Stereoselective Synthesis of (±)-Veadeiroic Acid and (±)-Veadeirol by Cyclisation of a 2-(2-Arylethyl)-1,3,3-trimethylcyclohexyl Cation: Mechanism and Stereochemistry of Related Cycloalkylation Reactions

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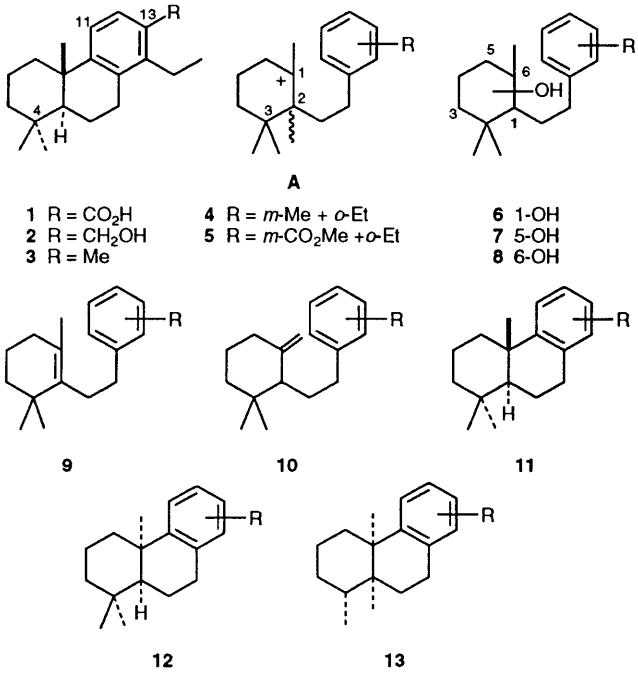
(±)-Veadeiroic acid **1** and (±)-veadeirol **2**, two new cleistanthoid diterpenes, have been synthesized by stereoselective cyclisation of the carbocation **5** generated from the cyclohexanol **26**. The latter is prepared from 2-ethyl-3-formylbenzoic acid (with CO_2H masked as an oxazoline ring) by successive reaction with 3-methylbutan-2-one, Robinson annulation, and reduction of the styrylcyclohexenone **24**. The stereochemistry of cycloalkylation of the carbocations **A**, which ranges from 100% *trans* to 50:50 *cis–trans* ring-fusion as a non-activated aryl ring becomes activated by substitution, has been rationalised on the basis of the shift of the rate-determining step from the formation of σ-complexes to that of π-complexes and the steric interactions therein.

In 1978, a Brazilian group isolated two new diterpenes, (+)-veadeiroic acid **1** and (+)-veadeirol **2** from *Vellozia flavicans*,[1] with the rare cleistanthane skeleton.[2] Our first attempt to synthesize these compounds by cyclisation of compound **4** to 14-ethyl-13-methylpodocarpatriene **3** and subsequent selective oxidation of the 13-Me group was frustrated due to the product being a 50:50 *cis–trans* mixture.[3] Cyclohexyl cations such as **A** have long been used for the synthesis of tricyclic ring C aromatic diterpenes. They are generated from a variety of substrates (in acidic medium), *viz.*, cyclohexanols **6**,[4,5] **7**,[6] and **8**,[7] cyclohexenes **9**,[8] and even methylenecyclohexanes **10**.[9] The major products of cyclisation are the *trans* **11** and the *cis* **12** isomers sometimes admixed with by-products, especially the octahydrophenanthrenes **13**.[10,11] Recently, Davis and co-workers[8] obtained better yields and cleaner products by using P_2O_5–$MeSO_3H$ (1:10) at ambient temperature in place of polyphosphoric acid (PPA) at 90 °C. Of immediate interest, however, is the observation of Ghatak's group[7,9] that while



A

1 R = CO_2H
2 R = CH_2OH
3 R = Me
4 R = *m*-Me + *o*-Et
5 R = *m*-CO_2Me + *o*-Et
6 1-OH
7 5-OH
8 6-OH

9 **10** **11**

12 **13**

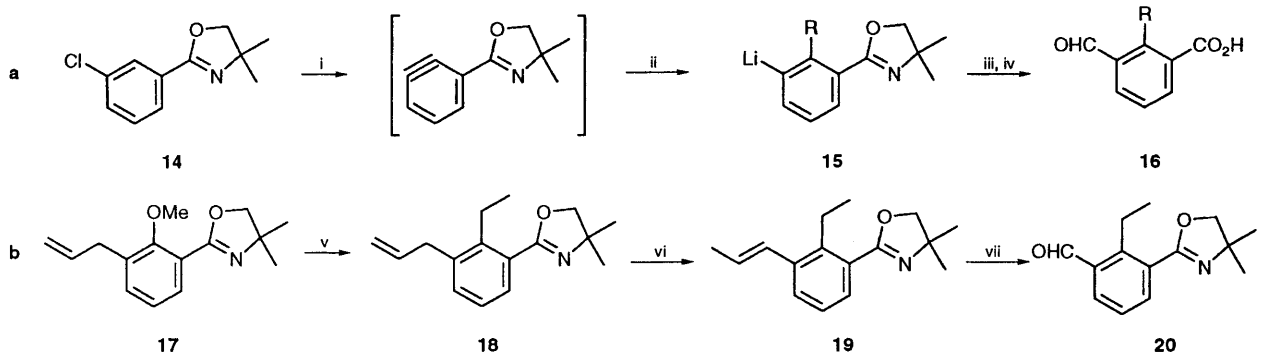
substrates with an activated aromatic ring cyclise to give a near 50:50 mixture of *cis–trans* isomers, those with a non-activated one cyclise predominantly to the *trans* isomer **11**. It is, therefore, expected that a substrate with a deactivated aromatic ring would give the *trans* isomer exclusively. This is indeed the case: cyclisation of the cyclohexyl cation **5** with a CO_2Me group in the aromatic ring gave the *trans* isomer with complete exclusion of the *cis*, thus providing a simple and convergent synthesis of racemic veadeiroic acid **1** (and veadeirol **2**).[12,†] A rationalisation of the stereochemical dichotomy mentioned above is also provided with one or two pieces of supporting evidences.

