Use of an Electrocyclic Reaction of *o*-Quinodimethane and an Intramolecular Mannich-type Cyclisation in Diterpene Alkaloid Synthesis: a Synthesis of Nagata's Intermediate for (±)-Atisine

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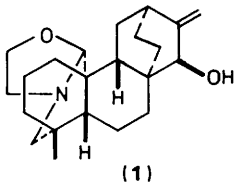
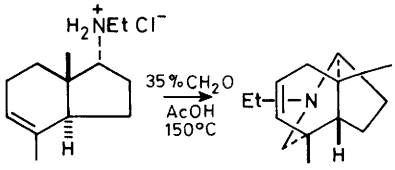
A synthesis of the tetracyclic amine hydrochloride (**2**), a pivotal intermediate for Nagata's total synthesis of (±)-atisine, is described. The synthesis commenced with an electrocyclic reaction of the *Z*-*o*-quinodimethane (**10**), generated *in situ* by thermolysis of the benzocyclobutene (**9**), leading to the dihydronaphthalene (**8**). The hydrophenanthrene portion in (**2**) was elaborated by an intramolecular Diels–Alder reaction of the transient triene (**6**), which was produced from (**8**) *via* a nine-step sequence. The piperidine ring construction was accomplished by employing an intramolecular Mannich-type cyclisation (or an intramolecular iminium-ene reaction) of the hydrochloride (**4**); the resulting tetracycle (**3**) was then finally converted into (**2**) by catalytic hydrogenation. The *cis*-hydrochloride (**27**) was similarly converted into the *cis*-tetracycle (**31**) *via* (**30**), whose structure was established by a single-crystal *X*-ray analysis, by the same manner.

Synthetic studies on the diterpene alkaloid atisine (**1**), the principal alkaloid of *Aconitum heterophyllum*, continue to occupy the attention of synthetic organic chemists worldwide.[1] Much of the activity in this area has been due to its chemical features and complex molecular structure.



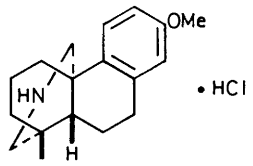
(**1**)

During the course of our synthetic studies of diterpene alkaloids, we have previously explored a method of efficient construction of the piperidine ring entity, one of the crucial points in the total synthesis, by intramolecular Mannich-type cyclisation and defined the scope and limitation[2] (Scheme 1).



Scheme 1.

In connection with a possible synthetic approach to atisine, we focussed our attention on the synthesis of the tetracyclic amine hydrochloride (**2**),[1g,1h,3] which has served as the pivotal intermediate not only in the first total synthesis[1c] of (±)-atisine but also in the syntheses of veatichine,[4] garryine,[4] and gibberellin A_{15}[5] by Nagata, employing the developed cyclisation



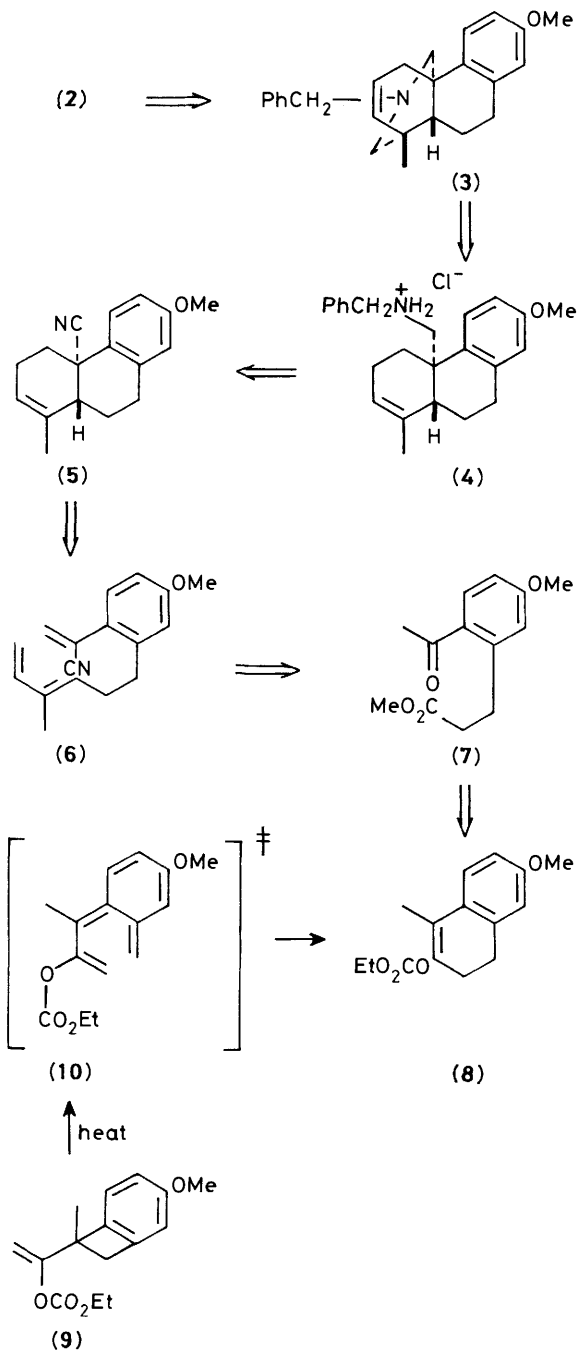
(**2**)

as a key step. In this paper, we detail our experiments in which Nagata's intermediate (**2**) was successfully synthesized.[6]

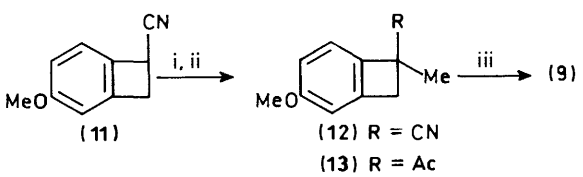
Scheme 2 outlines the key features of our strategy for the synthesis of (**2**). The pivotal step in this approach is the Mannich-type cyclisation of the olefinic amine hydrochloride (**4**). This process would be predicted to give regioselectively the tetracyclic amine (**3**), which could then be transformed to the target compound by catalytic hydrogenation. Intramolecular Diels–Alder reaction of the triene (**6**) would provide access to (**4**) through the *trans*-cycloadduct (**5**). The triene (**6**) would, in turn, be prepared from the keto ester (**7**), which might be derived from the dihydronaphthalene (**8**) by oxidative cleavage of the double bond. Recently, we have reported a preferential electrocyclic reaction of *Z*-*o*-quinodimethane, generated *in situ* by thermolysis of 1-alkenyl-1-alkylbenzocyclobutenes, leading to dihydronaphthalenes.[7] Even though the alkenyl part at C-1 is an enol carbonate, the thermolysis of (**9**) proceeds cleanly *via* the *Z*-*o*-quinodimethane (**10**) to provide the desired dihydronaphthalene (**8**). Thus, the proposed strategy could conceivably produce Nagata's intermediate (**2**) beginning with the benzocyclobutene (**9**) (Scheme 2).

