Diterpene Synthesis. Part 2.[1] Acid-catalysed Cyclisation of *p*-Methoxyphenylethyltrimethylcyclohexanols

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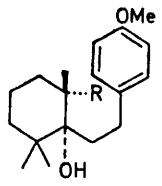
The acid-catalysed reactions of two phenylethylcyclohexanols, precursors to tricyclic diterpenoids, are reported. The reaction produced both a bicyclic alkene and a tricyclic molecule; the former was converted into the latter in protic media. Conditions for the formation of the naturally occurring *trans* A–B ring stereochemistry were defined and the mechanism was explored by the use of a deuterium label. Polyphosphoric acid-catalysed cyclisation produced a more complex mixture.

THE mechanism and stereochemistry of the acid-catalysed cyclisation of phenylethylcyclohexanols to ring C-aromatic tricyclic diterpenoids has been of considerable interest for many years. For example, King *et al.*[2] treated the cyclohexanol (1) with polyphosphoric acid to give a mixture of products which contained the tricyclic *trans*-ring-A–B isomer (3), as shown by its subsequent conversion into the naturally occurring phenol ferruginol; the oily residue from the cyclisation reaction was thought to contain the *cis*-isomer. Barltrop and Rogers[3] reported a similar reaction with the *meta*-methoxy-compound and claimed to obtain only the *trans*-isomer, although from the related cyclohexanol Church *et al.*[4] isolated the *trans*-product together with an oily material presumed to have been the *cis*-compound. Ireland *et al.*[5] repeated the reaction reported by Barltrop and Rogers and obtained the *trans*-isomer in only 24% yield and the *cis*-isomer as an oil in greater than 60% yield; however, no experimental details were reported.

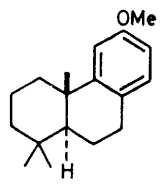
In an attempt to clarify the situation Nasipuri and Dalal[6] synthesised the *ortho*-, *meta*-, and *para*-methoxyphenylethylcyclohexanols and studied their reactions with polyphosphoric acid, and also the equilibration of the tricyclic *cis*- and *trans*-products under the cyclisation conditions. French workers[7] had shown earlier that the tricyclic *cis*-isomers in this series are identified readily by the appearance in the ^{1}H n.m.r. spectrum of a singlet resonance at high field (*ca.* δ 0.35) due to shielding of the 4α-methyl group by the aromatic ring, and we have used this diagnostic feature in other work.[8] Although Nasipuri and Dalal[6] reported the ^{1}H n.m.r. spectrum of a mixture claimed to consist of *cis*- and *trans*-isomers, no signal was recorded at higher field than δ 0.90.

In view of our interest in the stereoselective synthesis of tricyclic diterpenoids, and in cognisance of the apparent contradictions and confusion in the literature reports, we undertook a detailed study of the cyclisation reactions which lead to racemic 12-methoxypodocarpa-8,11,13-triene (3). Moreover, whereas earlier workers had used polyphosphoric acid as the cyclising medium, it was apparent from the related work of Johnson and his group[9] that other catalysts, which include the Lewis acids tin(IV) chloride and boron trifluoride–ether, could well result in clean reactions and deliver the cyclised products in high yield.

The phenylethylcyclohexanol (1) was synthesised by a modification of a reported method.[2] Reaction of 2,2,6-trimethylcyclohexanone with *p*-methoxyphenylethynyllithium in hexamethylphosphoric triamide resulted in smooth alkylation to give two diastereoisomeric cyclohexanols. The major isomer (4) is formed by axial



(1) R = H
(2) R = D



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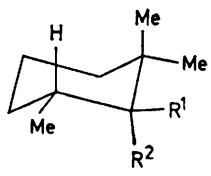
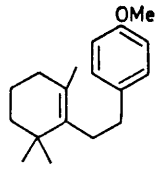


(4) R^1 = OH, R^2 = $-C\equiv C-C_6H_4OMe-p$
(5) R^1 = $-C\equiv C-C_6H_4OMe-p$, R^2 = OH

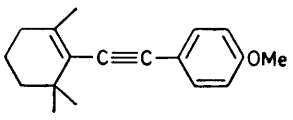


(6)

attack of the alkynyl anion on the carbonyl group, while the minor isomer (5) results from equatorial attack of the carbanion. The ^{1}H n.m.r. spectra of these alcohols are similar to those reported by Olson *et al.*[10] for the two alcohols produced by the attack of other alkynyl anions on 2,2,6-trimethylcyclohexanone. Hydrogenation of the alkynols (4) and (5) gave the corresponding methoxyphenylethylcyclohexanols. We also synthesised the 6-deuterio-isotopomer, compound (2), in order to trace the label, which must either undergo an intramolecular shift or be lost from the molecule altogether during formation of the tricyclic system. The required 2,2,6-trimethyl[6-$^2H_1$]cyclohexanone was prepared by exchange of the protiated ketone in phosphorus(V) chloride–deuterium oxide; repetition of the foregoing sequence then gave the labelled cyclohexanol (2).

