Registry No.—**1**, 24343-81-5; **2**, 24298-76-8; **4**, 24299-76-1; **6**, 24298-77-9; **8**, 24299-77-2; **9**, 24343-82-6; **13**, 24299-78-3 **14**, 24299-79-4; **15**, 24298-78-0; **16**, 24298-79-1; **17**, 24343-83-7.

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4-Carbomethoxy-5α-androstane Derivatives. Synthesis of (−)-Sandaracopimaric Acid

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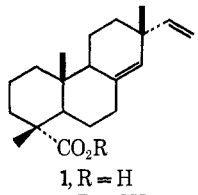
Novel steroidal β-keto esters **4** and **6** were prepared by direct carbonation of 17β-acetoxy-5α-androst-1-en-3-one (**3**) or by the reductive carbomethoxylation of testosterone acetate, respectively. Methylation of **6** affords selectively **7**, the expected product of stereoelectronically controlled axial alkylation. A reversal in the predicted stereochemical course of alkylation was observed with **4**, which afforded **11** as its exclusive methylation product. The configurations at C-4 in **7** and **11** were established through the corresponding 3-deoxy esters **9** and **10**. Ester **9** was converted by a series of reactions into (−)-sandaracopimaric acid (**1**).

Considerable support for the stereochemistry of the isomeric pimaric acids was provided by the syntheses of racemic pimaradiene and sandaracopimaradiene.[1] The stereochemical ambiguity at C-13[2] of the synthetic hydrocarbons was subsequently resolved by the conversion of testosterone into (−)-sandaracopimaradiene by three independent routes.[3] The synthesis of a pimaric acid-type natural product possessing a carboxyl group at C-4, however, has not been described in the literature. In this paper[4] we report the first synthesis of (−)-sandaracopimaric acid[5] (**1**) a diterpenoid resin acid isolated from *Callitris quadrivalvis*, starting from testosterone acetate. The present work provides a direct confirmation of the assigned structure **1** and absolute stereochemistry for the natural acid.



1, R = H
2, R = CH_3

Sandaracopimaric acid (**1**) has the same absolute stereochemistry at carbons 5, 9, 10, and 13 as steroids of the 5α series. Hence, the only stereochemical prerequisite for the conversion of a 5α steroid into **1** is the construction of the abietic acid type[6] of substitution pattern at C-4 of the steroid. Such a substitution pattern or the epimeric podocarpic acid type[6] of arrangement has been attained by a variety of approaches[7] in the syntheses of other resin acids from bi- and tricyclic intermediates. Among these approaches, the most direct method has been the selective methylation of β-keto esters.[8-10] We utilized this approach in preparing the epimeric keto esters **7** and **8**. Our interest in this area evolved from a program involving the preparation of novel 4-substituted androstane and pregnane derivatives for biological studies.

4-Carbomethoxy-5α-androstanes.—By analogy with the tricyclic series,[8] keto esters **4** and **6** would be the substrates of choice since methylation of either of these compounds would be expected to proceed by β attack, thereby providing the desired abietic acid type[6] of stereochemistry at C-4. Two methods were used for the introduction of the carbomethoxy group at C-4 of the appropriate steroid substrate. Using the direct carbonation procedure,[11,12] 17β-acetoxy-5α-androst-1-en-3-one[13] (**3**) was treated with an excess of tritylsodium followed by the introduction of carbon dioxide and conversion of the resulting acid into its methyl ester by reaction with diazomethane. Tlc indicated that the product was a complex mixture of keto esters and starting enone **3** in which the 17-acetate group had partially hydrolyzed and also had partially undergone carbona-

(1) (a) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963); (b) for a review, see R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

(2) Diterpene numbering as in ref 1b. This numbering will also be used for steroidal derivatives that do not contain C-15.

(3) (a) A. K. Bose and S. Harrison, *Chem. Ind.* (London), 1307 (1961); (b) M. Fetizon and M. Golfier, *Bull. Soc. Chim. Fr.*, 167 (1963); (c) P. Johnston, R. C. Sheppard, C. E. Stehr, and S. Turner, *J. Chem. Soc., C*, 1847 (1966).

(4) A preliminary report on this work has been published: A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968).

(5) (a) O. E. Edwards, A. Nicholson, and M. N. Rodger, *Can. J. Chem.*, **38**, 663 (1960); (b) V. Galik, J. Kulhan, and F. Petru, *Chem. Ind.* (London), 722 (1960); (c) A. K. Bose, *ibid.*, 1104 (1960).

(6) The term "abietic acid type" is used herein to denote an asymmetric center containing a β-methyl and an α-carboxyl group. "Podocarpic acid type" denotes the alternative arrangement (α-methyl, β-carboxyl).

(7) *Cf.* citations in ref 8–10.

