3β,21-Diacetoxy-4,4,14α-trimethyl-Δ^8-5α-pregnene-7,11,20-trione (XXV).—To a solution of 23 mg. of the Δ^8-pregnene 3,21-diacetate (XVIIIa) in 2 ml. of glacial acetic acid maintained at 77–78° was added with stirring over a 20-min. period a solution of 20 mg. of chromium trioxide in 1 ml. of glacial acetic acid. After a total reaction time of 25 min. the mixture was cooled to room temperature, the bulk of the acetic acid removed *in vacuo* and the residue taken up in water and chloroform. The chloroform extract was washed three times with water, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue (24 mg.) crystallized readily from methanol furnishing 18 mg. of the trione diacetate XXV, 75% yield, m.p. 191–192°, $[\alpha]^{23}\text{D}$ +107° (*c* 0.59), $\lambda_{\max}^{\text{alc}}$ 268 mμ (ε 8100); $\lambda_{\max}^{\text{Nujol}}$ 5.74, 5.82, 6.00, and 8.00–8.10 μ.

Anal. Calcd. for $C_{28}H_{38}O_7$ (486.58): C, 69.11; H, 7.83. Found: C, 68.82; H, 7.89.

4,4,14α-Trimethyl-Δ^8-5α-pregnene-3β,21-diol-20-one (XVIII). A solution of 684 mg. (1.56 mmoles) of the triene diol IX in 40 ml. of ethyl acetate was ozonized at −20° with 2.1 mole equivalents of ozone containing 0.81 mmole of ozone per liter of gas. The ozonolysis mixture was allowed to stand at −20° for 30 min. It was then decomposed at room temperature by the addition of 2 ml. of glacial acetic acid and 10 g. of zinc dust (in portions). The mixture was stirred for 1 hr., when it no longer gave a positive test with potassium iodide–starch reagent, filtered, washed with water, dried over sodium sulfate, and the solvent removed *in vacuo*. A crystalline residue remained (605 mg.) which on recrystallization from methanol–ethyl acetate furnished 358 mg. (62%) of the ketol XVIII melting at 214–216°. Crystallization from the same solvent furnished the pure compound, m.p. 225–227°, $[\alpha]^{23}\text{D}$ +113°, $\lambda_{\max}^{\text{Nujol}}$ 2.80 and 5.88 μ.

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.85; H, 10.20.

21-Acetoxy-4,4,14α-trimethyl-Δ^8-5α-pregnene-3β-ol-20-one (XIX).—To a solution of 1.0 g. of the carefully vacuum-dried (100°) pregnenediol XVIII in 25 ml. of pyridine was added 299 mg. of acetic anhydride (1.1 equiv.) and the mixture allowed to stand at room temperature for 18 hr. The reagents were evaporated *in vacuo* and the residual crystalline residue recrystallized from chloroform–methanol. There was obtained 800 mg. of the 21-monoacetate XIX, m.p. 198–199°, $[\alpha]\text{D}$ +119° (*c* 1.10); $\lambda_{\max}^{\text{Nujol}}$ 2.71, 5.72, 5.80, and 8.10 μ; n.m.r.: two protons in two doublets at 5.33 τ (*J* 17 c.p.s.) and 5.45 τ (*J* 17 c.p.s.) (21-CH_2).

Anal. Calcd. for $C_{26}H_{40}O_4$ (416.58): C, 74.97; H, 9.70. Found: C, 74.97; H, 9.48.

21-Acetoxy-4,4,14α-trimethyl-Δ^8-5α-pregnene-3,20-dione (XXIV).—A solution of 25 mg. of the 21-acetate XIX in 5 ml. of acetone was oxidized with 0.5 ml. of a solution containing 20 mg. of chromium trioxide and 32 mg. of concentrated sulfuric acid per milliliter of 90% aqueous acetone. The reaction was allowed to proceed for 15 min. when excess chromium trioxide was decomposed by the addition of methanol. Water and chloroform were added and the chloroform extract washed with water, dried over sodium sulfate, and evaporated to dryness. The diketone XXIV crystallized readily from methanol and melted at 172–173°, $[\alpha]^{23}\text{D}$ +131° (*c* 1.13); $\lambda_{\max}^{\text{Nujol}}$ 5.71, 5.78, 5.90, and 8.10 μ.

Anal. Calcd. for $C_{26}H_{38}O_4$ (414.56): C, 75.32; H, 9.24. Found: C, 75.27; H, 9.28.

Acknowledgment.—The authors wish to thank the following members of the staff of The Squibb Institute for their contributions to this work: Mr. J. Alicino and Mr. C. Sabo for the microanalyses, Miss B. Keeler and Miss R. Karitzky for the infrared spectra, Mr. W. Bullock for the ultraviolet spectra, and Dr. A. Cohen for most of the n.m.r. spectra. Some of the n.m.r. spectra were kindly supplied by Dr. H. Agahigian of the Olin Central Analytical Laboratory, New Haven, Conn.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL., AND THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

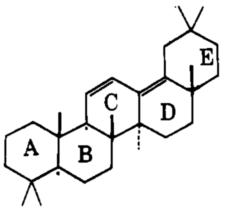
Synthesis of a β-Amyrin Derivative, Olean-11,12;13,18-diene[1]

BY E. J. COREY, HANS-JÜRGEN HESS, AND STEPHEN PROSKOW

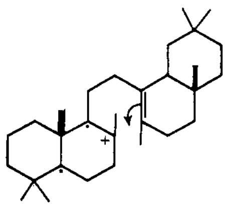
RECEIVED JULY 23, 1963

The construction of the pentacyclic ring system of the β-amyrin derivative olean-11,12;13,18-diene has been accomplished by joining a precursor containing the A and B rings to a monocyclic intermediate with a preformed E ring and then closing ring D by an internal aldol reaction and ring C by internal cation–olefin addition.