In seeking a clean, high yield route to the naturally

occurring *trans*-ring-A–B stereochemistry, our attention was directed initially to the cyclisation catalysed by Lewis acids. Thus, treatment of the cyclohexanol (1) with boron trifluoride–ether in dichloromethane at 0—5 °C for 1.5 h gave three compounds in yields (g.l.c.) of 25, 56, and 15%, respectively. The first product was identified as the *trans*-fused tricyclic ether (3), while the last remains unidentified. A portion of the major product was purified by high pressure liquid chromatography (h.p.l.c.) and was shown by its ^{1}H n.m.r. spectrum to retain the *para*-disubstituted aromatic ring, and also to include a methyl group subtended on a tetra-substituted double bond. Clearly, this product was not tricyclic. It was assigned the structure 2-(*p*-methoxyphenylethyl)-1,3,3-trimethylcyclohexene (6), which was confirmed by an independent synthesis. On treatment with



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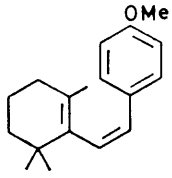

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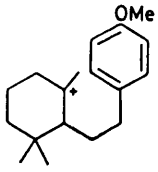

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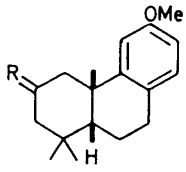


(10) R = H_2
(11) R = O

commercial 10% palladium-on-charcoal the alkynol (4) underwent elimination to give only the ethynyl-ene (7). The formation of compound (7) is attributed to the *in situ* generation of hydrochloric acid from hydrogenation of the residual palladium(II) chloride.[11] The products of reduction could, in fact, be obtained by hydrogenation of the catalyst, followed by an ethanol washing, prior to introduction of the substrate. This serendipitous elimination reaction provided a route to the desired tetra-substituted alkene (6) by selective saturation of the triple bond in a subsequent reaction. In a separate reaction the diene (8) was produced by controlled reduction of the ethynylene (7).

Reaction of the cyclohexanol (1) with tin(IV) chloride in benzene at room temperature for 15 min similarly produced the cyclised *trans*-isomer, albeit in much higher yield (83%, based on unconverted starting material), together with the alkene (6) (12%). The use of methanesulphonic acid–phosphorus(V) oxide [12] afforded these two products in yields of 95 and 5%, respectively.

These experiments show that the main two products from treatment of the cyclohexanol (1) with various acids are compounds (3) and (6). Obviously, the latter could be an intermediate which gives the former. With regard to this hypothesis the alkene (6) was treated with tin(IV) chloride in thoroughly dried benzene under an atmosphere of dry nitrogen and was recovered unchanged; with methanesulphonic acid–phosphorus(V) oxide, however, the tricyclic compound (3) was produced in 93% yield. Treatment with boron trifluoride–ether left mainly the unchanged cyclohexene (6), while tin(IV) chloride in benzene produced the tricycle (64%); the remainder was unchanged. In view of the result in thoroughly dried benzene this latter result is attributed to the presence of traces of water, and hence a proton source. Reaction of the cyclohexanol (1) with tin(IV) chloride under anhydrous conditions gave a mixture of the tricyclic compound (3) and the alkene (6) in a ratio of *ca.* 1 : 1. Thus it appears that a carbocation such as (9) is partitioned between reactions of electrophilic aromatic substitution and elimination, and that in the presence of a proton source the latter reaction is reversible. Importantly, the evidence accumulated above demonstrates the absence of any *cis*-fused ring-A–B products under these conditions.

The availability of (+)-12-methoxypodocarpa-8,11,13-triene [(+)-(3)], prepared by known methods from naturally occurring (+)-podocarpic acid, allowed an investigation of the potential reversibility of the ring-closure reaction under the cyclisation conditions. In the event, the optically active tricyclic ether (3) was inert to tin(IV) chloride in anhydrous benzene, to methanesulphonic acid, and even to polyphosphoric acid at 90 °C for 1 h.

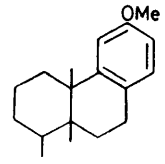
In order to confirm the pathway proposed above, cyclisation reactions of the deuteriated cyclohexanol (2) were investigated. The substrate was shown to contain 80% of the monodeuterio-isotopomer by mass spectrometry, and the location of the label at C(6) was confirmed by ^{13}C n.m.r. spectroscopy. Treatment of (2) with methanesulphonic acid–phosphorus(V) oxide, as before, gave a high yield of racemic 12-methoxypodocarpa-8,11,13-triene (3) which contained (mass spectroscopy) only 32% deuterium; variation of the reaction time between 15 min and 24 h resulted in the same deuterium value, within experimental error. This result indicates that under these conditions the alcohol generates a carbocation which may undergo either elimination (60%, loss of deuterium), or electrophilic aromatic substitution (40%, retention of deuterium) subsequent to intramolecular hydride (deuteride) migration. The deuterium atom in the cyclised *trans*-product was expected to be located at C(5) and this was confirmed by a detailed analysis of its mass spectral fragmentation pattern in comparison with that of the protiated compound. The electron-impact induced decompositions of a number of podocarpatrienes have been reported [13] and the modes of formation of most of the major ions established by the use of specifically deuteriated analogues.

In the converse experiment, the protiated cyclohexanol (1) was treated with deuteriomethanesulphonic acid–phosphorus(V) oxide. Spectroscopic analysis showed, not unexpectedly, that the tricyclic product had incorporated deuterium into the aromatic ring and this

was substantially removed by treatment with protiomethanesulphonic acid–phosphorus(v) oxide; we have shown above that, once formed, the C(9)–C(10) bond is not cleaved under these conditions. Although the interpretation of the mass spectral data from this product is complicated, to some extent, by the presence of residual di- and tri-deuteriated species, the total deuterium incorporated at C(5) was calculated to be 56% on the reasonable assumption that not only the [$^2H_1$]- but also the [$^2H_2$]- and [$^2H_3$]-isotopomers contain a label at this site. This value is in good agreement with that reported above, *viz. ca.* 60% of the tricyclic compound was produced from the cyclohexanol *via* the alkene using methanesulphonic acid–phosphorus(v) oxide as the catalyst.