Results and Discussion

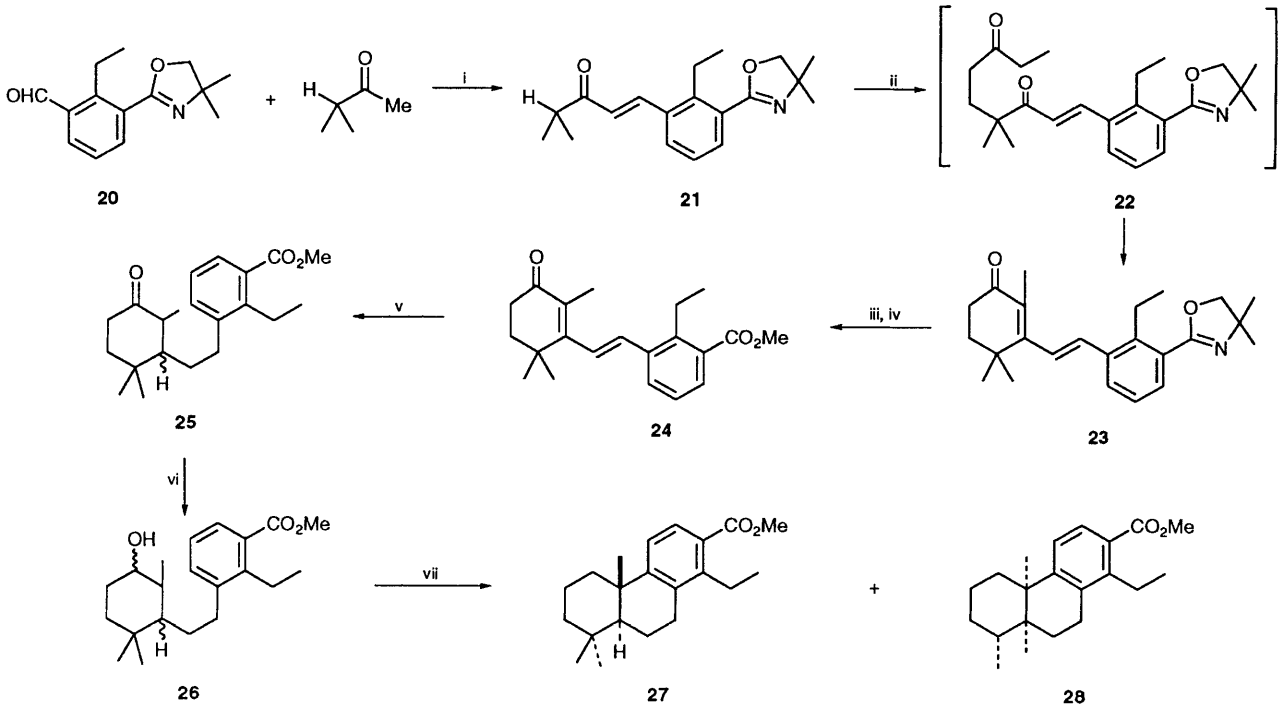
Methyl 2-ethyl-3-[2-(5-hydroxy-2,2,6-trimethylcyclohexyl)-ethyl]benzoate **26** is a requisite precursor of the carbocation **5**. 2-Ethyl-3-formylbenzoic acid served as the necessary starting material for the synthesis of compound **26** through a series of reactions first initiated by Ireland and co-workers[6] and subsequently elaborated by Nasipuri and De Dalal.[14] Preparation of 2-alkyl-3-formylbenzoic acids **16** has earlier been reported[15] from *m*-chlorobenzoic acid by first masking the CO_2H group in a 2-oxazoline ring (by reaction of the derived acid chloride with 2-amino-2-methylpropanol) and then treating the product **14** with BuLi. The benzyne intermediate (Scheme 1a) underwent regioselective addition of RLi to give intermediate **15** which, on formylation with dimethylformamide (DMF) followed by hydrolysis, afforded the 2-alkyl-3-formylbenzoic acid **16**. Although the method worked very well for 2-butyl-3-formylbenzoic acid, it went poorly for 2-ethyl-3-formylbenzoic acid (15%) when using EtLi for RLi, possibly due to the poor solubility of EtLi in hexane. In an alternative procedure (Scheme 1b), 3-allyl-2-methoxybenzoic acid was converted into 2-(3-allyl-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole **17**[16] and this was then treated with EtLi. The OMe group was smoothly replaced by Et through an addition–elimination sequence[17] to furnish compound **18**. The double bond in the allyl chain was brought into conjugation with the benzene ring by boiling alkali and the product **19**, after ozonolysis and reductive work-up, afforded the aldehyde **20** with the CO_2H group masked in an oxazoline ring. Although a number of steps were involved, the overall yield was very good and the procedure may serve as a convenient method for the preparation of 2-alkyl-3-formylbenzoic acids **16**.

The aldehyde **20** was condensed with 3-methylbutan-2-one

† A preliminary report of an alternative synthesis of these two diterpenes has also appeared[13] from our laboratory.