We have previously reported in a preliminary note[2] a synthetic route to olean-11,12;13,18-diene (I), a well-known pentacyclic triterpene derivative in the β-amyrin series. Details of this synthesis are provided in the present paper. The main object of the investigation was to test the possibility of forming the pentacyclic nucleus by cyclization of a tetracyclic intermediate containing rings A, B, D, and E *via* cationic intermediates, *e.g.*, II. This general approach to the pentacyclic nucleus is attractive because the synthesis of the necessary intermediates is clearly feasible and because the total number of steps required appears to be smaller than for the other routes which have been considered.



I



II

In addition there is a parallel with the proposed biosynthetic processes[3,4] and the reactions which have been employed for the synthesis of pentacyclosqualene (8,8′-cycloonocerene).[5,6] As in previous work,[6] we chose to deal with substances lacking the 3-hydroxyl group of the naturally occurring β-amyrin derivatives for the sake of operational convenience. The choice of the diene I as the synthetic objective was governed in part by the fact that this substance is resistant to isomerization under the acidic conditions which are generally used for cationic cyclization of olefins as is dramatically illustrated by the formation of this system from the ursan-11,12;13,18-diene system under drastic conditions.[7]

In general terms the synthesis of I was carried out along the following lines. An intermediate which contained rings A and B (VI) was prepared and coupled to a monocarbocyclic structure (X) ultimately to comprise ring E. The D ring was then produced by an aldol cyclization and finally the C ring was closed by an acid-catalyzed internal addition reaction.

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(1) This work was supported by the National Science Foundation.

(2) E. J. Corey, H.-J. Hess, and S. Proskow, *J. Am. Chem. Soc.*, **81**, 5258 (1959).

(3) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953).

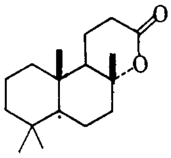
(4) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(5) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

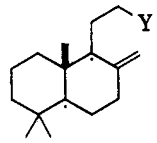
(6) E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 3925 (1957); **81**, 1739 (1959).

(7) G. G. Allen, J. M. Beaton, J. I. Shaw, F. S. Spring, R. Stevenson, J. L. Stewart, and W. S. Strachan, *Chem. Ind.* (London), 281 (1955).

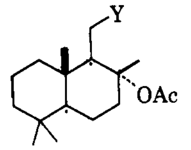
The intermediate VI which served as the precursor for the A and B rings was synthesized by two routes. In the first (+)-ambreinolide (III)[8] was converted by saponification and methylation (CH_2N_2) to a hydroxy methyl ester which was dehydrated with phosphorus oxychloride–pyridine and saponified to the unsaturated acid IV. Reduction of IV with lithium aluminum hydride led to the corresponding primary alcohol V which was transformed *via* the tosylate to the bromide VI with lithium bromide in acetone. The acid IV was also prepared from the acetoxyaldehyde VII[6] *via* the corresponding alcohol (VIII) ($NaBH_4$), brosylate, and cyanide (IX). Treatment to the acetoxynitrile IX with quinoline at reflux caused elimination of acetic acid to form an unsaturated nitrile from which IV was produced by basic hydrolysis.



III

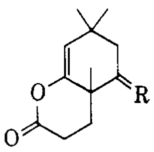


IV, Y = COOH
V, Y = CH_2OH
VI, Y = CH_2Br

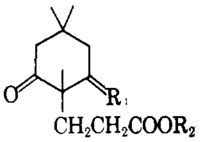


VII, Y = CHO
VIII, Y = CH_2OH
IX, Y = CH_2CN

The (±)-enol lactone X[9] was prepared from 2,5,5-trimethylcyclohexane-1,3-dione[10] *via* the diketo ester XI (methyl acrylate–potassium *t*-butoxide) and the acid XII. The reaction of this acid with phosphorus pentachloride gave the crystalline keto enol lactone XIII which upon hydrogenation with platinum catalyst in acetic acid afforded the acid XIV. The (±)-enol lactone X, m.p. 64–65°, infrared max. 1755 and 1673 cm.$^{-1}$, was formed by further treatment of the keto acid XIV with phosphorus pentachloride.

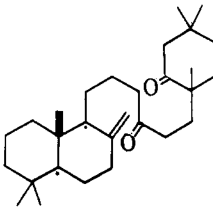


X, R = H_2
XIII, R = O

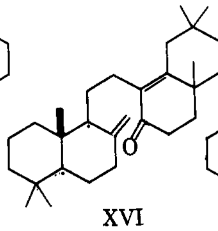


XI, R_1 = O, R_2 = CH_3
XII, R_1 = O, R_2 = H
XIV, R_1 = H_2, R_2 = H

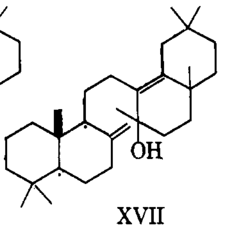
The coupling of the two precursors of the oleanane ring system was carried out by converting the (+)-bromide VI to the Grignard reagent by reaction with a large excess of magnesium under carefully controlled conditions and subsequently adding this intermediate slowly to the lactone X (in excess) at −70°. The diketone XV was thus obtained as an oily mixture of stereoisomers. The infrared spectrum of this intermediate showed carbonyl absorption at 1710 cm.$^{-1}$ and bands due to the terminal methylene grouping at 1640 and 890 cm.$^{-1}$, as expected. The reaction of XV with potassium *t*-butoxide–*t*-butyl alcohol gave a mixture of epimeric conjugated ketones (after chromatography) with infrared absorption 1668 and 1606 cm.$^{-1}$ and ultraviolet absorption (in ethanol) at 252 mμ (ϵ 14,600) and hence it was clear that cyclization to form ring D as in XVI had occurred. The cyclization reaction was quite slow, however, even in the presence of a large amount of the base and by-products containing unconjugated ketonic and hydroxyl groups were invariably found in the crude reaction product. These were easily separated from the ketone XVI, but further separation of XVI into pure stereoisomers was not realized. Treatment of the isomeric ketones XVI with methyllithium yielded the corresponding C_{30}-tertiary alcohol mixture XVII and this was used directly in the acid-catalyzed cyclization step which followed.