Finally, the cyclisation of (1) catalysed by polyphosphoric acid was examined more closely. In contrast with the high-yield reagents used above to prepare the *trans*-isomer, this catalyst is clearly not the medium of choice for preparative reactions. Thus, reaction of the cyclohexanol (1) with polyphosphoric acid for 1 h at 90 °C gave a mixture of products identified (g.l.c., ^1H n.m.r. spectroscopy) as 12-methoxypodocarpa-8,11,13-triene (3) (49%), the cyclohexene (6) (5%), and the *cis*-isomer, 12-methoxy-5β-podocarpa-8,11,13-triene (10) (4%). The latter compound (obtained consistently in low yield from different batches of polyphosphoric acid) was identical with an authentic sample obtained by the Wolff–Kishner reduction of the racemic 5β-ketone (11), itself available as a result of earlier work;[8] both the ketone and its reduction product showed the expected high-field singlet at *ca.* δ 0.35 in the ^1H n.m.r. spectra. The cyclisation mixture also contained another tricyclic molecule (30%). The ^1H n.m.r. spectrum of this new compound showed signals typical of the aromatic substitution pattern of 12-methoxypodocarpa-8,11,13-trienes and, notably, a doublet (*J* 7 Hz) at δ 0.83 characteristic of a methyl group attached to a carbon atom which bears a hydrogen atom. The single-frequency off-resonance decoupled (SFORD) ^{13}C n.m.r. spectrum contained five singlets due to quaternary carbon atoms. These data implied either that migration of one of the methyl groups on C(2) had occurred to give the condensed tricycle (12) or that the aromatic ring had attacked the carbocation generated at C(1) to give the spiran (13). The former possibility was proven on the basis of spectral comparison with authentic stereoisomers synthesised independently,[14] although there are analogies in the literature for the formation of the spiran (13).[15] Both the ^1H and ^{13}C n.m.r. spectra were consistent with structure (12) and particularly informative was the intense peak in the mass spectrum at *m/z* 187 due to the allylic cation (14).

The work reported herein casts doubt on the analyses reported by Nasipuri and Dalal[6] who claimed to have obtained the *trans*- and *cis*-isomers in the ratio 55 : 45, although it must be emphasised that in our hands the alkene (6) and the authentic *cis*-isomer (10) had very similar retention times on g.l.c. and were separated only with difficulty. Nasipuri and Dalal[6] treated the cyclohexanol (15) with polyphosphoric acid. In order to determine if the initial location of the hydroxy-group resulted in a different product distribution, we synthesised the alcohol (15) according to published procedures.[4,6] Reaction with tin(IV) chloride in benzene at



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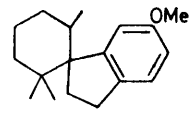

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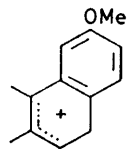

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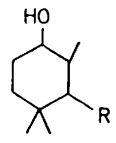
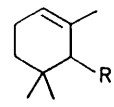


(15)

R = $CH_2CH_2C_6H_4OMe$-*p*



(16)

reflux temperature for 2.5 h (in this case, only the starting material was recovered from reaction at room temperature for 15 min) afforded (g.l.c., ^1H n.m.r. spectroscopy) 12-methoxypodocarpa-8,11,13-triene (3) (25%) and an inseparable mixture of the isomeric alkenes (6) and (16) (4 : 3, 67%). The use of methanesulphonic acid–phosphorus(v) oxide gave the tricyclic compound (3) (80%) and the alkene (6) (2%), while polyphosphoric acid gave a more complex mixture shown (g.l.c.) to be very similar in composition (Table 1) with that obtained

TABLE 1

Products (%) from reaction with polyphosphoric acid

Compound	From (1)	From (15)	From (+)-(3)
(3)	49	42	38
(10)	4	9	10
(6)	5	1	
(12)	30	37	20

previously from the isomeric alcohol (1) under the same conditions. The slight differences are not regarded as significant. For comparison, the composition of the product mixture obtained from treatment of (+)-12-methoxypodocarpa-8,11,13-triene with polyphosphoric acid at 170 °C for 3 h is included in Table 1.

In summary, our results demonstrate that either methanesulphonic acid–phosphorus(v) oxide or tin(IV) chloride is preferred to polyphosphoric acid as the catalyst for cyclisation of the alcohols (1) or (15) to the naturally occurring *trans*-A–B tricyclic molecules. The cyclisation reaction is initiated by protonation and loss of

water from the alcohol, the derived carbocation undergoing either intramolecular attack by the aromatic ring or elimination, as shown both by the isolation of the alkene and its behaviour in acid and also by the experiments using substrates specifically labelled with deuterium. Of the tricyclic compounds, the *trans*-isomer is clearly the product of kinetic control. Vigorous, even harsh, conditions are required to establish a mixture which approaches the thermodynamic ratio; again, however, the *trans*-isomer predominates, while the yield of the *cis*-isomer is overshadowed by that of the previously undetected product of methyl migration.

EXPERIMENTAL

For general experimental details see Part 1.[1]