Scheme 1 *Reagents:* i, BuLi in hexane; ii, RLi in hexane; iii, DMF; iv, aq. HCl; v, EtLi in hexane; vi, aq. KOH; vii, O_3

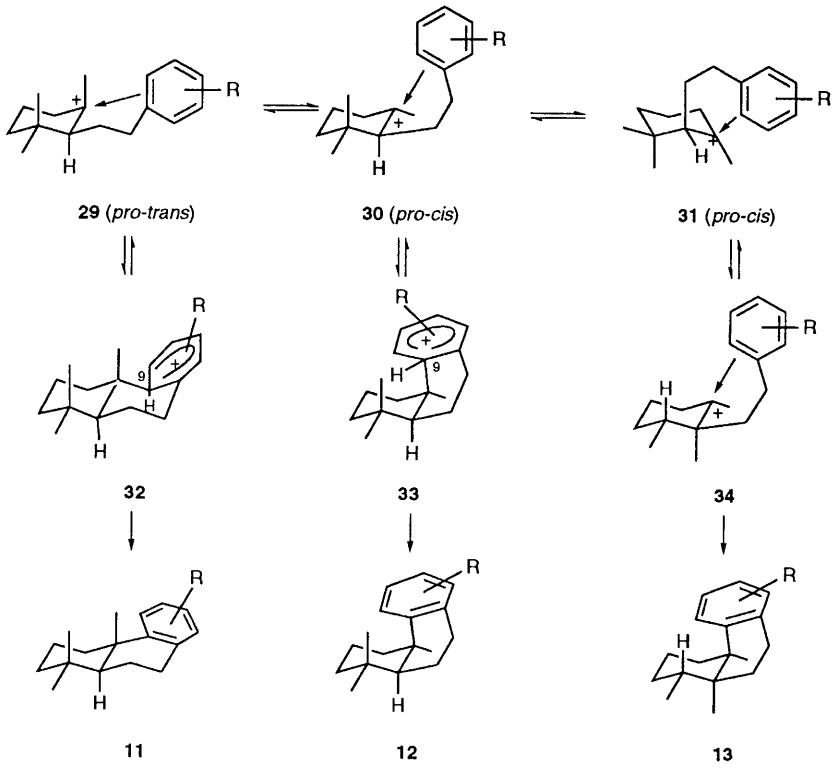


Scheme 2 *Reagents:* i, aq. NaOH; ii, $EtCOCH_2CH_2NEt_2$·MeI + KOEt; iii, aq. HCl; iv, CH_2N_2; v, H_2–Pd/C; vi, $NaBH_4$; vii, P_2O_5–$MeSO_3H$ (3:10)

and the styryl ketone **21** (Scheme 2) thus prepared, was subjected to Robinson annulation using ethyl vinyl ketone (generated *in situ*) to furnish the diketone **22** which spontaneously cyclised to give the styrylcyclohexenone **23** as a viscous gum in 40% overall yield. The CO_2H group was released by refluxing in aq. HCl and was esterified with CH_2N_2 to yield the methyl ester **24**. Catalytic hydrogenation afforded the saturated ketone **25**, which on further reduction with $NaBH_4$ furnished the desired cyclohexanol **26** as a mixture of diastereoisomers. Cyclisation of alcohol **26** with P_2O_5–$MeSO_3H$ (3:10)* at 30 °C afforded mainly methyl *trans*-14-ethylpodocarpa-8,11,13-triene-13-carboxylate **27**, *i.e.*, methyl (±)-veadeiroate with complete exclusion of the *cis* isomer, as evidenced by the absence of any high-field proton signal around δ 0.40 in the NMR spectrum which is diagnostic for the *cis* structure.[18] The crude product was, however, contaminated with the rearranged product **28** (~15%) shown by a high-field doublet at δ 0.83 which has been assigned by Davis *et al.*[8,11] to Me^{eq} at C-1 of the octahydrophenanthrenes **13** (see Scheme 3). A few crystallisations from methanol removed this impurity and methyl (±)-veadeiroate **27**, m.p. 78–80 °C, was obtained in a pure state. Hydrolysis of ester **27** afforded (±)-veadeiroic acid **1**, m.p. 204–205 °C and reduction with $LiAlH_4$ afforded (±)-veadeirol **2**, m.p. 104–105 °C. The spectral properties (UV, IR and NMR) of the two synthetic diterpenes corresponded well with those reported for the natural ones. To our knowledge, this is the first synthesis of these diterpenes (in racemic form) and probably the first ever synthesis of a cleistanthoid diterpene. A second, more expeditious synthesis has also been reported by us.[13]

Stereochemical data on cyclisations of a large number of substrates such as **6**–**10** with varying patterns of aromatic substitution are now available especially from the work of Ghatak's group[7,9] and Davis' group.[8,11] The substituents have so far been confined to OMe, Me and other alkyl groups (all electron-donating). The present synthesis provides a substrate with electron-withdrawing CO_2Me. The effect of OMe (one or two) on stereochemistry has been studied for all positions, *ortho*, *meta* and *para*, with respect to the side-chain but that of Me (alkyl) for the *meta* position only where it activates the reaction site. To complete the pattern, we have now synthesized cyclohexanols of type **7** with R = *o*-Me and R = *p*-Me from *o*-tolualdehyde and *p*-tolualdehyde following the reaction sequence shown in Scheme 2. True to expectations, unlike the

* For unreactive substrates, a higher percentage of P_2O_5 was found to be more effective.