The substrate (**9**) for thermolysis was prepared from 1-cyano-4-methoxybenzocyclobutene[1g] (**11**) as shown in Scheme 3. Methylation of (**11**) with methyl iodide using lithium diisopropylamide (LDA) as a base afforded (**12**) which was transformed to the methyl ketone (**13**) in one step by treatment with methyl iodide and lithium and ultrasound irradiation for 5 min.[8] Treatment of (**13**) with LDA in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) followed by addition

† Deceased October 1988.



Scheme 2.

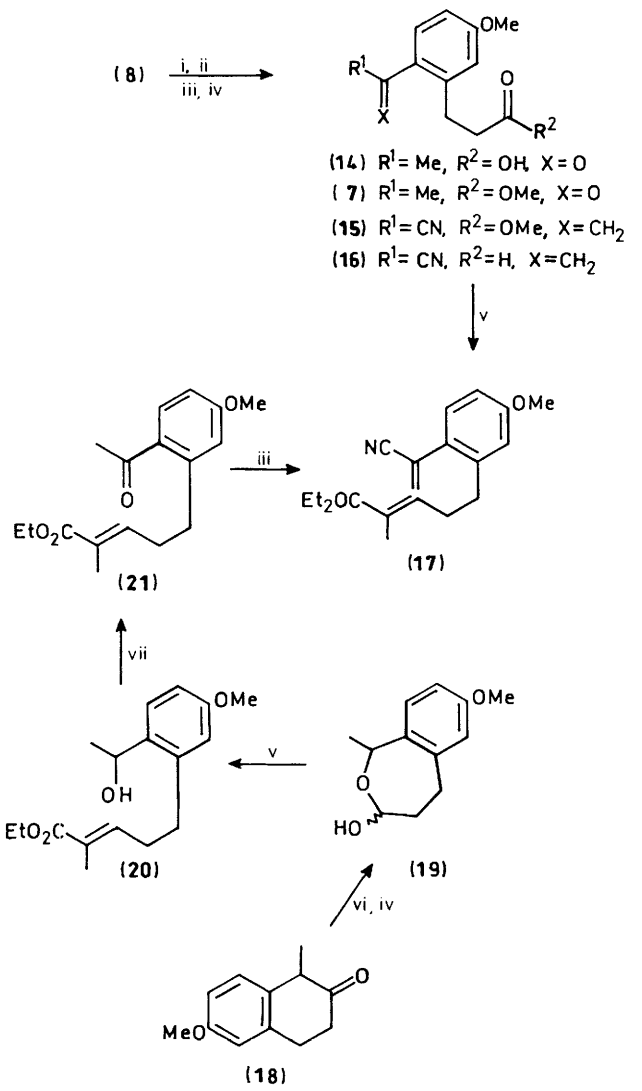


Scheme 3. *Reagents:* i, LDA, MeI, THF, HMPA; ii, MeI, Li, THF, HMPA, ultrasound; iii, LDA, $ClCO_2Et$, THF, HMPA

of ethyl chloroformate[9] provided the enol carbonate (**9**) in 82% yield from (**11**) (Scheme 3).

On heating a solution of (**9**) in *o*-dichlorobenzene at 180 °C for 2 h, the dihydronaphthalene (**8**) was obtained in 94% yield. None of the competitive [1,5]sigmatropic product *via* the *E*-*o*-quinodimethane[10] could be detected in the crude product. Lemieux oxidation of the double bond in (**8**) with catalytic osmium tetraoxide in the presence of sodium metaperiodate produced the keto acid (**14**) which, without purification, was converted into the keto ester (**7**) in 65% yield by treatment with toluene-*p*-sulphonic acid as catalyst in methanol. In an attempt to introduce the dienophile portion, we treated (**7**), according to the procedure reported by Oda,[11] with trimethylsilyl cyanide[12] in the presence of a catalytic amount of zinc iodide; this was followed by exposure to phosphorus oxychloride in pyridine in a one-pot operation to give the vinyl cyanide (**15**) in 79% yield. An initial attempt to construct a diene entity directly by means of the one-pot procedure, established by Yamamoto,[13] involving treatment of the aldehyde (**16**), prepared by chemoselective reduction of the ester group in (**15**) with di-isobutylaluminium hydride (DIBAH), with 1-methylallyldiphenylphosphine oxide produced either intractable mixtures or decomposition of starting material. After a considerable amount of experimentation, we have found that the transformation and subsequent cycloaddition could best be achieved by the following stepwise sequence. Wittig reaction of (**16**) with ethyl triphenylphosphoranylidenepropionate[14] provided stereoselectively the unsaturated ester (**17**) with *E*-configuration. Alternatively, (**17**) was also prepared from the known 3,4-dihydro-6-methoxy-1-methylnaphthalen-2(1*H*)-one[15] (**18**) as outlined in Scheme 4. Thus, sequential Baeyer–Villiger oxidation of (**18**) with *m*-chloroperbenzoic acid and immediate reduction with DIBAH provided the hemiacetal (**19**), which was treated with the stable ylide to afford the alcohol (**20**). Oxidation of (**20**) with pyridinium dichromate (PDC) in *N*,*N*-dimethylformamide then provided the ketone (**21**) which could be converted into (**17**) by treatment under the same conditions as used for (**7**); this gave a 44% overall yield from (**18**) (Scheme 4).

Reduction of (**17**) with DIBAH followed by oxidation of the resulting alcohol (**22**) with PDC provided the aldehyde (**23**), which was immediately treated with methylenetriphenylphosphorane; this failed to give the desired triene (**6**), resulting in only decomposition of starting material. Attempted conversions of (**23**) into (**6**) using zinc, methylene dibromide, and titanium tetrachloride as described by Nozaki[16] as well as the modified procedure employing zinc, methylene di-iodide, and trimethylaluminium which has also been described by Nozaki[16] produced directly the tricyclic cyanides (**5a**,**b**) [$\nu_{max.}(CHCl_3)$ 2 220 cm^{-1}; $\delta_H(CDCl_3)$ 5.57 (1 H, br); *m*/*z* 253 (M^+)], generated *via* sequential triene formation and spontaneous intramolecular Diels–Alder reaction, as a mixture of diastereoisomers in 9 and 19% yield, respectively. The problem of the low yield was nicely solved by employing the conditions of Peterson olefination. Thus, treatment of the crude aldehyde (**23**) with trimethylsilylmethylmagnesium chloride[17] in ether followed by exposure of the resulting alcohol (**24**) to methanesulphonyl chloride and triethylamine in methylene dichloride at −78 °C[18] to room temperature led to the desired cycloadducts (**5a**,**b**), as 1.25:1 (from ^1H n.m.r.) mixture of inseparable diastereoisomers; this was achieved in 61% overall yield from (**17**). Separation of the two diastereoisomers could easily be achieved by the following conversion. Reduction of a diastereoisomeric mixture of (**5a**,**b**) with lithium aluminium hydride ($LiAlH_4$) led to the corresponding primary amine, which upon exposure to one-pot benzoylation conditions, reported by Harding,[19] with potassium carbonate and benzoyl chloride gave rise to a chromatographically separable mixture of the desired *trans*-benzoate (**25**) and the *cis*-isomer (**26**) in a ratio of 1:1.2, in a combined yield of 97%. Although the relative stereochemistry of the two diastereoisomers could not be determined at this stage, confirmation was made by the eventual conversion of (**25**) into (**2**) and by the *X*-ray analysis of (**30**), derived from (**26**) as described below. The benzoates (**25**) and (**26**) were independently reduced