Synthesis of Substrates.—(a) cis- *and* trans-1-(p-*Methoxyphenylethynyl*)-2,2,6-*trimethylcyclohexanol* (4) *and* (5). To a solution of *p*-methoxyphenylacetylene (9.4 g, 72 mmol) in hexamethylphosphoric triamide (10 ml) under nitrogen was added butyl-lithium (47.1 ml, 79 mmol) and the mixture was stirred for 10 min. 2,2,6-Trimethylcyclohexanone (10.6 g, 76 mmol) was added and the mixture was stirred for 1 h. Work-up gave an orange oil (19.2 g) which was purified by preparative layer chromatography (p.l.c.) (hexane–ether, 9 : 1) to give (i) *trans*-1-(*p*-methoxyphenylethynyl)-2,2,6-trimethylcyclohexanol (4) (68%), m.p. 68—69 °C, (lit.,[2] 71—72 °C); δ_H 1.07 (3 H, s, 2-*eq*-Me), 1.12 (3 H, d, *J* 7 Hz, 6-Me), 1.20 (3 H, s, 2-*ax*-Me), 1.30—2.05 (8 H, m, methylene H and OH), 3.82 (3 H, s, OMe), and 6.80 and 7.36 (4 H, 2d, Ar-H); δ_C 16.6 (6-Me), 19.9 (2-*ax*-Me), 21.3 (C-4), 27.0 (2-*eq*-Me), 32.9 (C-5), 37.0 (C-6), 38.2 (C-2), 39.2 (C-3), 55.2 (OMe), 78.8 (C-1), 87.0 and 88.3 (C≡C), 113.8 (C-3′ and -5′), 115.2 (C-1′), 132.8 (C-2′ and -6′), and 159.3 (C-4′); (ii) cis-1-(p-*methoxyphenylethynyl*)-2,2,6-*trimethylcyclohexanol* (5) (22%), m.p. 50—51 °C (Found: C, 79.5; H, 9.1. $C_{18}H_{24}O_2$ requires C, 79.4; H, 8.9%); δ_H 1.18 (6 H, s, 2-Me), 1.21 (3 H, d, *J* 7 Hz, 6-Me), 1.25—2.20 (8 H, m, methylene H and OH), 3.82 (3 H, s, OMe), and 6.81 and 7.38 (4 H, 2d, Ar-H); *m/z* 272 ($M^{+\bullet}$); δ_C 17.4 (6-Me), 21.3 (C-4), 23.4 (2-*ax*-Me), 26.5 (2-*eq*-Me), 29.0 (C-5), 33.4 (C-3), 36.4 (C-6), 38.7 (C-2), 55.3 (OMe), 76.5 (C-1), 84.8 and 90.5 (C≡C), 113.9 (C-3′ and -5′), 115.3 (C-1′), 133.0 (C-2′ and -6′), and 159.5 (C-4′).

(b) trans-1-(p-*Methoxyphenylethyl*)-2,2,6-*trimethylcyclohexanol* (1). The ethynylcyclohexanol (4) (1.1 g, 4.0 mmol) in ethanol (25 ml) was hydrogenated at 1 atm using a palladium catalyst (100 mg, 10% on charcoal). Removal of the catalyst and solvent gave the cyclohexanol (1) (1.04 g, 95%), n_D^{21} 1.5305 (lit.,[2] n_D^{23} 1.5294); δ_H 0.98 (6 H, s, 2-Me_2), 1.02 (3 H, d, 6-Me), 1.20—1.60 (8 H, m, methylene H and OH), 1.60—2.00 and 2.45—2.85 (4 H, 2m, CH_2CH_2), 3.84 (3 H, s, OMe), and 6.80 and 7.12 (4 H, 2d, Ar-H); δ_C 16.1 (6-Me), 20.4 (C-4), 23.1 (2-*ax*-Me), 25.2 (2-*eq*-Me), 30.4 and 30.9 (CH_2CH_2), 33.2 (C-5), 37.8 (C-3 and -6), 39.3 (C-2), 55.1 (OMe), 76.7 (C-1), 113.8 (C-3′ and -5′), 129.1 (C-2′ and -6′), 135.4 (C-1′), and 157.6 (C-4′).

Cyclisation of the Cyclohexanol (1).—(a) *With boron trifluoride–ether.* In a typical cyclisation reaction the cyclohexanol (1) (50 mg, 0.18 mmol) was dissolved in dichloromethane (4 ml) under nitrogen and the mixture was cooled to 0 °C. Boron trifluoride–ether (5.0 μl, 0.035 mmol) was added and the mixture stirred for 1.5 h. Work-up gave an oil (46 mg, 99%) which was shown by g.l.c. to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (25%), (ii) 2-(*p*-methoxyphenylethyl)-2,6,6-trimethylcyclohex-1-ene (6) (56%), a sample was obtained pure by reverse-phase h.p.l.c. (methanol–water, 9 : 1), δ_H 0.98 (6 H, s, 6-Me_2), 1.20—2.70 (10 H, m, methylene H), 1.63 (3 H, s, 2-Me), 3.64 (3 H, s, OMe), and 6.50 and 6.84 (4 H, 2d, Ar-H), and (iii) an unknown compound (19%) not obtained pure.

(b) *With tin*(IV) *chloride.* In a typical experiment tin(IV) chloride (100 μl, 0.85 mmol) was added to a solution of the cyclohexanol (1) (190 mg, 0.69 mmol) in benzene (3 ml) and the mixture was stirred at room temperature for 15 min. Work-up gave an oil which was shown by g.l.c. to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (77%), (ii) the cyclohexene (6) (11%), (iii) unchanged (1) (7%), and (iv) other products (5%).

(c) *With methanesulphonic acid–phosphorus*(V) *oxide.* The methanesulphonic acid–phosphorus(V) oxide reagent was made from phosphorus(V) oxide (1.0 g) and methanesulphonic acid (10 g). In a typical cyclisation reaction the acid mixture (1.87 g) was added to the cyclohexanol (1) (25 mg, 0.09 mmol) and the mixture was stirred at 20 °C for 15 min. Work-up gave an oil (22.4 mg, 96%) which was analysed by g.l.c. and ^{1}H n.m.r. spectroscopy, and shown to contain 12-methoxypodocarpa-8,11,13-triene (3) (95%), the cyclohexene (6) (2%), and other products (3%).

