# Conversion of Pimaric Acid into Cleistanthane † Derivatives

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A method for the conversion of pimarenes (a) into cleistanthanes (c) *via* 4,4-dimethyl-17-nor-5a,13α-androst-8-en-16-one (18) is described. Several unsuccessful attempts to induce the pimarane ⟶ cleistanthane rearrangement with pimarane derivatives such as the triol diacetate (7), the diol acetate (8), and the mono-alcohol (17) are also reported.

The cleistanthane group of diterpenoids is represented in nature by a limited number of compounds including cleistanthol (1),[1] veadeirol (2),[2] veadeiroic acid (3),[2] and the ketone (4).[3] It has been suggested that the cleistanthane framework (c) is derived from a pimara-8(14),15-diene precursor (a) through protonation of the nuclear double bond at C-8 (b) and shift of the C-13 vinyl group to C-14[1b] (Scheme). The role of (b) as a biological intermediate has prompted several groups to initiate non-enzymic experiments in order to promote the migration of the vinyl side chain. To our knowledge, the pimarane–cleistanthane rearrangement has been effected only by treatment of the highly functionalized pimaradiene lactone (5) with Lewis acid.[4]

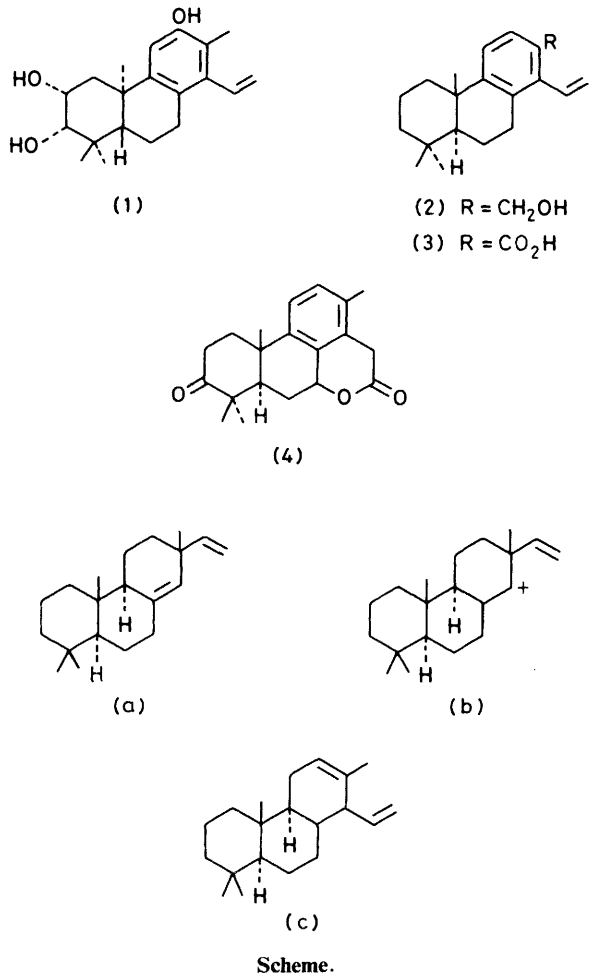
The work outlined in this paper is concerned with the conversion of the pimarenes into the cleistanthanes. Our attention was focused initially on the reactivity toward a Lewis acid of simple pimarenic models functionalized so as to generate the requisite pimarenyl cation [*e.g.* (b)].

The allylic alcohols (7) and (8)[6] represent potential intermediates for the conversion (a) ⟶ (c). Treatment of (7) with toluene-*p*-sulphonic acid in acetic anhydride at room temperature gave, after chromatographic separation, three products, the triene (9) and a mixture of the isomeric dienes (10) and (11). The structure of (9) was elucidated by the spectroscopic data and confirmed by comparison with an authentic sample.[5] The n.m.r. spectrum of the mixture of isomers (10) and (11) revealed two singlets at δ 5.05 and 5.56 (14-H) which are typical for the proposed structures; the downfield value is associated with the quasi-equatorial β-C-14 proton of (10). Under the same conditions the alcohol (8) is only transformed into the triene (12).