Scheme 3

m-Me derivative these alcohols on cyclisation with P_2O_5–$MeSO_3H$ afforded the *trans* isomers with almost complete exclusion of the *cis* but along with some of the rearranged products **13**. Cyclisation with PPA at 90 °C, however, gave 5–7% of the *cis* isomers. Davis' reagent is thus more stereoselective than is PPA. Cyclisation of a few alcohols of type **7** (R = H, *o*-OMe, *m*-OMe, and *p*-OMe) previously carried out in our laboratory[14] with PPA at 90–100 °C with discordant results has also been repeated with P_2O_5–$MeSO_3H$ and the stereochemical data for the products agreed fairly well with those reported by Davis.

The stereochemical cyclisation of some dozen substrates, all precursors of cation **A**, reported earlier and now by us falls under two broad categories. Substrates in which the aromatic ring is activated at the reaction site by OMe, Me, and/or alkyl cyclise to an almost 50:50 mixtue of *cis*–*trans* isomers. Substrates in which the aromatic ring is not so activated or is deactivated cyclise to the *trans* isomer with total stereoselectivity. Ghatak and co-workers[7,9] suggested that, for the unreactive substrates, the reaction goes entirely through the cyclohexyl cation **A** (a strong electrophile) and the *trans* isomers **11** are formed *via* the sterically favoured transition state **29** (Scheme 3). For the reactive substrates, the cyclohexenes **9** present in the medium provide an alternative pathway by undergoing 1,2-*anti* addition of H^+ and Ar to the double bond leading to the *cis* isomers, as proposed by Harding.[19] The second mechanism, however, lacks conviction: an aryl ring even activated by OMe is too weak a nucleophile[20] to add to a C=C bond in unison with a proton, particularly when such an addition incurs a severe 1,3-diaxial (Me/Me) interaction and when an easier pathway through cation **A** is available. In the concerted biomimetic cyclisations which follow this mechanism, there is often an initiating group such as an epoxide ring or an allylic alcohol group which triggers the reaction from one end.[20] In the absence of such a group, the cyclisation follows a non-concerted (stepwise) pathway.[21]

An alternative explanation is given here based solely on the mechanism of aromatic electrophilic substitution. With an activated aromatic ring, the transition states of the cyclisation are probably reactant-like, closely resembling the three π-complexes **29**, **30** and **31** (Scheme 3) with 'fixed geometry' as suggested by Goldsmith and Phillips.[22] A conformational analysis of cations **29**, **30** and **31** was made by Ireland *et al.*[23] who ignored isomer **30** on steric grounds and preferred species **31** over **29** (an allylic 1,2-strain in **29** versus an extra *gauche* in **31**)[14] and predicted the *cis* product to be the major isomer in the kinetically controlled reaction. The picture is, however, oversimplified: the extent of $A^{1,2}$-strain can never be known for sure[14] and even species **30** would contribute significantly since it can release its steric strain by having a twist-boat conformation.[24] On balance, a near 50:50 *cis*–*trans* mixture as product is reasonable if formation of the π-complexes is the rate-determining step, which explains one aspect of the stereochemical dichotomy.

When the aromatic ring is not activated or deactivated, the product-forming transition states shift farther along the reaction coordinate and resemble the σ-complexes which are more product-like. That derived from cation **31** (*cis*) is ignored since the *cis* isomer is known to exist in conformation **12** in the ground state.[14] In the σ-complexes **32** and **33**, C-9 is sp^3-hybridised with an extra H and so is effectively bulkier than its counterpart in species **11** and **12**. The difference in the free energies of their formation, *i.e.* $\Delta G^{\ddagger}_{\sigma}$ would, therefore, exceed the difference in the free energies of the ground states, $\Delta G°$ which is known to have a value of 4 kJ mol^{-1} (from equilibrium data[11]) corresponding to a 20:80 *cis*–*trans* mixture. Preponderant or even exclusive formation of the *trans* isomer in these cases, therefore, is not unlikely, which explains the other aspect of the stereochemical dichotomy.

The above argument is essentially based on the shift of the rate-determining step from the formation of the σ-complexes to that of the π-complexes as the aromatic ring is activated. Unfortunately, no additional experimental proof can be given. One may note, however, that the relative stability of the σ-complexes in going from toluene to *m*-xylene increases by a factor of 1300 while that of the π-complexes increases only

fractionally.[25] The aromatic ring in cation **A** when unsubstituted resembles toluene with the side-chain acting as Me. Introduction of a *meta*-Me group converts it into a *m*-xylene system which is reactive enough to have the formation of the π-complexes as the rate-determining step.

The carbocation **A** in acidic medium undergoes rearrangement (H- and Me-shifts, concerted or non-concerted) leading to the carbocation **34**, which cyclises to the all-*cis* **13**. Now that the 1,3-diaxial (Me/Me) interaction is absent, the axial attack is preferred,[26] for both reactive and unreactive aryl groups.

Experimental

M.p.s and b.p.s are uncorrected. M.p.s were measured in open capillaries using a sulfuric acid bath. IR spectra were taken on a Perkin-Elmer 177 instrument and UV spectra on a Hitachi U–3200 spectrophotometer. ^{1}H NMR spectra were recorded in a JEOL FX-100 instrument using $SiMe_4$ as internal standard for solutions in $CDCl_3$; *J*-values are given in Hz. Mass spectra (EI) were obtained on a Hitachi RMU 6L instrument. GLC (analytical) was performed in a Hewlett-Packard Model 5730A using stainless steel columns packed with 15% FFAP and 10% Carbowax on Chromasorb W with N_2 as carrier gas. An ultrasound bath (Nuclear Products; 117 V. 60 Hz, 40 W) was used for sonication. Light petroleum A refers to the fraction boiling in the range 40–60 °C and light petroleum B to that fraction boiling in the range 60–80 °C. Organic extracts were dried over anhydrous Na_2SO_4 and all reaction products were routinely checked by TLC in different solvent systems. All chiral compounds described are racemic.