Scheme 4. *Reagents*: i, OsO_4, $NaIO_4$, Et_3O, H_2O; ii, MeOH, *p*-TsOH; iii, Me_3SiCN, ZnI_2 then $POCl_3$, pyridine; iv, DIBAH, DME, CH_2Cl_2; v, $Ph_3P{=}C(Me)CO_2Et$, benzene; vi, *m*-$ClC_6H_4CO_3H$, $KHCO_3$, CH_2Cl_2; vii, PDC, DMF

with $LiAlH_4$ to the secondary amine hydrochlorides (**4**) and (**27**), after treatment with hydrogen chloride in ether, in 94 and 87% yield, respectively. Having the desired amine hydrochlorides (**4**) and (**27**) in hand, we proceeded to examine the key transformations of the synthetic sequence. On heating (**4**) and (**27**) with 37% aqueous formaldehyde in acetic acid in a sealed tube at 150 °C for 1 h, the tetracyclic amines (**3**) [*m/z* 359 (M^+)] and (**30**) [*m/z* 359 (M^+)] were obtained in 98 and 92% yield, respectively. The two products were each shown to be homogeneous by the gamut of analytical and spectroscopic techniques. Examination of the ^1H n.m.r. spectra of (**3**) and (**30**) at 500 MHz revealed the two olefinic protons at δ_H 5.89 (dt, *J* 9.2 and 3.4 Hz) and 5.51 (dt, *J* 9.2 and 2.1 Hz) for (**3**), and at δ_H 5.82 (dt, *J* 9.8 and 3.4 Hz) and 5.36 (dd, *J* 9.8 and 1.2 Hz) for (**30**), respectively, and the higher-field shifted methyl signals at δ_H 1.01 for (**3**) and at δ_H 0.99 for (**30**), which were indicative of the desired structures. Eventually, the whole structure and the stereochemistry of the *cis*-isomer (**30**) was unambiguously established by a single-crystal *X*-ray analysis (see Tables 1–3 and Figure).

In the cyclisation experiments, the tetracyclic amines (**3**) and (**30**) were obtained quantitatively in a completely regioselective manner. This observation suggests an iminium-ene[20] mechanism *via* aza-adamantane-type transition states (**28**) and (**29**) for this transformation. Finally, catalytic hydrogenation of the hydrochloride of *trans*-isomer (**3**) over 10% palladium on carbon under hydrogen in methanol produced smoothly the target compound (**2**) quantitatively. This material exhibited a melting point (274—275 °C) completely consistent with that previously reported (274—276 °C).[1c,1g] Alternatively, the *cis*-isomer (**30**) was also converted into (**31**) in 86% yield (Scheme 5).

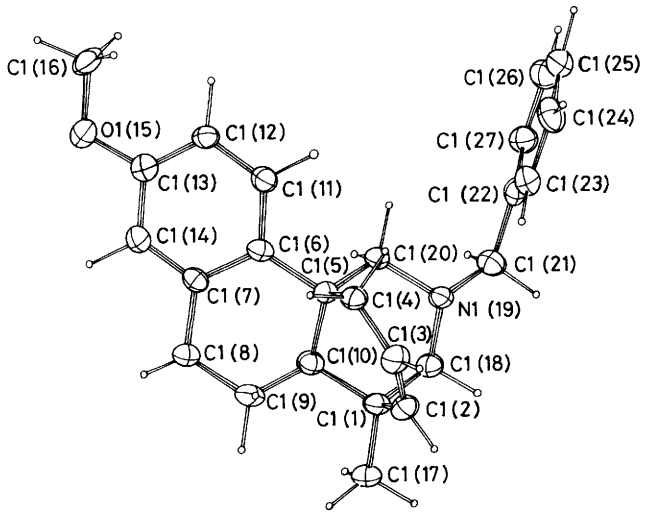


Figure. View of one of the two virtually identical molecules in crystals of (**30**). The atoms of the second molecule are numbered C2(28)–C2(54) and follow the same order as that shown above

In summary, we have completed a novel synthesis of Nagata's intermediate for (±)-atisine starting from ethyl 6-methoxy-1-methyldihydronaphthalene-2-carboxylate, which can be prepared by a preferential electrocyclic reaction of *Z*-*o*-quinodimethane developed by us. The crucial role which an intramolecular Mannich-type cyclisation (of an iminium-ene reaction) has played in the construction of the piperidine ring during the present synthesis is certainly worthy of note.

Experimental

M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H N.m.r. spectra were recorded at 60 MHz on a JEOL JNM-PMX-60, at 90 MHz on a JEOL JNM-FX-90A, or at 500 MHz on a JEOL JNM-GX500 spectrometer. ^{13}C N.m.r. spectra were recorded on a JEOL JNM-GX500 instrument, and all samples for n.m.r. analyses were dilute solutions in deuteriochloroform unless otherwise stated. Mass spectra were recorded on a Hitachi M-52G spectrometer, and microanalytical data were obtained on a JEOL TMS-01SG-2 spectrometer. All reactions were carried out under an atmosphere of dry argon or nitrogen. Column chromatography was carried out with silica gel (Kieselgel 60, 70—230 mesh, Merck). All organic solvents were evaporated under reduced pressure on a rotary evaporator. All new compounds described in this Experimental section were homogeneous on t.l.c.

4-Methoxy-1-methylbenzocyclobutene-1-carbonitrile (**12**).—A stirred solution of di-isopropylamine (4.07 g, 40.2 mmol) in dry THF (40 ml) was cooled to −78 °C and treated with 1.59M butyl-lithium in hexane solution (24.1 ml, 38.3 mmol) during several min. After the mixture had been stirred for an additional 20 min at −78 °C, 4-methoxybenzocyclobutene-1-carbonitrile (**11**)[1g] (3.05 g, 19.2 mmol) and HMPA (3.78 g, 21.1 mmol) were

Table 1. Atomic parameters ($\times 10^4$)