XV



XVI



XVII

Since a major goal of this research was the evaluation of methods of forming the hydropicene nucleus of the pentacyclic triterpenes from tetracyclic intermediates lacking ring C, a considerable number of experiments was carried out with the tetracyclic alcohol XVII. Before reviewing these, a more general discussion is in order. First of all, the intermediate XVII was chosen for study over other possible precursors for a number of reasons. As mentioned above, the expected product I is admirably stable to acid-catalyzed rearrangement and, further, it can be detected and identified easily because of its intense and characteristic ultraviolet absorption.

It is apparent that the direction of the cation–olefin addition to form ring C should ideally be under control, or at least unique. In principle, the C ring can be formed by addition of an A/B ring cation to a D/E ring unsaturation *or vice versa*. With symmetrical tetracyclic compounds such as the onoceradienes[5,6] the direction of cyclization is immaterial, but in other instances it is a matter of consequence. It was considered that under mildest conditions XVII would be converted by acids to a mixture of tetracyclic species consisting chiefly of (1) A/B monoene–D/E diene, (2) A/B cation–D/E diene, and (3) A/B monoene–D/E allylic cation structures. It was also thought that a mobile equilibrium would exist between these species which would be very fast compared to the cyclization process.[11] The possibility of directional specificity in this case seemed reasonable and it was initially thought possible that the species 2 above might be the most important intermediate for cyclization. Addition of the A/B cation to the D/E diene system to form the sterically strained pentacyclic system should derive large impetus from the generation of a stable D/E allyl cation in the transition state; indeed, a concerted proton addition–cyclization of this genre can be entertained. Clearly, a plurality of factors, including the relative concentrations of the various species, will operate to determine the direction of cyclization; it was hoped that the intermediate XVII would allow control over the distribution of products, at least by the modification of reaction conditions. In fact, however, the cyclization process has thus far not been developed into a highly efficient one.

A large number of attempts to cyclize XVII were unpromising as judged by ultraviolet assay of the crude reaction product. These included the use of sulfuric, perchloric, hydrobromic, hydrofluoric, hydriodic, *p*-toluenesulfonic, phosphoric, and trifluoroacetic acids in solvents such as acetic acid, benzene, methylene chloride, and formic acid. In most cases control experiments were performed to verify that the desired product I was stable under the reaction conditions. In contrast, the experiments with hydrogen chloride as acid

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(8) (±)-Ambreinolide has been made by total synthesis previously by P. Dietrich and E. Lederer, *Helv. Chim. Acta*, **35**, 1148 (1952).

(9) In ref. 2 this intermediate is labeled (+) in one place through a typographical error.

(10) E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 811 (1953).

(11) The cyclization of the onoceradienes to *sym*-pentacyclosqualene requires several hours even in 10% perchloric acid–acetic acid solution; see ref. 6 p. 1742.

catalyst seemed to yield more encouraging results since the product was found to have a broad ultraviolet maximum at 245 mμ which could be interpreted as a superposition of the absorption of the diene I and other conjugated dienes, including the tetracyclic D/E diene formed by dehydration of the starting alcohol XVII. The diene I shows a triple-peak absorption maximum at 242, 250, and 259 mμ (ε at 250 mμ *ca.* 30,000) and the diene produced by dehydration of XVII under mild conditions, *e.g.*, passage through acid-washed alumina (Merck) in hexane solution, showed absorption at 235, 245, and 254 mμ. The addition of these absorption spectra gave a synthetic spectrum similar to those observed for the crude cyclization product. Further, chromatography of the product from certain of the cyclizations using hydrogen chloride as catalyst led to fractions showing clear and strong absorption at 241, 250, and 260 mμ. The yield of this material was very poor, however. Similar chromatographic treatment of the cyclization product obtained using the other acids listed above did not yield fractions with the 241, 250, and 260 mμ absorption.

It seemed clear that the hydrogen chloride system was deserving of more intensive study despite the very poor conversion to material having the required absorption and consequently about thirty experiments were performed using this catalyst under varying conditions. The reaction product was assayed by ultraviolet analysis of the fractions obtained after chromatography on alumina. Runs were made with the solvents: benzene, formic acid, acetic acid, phenol, chloroform, chloroform–ethanol, and ethylene dichloride at temperatures ranging from 0–80°. Acetic acid appeared to afford the best results and so a series of about fifteen experiments was carried out with hydrogen chloride in acetic acid at various temperatures and for a range of reaction times.

The optimum conditions found involve the use of a saturated solution of anhydrous hydrogen chloride in acetic acid at 25° for 20 hr. and then at 55° for a further 3 hr. In the best runs the yield of I estimated by ultraviolet spectral analysis of partially purified chromatographic fractions was roughly 5%. Extensive chromatography of a run using 500 mg. of the tetracyclic alcohol XVII afforded crystalline I in *ca.* 1.5% yield. The purified product was identical with an authentic sample of pure I synthesized from β-amyrin[12] on the basis of comparison of infrared and ultraviolet absorption spectra, optical rotation, melting point, and mixture melting point.