Ethyllithium Suspension in Hexane.—EtLi suspended in hexane required for the present experiments was prepared in the usual way from Li powder (28.0 g, 2 mol) suspended in hexane (200 cm^3) to which EtBr (109.0 g, 75 cm^3, 1 mol) was added dropwise while the reaction mixture was kept irradiated with ultrasound using an untrasonic bath (60 Hz). The Li was attacked almost immediately and sonication was continued for another 1 h after the complete addition of EtBr.

2-(3-*Allyl*-2-*ethylphenyl*)-4,4-*dimethyl*-4,5-*dihydrooxazole* **18**.—To a vigorously stirred solution of 2-(3-allyl-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole **17** (49.0 g, 0.2 mol) in dry tetrahydrofuran (THF) (400 cm^3) cooled to −45 °C in a solid CO_2–acetone-bath was added dropwise a suspension of EtLi (0.4 mol) in hexane under N_2. After being stirred for 3 h at −45 °C, the mixture was allowed to attain room temperature slowly and was stirred overnight. Half of the solvent was removed under reduced pressure and the residue was decomposed with saturated aq. NH_4Cl. Work-up followed by distillation afforded the *ethylated oxazoline* **18** (43.0 g, 89%) as a yellow oil, b.p. 107–108 °C (0.1 mmHg) (Found: C, 78.7; H, 8.8. $C_{16}H_{21}NO$ requires C, 79.0; H, 8.6%); ν_{max}(neat)/cm^{-1} 1652; δ_H 1.15 (3 H, t, *J* 7, $ArCH_2Me$), 1.38 (6 H, s, 4-Me_2), 2.94 (2 H, q, *J* 7, $ArCH_2Me$), 3.46 (2 H, d, *J* 6, Ar3-CH_2), 4.08 (2 H, s, OCH_2), 4.90–5.16 (2 H, m, 2 × vinylic H), 5.80–6.20 (1 H, m, vinylic H), 7.20 (2 H, m, Ar 4- and 5-H) and 7.50 (1 H, dd, *J* 2 and 8, Ar 6-H).

2-[2-*Ethyl*-3-(*prop*-1-*enyl*)*phenyl*]-4,4-*dimethyl*-4,5-*dihydrooxazole* **19**.—A solution of the preceding oxazoline **18** (39.0 g, 0.16 mol) in MeOH (150 cm^3) was mixed with saturated aq. KOH (75 cm^3) and the container was set for downward distillation. When the temperature reached 110 °C, the residue was refluxed gently for 8 h. The mixture on acidification and usual work-up furnished the *oxazoline* **19** in quantitative yield as an oil, b.p. 105–106 °C (0.1 mmHg) (Found: C, 78.65; H, 8.9%); ν_{max}(neat)/cm^{-1} 1652; δ_H 1.16 (3 H, t, *J* 7, $ArCH_2Me$), 1.38 (6 H, s, 4-Me_2), 1.90 (3 H, dd, *J* 6 and 1.5, allylic Me), 2.94 (2 H, q, *J* 7, $ArCH_2Me$), 4.08 (2 H, s, OCH_2), 5.98–6.25 (1 H, m, vinylic H) and 6.70 (1 H, br d, *J* 15), and 7.10–7.60 (3 H, m, ArH). GLC gave a single peak.

3-(4,4-*Dimethyl*-4,5-*dihydrooxazol*-2-*yl*)-2-*ethylbenzaldehyde* **20**.—A solution of the styrene **19** (29.0 g, 0.12 mol) in dry MeOH (150 cm^3) was cooled to −20 °C and ozone was passed into it until the colour changed from light yellow to green (1 h). N_2 was then bubbled through the solution at 0 °C for 1.5 h, when the yellow colour reappeared. This was dropped into a stirred solution of thiourea (4.60 g, 60 mmol) in dry MeOH (25 cm^3) at 0 °C, when thiourea *S*,*S*-dioxide separated out and was filtered off. MeOH was removed from the filtrate under reduced pressure and the residue was taken up in diethyl ether. The ethereal extract was washed successively with aq. $NaHCO_3$ (2%) and then with water. Distillation afforded the *aldehyde* **20** (24.8 g, 90%) as an oil, b.p. 116–118 °C (0.1 mmHg) (Found: C, 72.4; H, 7.4. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4%); ν_{max}(neat)/cm^{-1} 1700 and 1652; δ_H 1.26 (3 H, t, *J* 7, $ArCH_2Me$), 1.40 (6 H, s, 4′-Me_2), 3.32 (2 H, q, *J* 7, $ArCH_2Me$), 4.12 (2 H, s, OCH_2), 7.40 (1 H, d, *J* 8, Ar 5-H), 7.90 (2 H, m, Ar 4- and 6-H) and 10.42 (1 H, s, CHO); M^+, 231.

2-*Ethyl*-3-*formylbenzoic Acid* **16** (R = Et).—In an alternative method for the preparation of the oxazolinylbenzaldehyde **20**, a solution of 2-(*m*-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole **14** (10.5 g, 50 mmol) in dry pentane (50 cm^3) was treated with BuLi solution (1 mol dm^{-3} in hexane; 50 cm^3) at −78 °C according to a known procedure. After being stirred for 15 min, the reaction mixture was allowed to warm up slowly to −10 °C and was stirred for another 10 min. A suspension of EtLi in hexane (5 mol dm^{-3}; 10 cm^3, 50 mmol) was then added rapidly and the mixture was stirred for 30 min at −10 °C and then slowly warmed up to 20 °C. The mixture was sonicated for 15 min, DMF (15 cm^3) was added dropwise, and sonication was continued for 30 min more. The reaction mixture was quenched with dry EtOH. The product after usual work-up was subjected to chromatography and the aldehyde **20** was eluted by ethyl acetate–benzene (5:95) to furnish an oil (2.2 g, 20%), having identical IR and NMR spectra as described before.