(d) *With deuteriomethanesulphonic acid–phosphorus*(V) *oxide.* Deuterium oxide (3.8 g, 192 mmol) was added slowly to methanesulphonyl chloride (20.0 g, 175 mmol) and the mixture was heated under reflux for 2 h. The product was distilled (b.p. 140 °C at 0.5 mmHg) to give deuteriomethanesulphonic acid. The cyclisation reagent was made from the deuteriated acid (10.8 g) and phosphorus(V) oxide (1.08 g). This reagent (620 mg) was added to the cyclohexanol (1) (211 mg, 0.77 mmol) and the mixture was stirred for 1 h. Work-up gave an oil (149 mg, 75%) which was shown (^{1}H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (82%), (ii) the cyclohexene (6) (9%), and (iii) other products (9%). The ^{1}H n.m.r. spectrum showed a decreased integral ratio for the aromatic protons; *m/z* (crude mixture) 258, 259, 260, and 261 ($M^{+\bullet}$); the ^{13}C n.m.r. spectrum was consistent with the product being mainly 12-methoxypodocarpa-8,11,13-triene (3). The crude reaction mixture (71 mg, 0.22 mmol) was then treated twice with methanesulphonic acid–phosphorus(V) oxide (220 mg) for 1 h. Work-up gave an oil (64 mg, (90%) which had an identical ^{1}H n.m.r. spectrum to the previous sample except that the relative integral ratio for the aromatic protons had increased; *m/z* 258 and 259 ($M^{+\bullet}$), and some residual *m/z* 260 and 261, showed 56% deuterium incorporation, mass spectral data are given in Table 2.

TABLE 2

Mass spectrum of products from reaction of compound (1) with $MeSO_3D$–P_2O_5

	Relative abundance (%)			
Abundant peaks (*m/z*)	*M*	*M* + 1	*M* + 2	*M* + 3
258	67	71	36	13
243	35	44	21	6
187	23	25	14	4
173	47	27	19	9
161	100	25	6	
147	62	39	12	
69	60	10		

6-*Deuterio*-2,2,6-*trimethylcyclohexanone.*—Phosphorus(V) chloride (4.0 g, 22.5 mmol) was slowly added to deuterium

oxide (16 ml) and the resultant acid was diluted with deuterium oxide (20 ml). 2,2,6-Trimethylcyclohexanone (1.15 g, 8.2 mmol) was dissolved in anhydrous 1,2-dimethoxyethane and the deuteriated acid mixture (12.0 g) added. The mixture was shaken for 12 h then diluted with deuterium oxide and worked up to give a liquid which was subject twice more to the exchange procedure. The product was distilled (Kugelrohr) to give 6-deuterio-2,2,6-trimethylcyclohexanone (500 mg, 43%), b.p. 60 °C at 20 mmHg, δ_H 0.92 (3 H, s, 6-Me), 0.98 (3 H, s, 2-*eq*-Me), 1.12 (3 H, s, 2-*ax*-Me), and 1.10—2.30 (6 H, m, methylene H); *m/z* 141 ($M^{+\cdot}$).

6-*Deuterio*-1-(p-*methoxyphenylethynyl*)-2,2,6-*trimethylcyclohexanol*.—Butyl-lithium (2.2 ml, 3.3 mmol) was added to a cooled solution of *p*-methoxyphenylacetylene (400 mg, 3.0 mmol) in hexamethylphosphoric triamide (1 ml) under nitrogen and the mixture was stirred for 1 h. 6-Deuterio-2,2,6-trimethylcyclohexanone (430 mg, 3.0 mmol) was added and the mixture stirred for 12 h. Work-up followed by p.l.c. (hexane–ether, 9 : 1) gave *trans*-6-deuterio-1-(*p*-methoxyphenylethynyl)-2,2,6-trimethylcyclohexanol (310 mg, 37%), m.p. 64—67 °C; δ_H 0.99 (3 H, s, 2-*eq*-Me), 1.05 (3 H, s, 2-*ax*-Me), 1.11 (3 H, s, 6-Me), 1.30—1.65 (6 H, m, methylene H), 2.19 (1 H, s, OH), 3.70 (3 H, s, OMe), and 6.68 and 7.25 (4 H, 2d, Ar-H); *m/z* 273 ($M^{+\cdot}$); δ_C 16.6 (6-Me), 19.9 (2-*ax*-Me), 21.2 (C-4), 26.9 (2-*eq*-Me), 32.8 (C-5), 37.1 (C-6, very low intensity), 38.2 (C-3), 39.2 (C-2), 55.0 (OMe), 78.8 (C-1), 86.9 and 88.3 (C≡C), 113.8 (C-3′ and -5′), 115.2 (C-1′), 132.9 (C-2′ and -6′), and 159.3 (C-4′).

trans-6-*Deuterio*-1-(p-*methoxyphenylethyl*)-2,2,6-*trimethylcyclohexanol* (2).—To the ethynyl-cyclohexanol prepared above (95 mg, 0.35 mmol) in ethanol (15 ml) was added a palladium catalyst (20 mg, 10% on charcoal, pre-hydrogenated and washed) and the mixture was hydrogenated at 1 atm. Removal of the catalyst and solvent gave *trans*-6-deuterio-1-(*p*-methoxyphenylethyl)-2,2,6-trimethylcyclohexanol (2) (89 mg, 91%); δ_H 0.96 (6 H, s, 2-Me), 0.97 (3 H, s, 6-Me), 1.20—1.50 (7 H, m, methylene H and OH), 1.45—1.85 (2 H, m, Ar-CH_2CH_2), 2.35—2.70 (2 H, m, Ar-CH_2), 3.70 (3 H, s, OMe) and 6.60 and 6.92 (4 H, 2d, Ar-H); *m/z* 277 ($M^{+\cdot}$); δ_C 16.0 (6-Me), 20.3 (C-4), 23.1 (2-*ax*-Me), 25.2 (2-*eq*-Me), 30.4 and 30.7 (CH_2CH_2), 33.2 (C-5), 37.7 (C-3 and -6, very low intensity), 39.3 (C-2), 55.2 (OMe), 76.7 (C-1), 113.8 (C-3′ and -5′), 129.1 (C-2′ and -6′), 135.5 (C-1′), and 157.7 (C-4′).