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Cl(1)	−6 572(6)	−3 489(2)	1 224(7)	C2(28)	3 748(7)	−1 501(3)	6 487(8)
C1(2)	−5 963(7)	−2 981(2)	743(8)	C2(29)	4 220(8)	−2 017(2)	5 837(8)
C1(3)	−4 607(8)	−2 894(2)	178(8)	C2(30)	4 825(8)	−2 094(3)	4 475(9)
C1(4)	−3 551(6)	−3 299(2)	−100(7)	C2(31)	5 134(8)	−1 686(2)	3 435(8)
C1(5)	−4 153(6)	−3 825(2)	401(6)	C2(32)	4 632(7)	−1 158(2)	4 069(7)
C1(6)	−3 436(6)	−4 238(2)	−611(7)	C2(33)	5 640(6)	−748(2)	3 389(7)
C1(7)	−4 250(6)	−4 552(2)	−1 847(7)	C2(34)	6 879(7)	−451(2)	4 236(7)
C1(8)	−5 934(6)	−4 523(3)	−2 184(8)	C2(35)	7 198(8)	−495(3)	5 951(8)
C1(9)	−6 453(7)	−4 020(3)	−1 474(8)	C2(36)	6 421(8)	−984(3)	6 430(7)
C1(10)	−5 910(6)	−3 925(2)	235(7)	C2(37)	4 765(7)	−1 071(2)	5 853(7)
C1(11)	−1897(6)	−4 289(2)	−384(7)	C2(38)	5 468(7)	−683(3)	1 827(7)
C1(12)	−1 158(7)	−4 643(3)	−1 331(7)	C2(39)	6 422(8)	−340(3)	1 113(8)
C1(13)	−1 988(7)	−4 942(2)	−2 530(7)	C2(40)	7 602(7)	−52(2)	1 990(8)
C1(14)	−3 522(7)	−4 897(2)	−2 785(8)	C2(41)	7 855(7)	−114(2)	3 537(8)
O1(15)	−1 390(5)	−5 301(2)	−3 540(6)	O2(42)	8 637(6)	310(2)	1 437(6)
C1(16)	215(8)	−5 326(3)	−3 396(9)	C2(43)	8 496(9)	355(3)	−185(10)
C1(17)	−8 336(7)	−3 571(3)	1 158(9)	C2(44)	3 796(9)	−1 446(3)	8 249(8)
C1(18)	−6 042(6)	−3 505(2)	2 931(8)	C2(45)	2 077(8)	−1 474(3)	5 929(8)
N1(19)	−4 386(5)	−3 450(2)	3 125(5)	N2(46)	1 906(5)	−1 524(2)	4 231(6)
C1(20)	−3 719(6)	−3 841(2)	2 101(7)	C2(47)	2 928(7)	−1 142(2)	3 594(7)
C1(21)	−3 937(7)	−3 454(2)	4 754(7)	C2(48)	308(7)	−1 494(3)	3 759(8)
C1(22)	−2 236(7)	−3 333(2)	5 131(7)	C2(49)	−71(6)	−1 684(2)	2 065(8)
C1(23)	−1 367(7)	−2 939(2)	4 522(8)	C2(50)	553(8)	−2 103(3)	1 332(8)
C1(24)	178(8)	−2 826(3)	4 914(9)	C2(51)	131(9)	−2 302(3)	−175(8)
C1(25)	868(7)	−3 104(3)	5 916(8)	C2(52)	−898(10)	−2 076(4)	−993(9)
C1(26)	36(8)	−3 489(3)	6 517(8)	C2(53)	−1 521(9)	−1 676(4)	−297(10)
C1(27)	−1 530(7)	−3 602(3)	6 128(7)	C2(54)	−1 115(8)	−1 467(3)	1 257(9)

Table 2. Bond lengths (Å)

Atom 1 Atom 2	Lengths	Atom 1 Atom 2	Lengths
C1(1)–C1(2)	1.510(9)	C2(28)–C2(29)	1.528(9)
C1(1)–C1(10)	1.539(9)	C2(28)–C2(37)	1.538(9)
C1(1)–C1(17)	1.538(9)	C2(28)–C2(44)	1.521(10)
C1(1)–C1(18)	1.550(9)	C2(28)–C2(45)	1.545(9)
C1(2)–C1(3)	1.309(9)	C2(29)–C2(30)	1.314(9)
C1(3)–C1(4)	1.504(9)	C2(30)–C2(31)	1.505(9)
C1(4)–C1(5)	1.559(9)	C2(31)–C2(32)	1.564(9)
C1(5)–C1(6)	1.527(7)	C2(32)–C2(33)	1.515(7)
C1(5)–C1(10)	1.535(7)	C2(32)–C2(37)	1.539(9)
C1(5)–C1(20)	1.523(7)	C2(32)–C2(47)	1.548(9)
C1(6)–C1(7)	1.399(7)	C2(33)–C2(34)	1.400(9)
C1(6)–C1(11)	1.386(9)	C2(33)–C2(38)	1.397(9)
C1(7)–C1(8)	1.513(9)	C2(34)–C2(35)	1.532(9)
C1(7)–C1(14)	1.378(9)	C2(34)–C2(41)	1.378(9)
C1(8)–C1(9)	1.527(9)	C2(35)–C2(36)	1.511(9)
C1(9)–C1(10)	1.529(9)	C2(36)–C2(37)	1.508(9)
C1(11)–C1(12)	1.403(9)	C2(38)–C2(39)	1.385(9)
C1(12)–C1(13)	1.366(9)	C2(39)–C2(40)	1.366(9)
C1(13)–C1(14)	1.381(9)	C2(40)–C2(41)	1.390(9)
C1(13)–O1(15)	1.377(7)	C2(40)–O2(42)	1.389(9)
O1(15)–C1(16)	1.422(9)	O2(42)–C2(43)	1.433(9)
C1(18)–N1(19)	1.449(7)	C2(45)–N2(46)	1.468(9)
N1(19)–C1(20)	1.470(7)	N2(46)–C2(47)	1.451(9)
N1(19)–C1(21)	1.462(7)	N2(46)–C2(48)	1.465(9)
C1(21)–C1(22)	1.509(9)	C2(48)–C2(49)	1.510(9)
C1(22)–C1(23)	1.394(9)	C2(49)–C2(50)	1.393(9)
C1(22)–C1(27)	1.370(9)	C2(49)–C2(54)	1.363(9)
C1(23)–C1(24)	1.379(9)	C2(50)–C2(51)	1.374(10)
C1(24)–C1(25)	1.383(10)	C2(51)–C2(52)	1.372(12)
C1(25)–C1(26)	1.357(10)	C2(52)–C2(53)	1.341(12)
C1(26)–C1(27)	1.396(9)	C2(53)–C2(54)	1.415(12)

added successively. After an additional 20 min, methyl iodide (5.44 g, 38.3 mmol) was added dropwise to the mixture and the cooling bath was then removed. The reaction mixture was allowed to warm to room temperature. After being stirred for 1 h at ambient temperature, saturated aqueous ammonium chloride was added dropwise to the reaction mixture at 0 °C. After evaporation of the solvent, water was added to dissolve any suspended material, and the mixture was then extracted with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by column chromatography with hexane–ethyl acetate (85:5, v/v) as eluant to give the *carbonitrile* (**12**) (3.25 g, 98%) as an oil (Found: C, 76.3; H, 6.5; N, 7.85. $C_{11}H_{11}NO$ requires C, 76.25; H, 6.4; N, 8.1%); $\nu_{max.}(CHCl_3)$ 2 230 cm^{-1}; δ_H(90 MHz) 1.75 (3 H, s, Me), 3.18 (1 H, d, *J* 14.0 Hz, C*H*H), 3.74 (1 H, d, *J* 14.0 Hz, CH*H*), 3.79 (3 H, s, OMe), 6.65—6.90 (2 H, m, ArH), and 7.11 (1 H, d, *J* 8.1 Hz, ArH); *m/z* 173 (M^+).