(8) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Amer. Chem. Soc.*, **86**, 2038 (1964), and earlier papers cited.

(9) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

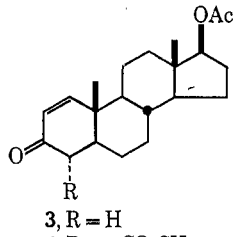
(10) T. A. Spencer, R. J. Friary, W. W. Schniegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968).

(11) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

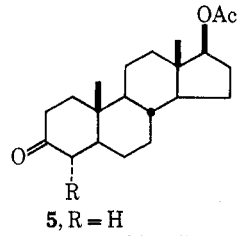
(12) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **81**, 5601 (1959).

(13) R. E. Counsell, P. D. Klimstra, and F. B. Cotton, *J. Org. Chem.*, **27**, 248 (1962).

tion. The crude reaction product was subjected to a selective hydrolysis of the 17-ester functions under acidic conditions, followed by acetylation. The product resulting from this treatment was predominantly a mixture of **3** and **4** and upon chromatography afforded the desired 4α-carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (**4**) in 30% yield. Catalytic reduc-



3, R = H
4, R = $-CO_2CH_3$

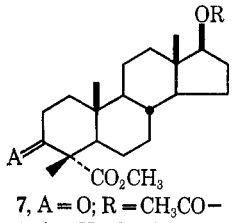


5, R = H
6, R = $-CO_2CH_3$

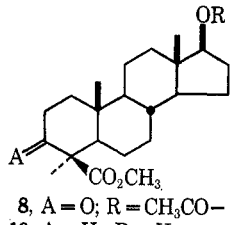
tion of **4** led to the formation of **6**. Alternatively, **6** was prepared by using Stork's procedure[14] for reductive carbomethoxylation.[9] Thus, testosterone acetate was treated with lithium in ammonia followed by carbon dioxide and, upon acidification, treated with diazomethane followed by acetylation. Chromatography of the reaction product resulting from this sequential treatment afforded 4α-carbomethoxy-17β-acetoxy-5α-androstan-3-one (**6**) in 24% yield. From the same reaction 17β-acetoxy-5α-androstan-3-one (**5**) was also isolated. No carbonation at C-2, which would result from equilibration of the C-4 anion,[9] was detectable in the reaction product.

In the nmr, the 4β-proton resonance of both **4** and **6** appears as a doublet with an axial–axial coupling of 12.5 cps. As has been observed in other *trans*-fused 4-carbalkoxy-3-ones,[9,12] neither of the keto esters **4** or **6** exhibits spectral properties of an enolized β-keto ester.

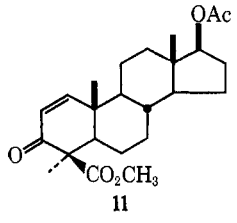
The keto esters **4** and **6** were alkylated with methyl iodide in benzene using sodium hydride as the base. Methylation of **6** proceeded selectively to afford **7** as the major product. From the same alkylation, a small yield of the epimeric compound **8** was also isolated, the ratio of **7** to **8** being 9.2:0.8. Under the same condi-



7, A = O; R = CH_3CO-
9, A = H_2; R = H



8, A = O; R = CH_3CO-
10, A = H_2; R = H



11

tions, the methylation of **4** was stereospecific, **11** being the only alkylated product formed in the reaction. Catalytic reduction of **11** afforded **8**, the minor methylation product of **6**.

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

The nmr spectrum of **8** shows a sextet (J = 14.5, 14.5, and 6 cps) with an intensity of 1 H centered at δ 2.93. It is noteworthy that this resonance, assigned to the 2β proton of **8**, is absent in **7** and **10**. Large values for J_{aa} and J_{ae} such as the ones above, observed for **8**, are not unusual.[15] The downfield position of the chemical shift of the 2β proton of **8** is interpreted as indicative of a chair conformation for ring A, wherein the carbonyl of the ester group can exert a deshielding effect on the 2β proton. Similar deshielding effects on protons held in the plane of a carbonyl group have been observed.[16]

Clemmensen reduction of the methylated keto esters **7** and **8** afforded the epimeric 3-deoxy esters **9** and **10**, respectively. A comparison of the relative susceptibility of the esters to basic hydrolysis showed that **10** is resistant to hydrolysis while **9** is not. In agreement with the hydrolytic data, the 19-methyl proton resonance of **10** appears at δ 0.70 shielded[17] by 0.19 ppm relative to the corresponding resonance of **9** at δ 0.89. The 1,3-diaxial shielding by a carbonyl group has been used as a diagnostic test to distinguish between analogous C-4 stereoisomers in other series.[9,18] The above hydrolytic and nmr data established unequivocally the stereochemistry at C-4 in compounds **9** and **10** and hence in **7**, **8**, and **11**.