At present it is not possible to define the side reactions which interfere so seriously with the formation of the pentacyclic triterpene nucleus by the approach described above. It is clear that our limited success constitutes only a first step in the direction of using cationic cyclization reactions to form ring C from a tetracyclic precursor. Much additional study is in order.[13,14]

Experimental[15]

Acetoxyaldehyde VII from Sclareol.—To a solution of 23.1 g. of sclareol in 693 ml. of freshly distilled *t*-butyl alcohol was added 231 ml. of water, 88.35 g. of sodium metaperiodate, and 0.177 g. of osmium tetroxide. The mixture was stirred vigorously at 25–30° for 5.5 hr. under nitrogen and then poured into 3 l. of water. The combined extracts from four 500-ml. ether extractions were washed twice with potassium carbonate solution and once with water. Evaporation of the dried extracts gave a dark viscous residue, which was dissolved in a minimum amount of *n*-hexane and then purified by filtration through a column (3 × 60 cm.) of 150 g. of Florisil. The *n*-hexane eluate, 1.5 l., was evaporated, yielding 15 g. (68%) of colorless crystalline acetoxy aldehyde VII.[6] The infrared spectrum in carbon tetrachloride showed broad carbonyl absorption at 1725 cm.$^{-1}$ and C–O stretching at 1250 cm.$^{-1}$. This procedure is superior to that given earlier.[6]

Diol Monoacetate VIII.—Sodium borohydride (2.3 g.) was dissolved in 230 ml. of cold methanol, and to the stirred solution was quickly added, with cooling, a solution of 9.53 g. of acetoxyaldehyde VII in 230 ml. of methanol. After stirring for 3 min., the excess sodium borohydride was decomposed by dropwise addition of acetic acid and the methanolic solution was concentrated *in vacuo* to a small volume. Water and ether were added and the separated ethereal phase was washed twice with small portions of water and dried with anhydrous sodium sulfate. Evaporation of the ether gave 9.15 g. (95%) of the crude diol monoacetate VIII, a viscous liquid, which was sufficiently pure for reaction in the next step.

Cyanoacetate IX.—The crude diol monoacetate VIII (9.15 g.) was dissolved in a mixture consisting of 67 ml. of dry pyridine and 67 ml. of dry collidine and to this, at 0°, was added with stirring 29.5 g. of *p*-bromobenzenesulfonyl chloride. The reaction mixture was maintained at +4° for 4 hr., the excess of *p*-bromobenzenesulfonyl chloride was then destroyed by dropwise addition of water at 0°, and the solution was transferred into a mixture of 850 ml. of water and cracked ice. The organic layer was extracted with ether twice and the combined ethereal phase washed successively with ice-cold portions of dilute hydrochloric acid, water, 1 *M* sodium carbonate solution, and again with water. The ethereal solution was dried with anhydrous sodium sulfate, the ether was evaporated *in vacuo*, and the oily residue was triturated with 40 ml. of *n*-hexane. After cooling at −10° overnight, 9.57 g. (60%) of crude crystalline brosylate was collected by filtration; m.p. 90–94°. Recrystallization from *n*-hexane furnished colorless plates of m.p. 94–97° which were unstable in the laboratory atmosphere at room temperature and decomposed slowly to a viscous liquid smelling strongly of acetic acid. The product was stable for long periods when stored under nitrogen at −10°.

A well stirred mixture of 8.7 g. of sodium cyanide and 9.0 g. of this brosylate in 220 ml. of purified, dry dimethyl sulfoxide was heated under nitrogen to 65°. The resulting solution was then maintained at 60–65° for 20 hr. After cooling, the solution was poured into 2.4 l. of water and the precipitate was extracted with two 600-ml. portions of ether. The combined ether extracts were then washed with water, dried with anhydrous sodium sulfate, and the ether evaporated giving 5.70 g. of the crude hydroxynitrile acetate (IX) as a crystalline residue. This was recrystallized once from *n*-hexane, furnishing 4.5 g. of silk-like needles, m.p. 84–86°.

A sample recrystallized several times from *n*-hexane gave crystals of unchanged melting point, $[\alpha]^{20}_{D}$ −10.1° (chloroform, *c* 2.250). The infrared spectrum in carbon tetrachloride showed nitrile absorption at 2250 cm.$^{-1}$ and acetate absorption at 1725 and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 75.10; H, 10.02; N, 4.62.

Unsaturated Acid IV.—A solution of 10.77 g. of hydroxynitrile acetate (IX) in 60 ml. of purified, dry quinoline was refluxed under nitrogen for 30 min. The cooled solution was taken up in ether and the ethereal solution washed successively with ice-cold portions of dilute hydrochloric acid, water, 1 *M* sodium carbonate solution, and again with water. After drying and ether evaporation, an oily crystalline residue was obtained. This was redissolved in boiling aqueous methanol, decolorized with charcoal, and gradually cooled to −10°; 5.36 g. (62%) of crude unsaturated nitrile was obtained, m.p. 88–90°. The crude product was then used advantageously in the next step since purification could be accomplished at that point with minimum loss of material.

A sample of the above crude product was recrystallized four times from methanol–water, giving the pure crystals, colorless transparent plates, m.p. 92–94°, $[\alpha]^{20}_{D}$ +46.6° (*c* 2.270); infrared max. (carbon tetrachloride) 2250, 1645, and 897 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{27}N$: C, 83.20; H, 11.09; N, 5.71. Found: C, 83.63; H, 10.89; N, 6.07.