Cyclisation of the Cyclohexanol (2).—(a) *With boron trifluoride–ether*. Boron trifluoride–ether (2.0 μl, 0.014 mmol) was added to a cooled solution of the cyclohexanol (2) 16 mg, 0.058 mmol) in dichloromethane (1 ml). The mixture was stirred for 15 min then worked up to give an oil (15 mg, 98%) which was shown (^{1}H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (24%), (ii) the cyclohexene (6) (54%), and (iii) an unknown compound (22%); *m/z* (crude mixture) 258 and 259 ($M^{+\cdot}$).

(b) *With tin*(IV) *chloride*. To a solution of the cyclohexanol (2) (26 mg, 0.094 mmol) in benzene (1 ml) was added tin(IV) chloride (20 μl, 0.17 mmol) and the mixture was stirred for 15 min. Work-up gave an oil (24 mg, 99%) which was shown (^{1}H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (91%) and (ii) the cyclohexene (6) (9%); *m/z* (crude mixture) 258 and 259 ($M^{+\cdot}$), 51% deuterium present.

(c) *With tin*(IV) *chloride under dry conditions*. Benzene, which had been distilled and stored over sodium, was redistilled from lithium aluminium hydride under nitrogen directly into a reaction vessel which contained the cyclohexanol (2) (11 mg, 0.04 mmol). While the flow of nitrogen was maintained some of the benzene was distilled off to remove any trace of moisture from the flask. The solution was cooled to room temperature, tin(IV) chloride (10 μl, 0.085 mmol) was added, and the reaction mixture was stirred for 15 min. Work-up gave an oil (10 mg, 96%) which was shown (^{1}H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (48%) and (ii) the cyclohexene (6) (52%); *m/z* (crude mixture) 258 and 259, ($M^{+\cdot}$), 48% deuterium incorporation.

(d) *With methanesulphonic acid–phosphorus*(V) *oxide*. The cyclohexanol (2) (53 mg, 0.19 mmol) was stirred with methanesulphonic acid–phosphorus(V) oxide (10 : 1, 4.0 g) for 24 h. Water was then added and the mixture was stirred for 15 min. Work-up gave an oil (41 mg, 84%) which was shown (^{1}H n.m.r. spectroscopy) to be 12-methoxypodocarpa-8,11,13-triene (3); *m/z* 258 and 259 ($M^{+\cdot}$), 30% deuterium incorporation (Table 3). Repetition of the above reaction, but for only 15 min reaction time, gave a similar result, but with 32% deuterium incorporation.

TABLE 3

Mass spectrum of products from reaction of the cyclohexanol (2) with $MeSO_3H$–P_2O_5

	Relative abundance (%)	
Abundant peaks (*m/z*)	*M*	*M* + 1
258	60	39
243	40	26
187	29	15
173	43	17
161	100	19
147	54	28
69	39	3

1-(p-*Methoxyphenylethynyl*)-2,6,6-*trimethylcyclohex*-1-*ene* (7).—In an attempted hydrogenation reaction the cyclohexanol (4) (9.7 g, 35.7 mmol) in ethanol (150 ml) was treated with hydrogen in the presence of a freshly opened, commercial palladium catalyst (150 mg, 10% on charcoal). Removal of the catalyst and solvent gave an oil (9.0 g, 100%). A sample was purified by p.l.c. (hexane–ether, 9 : 1) followed by distillation (Kugelrohr) to give the *cyclohex*-1-*ene* (7), b.p. 128 °C at 0.5 mmHg; $\nu_{max.}$ 2 220 (C≡C) and 1 605 cm^{-1} (C=C); δ_H 1.17 (6 H, s, 6-Me_2), 1.93 (3 H, s, 2-Me), 1.50—2.15 (6 H, m, methylene H), 3.74 (3 H, s, OMe), and 6.68 and 7.23 (4 H, 2d, Ar-H); (Found: $M^{+\cdot}$ 254.1670. $C_{18}H_{22}O$ requires *M* 254.1670); δ_C 19.1 (C-4), 22.7 (2-Me), 29.1 (6-Me_2), 31.9 (C-3), 34.0 (C-6), 37.8 (C-5), 55.1 (OMe), 87.0 and 92.9 (C≡C), 113.9 (C-3′ and -5′), 116.6 (C-1′), 124.1 (C-2), 132.5 (C-2′ and -6′), 140.1 (C-1), and 159.0 (C-4′).

1-(p-*Methoxyphenylethyl*)-2,6,6-*trimethylcyclohex*-1-*ene* (6).—Palladium catalyst was placed in ethanol and treated with hydrogen as for a normal hydrogenation reaction. The catalyst was filtered off and washed with ethanol, and the treatment was repeated. This active palladium catalyst (20 mg, 10% on charcoal) was added to a solution of the cyclohexene (7) (143 mg, 0.56 mmol) in ethanol (20 ml). The mixture was hydrogenated for 3.5 h after which time 2 mol equiv. of hydrogen had been consumed. Removal of the catalyst and solvent gave the *cyclohexene* (6) (130 mg, 90%), b.p. 140 °C at 0.5 mmHg (Found: C, 83.7; H, 10.1. $C_{18}H_{26}O$ requires C, 83.7; H, 10.1%); δ_H 1.04 (6 H, s, 6-Me_2), 1.63 (3 H, s, 2-Me), 1.10—2.80 (10 H, m, methylene H), 3.67 (3 H, s, OMe), and 6.59 and 6.93 (4 H, 2d, Ar-H); *m/z* 258 ($M^{+\cdot}$).

