucourt, D. Hinaut, J. C. Gasc, and G. Nominé, *Bull. Soc. Chim. Fr.*, 1920 (1969); A. H. Emasry and O. Gisvold, *J. Pharm. Sci.*, **59**, 449 (1970); von C. Rufer, E. Schröder, and H. Gibian, *Justus Liebigs Ann. Chem.*, 211 (1967).

(5) (a) W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.*, **81**, 4060 (1959); J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J. Chem. Soc.*, 1159 (1959); S. J. Halkes and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 889 (1965); H. Els, G. Englert, A. Fürst, P. Reusser, and A. J. Schocher, *Helv. Chim. Acta*, **52**, 1157 (1969). (b) J. W. ApSimon and R. R. King, *Can. J. Chem.*, **47**, 1989 (1969).

(6) The antibiotic activity of these compounds is described by W. O. Godtfredsen, W. von Daehne, L. Tybring, and S. Vangedal, *J. Med. Chem.*, **9**, 15 (1966).

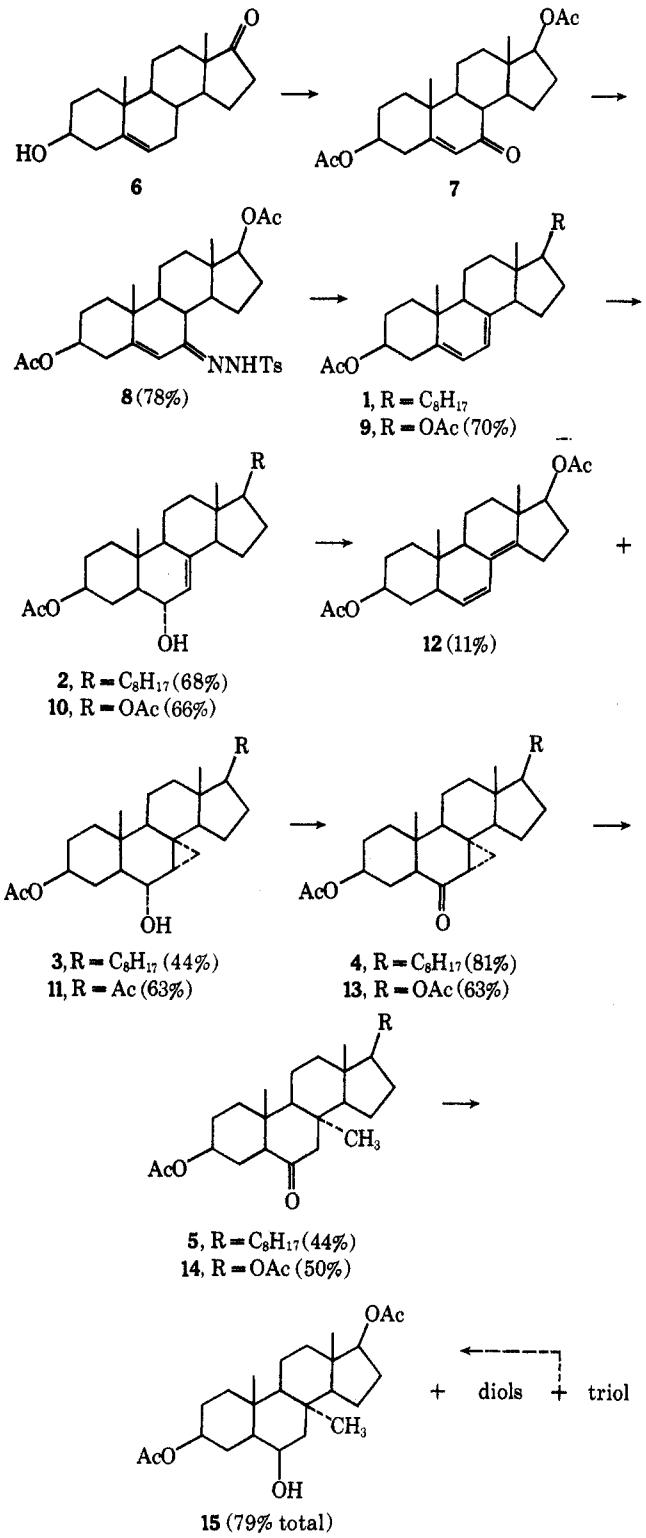
(7) W. Nagata and coworkers have stereoselectively made 8β-methyl steroids: W. Nagata, Proceedings of the Symposium on Drug Research, Montreal, Canada, June 1966; Japanese Patent 3166 (1967).

(8) G. Amiard, R. Heymés, T. V. Thuong, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 2321 (1965).

(9) G. Amiard, J. Mathieu, R. Heymés, and T. V. Thuong, *ibid.*, 1031 (1961).

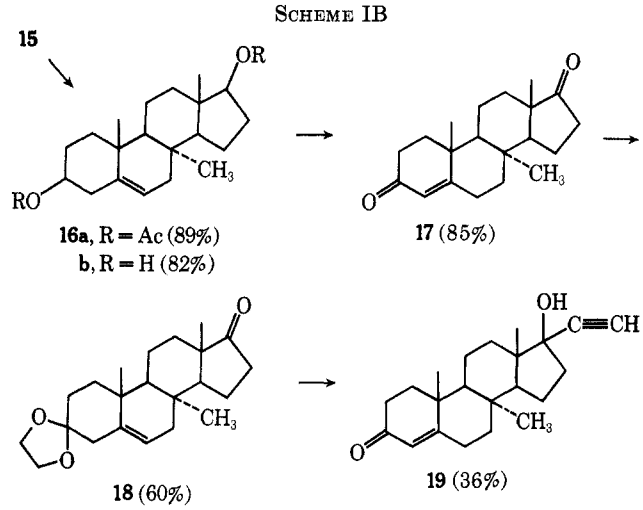
(10) E. Galantay, N. Paolella, S. Barcza, R. V. Coombs, and H. P. Weber, *J. Amer. Chem. Soc.*, **92**, 5771 (1970).