To a solution prepared from 2.8 g. of potassium hydroxide, 70 ml. of water, and 280 ml. of freshly distilled ethylene glycol was added 2.8 g. of crude unsaturated nitrile (m.p. 88–90°), and the mixture was stirred and refluxed under nitrogen at 140–145° for 24 hr. The clear solution was concentrated *in vacuo* to a small volume, water and ether were added, and the aqueous phase separated after extraction. Crushed ice and sodium chloride were then added to this aqueous phase, and the mixture acidified by addition of cold, dilute hydrochloric acid. After extraction of the precipitate with ether and washing the combined extract with two portions of saturated aqueous sodium chloride, the ethereal phase was dried and evaporated. The crystalline

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(12) J. Green, N. Mower, C. W. Picard, and F. S. Spring, *J. Chem. Soc.*, 527 (1944).

(13) For a recent review of this field see N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.* (London), **16**, 117 (1962).

(14) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1620 (1962), describe another aspect of the problem.

(15) All melting points were determined with a micro hot stage and are corrected. Rotations were measured with chloroform solutions.

residue of crude unsaturated acid IV was recrystallized once from methanol–water giving 2.53 g. (84%) of silk-like needles, m.p. 113–115°, $[\alpha]^{20}\mathrm{D}$ +52.1° (chloroform, *c* 0.700); infrared max. (carbon tetrachloride) 1710, 1645, and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.13; H, 10.67. Found: C, 76.95; H, 10.94.

(+)-Ambreinolide (III) from the Acetoxynitrile IX.—The hydroxynitrile acetate IX (2.38 g.) was added to 2.38 g. of potassium hydroxide in 50 ml. of water and 200 ml. of freshly distilled ethylene glycol. The mixture was then stirred at 140–145° for 24 hr. An atmosphere of nitrogen was maintained throughout the reaction period. The clear solution was distilled *in vacuo* to a small volume, water was added to the residue, and the aqueous solution extracted once with ether. The aqueous phase was then acidified with an excess of dilute hydrochloric acid, and after sodium chloride saturation the product was extracted with ether. The oily residue from evaporation of the dried ethereal extract gradually solidified when heated *in vacuo* on the steam bath, giving 2.09 g. of crude (+)-ambreinolide (III), m.p. 125–140°. One recrystallization from 95% ethanol gave 1.57 g. (76%) of long needles, m.p. 136–143°, which were used in the next step.

A small sample was recrystalized two more times to give crystals of m.p. 142–144°, $[\alpha]^{20}\mathrm{D}$ +33.3° (chloroform, *c* 2.565); reported m.p. 142°, $[\alpha]^{20}\mathrm{D}$ +34° (ethanol); identical by infrared spectrum and mixture m.p. with authentic (+)-ambreinolide.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.13; H, 10.67. Found: C, 77.36; H, 10.81.

Conversion of Ambreinolide (III) to the Unsaturated Acid IV.—One ml. of pure dioxane, and 0.716 g. of (+)-ambreinolide (m.p. 136–143°), were added to 41 ml. of 0.10 *M* aqueous sodium hydroxide solution, and the two-phase mixture was stirred and refluxed under nitrogen for 4 hr. The clear solution (at 0°) was treated with 41 ml. of 0.10 *M* hydrochloric acid, saturated with sodium chloride and quickly extracted with ether. The ether solution was then washed twice with ice-cold sodium chloride-saturated water. This ether solution of the hydroxy acid was maintained at 0° and treated with ethereal diazomethane. After carefully neutralizing the excess diazomethane with acetic acid, the solution was quickly washed with ice-cold portions of sodium carbonate solution and sodium chloride-saturated water. The dried ethereal solution on evaporation yielded 0.63 g. (79%) of the colorless, crystalline hydroxy acid methyl ester, m.p. 75–80°. This product was sufficiently pure for reaction in the next step.

The pure hydroxy acid methyl ester was obtained after two more recrystallizations from *n*-hexane; m.p. 83–85°, $[\alpha]^{20}\mathrm{D}$ −5.26° (*c* 2.280). The infrared spectrum in carbon disulfide showed alcohol absorption at 3490 cm.$^{-1}$ and ester carbonyl absorption at 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.95; H, 10.88. Found: C, 73.17; H, 10.64.

Freshly distilled phosphorus oxychloride (2 ml.) was added in portions to a solution, at 0°, of 0.4 g. of the above crude hydroxy acid methyl ester (m.p. 75–80°) in 40 ml. of dry pyridine. After 30 min. at 0°, the solution was allowed to stand at room temperature for 24 hr. longer. The excess phosphorus oxychloride was destroyed by dropwise addition of water at 0°, and 15 min. later the solution was transferred into a mixture of dilute hydrochloric acid (excess) and crushed ice. The cold mixture was then extracted with ether and the separated ethereal extract washed with 1 *M* sodium carbonate solution and water. After drying and evaporation, the ethereal solution afforded 0.375 g. (100%) of the colorless liquid unsaturated methyl ester of IV. This crude product had $[\alpha]^{20}\mathrm{D}$ +37.3° (*c* 4.140) and exhibited ester carbonyl absorption at 1740 cm.$^{-1}$ and the 890, 1640 cm.$^{-1}$ bands associated with the exocyclic methylene unsaturation. It was used in the next step without further purification.

The crude liquid unsaturated methyl ester (0.2 g.) was added to 0.2 g. of potassium hydroxide in 20 ml. of ethanol and 5 ml. of water and the clear solution was refluxed under nitrogen for 24 hr. The product was isolated as described in the preparation of the unsaturated acid IV from the unsaturated nitrile IX. The crude crystalline residue (0.18 g.) was recrystallized three times from methanol–water and furnished 0.09 g. (47%) of silk-like needles, m.p. 113–115°, $[\alpha]^{20}\mathrm{D}$ +48.9° (*c* 1.140) identical by infrared spectrum and mixture m.p. with the unsaturated acid IV obtained as described above from the unsaturated nitrile IX.