Stereochemistry of Alkylation.—As expected,[8] the methylation of **6** proceeds selectively to afford **7**, the product of stereoelectronically controlled alkylation (axial attack by the alkylating agent). The stereochemical course of the methylation of **4**, however, is opposite (exclusive α attack by the alkylating agent to form **11**) to that observed in analogous substrates.[19] Examination of Dreiding models of **4** and **6** does not reveal overwhelming differences, in either the steric shielding due to the angular group or in *peri* interactions between C-4, C-6 and C-11, C-1 that would account for the impressive reversal of the stereochemical course of alkylation of **4**. It is obvious that extraordinarily subtle factors in **4** affect the approach of the alkylating agent. Exclusive α-methylation of **4** can be regarded to be stereoelectronically controlled if ring A acquires a boat conformation in the transition state of its alkylation. Dreiding models indicate that twisting of ring A, which is easier in **4** than in **6**, somewhat relieves the *peri* interactions.

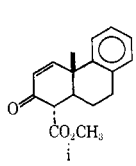
(15) (a) S. G. Levine and R. E. Hicks, *Tetrahedron Lett.*, 5409 (1968), and citation 9 therein; (b) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

(16) D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2810 (1963).

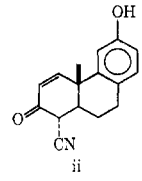
(17) The magnitude of the shielding effect in the corresponding 3-keto compound **8** is much reduced (0.06 ppm) relative to **10**.

(18) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

(19) The methylation of the analogous keto ester i, in contrast to that of **4**, proceeds by attack of the alkylating agent from the β side, exclusively.[8] It is noteworthy that the methylation of the related substrate ii, originally



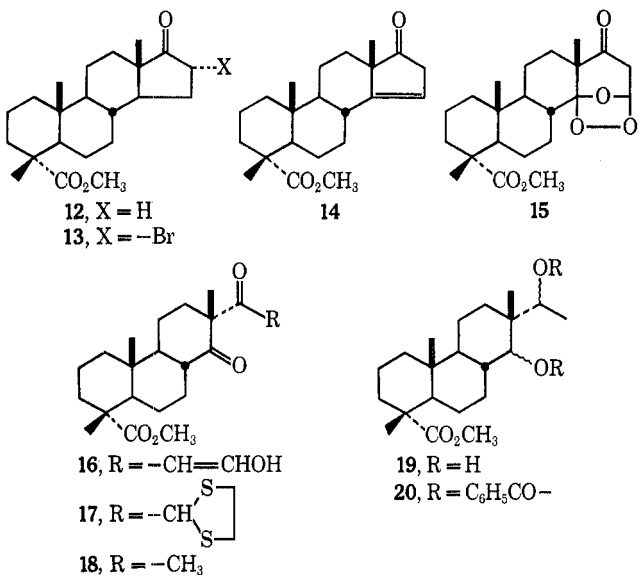
i



ii

reported to following the same stereochemical course as i [M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961)], has now been reinvestigated and found to proceed from the α side [M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970)].

Cleavage of Ring D.—With the conclusion of the construction of the desired substitution pattern at C-4 as in ester **9**, formation of an olefinic bond at C-14(15) in **9** was necessary in order to carry out subsequent steps to cleave ring D. In the described conversions of steroidal derivatives into sandaracopimaradiene, this objective was achieved by the acid-catalyzed migration of a 5,6 olefinic bond[3b,c] or through a 16-benzylidene derivative.[3a] Our approach is based on the observation that steroidal 16-α-bromo-17-ones, on dehydrobromination with lithium bromide–lithium carbonate in dimethylformamide, afford the corresponding 14(15)-en-17-ones in reasonable yield.[20] Thus, Jones oxidation of **9** gave the 17-ketone **12** which was converted into the corresponding enol acetate by refluxing with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. The enol acetate without further purification