Rearrangement of the pimarane skeleton which involves the migration of the C-13 vinyl group was also observed on treatment of the 8,14β-epoxypimarene (13) with boron trifluoride–diethyl ether. The acid catalysed ring opening of this epoxide occurs by a concerted mechanism leading to the alcohol (14) and the triene (15); the latter has a framework which resembles the A and B rings of rosane and the C ring of cleistanthane.[7] Under the same conditions the α-epoxide (16) gave a mixture of pimaratrienic compounds.[8]

Following these previous observations,[7,8] and in an effort to prevent the backbone transposition observed in the acid treatment of (13), we prepared the 14β-alcohol (17)[9] as a model compound with which to attempt the pimarane ⟶ cleistanthane conversion. Under the influence of Lewis acid, the pimarol (17) was transformed into an inseparable mixture of several products: an n.m.r. investigation of these revealed the absence of vinylic protons, probably due to the migration of the C-13 methyl group to C-15.[10]

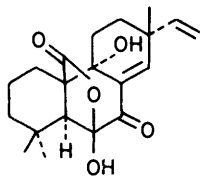
Since this initial exploration of the biomimetic migration of the vinyl group was unsuccessful, we decided to consider an alternative route for the pimarane ⟶ cleistanthane conversion. We herein describe the synthesis of the unsaturated cleistanthanes (23) and (27) which incorporate the aromatic C ring present in naturally occurring related diterpenes.




**Scheme.**

The key intermediate in our synthesis was the ketone (18), which was efficiently prepared by acid-catalysed intramolecular cyclization of the 16-diazopimar-8(14)-en-15-one.[11] Treatment of the ketone (18) with t-butyl hydroperoxide in tetrahydrofuran containing 10% aqueous sodium hydroxide [12] gave the desired γ-lactone (19). The spectroscopic data of this compound are in accordance with the assigned structure: the n.m.r. spectrum reveals that the signal due to the C-13 methyl protons (δ 1.36) is strongly deshielded compared with that (δ 1.18) of the starting ketone (18). The i.r. spectrum displays an absorption at 1 742 $cm^{-1}$. The stereochemistry at C-13 of the lactone (19) is deduced from the expected course of the

† Cleistanthane is 14-ethyl-15-methylpodocarpene.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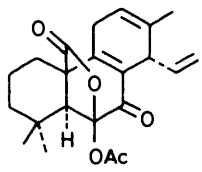
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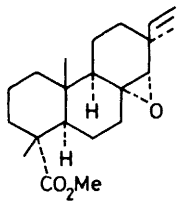
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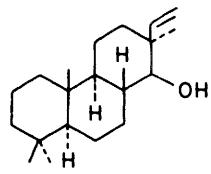
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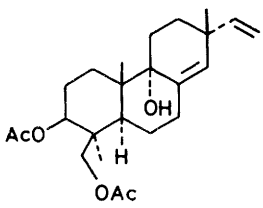
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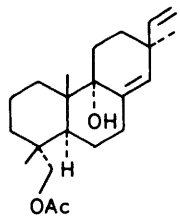
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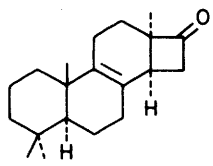
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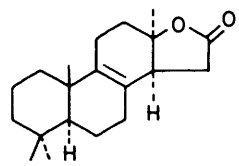
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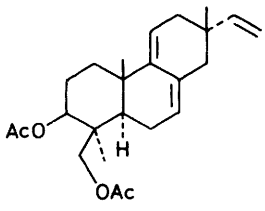
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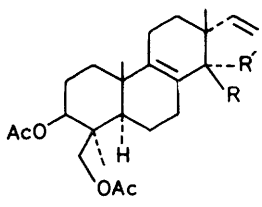
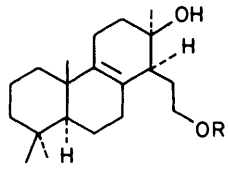

(10) R = OAc, R′ = H
(11) R = H, R′ = OAc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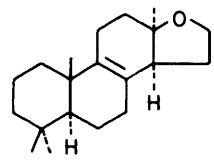
(21) R = Ac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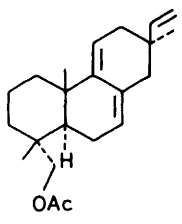
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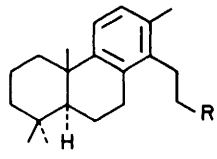
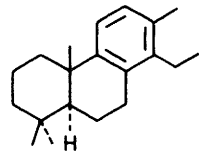

(24) R = OAc
(25) R = OH
(26) R = $SeC_6H_4NO_2$-*o*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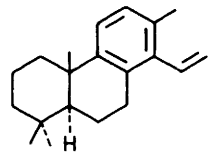
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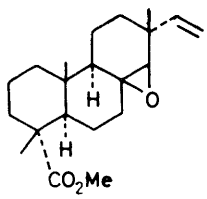
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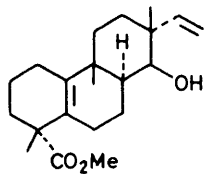
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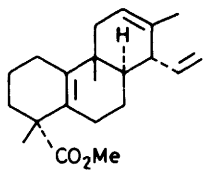
(15)

Baeyer–Villiger oxidation. Thus, the choice of the ketone (18) as the initial target allows for rapid construction of the carbon skeleton of cleistanthane.