SCHEME IA



would retain much of the androgenic and anabolic activities of their 8β isomers. Indeed, Djerassi found that 8-isotestosterone and 8-isoprogesterone have $^1/_3$ to $^1/_2$ the biological activity of the natural hormones.[11] Current receptor theory suggests that androgenic and anabolic receptors contact the β side of C-8 and that possibly the 8-iso steroids maintain significant biological activity by reacting at the receptors as the nearly planar intermediate between the C-boat and B-boat conformers.[11b] The introduction of the 8α-methyl group should affect this conformational situation and, in turn, the biological activity. However, it should be appreciated that drug–receptor interactions are not the only factors to be considered in studying androgenic and anabolic activities.[11c]

SCHEME IB



The general synthetic scheme followed was based upon previous findings in this laboratory and is shown in Scheme I. First, the methyl group was to be formed by a stereospecific reduction of the cyclopropyl ring of a 7α,8α-methano-6-one with lithium in liquid ammonia. In such a rigid ring system as that of a steroid, the cyclopropane bond that is better suited for the maximum π overlap in the transition state of the reduction[12] is clearly the one leading to the formation of an 8α-methyl group. The required cyclopropyl ketone was to be prepared from the related 6α alcohol, which in turn was to be obtained from the reaction of Simmons–Smith reagent (iodomethylzinc iodide) with the steroid 7-en-6α-ol. The stereospecific nature of the Simmons–Smith reaction with 2-cyclohexenols is well established,[13] the cyclopropane being formed on the same side of the molecule as the hydroxyl group. The desired steroid 7-en-6α-ol is known to be readily prepared by selective hydroboration of a 5,7 steroid diene.[14]

The portion of this synthetic route to cyclopropyl ketone **4** has been reported previously in the cholesterol series,[15] starting from the readily available steroid 5,7-diene **1**, but the experimental details were not given. In the present study, the reaction sequence was repeated and the yields obtained are given in Scheme I. The conversion of allylic alcohol **2** to cyclopropyl alcohol **3** was accompanied by a large production of a nonpolar side product which on the basis of detailed studies with the corresponding androstane compound **10** is certainly the product analogous to **12**. (Reaction

(11) (a) C. Djerassi, H. Bendas, and A. Segaloff, *J. Org. Chem.*, **21**, 1056 (1956); C. Djerassi, A. J. Manson, and H. Bendas, *Tetrahedron*, 22 (1957); (b) see J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1969. (c) A recent discussion with references is contained in a paper by M. E. Wolff and coworkers, *J. Med. Chem.*, **13**, 531 (1970).

(12) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966); T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).

(13) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963).

(14) S. H. Burstein and H. J. Ringold, *ibid.*, **89**, 4722 (1967); H. Laurent, H. Muller, and R. Wiechert, *Chem. Ber.*, 3836 (1966); F. T. Bond and R. H. Cornelia, *Chem. Commun.*, 1189 (1968).

(15) F. T. Bond and R. H. Cornelia, *ibid.*, 1189 (1968). We gratefully thank the authors for a copy of the thesis of R. H. Cornelia, Oregon State University, 1968.

conditions were found during these studies which maximized the yield of **11** while minimizing dehydration to **12**.)

The cyclopropyl ketone **4** was reduced with lithium and ammonia, and the crude product reacetylated to yield 8α-methylcholestan-6-on-3β-ol acetate (**5**). The finding of a positive Cotton effect clearly corroborates the 8α-methyl stereochemistry since 8β-6-keto steroids are known to possess a large negative Cotton effect.[16]

17-Ethynyl-8α-methyltestosterone (**19**) was prepared from the readily available 5-androsten-17-one-3β-ol (**6**). A variety of synthetic routes have been reported for the conversion of a steroid 5-ene to a 5,7-diene,which is the essential intermediate in the synthetic scheme. In the present study, the conversion was achieved by a modified sequence. The corresponding 3β,17β-diacetate of **6** was converted to the 7-ketone derivative **7**, in 75% yield, by oxidation with solid chromium trioxide–pyridine complex in methylene chloride.[17] The ketone upon reaction with *p*-toluenesulfonylhydrazine in methanol without an acid catalyst gave the tosylhydrazone **8** in 78% yield. Treatment of this derivative with lithium hydride in refluxing toluene[18] yielded the 5,7-diene **9** in 70% yield. The overall yield of 40% compares favorably with yields obtained by the commonly employed *N*-bromosuccinimide process. However, the advantage of the present route is that the difficultly removed 4,6-diene is not a by-product.

The diene was hydroborated and the resulting alcohol **10** showed in the nmr the C-7 vinyl proton as the expected singlet, consistant with a dihedral angle of 90° with the C-6 β proton.[14] (Angular methyl groups appeared as expected at δ 0.87 and 0.67.) This alcohol was found to be extremely sensitive toward dehydration with Simmons–Smith reagent. The reaction had to be run while keeping the reaction bath temperature low (35–38°) and the amount of Simmons–Smith reagent carefully controlled. With these precautions, cyclopropyl alcohol **11** and diene **12** were obtained in yields of 63 and 11%, respectively. The diene **12** was the major product when more Simmons–Smith reagent was used, or when the bath temperature was higher.