was treated with bromine to afford the 16α-bromo derivative **13**. The configuration of the bromo group is based on analogies.[21] Dehydrobromination of **13**, under the conditions mentioned earlier, afforded the 4β-methyl-4α-carbomethoxy-5α-androst-14-en-17-one (**14**) in 32% yield. The product does not absorb in the uv and its nmr spectrum shows the presence of one vinyl proton. Ozonization of **14** at low temperature led to the formation of a stable crystalline ozonide **15**. In the nmr, the protons at C-15 and C-16 of **15** show an ABX splitting pattern. Originally it was hoped that ozonization of **14** followed by oxidative work-up would afford a β-keto acid which would readily decarboxylate to form the diketone **18**. However, attempted oxidative work-up of the ozonization product by the conventional procedures led to the recovery of starting material. Reductive work-up using zinc–acetic acid was equally unsuccessful; however, catalytic hydrogenolysis of **15** in the presence of palladized carbon proceeded at a rapid rate, with the consumption of 1 equiv of hydrogen, to afford the hydroxymethylene derivative **16**. In agreement with structure **16**, the product gives a positive ferric chloride test and its absorption maximum undergoes the characteristic bathochromic shift in alkaline solution.[22] Decarbonylation of **16** using ethylene *p*-toluenethiolsulfonate,[23] proceeded smoothly to yield the thioketal **17**. This decarbonylation procedure was used in order to circumvent bond cleavages which could occur between carbons 13 and 14 or 13 and 17. Desulfurization of **17** with W-2 Raney nickel afforded the methyl ketone **18**. The formation of the new methyl group in **18** was evident from its nmr spectrum. Catalytic hydrogenation of **18** in the presence of platinum afforded a two-spot mixture of the epimeric diols **19** which, without further purification, was converted into the corresponding dibenzoates, **20**, and pyrolyzed at 440°. The distillate on chromatography afforded methyl sandaracopimarate (**2**, 55% from **18**), which on ester cleavage using lithium iodide in collidine[24] gave (−)-sandaracopimaric acid (**1**) identical in all respects with an authentic sample of the natural acids.[25]

Experimental Section[26]

4α-Carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (4).—A solution of tritylsodium in ether (3%, 450 ml) was added to a solution of 17β-acetoxy-5α-androst-1-en-3-one[13] (9 g) in dry ether until the red color persisted. A stream of dry carbon dioxide was then bubbled into the mixture for 2 hr. The mixture was then stirred vigorously with ice water for 5 min, and the aqueous layer, after separation, was rapidly acidified with cold 10% sulfuric acid and immediately extracted with methylene chloride. The organic extract was treated with an excess of ethereal diazomethane solution for 10 min and then evaporated. The residue (six-spot mixture on tlc) was stirred with methanolic sulfuric acid (1%, 200 ml) overnight at room temperature, and the insoluble nonsteroidal solid was then removed by filtration. The filtrate was concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. The extract was dried and evaporated under reduced pressure, and the residue was dissolved in pyridine (180 ml) containing acetic anhydride (40 ml). After being allowed to stand overnight at room temperature, the reaction mixture was diluted with ice water and after 15 min of stirring was extracted with ether. The extract was washed with cold 10% hydrochloric acid and water, dried, and evaporated. The resulting product (one major spot with trace contaminants) was applied as a plug on 600 g of Florisil. Elution with 20% ether–hexane afforded nonpolar materials and **3**. The material eluted with 30% ether–hexane was crystallized from ether–hexane to afford 3.17 g (30%) of **4** as colorless plates: mp 168–172°; $[\alpha]D$ −6.6°; λ_{max} 232 mμ (ε 10,400); λ_{max} 5.80, 6.00, and 8.10 μ; nmr δ 0.82 (3 H, s, 13-CH_3), 1.05 (3 H, s, 10-CH_3), 2.02 (3 H, s, 17-$OCOCH_3$), 3.38 (1 H, d, 4β-**H**, J = 12.5 cps), 3.76 (3 H, s, 4-CO_2CH_3), 5.92 and 7.21 (1 H, d, 2-**H** and 1-**H**, J = 10 cps) ppm.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.11; H, 8.59.

4α-Carbomethoxy-17β-acetoxy-5α-androstan-3-one (6). A. From 4.—A solution of **4** (0.7 g) in methanol (15 ml) was added to a presaturated suspension of 10% palladized carbon (0.175 g) in methanol (15 ml) and the hydrogenation allowed to proceed under atmospheric conditions. After the uptake of hydrogen

(20) A. Afonso, *Can. J. Chem.*, **47**, 3693 (1969).

(21) J. Fajkos, *Collect. Czech. Chem. Commun.*, **20**, 312 (1955); **23**, 1559 (1958).

(22) R. O. Clinton, *et al.*, *J. Amer. Chem. Soc.*, **83**, 1478 (1961).

(23) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(24) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

(25) The author thanks Dr. O. E. Edwards for a comparison sample of natural (−)-sandaracopimaric acid.

(26) Melting points were taken on a Reichert micro heating stage and are uncorrected. Infrared spectra were determined in Nujol mulls using a Perkin-Elmer Model 137 recording spectrophotometer. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. Nmr spectra, in $CDCl_3$ using TMS as the internal standard, were determined on a Varian A-60A spectrometer. Specific rotations were measured on 0.3% solutions in dioxane at 26° unless otherwise specified. Silica gel GF (250 μ) plates from Analtech, Inc., were used for thin layer chromatography; 2.5% ethyl acetate in chloroform was used as the developing solvent and sulfuric acid as the spraying agent. Microanalyses and the physical measurements were performed by the Analytical Research Services, Schering Corp.

was complete (10 min), the catalyst was removed by filtration and the residue obtained by evaporation of the filtrate was crystallized from ethyl acetate–ether to afford 0.6 g of **6** as prisms: mp 159–161°; $[\alpha]D$ −2.8°; λ_{max} 5.72, 5.78, 5.84, 8.05 μ; nmr δ 0.82 (3 H, s, 13-CH_3), 1.06 (3 H, s, 10-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.27 (1 H, d, 4β-**H**, J = 12.5 cps), 3.76 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.19; H, 8.97.