The above reaction was repeated, but using a less active catalyst. The cyclohexene (7) (1.08 g, 4.3 mmol) and palladium (50 mg, 10% on charcoal) in ethanol (50 ml) were hydrogenated as before. When the uptake of hydrogen had ceased the catalyst and solvent were removed to give an oil (1.07 g, 97%). A sample was purified by p.l.c. (hexane, four elutions) to give 1-(*p-methoxyphenylethenyl*)-2,6,6-*trimethylcyclohex-1-ene* (8) (233 mg), b.p. 140 °C at 0.5 mmHg (Found: C, 84.1; H, 9.7. $C_{18}H_{24}O$ requires C, 84.3; H, 9.4%); δ_H 1.06 (6 H, s, 6-Me_2), 1.42 (3 H, s, 2-Me), 1.40—2.16 (6 H, m, methylene H), 3.69 (3 H, s, OMe), 5.82 and 6.28 (2 H, 2d, *J* 12 Hz, CH=CH), and 6.63 and 7.25 (4 H, 2d, Ar-H); *m/z* 256 ($M^{+\cdot}$).

Cyclisation of the Cyclohexene (6).—(a) *With boron trifluoride–ether.* Boron trifluoride–ether (10 μl, 0.07 mmol) was added to the cyclohexene (6) (21 mg, 0.081 mmol) in dichloromethane (1 ml). The mixture was stirred for 15 min and worked up to give an oil (18 mg, 85%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (5%), (ii) the cyclohexene (6) (88%), and (iii) the cyclohexene (8) (7%), which was an impurity in the starting material.

(b) *With tin*(IV) *chloride.* Tin(IV) chloride (20 μl, 0.17 mmol) was added to the cyclohexene (6) (25 mg, 0.098 mmol) in benzene (1 ml). The mixture was stirred for 15 min, then worked up to give an oil (21 mg, 83%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (64%), (ii) the cyclohexene (6) (33%), and (iii) the cyclohexene (8) (3%).

(c) *With tin*(IV) *chloride under dry conditions.* Tin(IV) chloride (24 μl, 0.2 mmol) was added to the cyclohexene (6) (27 mg, 0.11 mmol) in benzene (1 ml), which had been rigorously dried as described earlier. The mixture was stirred for 15 min and worked up to give an oil (27 mg, 100%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to consist only of the starting material (6).

(d) *With methanesulphonic acid–phosphorus*(V) *oxide.* A methanesulphonic acid–phosphorus(V) oxide mixture (2.0 g) was added to the cyclohexene (6) (29 mg, 0.112 mmol) and the mixture was stirred for 15 min. Work-up gave an oil (22 mg, 74%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (93%), (ii) the cyclohexene (6) (3%), and (iii) the cyclohexene (8) (4%).

Preparation of 3-(p-*Methoxyphenylethyl*)-2,4,4-*trimethylcyclohexanol* (15).—This alcohol was prepared by published procedures [4,6] which involved reduction of 3-(*p*-methoxyphenylethyl)-2,4,4-trimethylcyclohex-2-en-1-one, itself prepared by the Robinson annulation of 1-(*p*-methoxyphenyl)-4-methylpent-1-en-3-one with 1-(*NN*-diethylamino)pentan-3-one.

Cyclisation of the Cyclohexanol (15).—(a) *With tin*(IV) *chloride.* Tin(IV) chloride (23 μl, 0.195 mmol) was added to the cyclohexanol (15) (30 mg, 0.11 mmol) in benzene (5 ml) and the mixture was stirred for 15 min. Work-up gave an oil (30 mg, 100%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to be the starting material.

The above reaction was repeated using the cyclohexanol (15) (16 mg, 0.058 mmol) and tin(IV) chloride (13 μl, 0.11 mmol) in benzene (3 ml), but the mixture was heated under reflux for 2.5 h. Work-up gave an oil (10.5 mg, 70%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (25%), (ii) an inseparable mixture (*ca.* 4 : 3) of the cyclohexene (6) and 3-(*p*-methoxyphenylethyl)-2,4,4-trimethylcyclohex-1-ene (16) (67% total), and (iii) the starting material (15) (8%).

(b) *With methanesulphonic acid–phosphorus*(V) *oxide.* A methanesulphonic acid–phosphorus(V) oxide mixture (1.5 g) was added to the cyclohexanol (15) (20 mg, 0.072 mmol) and the mixture was stirred for 15 min. Work-up gave an oil (18 mg, 97%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (80%), (ii) the cyclohexene (6) (2%), and (iii) starting material (18%). A cyclisation of 1-(*p*-methoxyphenylethyl)-2,2,6-trimethylcyclohexanol (1) (25 mg, 0.09 mmol) with methanesulphonic acid–phosphorus(V) oxide (1.87 g) using identical conditions gave identical results.

(+)-12-*Methoxypodocarpa*-8,11,13-*triene* (3).—This was obtained by published procedures [16] as an oil, $[\alpha]_D^{22}$ +65° (lit.,[16] $[\alpha]_D$ +72°), δ_H 0.90 (6 H, s, 4-Me_2), 1.14 (3 H, s, 10-Me), 1.15—2.88 (11 H, m, methylene H), 3.60 (3 H, s, OMe), and 6.32—6.84 (3 H, m, Ar-H); δ_C 19.2 (C-2 and -6), 21.7 (4β-Me), 24.8 (10-Me), 29.6 (C-7), 33.4 (C-4 and 4α-Me), 38.1 (C-10), 38.8 (C-1), 41.7 (C-3), 50.4 (C-5), 55.1 (OMe), 110.1 and 110.6 (C-11 and -13), 127.3 (C-8), 130.6 (C-14), 151.3 (C-9), and 157.6 (C-12).