The above aldehyde (2.0 g) was refluxed with aq. HCl (3 mol dm^{-3}, 15 cm^3) for 30 min, methanolic NaOH (20%; 25 cm^3) was added, and reflux was continued for another 30 min. On acidification and usual work-up, the product afforded 2-*ethyl*-3-*formylbenzoic acid* **16** as a gum (1.3 g, 15% from **14**) which could not be induced to crystallise. A sublimed fraction gave correct elemental analysis (Found: C, 67.1; H, 5.7. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%); ν_{max}(neat)/cm^{-1} 1700 and 1690; δ_H 1.28 (3 H, t, $ArCH_2Me$), 3.32 (2 H, q, 2-CH_2), 7.45–7.90 (3 H, m, ArH) and 10.43 (1 H, s, CHO); M^+, 178.

1-[3-(4,4-*Dimethyl*-4,5-*dihydrooxazol*-2-*yl*)-2-*ethylphenyl*]-4-*methylpent*-1-*en*-3-*one* **21**.—A mixture of the aldehyde **20** (23.0 g, 0.1 mol), 3-methylbutan-2-one (8.6 g, 0.1 mol), ethanol (70 cm^3), and aq. 5% NaOH (45 cm^3) was stirred at room temperature for 12 h. The product was worked up in the usual way and chromatographed over silica gel (100–200 mesh) using light petroleum B–ethyl acetate (95:5) as eluent. The *styryl ketone* **21** was obtained as an oil (19.1 g, 64%), b.p. 160–165 °C (0.1 mmHg) (Found: C, 76.0; H, 8.5. $C_{19}H_{25}NO_2$ requires C, 76.2; H, 8.4); ν_{max}(film)/cm^{-1} 1680 and 1652; δ_H 1.20 (3 H, t, *J* 7, $ArCH_2Me$), 1.21 (6 H, d, *J* 7, $CHMe_2$), 1.40 (6 H, s, 4′-Me_2), 2.80–3.20 (3 H, m, 4-H + $ArCH_2$), 4.12 (2 H, s, OCH_2), 6.74 (1 H, d, *J* 16, vinylic 2-H), 7.26 (1 H, m, Ar 5-H), 7.67 (2 H, d, *J* 8, Ar 4- + Ar 6-H) and 8.03 (1 H, d, *J* 16, vinylic 1-H).

3-{2-[3-(4,4-*Dimethyl*-4,5-*dihydrooxazol*-2-*yl*)-2-*ethylphenyl*]*vinyl*}-2,4,4-*trimethylcyclohex*-2-*enone* **23**.—To the vigorously stirred methiodide prepared from 1-(diethylamino)pentan-2-one (7.9 g, 50 mmol) and MeI (7.80 g, 55 mmol) was added a solution of the preceding styryl ketone (12.0 g, 40 mmol) in dry benzene (50 cm^3) under N_2 followed by a cold solution of KOEt [potassium metal (3.9 g, 0.1 mol) in dry ethanol (100 cm^3)] at 0 °C under N_2. After 2 h, the mixture was refluxed for 4 h on a water-bath. Most of the solvent was removed under reduced pressure. After usual work-up, the product was chromatographed on silica gel (100–200 mesh) with light petroleum B–ethyl acetate (90:10) as eluent. The *cyclohexenone* **23** was obtained as a light yellow gum (8.4 g, 63%), b.p. 180–185 °C (0.1 mmHg) (Found: C, 78.5; H, 8.8. $C_{24}H_{31}NO_2$ requires C, 78.9; H, 8.5%); ν_{max}(neat)/cm^{-1} 1670 and 1652; δ_H 1.18 (3 H, t, *J* 7, ArCH$_2$*Me*) 1.24 (6 H, s, 4-Me$_2$), 1.40 (6 H, s, CMe$_2$) 1.84–2.10 (2 H, m, 5-H$_2$), 1.94 (3 H, s, 2-Me), 2.56 (2 H, t, *J* 7, 6-H$_2$), 2.96 (2 H, q, *J* 7, ArC*H*$_2$), 4.10 (2 H, s, OCH$_2$), 6.60 (1 H, d, *J* 16, styryl H), 6.90 (1 H, d, *J* 16, styryl H), 7.28 (1 H, m, Ar 5-H) and 7.60 (2 H, d, *J* 8, Ar 4-H + Ar 6-H).

Methyl 2-*Ethyl*-3-[2-(2′,6′,6′-*trimethyl*-3′-*oxocyclohex*-1-*enyl*)*vinyl*]*benzoate* **24**.—The foregoing cyclohexenone **23** (8.0 g, 24 mmol) was hydrolysed first with refluxing aq. 3 mol dm^{-3} HCl (40 cm^3) for 30 min and then with refluxing methanolic 20% NaOH (100 cm^3) for 45 min. The solution was concentrated and acidified. The acidic material on work-up was esterified with diazomethane prepared from nitrosomethylurea (9.0 g) to furnish the *methyl ester* **24** (6.3 g, 81%), b.p. 190–193 °C (0.01 mmHg) (Found: C, 77.1; H, 8.2. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%); ν_{max}($CHCl_3$)/cm^{-1} 1725 and 1670; δ_H 1.20 (3 H, t, *J* 7, ArCH$_2$*Me*), 1.24 (6 H, s, 6-Me$_2$), 1.84–2.10 (2 H, m, 5′-H$_2$), 1.94 (3 H, s, 2′-Me), 2.56 (2 H, t, *J* 7, 4′-CH$_2$), 2.96 (2 H, q, *J* 7, ArC*H*$_2$), 3.90 (3 H, s, CO$_2$Me), 6.60 (1 H, d, *J* 16, styryl H), 6.90 (1 H, d, *J* 16, styryl H), 7.20–7.40 (1 H, m, ArH) and 7.64–7.80 (2 H, m, ArH).