B. By Reductive Carbomethoxylation.—Clean lithium (2.0 g) was added in small pieces to liquid ammonia (400 ml). After all of the lithium had dissolved (*ca.* 1 hr), a solution of testosterone acetate in dry tetrahydrofuran (100 ml) was added to it during 5 min. The mixture was stirred for 45 min and then a few crystals of ferric chloride were added. After the blue color had discharged (15 min), the ammonia was evaporated off on a hot water bath. The last traces of ammonia were displaced by a stream of argon. The white residue was suspended in dry ether (500 ml) and Dry Ice (200 g) was added carefully to the suspension. Stirring was continued until the reaction mixture attained room temperature. It was then cooled, and cold water (200 ml) was added with efficient stirring immediately followed by cold 10% sulfuric acid until the aqueous layer was acidic. Stirring was continued for a short period until the material liberated in the aqueous layer was extracted into the ether layer. The stirring was stopped and excess ethereal diazomethane was added to the two-phase reaction. After 15 min excess diazomethane was decomposed with acetic acid and the ether layer was separated, dried, and evaporated. The residue was acetylated overnight at room temperature with a mixture of pyridine (200 ml) and acetic anhydride (45 ml). The mixture was worked up in the usual way and the crude product (tlc showed one major spot; however, polar materials at origin were present) was chromatographed over 800 g of Florisil. Elution with 10% ether–hexane afforded 0.6 g of nonpolar material. With 20% ether–hexane was eluted 2.2 g of a material having the same R_f as 17β-acetoxy-5α-androstan-3-one (**5**). Continued elution with the same solvent afforded a material which on crystallization from ethyl acetate–ether gave 6.6 g (24%) of **6**, mp 157–160°, identical (ir, tlc) with the material prepared as in A. Further elution afforded only polar materials.

4α-Methyl-4β-carbomethoxy-17β-acetoxy-5α-androst-1-en-3-one (11).—A solution of **4** (0.7 g) in dry benzene (15 ml), from which 5 ml of the solvent had been distilled, was cooled and stirred under argon with sodium hydride (45% in mineral oil, 0.11 g) at room temperature for 10 min and then heated under reflux for 2 hr. The mixture was cooled and stirred with methyl iodide (0.5 ml) for 2 hr at room temperature and then heated under reflux overnight. The reaction mixture, upon cooling, was washed with dilute hydrochloric acid and water, then dried, and evaporated. The residue (one spot by tlc), on crystallization from ethyl acetate, afforded 0.527 g (71%) of **11** as shiny flakes: mp 193–195°; $[\alpha]D$ +30.9°; λ_{max} 231 mμ (ϵ 9900); λ_{max} 5.79, 5.92, 8.05 μ; nmr δ 0.81 (3 H, s, 13-CH_3), 0.98 (3 H, s, 10-CH_3), 1.44 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.63 (3 H, s, 4-CO_2CH_3), 6.00 and 7.05 (1 H, d, 2-**H** and 1-**H**, J = 10 cps) ppm.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.21; H, 8.34.

Examination by tlc of the mother liquor from crystallization of **11** showed a homogeneous spot with the same R_f as **11**.

4α-Methyl-4β-carbomethoxy-17β-acetoxy-5α-androstan-3-one (8).—A solution of **11** (0.1 g) in methanol (5 ml) was added to a presaturated suspension of 10% palladized carbon (0.05 g) in methanol (5 ml). The hydrogenation was allowed to proceed under atmospheric conditions, and after the uptake of hydrogen had ceased (6 min) the catalyst was removed by filtration. The residue obtained by evaporating the filtrate was crystallized from ether to afford 0.085 g (84%) of **8** as colorless prisms: mp 200–201°; $[\alpha]D$ −7.3°; λ_{max} 5.75–5.82, 9.09, 9.23 μ; nmr δ 0.80 (3 H, s, 13-CH_3), 1.0 (3 H, s, 10-CH_3), 1.34 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 2.96 (1 H, sextet, 2β-**H**), J_{gem} = 14.5, $J_{2\beta\text{-H},1\alpha\text{-H}}$ = 14.5, $J_{2\beta\text{-H},1\beta\text{-H}}$ = 6 cps), 3.70 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.54; H, 8.99.