Jones oxidation[19] of **11** gave cyclopropyl ketone **13**. The cyclopropyl ketone was reductively ring opened with lithium and ammonia, and the reaction product acetylated to give 8α-methylandrostan-6-one 3β,17β-diacetate (**14**). Since in the boat or twist conformation the angular methyl group C-18 is farthest away from the groupings at C-5 and C-6, the highest field resonance at δ 0.93 can be assigned to it. No definitive assignment can be given to the other two methyl group resonances since the exact conformation of ring B is not known. It is clear, however, that neither of the other two methyl nmr bands can be due to an 8β-methyl or the C-19 methyl group of an 8β steroid since either grouping would be expected to show a band at about δ 0.80. In agreement with this conclusion is the finding of a small positive Cotton effect in the CD of **14**. As mentioned earlier, this is unlike the large negative Cotton effect of 8β steroid 6-ones. Together, all these data indicate that the methylene bridge in cyclopropyl ketone **13** had to be α as predicted and assigned.

The reduction of the 6-ketone grouping in **14** with sodium borohydride was very slow, and as a result some hydrolysis (or reduction) of the acetate groups occurred. The reaction mixture was separated into a diacetoxy alcohol, two acetoxydiols, and a triol. It was found that these three materials could be selectively acetylated to yield **15**, indicating that the hydroxyl group at C-6 is sterically hindered. Thus, in a preparative run, the crude mixture could be directly reacetylated to give **15** in a total yield of 79%. No assignment of the 6-hydroxy stereochemistry can be made on the basis of spectral data or mechanistic predictions since the presence of an 8α-methyl group and the B twist conformations can give similar environments to both sides of the molecule around C-6.

Dehydration of the diacetoxy alcohol **15** with phosphorus oxychloride in pyridine gave the olefin **16** as the exclusive product (one vinyl proton multiplet at δ 5.35). The absence of any 6-ene product indicates that the hydroxyl in **15** possessed a β configuration since it is well established that dehydration of a 6β-ol in a 5α steroid under these conditions gives a 5-ene as the exclusive (or predominant) product.[20] Furthermore, equatorial (or pseudoequatorial) alcohols are known to dehydrate with difficulty,[21] while the dehydration of **15** was accomplished easily at 20°. The exclusive formation of the 5-ene may be also attributed to the fact that, when ring B is in a twist or boat conformation, no C-7 hydrogen atom can be trans coplanar with the leaving group. The assignment of a 6β-ol configuration to **15** permits assignments of its three nmr methyl resonances, *i.e.*, δ 0.92 to C-18 as discussed for **14**; the most deshielded methyl group must be C-19 (1.40 δ), leaving the 8α methyl to be at δ 1.08.

The diacetate olefin **16** was saponified and the resulting diol oxidized with Jones reagent.[19] The initial product was apparently a mixture of the Δ^4 and Δ^5 unsaturated ketones, but after alumina chromatography (activity III), only the pure Δ^4 isomer, 8α-methylandrost-4-ene-3,17-dione (**17**), was obtained. The ultraviolet spectrum of **17** [uv max 250 nm (ε 14,100)] reveals interesting information about the conformation. Since both 8β and 8-iso steroid Δ^4-3-ones display maxima at 242 nm,[4] the 8α-methyl group must introduce extra strain into ring A. A similar abnormal bathchromic shift has been reported for an 8α-methyl-1,4-dien-3-one and attributed to a slightly twisted boat conformation which developed to relieve steric interaction of the 8α-methyl group.[22] A similar conformation for **17** can be assumed.

For biological testing purposes, **17** was converted to 17-ethynyl-8α-methyltestosterone (**19**) *via* the monoketal **18**,[23] by reaction with solid lithium acetylide–EDTA,[24] and hydrolysis.

(16) P. Crabbé, "Optical Rotary Dispersion," Holden Day, San Francisco, Calif., 1965, pp 124–127.

(17) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).

(18) L. Caglioti and P. Casselli, *Chim. Ind. (Milan)*, 559 (1963).

(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(20) A. Schubert and C. Damker, *J. Prakt. Chem.*, **4**, 260 (1957); C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1786 (1952).

(21) The exception is when the carbon bearing the equatorial hydroxyl also bears a methyl group, in which case one of the methyl protons can line up for a trans coplanar *E*2 elimination to give an exocyclic methylene. These topics are discussed in depth by D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, pp 101–111.

(22) See ref 8; *cf.* R. Bucourt, *Bull. Soc. Chim. Fr.*, 2081 (1964).

(23) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, **76**, 1359 (1954).

(24) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).

Results of Biological Testing.—Using standard tests on **17** and **19**, it was found that the 8α-methyl group eliminates nearly all androgenic and anabolic activities found in the related 8β-H steroids. Only in the case of 8α-methylandrostenedione (**17**) was even slight androgenic activity maintained.