1-*Acetyl*-4-*methoxy*-1-*methylbenzocyclobutene* (**13**).—Methyl iodide (1.23 g, 8 mmol) and lithium (0.15 g, 21.5 mmol) were successively added to a solution of the carbonitrile (**12**) (0.75 g, 4.3 mmol) in ether (15 ml) and the mixture was sonicated at 20 °C for 5 min. After removal of the excess of lithium, 10% aqueous hydrochloric acid was added at 0 °C. The separated ether phase was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was submitted to column chromatography with hexane–ethyl acetate (93:7, v/v) as eluant to give the *methyl ketone* (**13**) (0.68 g, 82%) as an oil (Found: C, 75.85; H, 7.7. $C_{12}H_{14}O_2$ requires C, 75.75; H, 7.4%); $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1}; δ_H(90 MHz) 1.59 (3 H, s, Me), 2.16 (3 H, s, COMe), 2.92 (1 H, d, *J* 14.2 Hz, C*H*H), 3.56 (1 H, d, *J* 14.2 Hz, CH*H*), 3.78 (3 H, s, OMe), 6.65—6.89 (2 H, m, ArH), and 7.04 (1 H, dd, *J* 7.4 and 1.6 Hz, ArH); *m/z* 190 (M^+).

1-(1-*Ethoxycarbonyloxyvinyl*)-4-*methoxy*-1-*methylbenzocyclobutene* (**9**).—A solution of the ketone (**13**) (1.55 g, 8.15 mmol) in dry THF (10 ml) was added dropwise to a stirred solution of LDA [prepared as described for (**12**) from diisopropylamine (1.15 g, 11.4 mmol) and 1.55M butyl-lithium in hexane (6.83 ml, 10.6 mmol)] at −78 °C. After the mixture had been stirred for 15 min at the same temperature, it was allowed to warm to ambient temperature when a solution of ethyl chloroformate (1.15 g, 10.6 mmol) in HMPA (24 ml) was added

Table 3. Bond angles (°)

Atom 1	Atom 2	Atom 3	Angles	Atom 1	Atom 2	Atom 3	Angles
C1(2)	C1(1)	C1(10)	110.5(5)	C2(31)	C2(32)	C2(37)	110.7(5)
C1(2)	C1(1)	C1(17)	111.8(5)	C2(31)	C2(32)	C2(47)	110.0(5)
C1(2)	C1(1)	C1(18)	109.3(5)	C2(33)	C2(32)	C2(37)	111.0(5)
C1(10)	C1(1)	C1(17)	111.4(5)	C2(33)	C2(32)	C2(47)	110.1(5)
C1(10)	C1(1)	C1(18)	106.9(5)	C2(37)	C2(32)	C2(47)	106.9(4)
C1(17)	C1(1)	C1(18)	106.7(5)	C2(32)	C2(33)	C2(34)	122.2(5)
C1(1)	C1(2)	C1(3)	122.8(6)	C2(32)	C2(33)	C2(38)	121.0(5)
C1(2)	C1(3)	C1(4)	122.7(6)	C2(34)	C2(33)	C2(38)	116.5(5)
C1(3)	C1(4)	C1(5)	115.3(5)	C2(33)	C2(34)	C2(35)	121.2(5)
C1(4)	C1(5)	C1(6)	108.2(4)	C2(33)	C2(34)	C2(41)	120.5(5)
C1(4)	C1(5)	C1(10)	111.2(4)	C2(35)	C2(34)	C2(41)	118.3(5)
C1(4)	C1(5)	C1(20)	110.8(4)	C2(34)	C2(35)	C2(36)	112.7(5)
C1(6)	C1(5)	C1(10)	110.4(4)	C2(35)	C2(36)	C2(37)	110.2(5)
C1(6)	C1(5)	C1(20)	109.6(4)	C2(28)	C2(37)	C2(32)	109.0(5)
C1(10)	C1(5)	C1(20)	106.6(4)	C2(28)	C2(37)	C2(36)	116.2(5)
C1(5)	C1(6)	C1(7)	122.5(5)	C2(32)	C2(37)	C2(36)	111.0(5)
C1(5)	C1(6)	C1(11)	119.9(5)	C2(33)	C2(38)	C2(39)	123.8(6)
C1(7)	C1(6)	C1(11)	117.5(5)	C2(38)	C2(39)	C2(40)	117.8(6)
C1(6)	C1(7)	C1(8)	121.2(5)	C2(39)	C2(40)	C2(41)	120.8(6)
C1(6)	C1(7)	C1(14)	120.2(5)	C2(39)	C2(40)	O2(42)	124.2(6)
C1(8)	C1(7)	C1(14)	118.6(5)	C2(41)	C2(40)	O2(42)	115.0(6)
C1(7)	C1(8)	C1(9)	112.9(5)	C2(34)	C2(41)	C2(40)	120.6(6)
C1(8)	C1(9)	C1(10)	108.0(5)	C2(40)	O2(42)	C2(43)	116.7(5)
C1(1)	C1(10)	C1(5)	108.3(4)	C2(28)	C2(45)	N2(46)	111.9(5)
C1(1)	C1(10)	C1(9)	115.6(5)	C2(45)	N2(46)	C2(47)	111.9(5)
C1(5)	C1(10)	C1(9)	110.8(5)	C2(45)	N2(46)	C2(48)	109.9(5)
C1(6)	C1(11)	C1(12)	122.4(5)	C2(47)	N2(46)	C2(48)	110.6(5)
C1(11)	C1(12)	C1(13)	118.4(6)	C2(32)	C2(47)	N2(46)	112.5(5)
C1(12)	C1(13)	C1(14)	120.4(5)	N2(46)	C2(48)	C2(49)	113.4(5)
C1(12)	C1(13)	O1(15)	123.8(5)	C2(48)	C2(49)	C2(50)	120.9(6)
C1(14)	C1(13)	O1(15)	115.8(5)	C2(48)	C2(49)	C2(54)	120.1(6)
C1(7)	C1(14)	C1(13)	121.1(5)	C2(50)	C2(49)	C2(54)	118.8(6)
C1(13)	O1(15)	C1(16)	117.4(5)	C2(49)	C2(50)	C2(51)	121.4(7)
C1(1)	C1(18)	N1(19)	111.6(5)	C2(50)	C2(51)	C2(52)	119.5(7)
C1(18)	N1(19)	C1(20)	111.8(4)	C2(51)	C2(52)	C2(53)	119.7(8)
C1(18)	N1(19)	C1(21)	109.8(5)	C2(52)	C2(53)	C2(54)	121.8(8)
C1(20)	N1(19)	C1(21)	111.9(4)	C2(49)	C2(54)	C2(53)	118.7(7)
C1(5)	C1(20)	N1(19)	111.7(4)	C2(29)	C2(28)	C2(37)	109.9(5)
N1(19)	C1(21)	C1(22)	114.5(5)	C2(29)	C2(28)	C2(44)	110.0(6)
C1(21)	C1(22)	C1(23)	121.2(5)	C2(29)	C2(28)	C2(45)	109.1(5)
C1(21)	C1(22)	C1(27)	120.0(5)	C2(37)	C2(28)	C2(44)	112.9(6)
C1(23)	C1(22)	C1(27)	118.8(5)	C2(37)	C2(28)	C2(45)	107.3(5)
C1(22)	C1(23)	C1(24)	120.2(6)	C2(44)	C2(28)	C2(45)	107.6(6)
C1(23)	C1(24)	C1(25)	120.0(6)	C2(28)	C2(29)	C2(30)	122.2(6)
C1(24)	C1(25)	C1(26)	120.5(7)	C2(29)	C2(30)	C2(31)	123.6(6)
C1(25)	C1(26)	C1(27)	119.6(7)	C2(30)	C2(31)	C2(32)	114.9(5)
C1(22)	C1(27)	C1(26)	120.9(6)	C2(31)	C2(32)	C2(33)	108.2(5)