4β-Methyl-4α-carbomethoxy-17β-acetoxy-5α-androstan-3-one (7).—A solution of **6** (7.0 g) in dry benzene (150 ml), from which 50 ml of the solvent had been distilled, was alkylated with methyl iodide (5 ml) in the presence of sodium hydride (45% in mineral oil, 1.1 g) under conditions of reaction and work-up identical with those used for the preparation of **11**. The alkylation product on crystallization from ether afforded 3.18 g of **7** (one spot by tlc). The mother liquor (two spots by tlc) was evaporated to dryness and the residue was chromatographed over 200 g of Florisil. Elution with 10% ether–hexane afforded, after crystallization from ether, 0.428 g of **8**, mp 198–200°. The material was identical with **8** prepared by the hydrogenation of **11**.

Continued elution with the same solvent afforded, after crystallization from ether, an additional 1.46 g (total yield 4.64 g, 64%) of **7**. Recrystallization from ether–hexane afforded **7** as shiny plates: mp 166–168°; $[\alpha]D$ −24.1°; λ_{max} 5.75, 5.88, 9.23, 11.0 μ; nmr δ 0.80 (3 H, s, 13-CH_3), 1.06 (3 H, s, 10-CH_3), 1.37 (3 H, s, 4-CH_3), 2.02 (3 H, s, 17-OCOCH_3), 3.71 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.17; H, 8.99.

4β-Methyl-4α-carbomethoxy-5α-androstan-17β-ol (9).—A heterogeneous mixture consisting of **7** (4 g), toluene (40 ml), 15% hydrochloric acid (100 ml), and amalgamated zinc[27] (prepared from 90 g of zinc) was heated under reflux for 4 days (tlc indicated that the reaction was complete). During this period, concentrated hydrochloric acid (14 ml) was added to the mixture in 2-ml portions. The reaction mixture was cooled and extracted several times with ether, and the combined extracts were washed with water, dried, and evaporated. The residue (two spots by tlc due to partial hydrolysis of the 17-acetate) was dissolved in methanol (50 ml) and treated for 2.5 hr at room temperature with 10% sodium hydroxide (4 ml). The solution was concentrated under reduced pressure, acidified with dilute hydrochloric acid, diluted with ice water, and extracted with chloroform. The extract was dried and evaporated. The residue was taken up in 25 ml of methylene chloride and treated with an excess of an ethereal solution of diazomethane for 1 hr; the solution was then evaporated to dryness. The product on crystallization from methanol afforded 3.25 g (93%) of **9** as white plates: mp 173–178°; $[\alpha]D$ −6.7°; λ_{max} 2.89, 5.82, 7.61, 7.99, 8.46, 8.52, 9.73 μ; nmr δ 0.72 (3 H, s, 13-CH_3), 0.89 (3 H, s, 10-CH_3), 1.18 (3 H, s, 4-CH_3), 3.64 (3 H, s, 4-CO_2CH_3) ppm.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.90; H, 10.41.

4α-Methyl-4β-carbomethoxy-5α-androstan-17β-ol (10).—A mixture consisting of **8** (0.15 g), 15% hydrochloric acid (6 ml), toluene (1 ml), and amalgamated zinc[27] (from 6 g of zinc) was heated under reflux for 3 days. During this period concentrated hydrochloric acid (3.6 ml) was added in 0.6-ml portions. The reaction mixture was worked up as described in the preceding experiment, the hydrolysis step being carried out with 0.2 ml of 10% sodium hydroxide in 4 ml of methanol. Reesterification with diazomethane was not necessary. The product was crystallized from methanol to afford 0.085 g (66%) of **10** as needles: mp 180–184°; $[\alpha]D$ +37.1°; λ_{max} 2.85, 5.82, 7.51, 8.06, 8.52, 8.60, 8.92, 9.63 μ; nmr δ 0.70 (6 H, s, 13- and 10-CH_3), 1.16 (3 H, s, 4-CH_3), 3.65 (3 H, s, 4-CO_2CH_3) ppm.

Hydrolyses of Esters 9 and 10.—A solution of the ester (13 mg) in ethylene glycol (0.5 ml) containing 10% aqueous potassium hydroxide (0.1 ml) was heated in an oil bath at 150°. A micro cold finger was used instead of a condenser. Micro aliquots were taken at hourly intervals, acidified with dilute hydrochloric acid, and extracted with methylene chloride. The residue obtained from evaporation of the extract of each aliquot was analyzed by tlc. The 3-hr aliquots showed that ester **9** had hydrolyzed completely, while **10** was mainly unchanged.

The 3-hr aliquot of **9** was treated with ethereal diazomethane for 15 min and then examined by tlc. Complete regeneration of **9** was observed.