Experimental Section

Microanalyses and mass spectra were obtained from the Microchemical and Mass Spectrometry Laboratories, College of Chemistry, University of California. Optical rotations were taken in chloroform, nmr spectra in $CDCl_3$, and uv spectra in EtOH. Ir spectra were taken in chloroform and therefore may vary from expected CCl_4 values by 5–10 cm^{-1}. "Usual work-up" will be used to mean extraction of the crude reaction mixture with an appropriately large amount of ether and then washing the ether extract twice with 5% HCl, 5% $NaHCO_3$, saturated NaCl, and water. Each group of washings was individually back extracted with ether before further washing of the parent ether solution. The ether solution was dried over magnesium sulfate and rotary evaporated to give a crude product which was chromatographed and recrystallized. Unless otherwise specified, column chromatographies were with Woelm neutral alumina (activity III). Crystallizations were in a mixture of methylene chloride and methanol or (for alcohols) in methylene chloride and hexane.

7-Cholestene-3β,6α-diol 3β-Acetate (2).—A solution of 10 g (0.023 mol) of 5,7-cholestadien-3β-ol acetate (**1**) in 200 ml of tetrahydrofuran was cooled in an ice bath. To this rapidly stirred solution under nitrogen was added dropwise 14 ml (0.014 mol) of 1.0 *M* diborane in tetrahydrofuran solution (Alfa Inorganics, Inc.). The ice bath was removed, and the solution was allowed to stir for 1 hr. The rapidly stirred solution was cooled in an ice bath, and 10 ml of water was carefully added, followed by 10 ml of 3 *N* NaOH and 20 ml of 15% H_2O_2 solution. The ice bath was removed for 1 hr and replaced as 25 ml of 5% ferrous sulfate in 2% sulfuric acid was carefully added. The resulting solution was poured into 2.5 l. of ether. The ethereal extracts were carefully washed with acidic ferrous sulfate solution and worked up in the usual way to give 7.2 g (69%) of **2**: mp 141–144° (lit.[15] mp 143–144°); ir 3400, 1725, 1250 cm^{-1}; nmr δ 5.2 (s, 1, C-7 vinyl proton with singlet characteristic of a dihedral angle of 90° with the proton at C-6), 3.75 (m, 1, proton on C-6), 4,6 (m, 1, C-3 proton).

7α,8α-Methanocholestane-3β,6α-diol 3β-Acetate (3).—To 350 ml of anhydrous ether was added, with stirring, 7.5 g of methylene iodide and 14 g of zinc–copper couple (freshly prepared by the method of Friedrich[25]). After two tiny crystals of iodine were added, the solution was stirred for 30 min at reflux. At the end of that time, the bath temperature was reduced to 35–38°. A solution of 7.0 g (0.016 mol) of **2** and 12.5 g of methylene iodide in 1 l. of anhydrous ether was added over 30 min. The mixture was stirred at 35° for 17 hr; then further portions of 7.0 g of zinc–copper couple and 6.6 g of methylene iodide were added. The mixture was stored for an additional 8 hr, 25 ml of saturated ammonium chloride was slowly added, and the usual work-up (but omitting acid wash) was followed. Chromatography of the crude product on Woelm basic alumina (activity III) gave 3.0 g (44%) of **3**: mp 177–178° (lit.[15] mp 167–171°); ir 3400, 1725, 1230 cm^{-1}; nmr δ 3.70 (m, 1, proton on C-6), 0.2 (m, cyclopropyl protons). A major nonpolar side product was seen on tlc but not identified. On the basis of studies while making **11**, the material is certainly the diene corresponding to **12**.[26]

7α,8α-Methanocholestan-3β-ol-6-one Acetate (4).—To a solution of 1.5 g (3.0 mmol) of **3** in 600 ml of acetone at room temperature was added 1.8 ml of Jones reagent[19] with rapid stirring. The resulting solution was stirred for 10 min, and 5 ml of methanol was added dropwise to destroy excess Jones reagent. The usual work-up (but omitting the acid wash) was followed, including chromatography over basic alumina (activity III) to give 1.25 g (84%) of **4**: mp 167–169° (lit.[15] 165–168°); uv max 206 nm (ε 6000); ir 1685, 1725, 1250 cm^{-1}.

8α-Methylcholestan-3β-ol-6-one Acetate (5).—To 350 ml of dry[27] distilled liquid ammonia was added 0.2 g (0.028 mol) of lithium wire, and to the resulting blue solution which had been stirred for 20 min was added 1.0 g (0.014 mol) of anhydrous *tert*-butyl alcohol, followed by 1.25 g (3.0 mmol) of **4** and 1.0 g (0.014 mol) of anhydrous *tert*-butyl alcohol in 225 ml of anhydrous ether over 10 min. The resulting solution was stirred for 30 min under nitrogen and then 50 ml of saturated ammonium chloride solution was very carefully added dropwise, followed by 200 ml of glyme. The Dry Ice condenser and Dry Ice bath were removed and the ammonia was allowed to evaporate. The remaining glyme mixture was extracted with 3 l. of ether and worked up in the usual way. The crude product was dissolved in 25 ml of anhydrous pyridine containing 4 ml of acetic anhydride and the solution was heated on a steam bath for 1 hr. The usual work-up gave 550 mg (44%) of **5**: mp 150–151°; ORD (*c* 0.067, dioxane)[28] $[\Phi]_{317}$ +751°, $[\Phi]_{286}$ +217°; $[\alpha]^{26}D$ +17° (*c* 0.184); ir 1725, 1250, 1708 cm^{-1}; nmr δ 1.26 (new s, 3).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.57 H, 11.03.