Treatment of (+)-12-*Methoxypodocarpa*-8,11,13-*triene* (3).—(a) *With tin*(IV) *chloride under dry conditions.* Tin(IV) chloride (100 μl, 0.85 mmol) was added to (+)-12-methoxypodocarpa-8,11,13-triene (3) (100 mg, 0.39 mmol) in rigorously dried benzene (20 ml). The mixture was stirred for 336 h then worked up to give an oil (84 mg, 84%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to be the starting material, $[\alpha]_D^{22}$ +69°.

(b) *With methanesulphonic acid–phosphorus*(V) *oxide.* Methanesulphonic acid–phosphorus(V) oxide (4.0 g) was added to (+)-12-methoxypodocarpa-8,11,13-triene (3) (110 mg, 0.43 mmol) and the mixture was stirred for 15 min. Work-up gave an oil (94 mg, 86%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to be the starting material (3), $[\alpha]_D^{22}$ +64°. Repetition of the reaction for 18 h again gave only the starting material, $[\alpha]_D^{22}$ +49°.

Reactions with Polyphosphoric Acid.—(a) trans-1-(p-*Methoxyphenylethyl*)-2,2,6-*trimethylcyclohexanol* (1). Polyphosphoric acid was made by heating a mixture of phosphorus(V) oxide (6.5 g) and 85% phosphoric acid (4 ml) on a steam-bath for 4 h. The acid mixture (4.3 g) was added to the cyclohexanol (1) (130 mg, 0.47 mmol) and the mixture was stirred at 90 °C for 1 h. Work-up gave an oil (82 mg, 68%) which was shown (g.l.c., ¹H n.m.r. spectroscopy) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (49%), (ii) the cyclohexene (6) (5%), (iii) 12-methoxy-5β-podocarpa-8,11,13-triene (10) (4%), (iv) 6-methoxy-1,4a,10a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (12) (30%), and (v) unknown products (11%); g.c.–m.s. of the mixture showed all products to have *m/z* 258.

(b) 3-(p-*Methoxyphenylethyl*)-2,4,4-*trimethylcyclohexanol* (15). The cyclohexanol (15) (128 mg, 0.465 mmol) was treated with polyphosphoric acid (4.26 g) for 1 h at 90 °C. Work-up gave an oil (78 mg, 65%) which was shown (¹H n.m.r. spectroscopy, g.l.c.) to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (42%), (ii) the cyclohexene (6) (1%), (iii) 12-methoxy-5β-podocarpa-8,11,13-triene (10) (9%), (iv) the trimethyl-compound (12) (37%), and (v) unknown products (10%). After careful p.l.c. (run four times in hexane) a sample of the compound (12) was obtained; δ_H 0.83 (3 H, d, 1-Me), 0.89 (3 H, s, Me), 1.04 (3 H, s, Me), 1.10—2.83 (11 H, m, methylene H), 3.70 (3 H, s, OMe), and 6.36—6.94 (3 H, m, Ar-H); *m/z* 258 ($M^{+\cdot}$); δ_C 16.2 and 16.3 (1- and

10a-Me), 22.8 (C-3), 24.9 (C-10), 28.5 (C-9), 29.8 (4a-Me), 30.8 (C-2), 32.1 (C-4), 33.3 (C-1), 37.4 (C-10a), 42.1 (C-4a), 55.2 (OMe), 110.2 and 112.0 (C-5 and C-7), 128.5 (C-8a), 130.0 (C-8), 145.8 (C-4b), and 157.9 (C-6).

(c) (+)-12-*Methoxypodocarpa*-8,11,13-*triene* (3). (+)-12-Methoxypodocarpa-8,11,13-triene (3) (66 mg, 0.256 mmol) was treated with polyphosphoric acid (1.65 g) at 90 °C for 1 h. Work-up gave an oil (59 mg, 90%) which was shown (^{1}H n.m.r. spectroscopy, g.l.c.) to be the starting material $[\alpha]_D^{22}$ +63°. Similar treatment of compound (3) (100 mg, 0.39 mmol) with polyphosphoric acid, but at 170 °C for 3 h gave an oil which was shown by g.l.c. to contain (i) 12-methoxypodocarpa-8,11,13-triene (3) (38%), (ii) the cyclohexene (6) (10%), (iii) the compound (12) (20%), (iv) an unknown compound (21%), and (v) other products (11%); $[\alpha]_D$ of mixture +2°. When the reaction time was extended to 5 h the product distribution remained unchanged.

12-*Methoxy*-5β-*podocarpa*-8,11,13-*triene* (10).—Hydrazine hydrate (48.5 mg, 0.97 mmol) in 2-ethoxyethanol (1 ml) was added to 12-methoxy-5β-podocarpa-8,11,13-trien-2-one (11) [8] (19.4 mg, 0.071 mmol) in 2-ethoxyethanol (5 ml) and the mixture was heated under reflux under nitrogen for 2 h. The mixture was cooled, then potassium hydroxide (22 mg, 0.39 mmol) added and the water was boiled off. The mixture was heated under reflux overnight. Work-up gave an oil, purified by p.l.c. (hexane) to give 12-methoxy-5β-podocarpa-8,11,13-triene (10) (12 mg, 65%); δ_H 0.35 (3 H, s, 4α-Me), 0.91 (3 H, s, 4β-Me), 1.14 (3 H, s, 10-Me), 1.10—3.00 (10 H, m, methylene H), 3.76 (3 H, s, OMe), and 6.60—6.98 (3 H, m, Ar-H); *m/z* 258 ($M^{+\bullet}$).

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