4β-Methyl-4α-carbomethoxy-5α-androstan-17-one (12).—A solution of **9** (3.1 g) in acetone (300 ml) was cooled to 10° and treated with Jones reagent (2.44 ml). The mixture was then stirred at room temperature for 10 min and filtered through Celite. The filtrate was concentrated under reduced pressure, diluted with ice water, and extracted with chloroform. The extract was dried and evaporated. The residue was chromatographed over 60 g of Florisil. The eluates with hexane were discarded. The desired product was eluted with 2% ether–hexane. Crystallization from hexane afforded 2.63 g (85%) of

(27) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p 199.

12 as needles: mp 140–142°; $[\alpha]_D$ +42.9°; λ_{max} 5.72, 5.76, 9.26 μ.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.44; H, 9.55.

4β-Methyl-4α-carbomethoxy-16α-bromo-5α-androstan-17-one (13).—A solution of **12** (2.6 g) in isopropenyl acetate (300 ml) containing *p*-toluenesulfonic acid (0.26 g) was distilled slowly (200 ml of distillate was collected in 10 hr) and then refluxed for 3 days. The dark brown reaction mixture was concentrated under reduced pressure, cooled, diluted with ethyl acetate, washed with 5% sodium bicarbonate solution and with water, and then dried and evaporated under reduced pressure. The residue (mainly one spot by tlc) was dissolved in carbon tetrachloride (100 ml). The solution was cooled in an ice bath and to it was added rapidly a cold solution of bromine (1.3 g) in carbon tetrachloride (25 ml). The solution was filtered to remove a tan solid that had coagulated out, and the pale yellow filtrate was evaporated to dryness. The residue (one spot by tlc) on crystallization from ether afforded 2.56 g (79%) of **13** as long needles: mp 220–224° dec; $[\alpha]_D$ +51.9°; λ_{max} 5.70, 5.79, 8.50 μ.

Anal. Calcd for $C_{22}H_{33}O_3Br$: C, 62.10; H, 7.81. Found: C, 62.23; H, 7.76.

4β-Methyl-4α-carbomethoxy-5α-androst-14-en-17-one (14).—A mixture of **13** (2.5 g), lithium bromide (2.5 g), and lithium carbonate (2.5 g) in dimethylformamide (25 ml) was heated at 180° under argon, with efficient stirring. After 4 hr, the reaction mixture was cooled, diluted with water, acidified with dilute sulfuric acid, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was dissolved in ether and treated with an excess of ethereal solution of diazomethane for 15 min at room temperature. The solution was then evaporated and the residue was chromatographed on 60 g of Florisil. The major product was eluted with 10% ether–hexane and crystallization from hexane afforded 0.65 g (32%) of **14** as prisms: mp 102–103°; $[\alpha]_D$ +104.6°; λ_{max} 5.70, 5.79, 8.01 μ; nmr δ 0.98 (3 H, s, 10-CH_3), 1.10 (3 H, s, 13-CH_3), 1.20 (3 H, s, 4-CH_3), 2.89 (2 H, m, 16-H_2), 5.52 (1 H, m, 15-H), 3.67 (3 H, s, 4-CO_2CH_3) ppm.

Ozonization of 14.—A stream of ozonized oxygen was bubbled through a gas dispersion tube into a solution of **14** (0.6 g) in ethyl acetate (10 ml) at −70° until the solution acquired a light blue color. The solution was allowed to stand for 10 min, after which excess ozone was displaced with a stream of argon and the solution as evaporated to dryness under reduced pressure. The residue on crystallization from ethyl acetate–ether afforded the ozonide **15** (0.65 g, 75%) as colorless plates: mp 179–185° dec; λ_{max} 5.79, 8.01, 9.01, 10.42 μ; nmr δ 0.91 (3 H, s, 10-CH_3), 1.18 (6 H, s, 13-CH_3 and 4-CH_3), 3.66 (3 H, s, 4-CO_2CH_3) ppm; ABX splitting for C_{15}–C_{16} protons: δ H_A 2.58, H_B 2.86 (2 H, octet, J_{AB} = 17.5, J_{AX} = 1.5, J_{BX} = 3.0 cps), H_X 5.96 (1 H, m, J_{AX+BX} = 5 cps) ppm.

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.50.