5-Androstene-3β,17β-diol 7-Tosylhydrazone 3β,17β-Diacetate (8).—In 2 l. of methanol was dissolved 93 g (0.24 mol) of 5-androsten-7-one-3β,17β-diol diacetate (**7**)[17,29] and 100 g (0.54 mol) of *p*-toluenesulfonylhydrazine. The solution was refluxed for 5 hr under nitrogen and cooled, and the solvent was rotary evaporated at 30°. The resulting yellow oil was dissolved in 2 l. of methylene chloride and quickly washed through neutral alumina (activity III) with methylene chloride. The methylene chloride was rotary evaporated and the crude, oily product slowly crystallized to yield 105 g (78%) of **8** in three crops. (Rapid crystallization produced crystals contaminated with tosylhydrazine, which significantly lowers the yield of diene in the next step. The tosylhydrazine can be seen on tlc with phosphomolybdic acid, but is unstained by acidic ceric sulfate. Using less tosylhydrazine in the reaction gave much unreacted **8**.) The melting point of **8** is 201–203° dec; ir 3300 small peak, 1650 d, 1720, 1250 cm^{-1}; nmr δ 2.0 (s, 6, acetate), 4.7 (m, 2, C-3 and C-17 protons),[30] 7.2 and 7.7 (two d of d, 4, tosyl group aromatic protons), 6.1 (s, 1, vinyl).

Anal. Calcd for $C_{30}H_{40}O_6N_2S$: C, 64.51; H, 7.16. Found: C, 64.45; H, 7.18.

5,7-Androstadiene-3β,17β-diol 3β,17β-Diacetate (9).—A solution of 105 g (14.4 mol) of lithium hydride and 105 g (0.19 mol) of **8** in 4 l. of toluene was refluxed under nitrogen for 8 hr.[18] The solution was cooled and filtered through a sintered-glass funnel into a suction flask containing 200 ml 5% of sulfuric acid. The funnel was washed with toluene and anhydrous ether.[31] The toluene–ether solution was rotary evaporated to 2 l. and worked up in the usual way, chromatographed, and crystallized to yield 44.3 g (67%) of **9**.[32] The properties of **9** are mp 128–131° (lit.[33] mp 132°) and uv max 270, 280 nm (ε 10,500); no absorption at 230–240 nm was seen in the crude product or mother liquor of **9**, indicating no 4,6 diene product.

(25) L. Friedrich, Thesis, University of California, Berkeley, 1966; *cf.* R. E. Shank and H. Schechter, *J. Org. Chem.*, **24**, 1825 (1959). Friedrich's modification: "Into a 250-ml Erlenmeyer flask were placed 49.2 g of zinc dust and a large teflon magnetic stir bar. The zinc dust was washed with four 40-ml portions of 3% aqueous HCl. During each wash, the mixture was stirred vigorously for 1 min. The zinc was washed in the same manner with seven 100-ml portions of distilled water, and after the fifth wash the porous-looking zinc became a dense powder again. It was then washed with two 75-ml portions of 2% aqueous $CuSO_4$ $(H_2O)_4$ and six 100-ml portions of distilled water. After the fifth water wash, the material became a powder again. The zinc–copper couple was finally washed with four 100-ml portions of absolute ethanol and five 100-ml portions of anhydrous ether, and the last traces of ether were removed by a slow nitrogen stream passing over the couple's surface. The couple was stored over P_2O_5 under vacuum and used within 1 day of preparation."

(26) The procedure for making **11** was carefully developed so that the yield of cyclopropyl alcohol was high while keeping diene yield low. Thus, the procedure for **11** is recommended to be followed for making **3**.

(27) The ammonia must be dry to minimize reduction of the ketone.

(28) For comparison with **14**, this ORD corresponds to a CD of $[\theta]_{300} = +441$.

(29) H. J. Ringold, *J. Amer. Chem. Soc.*, **82**, 961 (1960).

(30) These absorptions appear for all the steroid acetates and will not be listed again.

(31) The large amount of recovered lithium hydride can be safely destroyed by suspending it in 1 l. of hexane and adding methanol, dropwise, over 3 days.

(32) Another 3.5 g of **9** was obtained by treating the dried mother liquor of **8** with lithium hydride in the same manner, bringing the total yield of diene **9** to 47.7 g or 40% from olefin **6**.

(33) R. Butenandt, *Ber.*, **71**, 1316 (1938).

7-Androstene-3β,6α,17β-triol 3β,17β-Diacetate (10).—In 4 l. of tetrahydrofuran was dissolved 45 g (0.12 mol) of diene **9** under nitrogen, and the mixture was cooled in an ice bath. To this rapidly stirred solution was added dropwise 100 ml (0.1 mol) of 1.0 *M* diborane in THF solution. The ice bath was removed, and the solution was allowed to stir for 1.5 hr. The rapidly stirred solution was cooled in an ice bath, and 50 ml of water was carefully added dropwise, followed by 9 ml of 5% NaOH solution. The 5% base solution was thereafter added dropwise until the pH of the reaction mixture reached just 9–10 as indicated on moist wide-range pH paper. (Excess base reduces the yield of **10** through saponification.) To the alkaline solution was added 60 ml of 15% hydrogen peroxide, and the pH of the mixture was checked again and adjusted if necessary. The ice bath was removed and the solution stirred under nitrogen for 1 hr. Acidic ferrous sulfate was added dropwise to the cooled mixture and work-up proceeded as with **2**. The yield after chromatography was 31 g (76% based on recovered diene) of **10** as amorphous dried flakes (one spot, tlc) and 5.6 g of recovered diene **9**. Product **10** resisted all attempts at crystallization, even after preparative tlc. The spectral properties of **10** are ir 3400, 1720, 1250 cm^{-1}; nmr δ 5.15 (s, 1, C-7 vinyl proton with singlet characteristic of a dihedral angle of 90° with the proton at C-6),[14] 3.75 (m, 1, proton on C-6), 0.87 (s, 3, C-19 methyl), 0.67 (s, 3, C-18 methyl).