Lithium Aluminum Hydride Reduction of the Unsaturated Acid.—The unsaturated acid IV (5.81 g.) in 75 ml. of absolute ether was slowly added at 25° with stirring to a mixture of 4.94 g. of lithium aluminum hydride and 300 ml. of ether (prestirred for 2 hr. under reflux). After addition, the mixture was refluxed 5 hr. more with stirring and then stirred at 25° overnight. To destroy excess hydride a minimum volume of water was added at 0°. The inorganic precipitate was removed by decantation and the combined ethereal solution was extracted with 1 *M* sodium carbonate solution. After washing with water and drying with anhydrous sodium sulfate, the ethereal phase was evaporated giving 5.45 g. (99%) of the hydroxy olefin V as a pale yellow liquid residue, $[\alpha]^{20}\mathrm{D}$ +33.3° (*c* 4.170). This crude product was used in the next step (see below) without further purification.

The infrared spectrum of the crude product showed alcohol OH absorption and exocyclic methylene unsaturation at 890 and 1645 cm.$^{-1}$. For analysis, a small sample was distilled into a micro-cup; b.p. about 150° (0.4 mm.).

Anal. Calcd. for $C_{17}H_{30}O$: C, 81.55; H, 12.08. Found: C, 81.95; H, 12.14.

Unsaturated Bromide VI.—A solution of the above hydroxy olefin V (2.57 g.) in 50 ml. of dry pyridine was maintained at 0°, and 7.64 g. of *p*-toluenesulfonyl chloride was added. After 30 min. at 0°, the solution was maintained at +4° for 18 hr. The excess acid chloride was destroyed by dropwise addition of water at 0°. The solution was then transferred into 500 ml. of water and the organic layer extracted twice with ether. Ice-cold portions of dilute hydrochloric acid and water were then used to extract the pyridine from the combined ethereal solution. After washing with 1 *M* sodium carbonate solution and water, the ethereal phase was dried with anhydrous sodium sulfate and evaporated. The viscous, pale yellow residue of the hydroxy olefin tosylate weighed 3.66 g. (90%) and had $[\alpha]^{20}\mathrm{D}$ +32.2° (*c* 3.390). The infrared spectrum (in carbon disulfide) was devoid of alcohol OH absorption and exhibited bands at 1370, 1180 cm.$^{-1}$ (arylsulfonic acid ester) and 1645, 890 cm.$^{-1}$ (exocyclic methylene unsaturation).

The product decomposed during an attempted distillation *in vacuo* (0.3 mm.) and was therefore used in the next step without further purification.

Dry lithium bromide (6.43 g.) was dissolved in 50 ml. of pure acetone and the solution added to 3.0 g. of the above liquid hydroxy olefin tosylate. The clear solution was then stored in the dark, at 25°, for 35 hr.

The acetone was removed *in vacuo* and ether and water were added to dissolve the residue. The separated ethereal solution was then washed with water, dried, and evaporated, giving the crude product as a pale yellow liquid residue. This was transferred with *n*-hexane on a column of Merck basic alumina (20 g., 2 × 10 cm.), and the column further eluated with *n*-hexane. The product obtained by evaporation of the first 200 ml. of eluent was the purified olefin bromide VI. It was a clear colorless liquid which, when thoroughly dried *in vacuo*, was suitable for use in the Grignard reaction (see below); weight 2.1 g. (91%), $[\alpha]^{20}\mathrm{D}$ +43.1° (*c* 2.805). The product exhibited exocyclic methylene unsaturation at 1645 and 890 cm.$^{-1}$ in the infrared spectrum (carbon disulfide) and silver bromide was precipitated when it was heated with ethanolic silver nitrate solution.

2,5,5-Trimethyl-2-carbomethoxyethylcyclohexane-1,3-dione (XI).—Potassium metal (6.2 g.) was dissolved in 2 l. of dry *t*-butyl alcohol under nitrogen, and 49.8 g. of 2-methyldimedone[10] was added. To this stirred solution at 20° was then slowly added 280 ml. of methyl acrylate over a period of 6 hr. and the solution was stirred at 25° for 12 hr. longer.

Most of the *t*-butyl alcohol was removed by distillation *in vacuo*, and water and ether were added to the residue. The ethereal phase after washing with 1 *M* sodium carbonate solution and water was then dried and evaporated, furnishing 57 g. (74%) of the diketo ester XI as a pale yellow oil. The infrared spectrum (in carbon disulfide) showed carbonyl doublet absorption at 1695 and 1730 cm.$^{-1}$ with widening of the 1730 cm.$^{-1}$ band due to ester carbonyl absorption.

2,5,5-Trimethyl-2-carboxyethylcyclohexane-1,3-dione (XII).—Diketo methyl ester XI (56.5 g.) was dissolved in a solution prepared from 33.5 ml. of 12 *M* hydrochloric acid, 150 ml. of water, and 675 ml. of acetone, and the new solution was refluxed for 24 hr. The bulk of the acetone was then removed *in vacuo* and the residual acidic aqueous solution extracted once with 200 ml. of ether. This ethereal extract was washed with portions of 1 *M* sodium carbonate solution in excess, and the combined basic aqueous extract added to the aqueous acidic phase above. The solution was then reacidified, saturated with salt, and extracted repeatedly with portions of ether. A white waxy solid residue (55 g.) was obtained from this combined ether extract after washing (aqueous saturated salt solution), drying, and evaporation.

The solid recrystallized once from cyclohexane–benzene (1:1) afforded 39.6 g. (75%) crystals of XII, m.p. 190–113°.