Lithium aluminium hydride reduction of the γ-lactone (19) yielded the diol (20) whose n.m.r. spectral characteristics reveal the presence of a hydroxyethyl group (complex multiplet at δ 3.45—3.90). Dehydration of the C-13 hydroxy group of the diol (20) with various Lewis acids as catalysts, such as toluene-*p*-sulphonic acid and boron trifluoride, led only to the cyclic ether (22). Much more promising results were obtained by using iodine to promote the dehydration.[13] Treatment of the diol (20) with a catalytic amount of iodine in toluene at reflux afforded an inseparable mixture of products whose n.m.r. spectra revealed the presence of two aromatic protons, appearing as an AB system, in accordance with the aromatization of the C ring. When the reaction was carried out on the acetate (21) the products consisted of a 1 : 1.2 mixture of (23) and (24), easily separated by chromatography. The less polar product (23) shows an i.r. absorption at 1 480—1 420 and 820 $cm^{-1}$ typical for a tetrasubstituted aromatic compound; the disappearance of the acetoxymethylene signals and the appearance of a methyl triplet (*J* 6 Hz) and two aromatic protons *ortho* to each other [δ 6.91, 7.02 (dd, *J* 7 Hz)] in the n.m.r. spectrum suggested this product to be cleistantha-8,11,13-triene (23). The n.m.r. and i.r. spectra of compound

(24) are in accordance with the assigned structure. A satisfactory rationale for the observed formation of the two aromatic compounds can be formulated assuming an initial dehydration of the olefin (21) to a diene intermediate which undergoes either an elimination followed by aromatization to give (23) (*via* a tautomeric process), or direct aromatization into the acetate (24).

With compound (24) in hand, we turned our attention to the preparation of the vinyl group at C-14, present in natural diterpenes [*e.g.* (1) and (4)]. The acetate (24) was converted into the corresponding alcohol (25), and then into the selenide (26) by treatment with *o*-nitrophenyl selenocyanate and tributylphosphine in tetrahydrofuran.[14] Oxidation of the selenide (26) with hydrogen peroxide, accompanied by elimination of the selenoxide moiety, led to the crystalline product (27) (m.p. 65—67 °C). The structure of compound (27) was corroborated by its n.m.r. spectrum which showed an ABX system characteristic of the vinylic protons.

## Experimental

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were obtained with a Beckman Acculab 5 spectrophotometer in $CHCl_3$ solution. $^1H$ N.m.r. spectra were recorded with a Varian EM-390 spectrometer (solution in $CDCl_3$ with internal $Me_4Si$ as standard). U.v. spectra were obtained with a Beckman DB-GT spectrophotometer in EtOH solution. Column chromatography was performed with Merck silica gel (0.063—0.200 mm particle size).

*Treatment of* 13β-*Methyl*-13-*vinylpodocarp*-8(14)-*ene*-3β,9α,-19-*triol* 3,19-*Diacetate* (7) *with Acetic Anhydride and Toluene*-p-*sulphonic Acid*.—A solution of the alcohol (7) (0.18 g) in acetic anhydride (3 ml) and toluene-*p*-sulphonic acid (20 mg) was stirred at room temperature for 30 min. It was then poured into ice–water and extracted with chloroform. The extract was washed with a saturated solution of sodium hydrogen carbonate and water, dried ($Na_2SO_4$), and evaporated under reduced pressure. Chromatography of the residue (160 mg) on silica gel and elution with benzene gave the triene (9) (0.05 g) (for analytical and spectroscopic data see ref. 5). Further elution yielded a semisolid mixture (0.1 g) of the isomeric *acetates* (10) [δ 0.93, 1.05, 1.05 (each s, 3 × Me), 2.03, 2.05, 2.07 (each s, 3 × OCOMe), 4.21, 4.38 (dd, *J* 11 Hz, 19-H), 4.55 (m, 3-H), 4.80, 5.84 (m, vinyl protons), 5.08 (s, 14-H)], and (11) [δ 0.96, 1.05, 1.05 (each s, 3 × Me), 2.03, 2.05, 2.07 (each s, 3 × OCOMe), 4.21, 4.38 (dd, *J* 11 Hz, 19-H), 4.55 (m, 2-H), 4.80—6.10 (m, vinyl protons), 5.53 (s, 14-H)] (Found: C, 70.1; H, 8.4. $C_{26}H_{38}O_6$ requires C, 69.93; H, 8.58%).