Anal. Calcd $C_{23}H_{34}O_5$: *m/e* 290.2406. Found: *m/e* 290.2406.

7α,8α-Methanoandrostane-3β,6β,17β-triol 3β,17β-Diacetate (11).—The following is the procedure found to maximize the yield of **11** while keeping the yield of diene **12** minimized. To 1.5 l. of anhydrous ether was added 8 g of fresh zinc–copper couple,[25] 33 g of methylene iodide, and three tiny crystals of iodine. The mixture was refluxed for 45 min and then 14.1 g (0.048 mol) of **10** in 150 ml of anhydrous ether was added in one portion. The bath under the reaction was maintained at 35–38° for 24 hr, causing a very slow rate of reflux. At the end of this reflux period, a solution prepared by refluxing 33 g of methylene iodide, 8 g of zinc–copper couple, and three tiny crystals of iodine in 100 ml anhydrous ether for 45 min was added to the reaction mixture. The bath was maintained at 35–38° for an additional 24 hr, and 15 ml of saturated aqueous ammonium chloride was added to the cooled solution. Usual work-up (but omitting acid wash), chromatography on basic alumina (activity III), and crystallization gave 9.1 g (63%) of **11** and 1.4 g (11%) of diene **12**. The properties of **11** are mp 221–222°; $[\alpha]^{26}D$ +43° (*c* 0.105); ir 3400, 1725 cm^{-1}; nmr δ 0.3 (broad m, 3).

Anal. Calcd for $C_{24}H_{36}O_5$ (**11**): C, 71.26; H, 8.79. Found: C, 71.19; H, 8.95.

The properties of diene **12** are mp 150–151°; $[\alpha]^{26}D$ +162° (*c* 0.10); uv max 248 nm (ε 23,500); ir 1725 cm^{-1}; nmr δ 6.1 (d of d, 1, J = 3, 9 Hz), 5.3 (d of d, 1, J = 3, 9 Hz), 0.85 (s, 6, angular methyls).

Anal. Calcd for $C_{23}H_{32}O_4$ (**12**): C, 74.16; H, 8.66. Found: C, 74.07; H, 8.75.

7α,8α-Methanoandrostane-3β,17β-diol-6-one 3β,17β-Diacetate (13).—In 1 l. of acetone was dissolved 9.5 g (24 mmol) of **11** and the mixture was cooled in an ice bath. To the cooled solution was added dropwise 10.0 ml of Jones reagent.[19] The ice bath was removed, the mixture was stirred for 10 min, 5 ml of methanol was added, and reaction mixture was stirred for an additional 2 min. The reaction was worked up in the usual way (but with no acid wash) and chromatographed over basic alumina (activity III) to yield 6.2 g (63%) of **13**: mp 174–175°; $[\alpha]^{26}D$ 0° (*c* 0.129); uv max 205 nm (ε 6100); ir 1725, 1685, 1250 cm^{-1}; nmr δ 0.83 (s, 6, angular methyl groups).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.61; H, 8.46.

8α-Methylandrostane-3β,17β-diol-6-one 3β,17β-Diacetate (14).—Following the procedure for **5**, 3.5 l. of anhydrous ammonia was distilled and to it was added 1.5 g (0.21 g-atom) of lithium wire. The lithium in ammonia solution was stirred for 20 min and 5.0 g (0.067 mol) of anhydrous *tert*-butyl alcohol was added, followed by a solution of 5.0 g (0.012 mol) of **13** and 10.0 g (0.135 mol) of anhydrous *tert*-butyl alcohol in 200 ml of anhydrous ether and 15 ml of anhydrous hexane. The solution of **13** was added over 10 min, the resulting mixture was stirred for 30 min, and 50 ml of saturated aqueous ammonium chloride solution was very carefully added dropwise, followed by 200 ml of glyme. The Dry Ice condenser and Dry Ice bath were removed, and the ammonia was allowed to evaporate. The remaining glyme mixture was processed in the usual fashion, and the crude product was acetylated as in the procedure for **5** and column chromatographed to give 2.5 g (50%) of **14**: mp 224–225°; $[\alpha]^{26}D$ +9° (*c* 0.129); CD (*c* 0.089, dioxane) $[\theta]_{298}$ +50; ir 1708, 1725, 1250 cm^{-1}; nmr δ 1.21 (s, 3), 1.06 (s, 3), 0.93 (s, 3).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 70.97; H, 8.88.