A small sample when recrystallized several times from cyclohexane–benzene gave a product, m.p. 109–113°, neut. equiv. 218 (calcd. 226).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.73; H, 7.98.

2,5,5-Trimethyl-2-carboxyethylcyclohexane-1,3-dione Enol Lactone (XIII).—Diketo acid XII (10 g.), m.p. 90–107°, was treated under nitrogen with 10 g. of phosphorus pentachloride. The initial vigorous reaction was controlled by cooling and the mixture was then heated on the steam bath for 1 hr.

The phosphorus oxychloride was removed by distillation *in vacuo* leaving a light brown oil from which crystalline enol lactone was obtained by sublimation through a short path at 100° (0.25 mm.). Resublimation gave 6.80 g. (75%) of product of m.p. 62–90°. Nearly pure crystals, m.p. 95–97°, were then obtained after one recrystallization from cyclohexane; yield 6.1 g. (66%). The enol lactone absorption in the infrared spectrum was characterized by two strong bands at 1765 and 1675 cm.$^{-1}$, and that of the isolated ketone function by a strong band at 1720 cm.$^{-1}$.

A small sample of XIII, repeatedly recrystallized from cyclohexane for analysis, showed m.p. 95.5–97° (subl.).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.18; H, 7.74. Found: C, 69.28; H, 7.88.

2,5,5-Trimethyl-2-carboxyethylcyclohexanone (XIV).—The keto-enol lactone XIII (10 g.), m.p. 95–97°, was dissolved in a prereduced mixture of 250 ml. of glacial acetic acid and 1.27 g. of Baker (no. 535) platinum oxide catalyst, and the mixture was hydrogenated at 25° and 1 atmosphere pressure. The hydrogenation was interrupted after 2.5 hr. at which time 2.025 l. of hydrogen gas was absorbed. The platinum was separated and the solvent was removed by distillation *in vacuo*. Ether was then added to the residual oil, and the ethereal solution was washed with portions of 1 *M* sodium carbonate solution in excess. The basic extract was acidified with 2.9 *M* hydrochloric acid, saturated with sodium chloride, and extracted repeatedly with ether. After drying, the combined ethereal phase was evaporated and the viscous liquid residue (7.86 g.) redissolved in boiling *n*-hexane. On gradual cooling to −10°, 5.67 g. (55%) of keto acid XIV, transparent plates of m.p. 68.5–70.5° deposited.

A small sample was recrystallized repeatedly from *n*-hexane for analysis. The m.p. of the analytical sample was 68–70°.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.00; H, 9.23.

The ethereal phase left from the sodium carbonate extraction above was washed with water, dried, and evaporated, giving 3.2 g. of a viscous oily residue. This oil was shown by its infrared spectrum to consist chiefly of 2,5,5-trimethyl-2-carboxyethyl-3-hydroxycyclohexanone lactone.

2,5,5-Trimethyl-2-carboxyethylcyclohexanone Enol Lactone (X).—The keto acid XIV (8.2 g.) was mixed under nitrogen with 8.2 g. of phosphorus pentachloride. The initial vigorous reaction was controlled by cooling, and the reaction mixture was then heated on the steam bath for 30 min. Subsequently, the formed phosphorus oxychloride was removed by distillation *in vacuo* and the light brown residue sublimed twice at 120–130° (0.3 mm.), yielding 5.6 g. (74%) of crystalline material, m.p. 68–70°. This product, which exhibited strong enol lactone absorption at 1755 and 1673 cm.$^{-1}$ in its infrared spectrum (carbon disulfide), was used immediately in the Grignard reaction.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.25; H, 9.40.

Grignard Reaction of Olefinic Bromide VI and Enol Lactone X.—To 55 g. of finely powdered magnesium and 50 ml. of anhydrous ether in a three-necked round-bottomed flask having an outlet with stopcock at the bottom and equipped with reflux condenser, stirrer, and dropping funnel was added 1 ml. of iodomethane in 50 ml. of ether. The mixture was stirred for 1 hr., and after removal of the ethereal methylmagnesium iodide, the residual activated magnesium was washed three times with 50-ml. portions of ether. The magnesium was then covered with 50 ml. of fresh ether and to this vigorously stirred mixture at reflux temperature (infrared heating lamp) was slowly added over a period of 2 hr. a solution of the olefinic bromide VI (4.2 g.) in 75 ml. of ether. The mixture was stirred and refluxed for an additional hour.

The Grignard reagent was then added dropwise (through the outlet at bottom) over a period of 2 hr. under nitrogen to a stirred solution of 5.6 g. of freshly prepared enol lactone X in 50 ml. of dry ether at Dry Ice–acetone temperature. The mixture was stirred for an additional 2 hr., then gradually warmed up to room temperature and stirred overnight. Saturated ammonium chloride solution was added for hydrolysis and the aqueous phase was extracted with ether. The combined ethereal phase was washed with water, dried, and the ether evaporated. To remove unreacted enol lactone, the residue was dissolved in 150 ml. of tetrahydrofuran, 3.0 g. of sodium hydroxide in 12.5 ml. of water was added, and the mixture was stirred magnetically under nitrogen for 1.5 hr. Ether and water were added; the aqueous phase was separated and extracted with ether. The combined ethereal extract was washed with water to neutrality, dried, and the ether evaporated. The residual oil (5.25 g.) exhibited strong carbonyl absorption in the infrared spectrum at 1710 cm.$^{-1}$ and exocyclic methylene absorption at 1640 and 890 cm.$^{-1}$. This material (crude XV) was used in the next step without further purification.

From the above alkaline solution, 3.75 g. of keto acid XIV, m.p. 74–76°, was recovered.