Methyl 2-*Ethyl*-3-[2-(2′,2′,6′-*trimethyl*-5′-*oxocyclohexyl*)*ethyl*]*benzoate* **25**.—The unsaturated keto ester **24** (6.0 g, 18.5 mmol) was mixed with Pd/C (500 mg; 10%) in dry methanol (50 cm^3) and hydrogenated at room temperature by being stirred under H_2 for 6 h. Work-up of the product furnished the *cyclohexanone* **25** (5.9 g, 97%) as an oil, b.p. 178–180 °C (0.1 mmHg) (Found: C, 76.5; H, 9.35. $C_{21}H_{30}O_3$ requires C, 76.4; H, 9.1%); ν_{max}(neat)/cm^{-1} 1725 and 1705.

Methyl 2-*Ethyl*-3-[2-(5′-*hydroxy*-2′,2′,6′-*trimethylcyclohexyl*)*ethyl*]*benzoate* **26**.—A solution of the foregoing cyclohexanone (5.6 g, 17 mmol) was reduced with sodium borohydride (2.5 g, 68 mmol) in dry ethanol (30 cm^3) in the usual way to furnish the cyclohexanol **26** as a thick oil in quantitative yield; ν_{max}(neat)/cm^{-1} 1725 and 3630br. GLC showed three major peaks of unequal intensity. The alcohol was used in the next experiment without further purification.

Methyl (±)-*Veadeiroate* **27**.—The foregoing cyclohexanol **26** (4.0 g) was mixed with a vigorously stirred solution of P_2O_5 in $MeSO_3H$ (3:10; 20.0 g) at 30 °C. A red colour developed and the mixture was stirred for 2 h more. The red slurry was decomposed with crushed ice and organic matter was extracted with dichloromethane. The crude gum (3.0 g) obtained on removal of the solvent showed a ^1H NMR spectrum which showed, in addition to the resonances of methyl veadeiroate **27** (see below), a doublet at δ 0.83 (*J* 4) accounting for 15–20% of the octahydrophenanthrene **28** as judged from relative intensity. On scratching, the gum solidified, the solid was chromatographed on silica gel (100–200 mesh), and finally crystallised from light petroleum A and diethyl ether (alternately from aq. acetone) to pure *methyl* (±)-*veadeiroate* **27**, m.p. 78–80 °C (Found: C, 80.0; H, 9.8. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%); ν_{max}(KBr)/cm^{-1} 1720; M^+, 314; δ_H 0.83 (trace), 0.94 (3 H, s, 4-Me^{eq}), 0.96 (3 H, s, 4-Me^{ax}), 1.20 (3 H, t, *J* 7, ArCH$_2$*Me*), 1.21 (3 H, s, 10-Me), 1.50–2.24 (9 H, m, 1-, + 2-, + 3-, + 6-H$_2$ + 5-H), 2.80–3.04 (4 H, m, 2 × ArC*H*$_2$), 3.88 (3 H, s, CO$_2$Me), 7.21 (1 H, d, *J* 8, 11-H) and 7.60 (1 H, d, *J* 8, 12-H).

The mother liquor from crystallisation was enriched with compound **28** as judged from the intensity of the δ_H 0.83 doublet but no crystalline compound could be isolated in a pure state.

(±)-*Veadeiroic Acid* **1**.—The methyl ester **27** (0.5 g) was hydrolysed with methanolic KOH (10%) to furnish (±)-*veadeiroic acid* which crystallised from aq. acetone in crystals, m.p. 204–205 °C [reported m.p. of the natural (+)-enantiomer is 226–227 °C] (Found: C, 79.8; H, 9.5. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.3%); λ_{max}/nm(EtOH) 221 and 238 (log ε 3.34 and 4.07 respectively); ν_{max}(KBr)/cm^{-1} 3450–2850br, 1690, 1575, 1560, 1455, 1410, 1270 and 790; *m*/*z* (relative intensity) 300 (M^+, 35), 285 (42) and 203 (100); δ_H 0.94 (3 H, s, 4-Me^{eq}), 0.96 (3 H, s, 4-Me^{ax}), 1.21 (3 H, t, *J* 7, ArCH$_2$*Me*), 1.23 (3 H, s, 10-Me), 1.50–2.40 (9 H, m, 1-, 2-, 3- + 6-H$_2$ + 5-H), 2.80–3.10 (4 H, m, 2 × ArC*H*$_2$), 7.22 (1 H, d, *J* 8, 11-H) and 7.80 (1 H, d, *J* 8, 12-H).