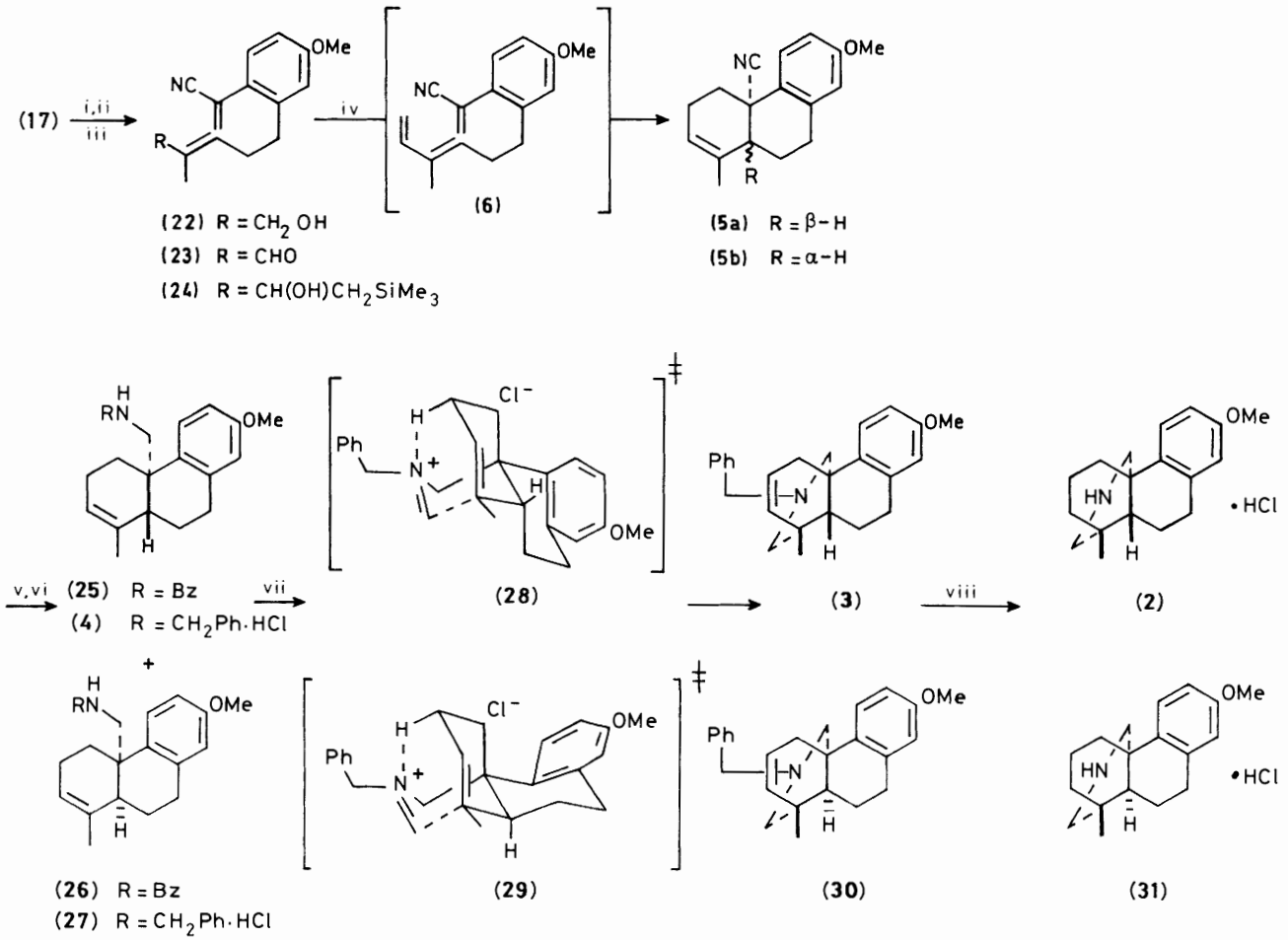
to it. After the mixture had been stirred for 30 min, saturated aqueous ammonium chloride was added to it at 0 °C, and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a residue. Column chromatography of the product with hexane–ethyl acetate (9:1, v/v) as eluant gave the *enol carbonate* (**9**) (2.13 g, 100%) as an oil; $\nu_{max.}$($CHCl_3$) 1 750 and 1 655 cm^{-1}; δ_H(90 MHz) 1.30 (3 H, t, *J* 7.2 Hz, OCH_2*Me*), 1.56 (3 H, s, Me), 2.95 (1 H, d, *J* 13.9 Hz, C*H*H), 3.37 (1 H, d, *J* 13.9 Hz, CH*H*), 3.77 (3 H, s, OMe), 4.20 (2 H, q, *J* 7.2 Hz, OCH_2Me), 4.89 (1 H, d, *J* 2.1 Hz, =C*H*H), 4.95 (1 H, d, *J* 2.1 Hz, =CH*H*), 6.65—6.85 (2 H, m, ArH), and 7.04 (1 H, dd, *J* 7.5 and 1.3 Hz, ArH); *m/z* 262 (M^+) (Found: M^+, 262.1183. $C_{15}H_{18}O_4$ requires *M*, 262.1205).

2-*Ethoxycarbonyloxy*-3,4-*dihydro*-6-*methoxy*-1-*methylnaphthalene* (**8**).—A solution of the enol carbonate (**9**) (2.13 g, 8.12 mmol) in dry *o*-dichlorobenzene (140 ml) was degassed for 5 min and heated and stirred at 180 °C for 2 h. After evaporation of the solvent, the residue was chromatographed with hexane–ethyl acetate (9:1, v/v) as eluant to afford the *dihydronaphthalene* (**8**) (2.01 g, 94%) as an oil; $\nu_{max.}$($CHCl_3$) 1 750 cm^{-1}; δ_H(90 MHz) 1.36 (3 H, t, *J* 7.2 Hz, OCH_2*Me*), 1.95 (3 H, br s, Me), 2.31—2.70 (2 H, m, CH_2), 2.80—3.07 (2 H, m, CH_2), 3.80 (3 H, s, OMe), 4.27 (2 H, q, *J* 7.2 Hz, OCH_2Me), 6.60—6.84 (2 H, m, ArH), and 7.15 (1 H, d, *J* 9.0 Hz, ArH); *m/z* 262 (M^+) (Found: M^+, 262.1212. $C_{15}H_{18}O_4$ requires *M*, 262.1205).