*Treatment of Pimara*-8(14),15-*diene*-9α,18-*diol* 18-*Acetate* (8) *with Acetic Anhydride and Toluene*-p-*sulphonic Acid*.—A solution of the alcohol (8) (0.15 g) in acetic anhydride (3 ml) and toluene-*p*-sulphonic acid (20 mg) was stirred at room temperature for 30 h. Work-up as above followed by chromatography on silica gel and elution with benzene gave *pimara*-7,14,15-*trien*-15-*yl acetate* (12) (0.12 g) as a colourless oil; $\lambda_{max.}$ 234, 238, and 248 nm (ε 14 000); δ 0.96, 0.96, 0.98 (each s, 3 × Me), 2.03 (s, OCOMe), 3.7, 3.83 (dd, *J* 11 Hz, 18-H), and 5.4 (m, 8- and 11-H) (Found: C, 80.6; H, 8.7. $C_{22}H_{32}O_2$ requires C, 80.44; H, 9.83%).

*Treatment of* 14α-*Hydroxypimar*-15-*ene with Boron Trifluoride–Diethyl Ether*.—To a solution of the alcohol (17) (0.05 g) in dry benzene (10 ml) was added freshly distilled $BF_3$–$Et_2O$ (1 ml). The solution was stirred at room temperature for 4 h. Work-up as above, chromatography on silica gel, and elution with benzene gave a single product (t.l.c.) (0.04 g) which resulted in a complex mixture ($^1H$ n.m.r. and g.c.).

*Baeyer–Villiger Oxidation of* 4,4-*Dimethyl*-17-*nor*-5α,13α-*androst*-8-*en*-16-*one* (18).—A solution of the ketone (18) (1.2 g) in tetrahydrofuran (25 ml) was mixed with t-butyl hydroperoxide (0.8 ml) and sodium hydroxide (10%; 1.2 ml) and stirred at 0 °C for 15 min. The reaction mixture was poured into water and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (0.9 g) on silica gel and elution with benzene–ethyl acetate (19 : 1) gave the γ-*lactone* (19) (0.75 g), $\nu_{max.}$ 1 753 $cm^{-1}$; δ 0.86, 0.90, 0.96, and 1.36 (each s, 4 × Me) (Found: C, 79.65; H, 9.9. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.00%).

*Lithium Aluminium Hydride Reduction of the* 4,4-*Dimethyl*-17-*oxa*-5α,13α-*androst*-8-*en*-16-*one* (19).—A solution of the γ-lactone (19) (0.75 g) in tetrahydrofuran (15 ml) was added to a suspension of lithium aluminium hydride (0.25 g) in tetrahydrofuran (15 ml) and the reaction mixture was stirred at reflux under nitrogen for 30 min. The reaction mixture was cooled, decomposed with water, acidified with dilute hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated under reduced pressure. Chromatography of the residue (0.7 g) on silica gel and elution with benzene–ethyl acetate (9 : 1) gave the semisolid *diol* (20) (0.65 g); δ 0.85, 0.90, 0.95, 1.20 (each s, 4 × Me), and 3.7 (m, 16-H) (Found: C, 78.1; H, 11.3. $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%).

*Treatment of* 5α-*Cleistanth*-8-*ene*-13β,16-*diol* (20) *with Boron Trifluoride–Diethyl Ether*.—To a solution of the diol (20) (0.1 g) in dry diethyl ether (5 ml) was added freshly distilled boron trifluoride–diethyl ether (10 drops) and the reaction mixture was stirred at room temperature for 15 min. Work-up as above, chromatography on silica gel, and elution with benzene led to 4,4-*dimethyl*-17-*oxa*-5α,13α-*androst*-8-*ene* (22) (0.08 g), δ 0.85, 0.91, 0.94, 1.19 (each s, 4 × Me), and 3.85 (m, 16-H) (Found: C, 83.4; H, 11.1. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

*Acetylation of* 5α-*Cleistanth*-8-*ene*-13β,16-*diol* (20).—A solution of the diol (20) (0.5 g) in pyridine (5 ml) and acetic anhydride (2 ml) was kept at room temperature for 2 h. The usual work-up, chromatography of the crude product on silica gel, and elution with benzene gave the 16-*acetate* (21) (0.5 g); $\nu_{max.}$ 1 720 (C=O), 0.85, 0.90, 0.95, 1.17 (each s, 4 × Me), 2.06 (s, OCOMe), and 4.17 (t, *J* 6 Hz, 16-H) (Found: C, 75.6; H, 10.6. $C_{22}H_{36}O_3$ requires C, 75.81; H, 10.47%).