8α-Methylandrostane-3β,6β,17β-triol 3β,17β-Diacetate (15).—To a solution of 1.4 g (3.5 mmol) of **14** in 3.5 l. of distilled ethanol under a nitrogen atmosphere and at room temperature there was added 75 mg (2.0 mmol) of sodium borohydride. The solution was stirred for 6 hr, an additional 70 mg (2.0 mmol) of sodium borohydride was added, and 14 hr later, another 65 mg (1.7 mmol) was added. Less stirring time left unreacted ketone. After 3 hr of additional stirring, 50 ml of 5% HCl was added, and the resulting ethanol solution was rotary evaporated at 35° to 200 ml. The resulting solution was worked up in the usual way and the crude product was chromatographed over neutral alumina (activity IV) to give 750 mg (52%) of **15**. In addition, 210 and 96 mg of two diol monoacetates were collected, as well as 180 mg of a triol. These side products were individually dissolved in 20 ml anhydrous pyridine and acetylated with 1 ml of acetic anhydride by stirring at room temperature under nitrogen for 5 hr. Individual work-up of each and chromatography over neutral alumina (activity IV) gave **15** in each case, 350-mg total, bringing the combined yield of **15** to 1.1 g (79%). The properties of **15** are mp 169–170°; $[\alpha]^{26}D$ −54° (*c* 0.090); ir 3400, 1725, 1250 cm^{-1}; nmr δ 1.40 (s, 3), 1.08 (s, 3), 0.92 (s, 3), 4.0 (m, 1).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.12; H, 9.65.

8α-Methyl-5-androstene-3β,17β-diol 3β,17β-Diacetate (16).—To an ice-bath cooled solution of 1.2 g (3.0 mmol) of **15** in 34 ml of pyridine was added 9.6 ml (26 g, 0.017 mol) of phosphorus oxychloride. The ice bath was removed and the mixture was allowed to stir under nitrogen at 20° overnight. Water was very carefully added dropwise to the mixture, and the reaction was worked up in the usual manner to give 1.023 g (89%) of **16**: mp 181–182°; $[\alpha]^{26}D$ 0° (*c* 0.149); ir 1725, 1250 cm^{-1}; nmr δ 5.32 (m, 1), 1.22 (s, 3), 1.00 (s, 3), 0.89 (s, 3).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.25.

8α-Methyl-4-androstene-3,17-dione (17).—To 900 mg (2.3 mmol) of **16** in 2.3 l. of methanol was added 1.0 g (17 mmol) of potassium hydroxide in 50 ml of methanol containing 2 ml of water. The resulting mixture was refluxed under nitrogen for 3.25 hr, after which 25 ml of saturated sodium chloride was added, and the methanol solution was rotary evaporated at 35° to 200 ml. Usual work-up, with last traces of water in the crude product removed by rotary evaporation of a benzene azeotrope, gave 580 mg (82%) of crude diol **15b**, mp 156–173°. The diol was oxidized with 60 ml of chromium trioxide–pyridine complex methylene chloride solution (6.0 g of chromium trioxide, 9.49 g of pyridine, in 150 ml of methylene chloride).[34] Usual work-up gave 520 mg of crude product which showed two major products on tlc. Chromatography and crystallization gave 410 mg (85%) of **17**: mp 164–165°; $[\alpha]^{26}D$ +220° (*c* 0.083); uv max 250 nm (ε 14,100); ir 1730, 1655 cm^{-1}; nmr δ 6.0 (s, 1), 1.35 (s, 3), 1.11 (s, 3), 1.08 (s, 3).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.77; H, 9.46.

8α-Methyl-4-androstene-3,17-dione 3-Ethylene Ketal (18).—A solution of 100 ml of 2-methyl-2-ethyl-1,3-dioxolane[23] in 500 ml of *n*-hexane was passed through 250 g of basic alumina (activity III). By this procedure, less than 0.5% ethylene glycol remained in the ketal after the hexane was rotary evaporated. In 30 ml of ketal was dissolved 250 mg (0.83 mmol) of **17** along with 8 mg of *p*-toluenesulfonic acid monohydrate. The mixture was very slowly distilled under dry nitrogen over 5.5 hr so that only 5 ml remained; 50 ml of reagent benzene was added and the mixture was extracted with 100 ml of dry ether. The ether–benzene solution was washed with 5% sodium bicarbonate and with water, and organic solvents were rotary evaporated. The residue, 310 mg of brown oil, was chromatographed over basic alumina (activity III) to give 128 mg of monoketal **18**, no diketal, and 96 mg of recovered starting material. The 96 mg of recovered starting material and 60 mg more of **17** was treated the same way to give an additional 105 mg of monoketal **18**.

(34) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

Thus, from 310 mg of **17**, 233 mg (66%) of **18** was obtained. The properties of **18** are mp 173–174°; ir 1730 cm^{-1}; nmr 5.3 (s, 1, vinyl), 4.0 (m, 4, ethylene), 1.05 (s, 3), 1.13 (s, 3), 1.20 (s, 3).

Anal. Calcd for $C_{22}H_{32}O_3$: *m/e* 344.2351. Found: *m/e* 344.2349.

17-Ethynyl-8α-methyltestosterone (19).—In 170 ml of spectroquality dioxane under nitrogen in a 500-ml three-neck flask was bubbled acetylene which had been passed through three sulfuric acid wash bottles, one empty trap, one KOH cylinder, and one calcium chloride trap. After 5 min of bubbling, 5.0 g (0.055 mol) of lithium acetylide–EDTA complex[24] (Foote Mineral Co.) was added. The mixture was stirred for 10 min while acetylene bubbling was continued, and then 185 mg (0.54 mmol) of **18** in 120 ml of dioxane was added dropwise over 25 min. Acetylene bubbling was continued for an additional 40 min. The resulting mixture, under nitrogen, was stirred overnight at room temperature (total 22.5 hr), 5 ml of saturated aqueous ammonium chloride solution was carefully added with a micropipette, and 100 ml of a 1:1 mixture of water and concentrated HCl was added. The resulting solution was heated on a steam bath 1.25 hr and cooled and usual work-up gave 205 mg of a yellow oil. The material was purified by preliminary chromatography on neutral alumina (activity IV) and the resulting 120 mg of a yellow semisolid was separated by preparative thin layer chromatography to give 63 mg (36%) of **19** and 20 mg of yellow oil containing **17**. The properties of **19** are mp 230–231°; $[\alpha]^{26}D$ +88° (*c* 0.025); uv max 250 nm (ε 14,100); ir 3350, 1660 cm^{-1}; nmr δ 6.0 (s, 1), 1.33 (s, 3), 1.10 (s, 3), 1.07 (s, 3).