Tetracyclic α,β-Unsaturated Ketone XVI.—Crude tricyclic diketone (5.25 g.) was treated under nitrogen with a solution of potassium *t*-butoxide in *t*-butyl alcohol (12.5 g. potassium in 300 ml. of *t*-butyl alcohol). The resulting clear solution was stirred for 42 hr. at 25° and then neutralized with dilute acetic acid. Isolation gave 5.2 g. of a yellow viscous oil, which exhibited α,β-unsaturated ketone absorption in the infrared spectrum at 1670 and 1605 cm.$^{-1}$ and also hydroxy absorption at 2800 cm.$^{-1}$ and carbonyl absorption at 1710 cm.$^{-1}$. The product was dissolved in *n*-hexane and then transferred on a column of Merck basic alumina (250 g., 70 × 2 cm.). Elution with *n*-hexane gave 1.07 g. of a colorless oil, which showed strong exocyclic methylene unsaturation in the infrared spectrum at 1640 and 890 cm.$^{-1}$ and which presumably is the coupling product derived from the olefinic bromide VI. The α,β-unsaturated ketone (1.37 g.) (25% from olefinic bromide VI) was eluted with *n*-hexane–ether (9:1), followed by fractions (0.2 g.) which contained α,β-unsaturated ketone and which also exhibited ketone absorption at 1710 cm.$^{-1}$ in the infrared spectrum. Elution with ether and methanol gave an unknown crystalline product (1.7 g.) with hydroxyl and ketone absorption at 1710 cm.$^{-1}$.

A sample of the α,β-unsaturated ketone was rechromatographed and then evaporatively distilled for analysis at 0.01 mm. and 150°, infrared maxima 1668 and 1606 cm.$^{-1}$, $\lambda_{\max}$ 252 mμ (ε 14,600) in ethanol.

Anal. Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.53; H, 11.52.

Conversion of the Tetracyclic α,β-Unsaturated Ketone XVI to the Tetracyclic Alcohol XVII.—A solution of 8.0 g. of iodomethane in 50 ml. of dry ether was slowly added to a stirred mixture, at 25°, of 2.14 g. of freshly cut lithium in 50 ml. of ether. It was stirred for 1 hr. at room temperature and 0.50 g. of α,β-unsaturated ketone in 50 ml. of dry ether was then added to the methyllithium and the mixture was refluxed for 3 hr. After filtration through glass wool, water was carefully added to the ether solution and the ethereal phase was washed with water to neutrality, dried, and the ether evaporated. A pale yellow oil, weighing 0.50 g., was obtained as a residue. The infrared spectrum exhibited alcohol OH stretching absorption, was entirely devoid of carbonyl absorption and had the 1645, 890 cm.$^{-1}$ bands characteristic of exocyclic methylene unsaturation. The product was used directly for the acid-catalyzed cyclization.

Acid-Catalyzed Cyclization of Tetracyclic Alcohol XVII.—The tetracyclic alcohol XVII (0.5 g.) was dissolved in 200 ml. of glacial acetic acid and a stream of anhydrous hydrogen chloride was bubbled through the solution at 25° for 20 hr. and then at 55° for 3 hr. The solution then was poured into ice–water, extracted with ether, and the ethereal extract was washed successively with water, 2 *N* sodium carbonate solution, water, and dried with anhydrous sodium sulfate. Evaporation of the ether yielded 0.430 g. of a pale yellow oil as a residue which showed strong end absorption and a broad maximum at 245 mμ in the ultraviolet spectrum.

Extensive chromatography was carried out first on ferric oxide.[16] A column 55 × 4 cm. was used and purified *n*-hexane was the solvent. Fractions of 15 ml. were collected and the ultraviolet spectra measured. The first fractions which contained eluted material showed strong end absorption; these were followed by fractions which had end absorption and maxima at 245, 255, and 265 mμ. Subsequent fractions (51–92) showed end absorption and the characteristic diene absorption of I with maxima at 242, 250, and 259 mμ.

The combined diene fractions 51–92 (0.185 g. as a colorless oil) were rechromatographed on acid-washed alumina which had been activated *in vacuo* for 11 hr. at 200° (0.5 mm.). The packed column was 9 ft. long and 2 cm. in diameter; *n*-hexane was again the solvent and 15-ml. fractions were collected.

Those showing diene absorption (39–51) in the ultraviolet spectrum had lower end absorption this time, were combined and evaporated, yielding 0.063 g. of a colorless glass.

Further purification was obtained by chromatography on neutral alumina; Woelm activity I reactivated for 11 hr. at 270° and then for 2 hr. *in vacuo* at 300° (0.8 mm.). The packed column was 10 ft. long and 2 cm. in diameter; solvent was purified *n*-hexane and the fractions were 15 ml.

The diene fractions were combined and evaporated giving 0.040 g. of residue, a colorless glass. Acetone was added, and crystals appeared shortly, which were filtered and washed successively with mixtures of acetone–methanol (9:1, 3:1, 1:1); yield 0.0085 g., m.p. 205–207°. Recrystallization from acetone raised the m.p. to 218° (hot-stage microscope), weight 0.004 g., identical by infrared spectrum, ultraviolet spectrum, ultraviolet max. (hexane) 242, 250, 259 mμ (ε 26,670, 29,860, 19,710), rotation $[\alpha]^{25}\text{D}$ −65° (*c* 2.2), and mixture melting point (218°) with an authentic sample[12] of olean-11,12;13,18-diene, m.p. 219°, ultraviolet max. (hexane) 242, 250, 259 mμ (ε 26,010, 29,070, 19,550), $[\alpha]^{25}\text{D}$ −66°.

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(16) Prepared according to O. Glemser and G. Rieck, *Angew. Chem.*, **69**, 91 (1957), and activated *in vacuo* for 17 hr. at 200° (0.5 mm.).