Methyl 3-(2-*Acetyl*-5-*methoxyphenyl*)*propionate* (**7**).—A solution of a catalytic amount of osmium tetraoxide and the dihydronaphthalene (**8**) (67 mg, 0.26 mmol) in a mixture of ether (3 ml) and water (3 ml) was stirred vigorously whilst sodium metaperiodate (820 mg, 3.83 mmol) was added in portions at room temperature. After 40 h, the reaction mixture was filtered through Celite. The filtrate was acidified with 10% aqueous hydrochloric acid and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to leave the acid (**14**) which was immediately taken up into methanol (5 ml). The solution was heated with a catalytic amount of toluene-*p*-sulphonic acid under reflux for 2 h, and was then allowed to cool to room temperature, whereupon the methanol was evaporated to give a residue. This was purified by column chromatography with hexane–ethyl acetate (4:1, v/v) as eluant to give the *ester* (**8**) (39 mg, 65%) as a yellow oil; $\nu_{max.}$ 1 730 and 1 670 cm^{-1}; δ_H(90 MHz) 2.56 (3 H, s, COMe), 2.65 (2 H, t, *J* 7.4 Hz, CH_2), 3.23 (2 H, t, *J* 7.4 Hz, CH_2), 3.66 (3 H, s, OMe), 3.85 (3 H, s, OMe), 6.68—6.90 (2 H, m, ArH), and 7.78 (1 H, d, *J* 9.5 Hz, ArH); *m/z* 236 (M^+) (Found: M^+, 236.1039. $C_{13}H_{16}O_4$ requires *M*, 236.1049).

Methyl 3-[2-(1-*Cyanovinyl*)-5-*methoxyphenyl*]*propionate* (**15**).—Trimethylsilyl cyanide (56 mg, 0.56 mmol) was added to a stirred solution of the ketone (**7**) (95 mg, 0.40 mmol) and a catalytic amount of zinc iodide in dry toluene (4 ml) at room temperature. After 10 h, phosphorus oxychloride (247 mg, 1.61 mmol) and pyridine (0.8 ml) was added at the same temperature and stirring was continued under reflux for 24 h. The reaction mixture was treated with 10% aqueous hydrochloric acid at 0 °C and filtered through Celite. The filtrate was extracted with ethyl acetate, and the combined extracts were then washed with brine, dried ($MgSO_4$), and concentrated to leave an oil. Purification by column chromatography with hexane–ethyl acetate (4:1, v/v) as eluant gave the *cyanide* (**15**) (78 mg, 79%) as an oil (Found: C, 68.5; H, 6.0; N, 5.75. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 5.85; N, 5.7%); $\nu_{max.}$($CHCl_3$) 2 225 and 1 740 cm^{-1}; δ_H(90 MHz) 2.51—2.79 (2 H, m, CH_2), 2.93—3.22 (2 H, m), 3.68 (3 H, s, OMe), 3.81 (3 H, s, OMe), 5.95 (1 H, d, *J* 0.6 Hz, =C*H*H), 6.21 (1 H, d, *J* 0.6 Hz, =CH*H*), 6.67—6.88 (2 H, m, ArH), and 7.17 (1 H, d, *J* 9.3 Hz, ArH); *m/z* 245 (M^+).

1,3,4,5-*Tetrahydro*-7-*methoxy*-1-*methyl*-2-*benzoxepin*-3-*ol* (**19**).—*m*-Chloroperbenzoic acid (70% purity; 40.1 g, 220 mmol) was added to a stirred solution of 3,4-dihydro-6-methoxy-1-methylnaphthalen-2(1*H*)-one (**18**)[15] (19.0 g, 99.9 mmol) and potassium hydrogen carbonate (22.0 g, 220 mmol) in dry methylene dichloride (700 ml) at room temperature. After 17 h, 5% aqueous sodium thiosulphate was added and the mixture stirred for a further 20 min. The white suspension was filtered through Celite and the filtrate was extracted with chloroform. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to leave a crude product which was immediately dissolved in a mixture of dry THF (190 ml) and dry hexane (190 ml). The solution was cooled to −70 °C whilst a solution of di-isobutylaluminium hydride (DIBAH) (1M solution in hexane; 120 ml, 120 mmol) was added dropwise. After a further 10 min, the solution was treated with water (140 ml), diluted with ether, and stirred for 1.5 h at room temperature. The mixture was



Scheme 5. *Reagents:* i, DIBAH, THF, hexane; ii, PDC, CH_2Cl_2; iii, $ClMgCH_2SiMe_3$, Et_2O; iv, $MeSO_2Cl$, NEt_3, CH_2Cl_2; v, $LiAlH_4$, Et_2O then K_2CO_3, BzCl; vi, $LiAlH_4$, THF then HCl, Et_2O; vii, 35% aqueous HCHO, AcOH, 150 °C; viii, HCl salt of (**3**) or (**30**), H_2, 10% Pd–C, MeOH, 6 kg/cm^2

filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated to leave a residue which was subjected to column chromatography with hexane–ethyl acetate (3:2, v/v) as eluant to afford the *hemiacetal* (**19**) (18.7 g, 90%) as needles after recrystallisation from ether, m.p. 77—83 °C (Found: C, 69.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%); $\nu_{max.}(CHCl_3)$ 3 580 and 1 720 cm^{-1}; δ_H(90 MHz) 1.42—1.69 (3 H, m, Me), 1.69—3.45 (5 H, m, one of them disappeared with D_2O, 2 × CH_2, OH), 3.79 (3 H, s, OMe), 4.58—5.67 (2 H, m, 2 × CH), 6.60—6.88 (2 H, m, ArH), and 7.08—7.25 (1 H, m, ArH); *m/z* 208 (M^+).

(E)-*Ethyl* 5-[2-(1-*Hydroxyethyl*)-5-*methoxyphenyl*]-2-*methylpent*-2-*enoate* (**20**).—A stirred solution of the hemiacetal (**19**) (3.12 g, 15.0 mmol) and (ethoxycarbonylethylidene)triphenylphosphorane (16.3 g, 44.9 mmol) in dry benzene (65 ml) was heated at 70 °C for 2 h. The solvent was evaporated to leave an oily residue which was subjected to column chromatography with hexane–ethyl acetate (7:3, v/v) to afford the *alcohol* (**20**) (4.0 g, 91%) as an oil (Found: C, 70.15; H, 8.25. $C_{17}H_{24}O_4$ requires C, 69.85; H, 8.25%); $\nu_{max.}(CHCl_3)$ 3 600, 3 450, and 1 700 cm^{-1}; δ_H(90 MHz) 1.29 (3 H, t, *J* 7.1 Hz, OCH_2Me), 1.48 (3 H, d, *J* 6.3 Hz, CH*Me*), 1.79 (3 H, d, *J* 1.5 Hz, HC=C*Me*), 1.88 (1 H, br s, disappeared with D_2O, OH), 2.28—2.62 (2 H, m, CH_2), 2.65—2.92 (2 H, m, CH_2), 3.80 (3 H, s, OMe), 4.19 (2 H, q, *J* 7.1 Hz, OCH_2Me), 5.11 (1 H, m, C*H*OH), 6.62—7.19 (3 H, m, *H*C=CMe, ArH), and 7.45 (1 H, d, *J* 8.3 Hz, ArH); δ_C(25 MHz) 12.39(q), 14.33(q), 24.83(q), 30.59(t), 31.12(t), 55.19(q), 60.59(t), 65.87(d), 111.96(d), 114.72(d), 126.70(d), 128.58(s), 135.91(s), 139.20(s), 140.61(d), 158.75(s), and 168.15(s); *m/z* 292 (M^+).