Anal. Calcd for $C_{22}H_{30}O_2$: *m/e* 326.2247. Found: *m/e* 326.2252.

Registry No.—**2**, 17181-88-3; **3**, 31327-29-4; **4**, 31327-30-7; **5**, 31327-31-8; **8**, 31327-32-9; **9**, 31327-33-0; **10**, 31327-34-1; **11**, 31337-76-5; **12**, 31337-75-4; **13**, 31327-35-2; **14**, 31327-36-3; **15**, 31428-83-8; **16a**, 31385-44-1; **17**, 31337-34-5; **18**, 31337-35-6; **19**, 31337-36-7.

Acknowledgments.—The authors are indebted to Dr. Alfred Boris, Endrocrine Section, Hoffmann-La Roche, Inc., for evaluation of the biological activity.

The Stereochemistry of Vinyl Phosphates from the Perkow Reaction and the Phosphorylation of Enolates[1]

IRVING J. BOROWITZ,*[2] STEVEN FIRSTENBERG, EDWARD W. R. CASPER, AND ROSALIE K. CROUCH

Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York 10033

Received December 28, 1970

The predominant stereochemistry of vinyl phosphates resultant from the reactions of α-halo ketones with trialkyl phosphites involves the *E* configuration, *i.e.*, $(RO)_2P(=O)O_A{>}C{=}C{<}^{H_B}_{Y}$ for A = Ph, H_A; Y = Ph, alkyl, Cl, Br. The assignment of stereochemistry is based on a combination of nmr spectral effects including (a) the differentiation of cis and trans 1,2-vinyl protons by their J_{HH} coupling constants, (b) a downfield shift for H_B when cis to phosphate and A = Ph in the presence of boron trifluoride etherate, and (c) the application of Tobey–Pascual substituent shielding constants. The phosphorylation of several potassium or lithium enolates with diethyl phosphorochloridate gives predominantly vinyl phosphates. In two cases these also have the *E* configuration. Several vinyl phosphates are found to have $J_{^{31}POCCH}$ coupling constants, trans > cis. Deuteriobenzene solvent induced shifts are briefly discussed.

The reactions of α-halo ketones with trialkyl phosphites lead to either ketophosphonates or, more usually, to vinyl phosphates (Perkow reaction).[3] The stereoisomerism of these vinyl phosphates has been previously discussed,[4] although rigorous assignment of structure has often been lacking. In one case, an unambiguous assignment[4c] was unfortunately inverted by error.[3a] We now report that the stereochemistry of vinyl phosphates can be determined, in a number of cases, by a combination of nmr techniques including the assignment of cis and trans groups on an ethylene by the method of Tobey[5a] and Pascual.[5b] We have also phosphorylated several enolates to give mainly vinyl phosphates whose stereochemistry can be correlated with those obtained from the Perkow reaction. Although some enolates have previously been phosphorylated on oxygen,[3a] the resultant vinyl phosphates have not previously been correlated with those arising from the Perkow reaction.[5c]

Results and Discussion

Phosphorylation of Enolates.—A number of potassium or lithium enolates were prepared under kinetic control conditions by the reaction of potassium or lithium triphenylmethide with the respective ketone (Scheme I).[6] Reaction of these enolates with diethyl phosphorochloridate gives the vinyl phosphate as the exclusive product (Table I) except in the case of acetophenone where some ketophosphonate (11%) is also formed. Equilibrium control formation of several enolates[6b] gave the same results.

Our phosphorylation results parallel the reactions of enolates with acetyl chloride or chlorotrimethylsilane in that bond formation occurs on oxygen in most cases.[6,7] The small yield of **16** could arise from either direct C-phosphorylation of the enolate or from the

(1) This investigation was supported by Grant No. AF-AFOSR 1170-66, 1170-67 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research, and by the National Science Foundation. This is part XV of the series, Organophosphorus Chemistry.

(2) To whom correspondence should be addressed.

(3) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965); (c) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(4) (a) J. C. Craig, M. D. Bergenthal, I. Fleming, and J. Harley-Mason, *Angew. Chem., Int. Ed. Engl.*, **8**, 429 (1969); (b) J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3712 (1963); (c) A. R. Stiles, C. A. Reilly, G. R. Pollard, C. H. Tieman, L. F. Ward, D. D. Philips, S. B. Soloway, and R. R. Whetstone, *J. Org. Chem.*, **26**, 3960 (1961).

(5) (a) S. W. Tobey, *ibid.*, **34**, 1281 (1969); (b) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966); (c) for recent work on the stereochemistry of the thiophosphorylation of enolates, see B. Miller, H. Margulies, T. Drabb, Jr., and R. Wayne, *Tetrahedron Lett.*, 3801, 3805 (1970).

(6) (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 272–275; (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(7) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462 (1968).