Thioketal 17.—A solution of the ozonide **15** (0.48 g) in ethyl acetate (25 ml) was hydrogenated in the presence of 10% palladized carbon (0.3 g) which had been presaturated with hydrogen. The theoretical uptake of hydrogen (31 ml) was complete in 3 min. Removal of the catalyst by filtration and evaporation of the filtrate afforded **4β-methyl-4α-carbomethoxy-14,15-*seco*-15-hydroxy-5α-androst-15-en-17-one (16)** as a resinous solid, λ_{max} 259 mμ (ε 2760) → $\lambda_{max}^{MeOH-NaOH}$ 296 mμ (ε 12,600). Without further purification, **16** was dissolved in methanol (20 ml) containing ethylene *p*-toluenethiolsulfonate[28] (0.64 g) and potassium acetate (0.8 g). The mixture, under an argon blanket, was heated on the steam bath for 0.5 hr. The resulting pale yellow solution was then concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The residue obtained by evaporation of the organic extract was applied on a 20 × 20 × 0.1 cm silica gel plate which was then developed in 2% ethyl acetate–chloroform. The major band was extracted with 20% methanolic chloroform. Evaporation of the extract left a residue (one spot by tlc) which was crystallized from ether to afford 0.18 g (34%) of **17** as colorless plates: mp 158–161°; $[\alpha]_D$ −14.1°; λ_{max} 5.80, 5.92 μ; nmr δ 1.00 (3 H, s, 10-CH_3), 1.20 (3 H, s, 4-CH_3), 1.45 (3 H, s, 13-CH_3), 3.38 (4 H, m, -S-(CH_2)$_2$-S-), 3.67 (3 H, s, 4-CO_2CH_3), 5.10 (1 H, s, -CH(-S-)-S-) ppm.

Anal. Calcd for $C_{23}H_{34}O_4S_2$: C, 62.96; H, 7.81. Found: C, 62.90; H, 7.42.

Methyl Ketone 18.—A solution of **17** (0.15 g) in methanol (30 ml) was treated with W-2 Raney nickel (2 g) and the resulting suspension was stirred efficiently while being heated under reflux for 2 hr. The catalyst was then removed by filtration and the residue was crystallized from hexane to afford 0.115 g (97%) of **18** as colorless prisms: mp 122–123°; λ_{max} 5.80–5.96 μ; nmr δ 1.00 (3 H, s, 10-CH_3), 1.18 (3 H, s, 4-CH_3), 1.38 (3 H, s, 13-CH_3), 2.15 (3 H, s, -$COCH_3$), 3.65 (3 H, s, -CO_2CH_3) ppm.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.49; H, 9.18.

Methyl Sandaracopimarate (2).—A suspension of platinum oxide (0.1 g) in methanol (10 ml) was prereduced and to it was added **18** (0.08 g). The hydrogenation was allowed to proceed under atmospheric conditions overnight (12 ml of hydrogen uptake), and the solution was then filtered. The filtrate was evaporated to dryness and the residue of the diol mixture **19** (two spots by tlc) was dissolved in pyridine (1.4 ml) containing benzoyl chloride (0.12 ml). The mixture was heated (argon blanket) at 140° for 6 hr and then was cooled, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, then with water, dried, and evaporated. The residue of the dibenzoate mixture **20** was pyrolyzed by distilling at 180° (0.05 mm) through a glass tube (45 cm long, 3-mm i.d.) filled with glass wool and maintained at 440°. The condensate from this pyrolysis was chromatographed on 2 g of Florisil. Elution with 5% ether–hexane afforded a chromatographically homogeneous oil (39 mg). The mobility on tlc and the infrared spectrum (film) of this oil was identical with that of authentic methyl (−)-sandaracopimarate (**2**).[29] The yield of **2** from **18** was 55%.

(−)-Sandaracopimaric Acid (1).—A mixture of synthetic methyl sandaracopimarate (**2**, 25 mg), obtained in the previous experiment, and anhydrous lithium iodide (0.1 g) in *s*-collidine (2.5 ml) was heated under reflux (argon blanket) for 8 hr. The reaction was then cooled, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water and then was dried and evaporated. The tan residue was applied on a column of 1 g of Florisil which was then eluted with ether. The residue obtained by evaporating the ether eluate was crystallized three times from methanol–water to afford colorless needles of (−)-sandaracopimaric acid (**1**, 12 mg, 50%): mp 165–168° (undepressed on admixture with authentic[29] **1**), $[\alpha]^{26}_D$ −19.8° (*c* 0.2, ethanol) (lit.[5a] $[\alpha]^{26}_D$ −20°). The mobility on thin layer chromatography and infrared spectrum of synthetic **1**, obtained as above, was identical with that of natural[25] **1**.

Registry No.—**1**, 23527-10-8; **2**, 1686-54-0; **4**, 24165-39-7; **6**, 23527-11-9; **7**, 23527-12-0; **8**, 23527-13-1; **9**, 23527-14-2; **10**, 23527-15-3; **11**, 24165-44-4; **12**, 23527-16-4; **13**, 23527-17-5; **14**, 23527-18-6; **15**, 24165-46-6; **16**, 24165-47-7; **17**, 24165-48-8; **18**, 23527-21-1.

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(29) Obtained by treating authentic (−)-sandaracopimaric acid[26] with diazomethane.