*Iodine Treatment of* 5α-*Cleistanth*-8-*ene*-13β-16-*diol* 16-*Acetate* (21).—A solution of the acetate (21) (0.5 g) and iodine (0.05 g) in xylene (30 ml) was stirred under nitrogen at 120 °C for 30 min. The mixture was diluted with water and extracted with chloroform. The organic phase was washed with saturated sodium thiosulphate solution and water, dried ($Na_2SO_4$), and concentrated under reduced pressure. Chromatography of the residue (0.43 g) on silica gel and elution with benzene–ethyl acetate (49 : 1) gave *cleistantha*-8,11,13-*triene* (23) (0.18 g); $\nu_{max.}$ 1 480, 1 420, 820 $cm^{-1}$ (arom); δ 0.91, 0.93, 1.20, 2.26 (each s, 4 × Me), 1.10 (t, *J* 6 Hz, 16-H), 2.60 (q, *J* 7 Hz, 15-H), and 6.91, 7.02 (dd, *J* 7 Hz, 11- and 12-H) (Found: C, 88.7; H, 11.4. $C_{20}H_{30}$ requires C, 88.92; H, 11.18%); and the acetate (24) (0.22 g); $\nu_{max.}$ 1 480, 1 420, 820 (arom), and 1 720 $cm^{-1}$ (acetate); δ 0.91, 0.93, 1.20, 2.30 (each s, 4 × Me), 2.03 (s, OCOMe), 2.93 (t, *J* 8 Hz, 15-H), 4.12 (t, *J* 8 Hz, 16-H), and

6.96, 7.06 (dd, *J* 7 Hz, 11- and 12-H) (Found: C, 80.65; H, 9.7. $C_{22}H_{32}O_2$ requires C, 80.44; H, 9.83%).

*Treatment of* 5α-*Cleistantha*-8,11,13-*trien*-16-*yl Acetate* (24) *with Sodium Methoxide*.—A solution of the acetate (24) (0.2 g) in methanol (10 ml) was treated with a 0.1M solution of sodium methoxide in methanol (8 ml) at room temperature for 5 h. It was then diluted with methanol (10 ml), filtered through an IR-120 resin column (previously washed with dilute hydrochloric acid) and the solution evaporated under reduced pressure. Chromatography of the residue (0.18 g) on silica gel and elution with benzene–ethyl acetate (49 : 1) gave the semisolid *alcohol* (25) (0.14 g); δ 0.93, 0.95, 1.2, 2.3 (each s, 4 × Me), 2.93 (t, *J* 8 Hz, 15-H), 4.1 (t *J* 8 Hz, 16-H), and 6.96, 7.06 (dd, *J* 7 Hz, 11- and 12-H) (Found: C, 83.6; H, 10.75. $C_{20}H_{30}O$ requires C, 83.86; H, 10.56%).

*Treatment of* 5α-*Cleistantha*-8,11,13-*trien*-16-*ol* (25) *with* o-*Nitrophenyl Selenocyanate*.—A solution of the alcohol (25) (0.14 g) in tetrahydrofuran (2 ml) containing *o*-nitrophenyl selenocyanate (0.22 g) under nitrogen was treated dropwise with tri-n-butylphosphine at room temperature. After the reaction had been stirred for 2 h, the solvent was removed under reduced pressure. Chromatography of the residue on silica gel and elution with benzene–ethyl acetate (49 : 1) gave the semisolid (26) (0.17 g); δ 0.93, 0.95, 1.2, 2.3 (each s, 4 × Me), 2.9 (m, 15- and 16-H), 6.96, 7.06 (dd, *J* 7 Hz, 11- and 12-H), and 7.2—8.4 (m, arom protons).

*Conversion of the Selenide* (26) *into* 5α-*Cleistantha*-8,11,13,-15-*tetraene* (27).—To a solution of the selenide (26) (0.15 g) in tetrahydrofuran (2 ml) at 0 °C was slowly added 36% aqueous hydrogen peroxide (90 μl). After the addition was complete, the reaction was warmed at 50 °C for 3 h, and then quenched by the addition of water (5 ml), and the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel and elution with light petroleum gave crystalline *olefin* (27) (0.06 g), m.p. 65—67 °C (methanol); δ 0.92, 0.95, 1.2, 2.2 (each s, 4 × Me), and an ABX system [A 5.18, B 5.48, X 6.65 ($J_{AB}$ 3, $J_{AX}$ 18, $J_{BX}$ 12 Hz, vinylic protons)] (Found: C, 89.25; H ,10.7. $C_{20}H_{28}$ requires C, 89.49; H, 10.51%).

**Acknowledgements**

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