(±)-*Veadeirol* **2**.—Methyl (±)-veadeiroate **27** (0.30 g) was reduced with an excess of lithium aluminium hydride solution (1 mol dm^{-3}) in diethyl ether and the product on work-up furnished (±)-*veadeirol* **2** (0.28 g) as a waxy solid, which was crystallised from methanol to afford flakes, m.p. 104–105 °C [reported m.p. for the natural (+)-enantiomer is 128–129 °C] (Found: C, 83.8; H, 10.7. $C_{20}H_{30}O$ requires C, 83.9; H, 10.5%); λ_{max}(EtOH)/nm 208 (4.59) and 270 (2.54); ν_{max}(KBr)/cm^{-1} 3250–2950br, 1480, 1455, 1410, 1375, 1010 and 825; *m*/*z* (relative intensity) 286 (M^+, 61), 271 (77), 189 (90) and 175 (100); δ_H 0.94 (3 H, s, 4-Me^{eq}), 0.96 (3 H, s, 4-Me^{ax}), 1.21 (3 H, t, *J* 7, ArCH$_2$*Me*), 1.23 (3 H, s, 10-Me), 1.70 (1 H, s, OH, D_2O-exchangeable), 1.55–2.38 (9 H, m), 2.60–3.00 (4 H, m, 2 × ArC*H*$_2$), 4.70 (2 H, s, ArC*H*$_2$OH) and 7.20 (2 H, s, 11- and 12-H).

4-*Methyl*-1-(2-*methylphenyl*)*pent*-1-*en*-3-*one*.—*o*-Tolualdehyde was condensed with 3-methylbutan-2-one in the manner previously described to furnish 4-*methyl*-1-(2-*methylphenyl*)-*pent*-1-*en*-3-*one* as an oil, b.p. 130 °C (10 mmHg) (Found: C, 82.6; H, 8.7. $C_{13}H_{16}O$ requires C, 82.9; H, 8.5%); ν_{max}(neat)/cm^{-1} 1662; δ_H 1.21 (6 H, d, *J* 7, CH*Me*$_2$), 2.35 (3 H, s, Ar*Me*), 2.80 (1 H, m, 4-H), 6.75 (1 H, d, *J* 16, 2-H), 7.20–7.50 (4 H, m, ArH) and 8.10 (1 H, d, *J* 16, 1-H).

2,4,4-*Trimethyl*-3-[2-(2-*methylphenyl*)*ethyl*]*cyclohexanol* (**7**, R = *o*-Me).—The foregoing unsaturated ketone was subjected to Robinson annulation reaction by using the methiodide of 1-(diethylamino)pentan-3-one as described before to afford 2,4,4-*trimethyl*-3-[2-(2-*methylphenyl*)*vinyl*]*cyclohex*-2-*enone* (60%), b.p. 160–165 °C (0.1 mmHg) (Found: C, 85.1; H, 8.9. $C_{18}H_{22}O$ requires C, 85.4; H, 8.7%); δ_H 1.24 (6 H, s, 4-Me$_2$), 1.82–2.10 (2 H, m, 5-H$_2$), 1.92 (3 H, s, 2-Me), 2.35 (3 H, s, Ar*Me*), 2.54 (2 H, t, *J* 7, 6-H$_2$), 6.62 (1 H, d, *J* 16, styryl H), 6.92 (1 H, d, *J* 16, styryl H) and 7.20–7.50 (4 H, m, ArH).

The cyclohexenone (4.0 g) was hydrogenated catalytically using Pd/C (400 mg; 10%) in dry methanol (30 cm^3) to yield the corresponding cyclohexanone. This in turn was reduced with an excess of sodium borohydride in ethanol to furnish the cyclohexanol (**7**, R = *o*-Me) (4.0 g) which was used in cyclisation experiments without further purification.

2,4,4-*Trimethyl*-3-[2-(4-*methylphenyl*)*ethyl*]*cyclohexanol* (**7**, R = *p*-Me).—In a parallel series of reactions, *p*-tolualdehyde was condensed with 3-methylbutan-2-one to furnish 4-*methyl*-1-(4-*methylphenyl*)*pent*-1-*en*-3-*one*, b.p. 130 °C (10 mmHg) (Found: C, 82.4; H, 8.8). The spectral data were very similar to those of the 2-methylphenyl analogue described above.

This was subjected to Robinson annulation in a similar fashion to afford 2,4,4-*trimethyl*-3-[2-(4-*methylphenyl*)*vinyl*]-*cyclohex*-2-*enone* (60%), b.p. 160–165 °C (0.1 mmHg) (Found: C, 85.3; H, 8.7%). The spectral data are very similar to those of the 2-methylphenyl analogue.

This was reduced successively with hydrogen in the presence of Pd/C (10%) and with sodium borohydride to furnish **7** (R = *p*-Me) as a gum, used in the next experiment.

Cyclisation of the Cyclohexanols (**7**, R = *o*-Me and R = *p*-Me).—The crude cyclohexanol (0.5 g) in each case was intimately mixed with a solution of P_2O_5 (4.0 g) in $MeSO_3H$ (20 cm^3) and stirred at room temperature for 2–3 h, when a red colour developed. After usual work-up, the residual oil was chromatographed on a column of silica gel (100–200 mesh) with light petroleum B as eluent. The product (0.45 g, 90%) was examined by ^1H NMR spectroscopy and also by GLC. A typical sample of 12-methylpodocarpatriene (obtained by cyclisation of **7**, R = *p*-Me) showed: δ_H 0.83 (trace, d, *J* 7, due to 4-Me^{eq} in **13**), 0.95 (3 H, s, 4-Me^{eq}), 0.97 (3 H, s, 4-Me^{ax}), 1.28 (3 H, s, 10-Me), 2.30 (3 H, s, 12-Me), 2.90 (2 H, m, 7-H_2) and 7.15–7.30 (3 H, m, ArH); the remaining Hs appeared as broad peaks in the region δ_H 1.00–1.80. The spectra showed complete absence of any peak around δ_H 0.4. The GLC showed two main peaks, the first one due to the rearranged product **13** and the second one (major) due to the *trans* isomer **11**. The NMR spectra of products obtained from PPA cyclisation (at 90 °C) was more complex, showing traces of a peak around δ 0.4 (due to *cis*-**12**).

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