(E)-*Ethyl* 5-(2-*Acetyl*-5-*methoxyphenyl*)*pent*-2-*enoate* (**21**).—A solution of the alcohol (**20**) (0.84 g, 2.87 mmol) in dry *N*,*N*-dimethylformamide (DMF) (7 ml) was added in one portion to a stirred solution of pyridinium dichromate (PDC) (1.62 g, 4.31 mmol) in dry DMF (6 ml) at room temperature. After 4 h, Florisil (2.5 g) was added to the mixture which was then diluted with dry ether (26 ml), and stirred for a further 20 min at room temperature. It was then filtered through Celite and the filtrate concentrated to give a residue which was purified by column chromatography with hexane–ethyl acetate (4:1, v/v) as eluant to afford the *ketone* (**21**) (0.81 g, 97%) as an oil (Found: C, 70.55; H, 7.65. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.65%); $\nu_{max.}(CHCl_3)$ 1 700 and 1 670 cm^{-1}; δ_H(90 MHz) 1.29 (3 H, t, *J* 7.1 Hz, OCH_2Me), 1.79 (3 H, d, *J* 1.5 Hz, HC=C*Me*), 2.30—2.63 (2 H, m, CH_2), 2.56 (3 H, s, COMe), 2.92—3.18 (2 H, m, CH_2), 3.85 (3 H, s, OMe), 4.18 (2 H, q, *J* 7.1 Hz, OCH_2Me), 6.67—6.89 (3 H, m, *H*C=CMe, ArH), and 7.77 (1 H, d, *J* 9.3 Hz, ArH); *m/z* 290 (M^+).

(E)-*Ethyl* 5-[2-(1-*Cyanovinyl*)-5-*methoxyphenyl*]-2-*methylpent*-2-*enoate* (**17**).—(*a*) DIBAH (1M solution in hexane; 0.38 ml, 0.38 mmol) was added to a solution of the ester (**15**) (85 mg, 0.35 mmol) in a mixture of dry dimethoxyethane (1.7 ml) and dry methylene dichloride (1.7 ml) at −78 °C. After the mixture had been stirred at −78 °C for 15 min, water (0.38 ml) was

added dropwise to it and stirring continued for 30 min at room temperature. The resulting mixture was filtered under suction through a pad of Celite, and the filter pad was washed with ether. The combined filtrates were dried ($MgSO_4$) and evaporated to leave a slightly unstable aldehyde (**16**) as an oil, which was used for the next reaction without purification.

(Ethoxycarbonylethylidene)triphenylphosphorane (0.31 g, 0.86 mmol) was added to a solution of the crude aldehyde (**16**) in benzene (4 ml). After the mixture had been stirred at 70 °C for 17 h, it was evaporated to afford a residue which was chromatographed using hexane–ethyl acetate (85:15, v/v) as eluant to give the *unsaturated ester* (**17**) (76 mg, 74%) as a pale yellow oil (Found: C, 72.25; H, 7.1; N, 4.65. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.05; N, 4.7%); $\nu_{max.}$($CHCl_3$) 2 220 and 1 700 cm^{-1}; δ_H(90 MHz) 1.29 (3 H, t, *J* 7.1 Hz, OCH_2Me), 1.78 (3 H, d, *J* 1.5 Hz, Me), 2.29—2.65 (2 H, m, CH_2), 2.71—3.02 (2 H, m, CH_2), 3.81 (3 H, s, OMe), 4.19 (2 H, q, *J* 7.1 Hz, OCH_2Me), 5.93 (1 H, d, *J* 0.7 Hz, =CH*H*), 6.20 (1 H, d, *J* 0.7 Hz, =C*H*H), 6.62—6.89 (3 H, m, =CH–, ArH), and 7.16 (1 H, d, *J* 9.3 Hz, ArH); *m/z* 299 (M^+).

(*b*) Trimethylsilyl cyanide (0.79 g, 8.0 mmol) was added to a stirred solution of the ketone (**21**) (1.66 g, 5.72 mmol) and zinc iodide (0.09 g, 0.29 mmol) in dry toluene (70 ml). The mixture was stirred at room temperature for 20 h, after which phosphorus oxychloride (3.51 g, 23 mmol) and pyridine (11.4 ml) were added to it; the mixture was then heated under reflux for a further 23 h. After the mixture had been cooled to 0 °C, 10% aqueous hydrochloric acid was added to it and the resulting suspension was filtered under suction through a pad of Celite. The filtrate was extracted with ethyl acetate, and the combined extracts were then washed with brine, dried ($MgSO_4$), and concentrated to leave an oil which was chromatographed using hexane–ethyl acetate (9:1, v/v) as eluant to give the cyanide (**17**) (0.95 g, 56%) as a pale yellow oil, showing spectral data identical with those described above.

(E)-5-[2-(1-*Cyanovinyl*)-5-*methoxyphenyl*]-1-*hydroxy*-2-*methylpent*-2-*ene* (**22**).—A solution of DIBAH (1M; 6.7 ml, 6.7 mmol) was added dropwise to a stirred, cooled (−78 °C) solution of the ester (**17**) (0.87 g, 2.91 mmol) in dry THF (35 ml). The mixture was stirred at −78 °C for 1.5 h after which water (6.7 ml) was cautiously added. The mixture was stirred at room temperature for 1 h and the precipitated aluminium salts were removed by filtration through a pad of Celite. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil which was chromatographed using hexane–ethyl acetate (7:3, v/v) as eluant to give the starting ester (**17**) (0.16 g). The later fractions eluted with hexane–ethyl acetate (3:2, v/v) gave the *alcohol* (**22**) (0.62 g, 100% based on the consumed starting ester) as an oil (Found: C, 74.2; H, 7.4; N, 5.45. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.45; N, 5.45%); $\nu_{max.}$($CHCl_3$) 3 600, 3 400, and 2 225 cm^{-1}; δ_H(90 MHz) 1.60 (4 H, br s, one of them disappeared with D_2O, OH, Me), 2.18—2.53 (2 H, m, CH_2), 2.67—2.92 (2 H, m, CH_2), 3.82 (3 H, s, OMe), 3.98 (2 H, br s, OCH_2), 5.45 (1 H, br t, *J* 5.9 Hz, =CH), 5.92 (1 H, d, *J* 0.7 Hz, =CH*H*), 6.20 (1 H, d, *J* 0.7 Hz, =C*H*H), 6.66—6.87 (2 H, m, ArH), and 7.15 (1 H, d, *J* 9.0 Hz, ArH); *m/z* 257 (M^+).

(E)-5-[2-(1-*Cyanovinyl*)-5-*methoxyphenyl*]-2-*hydroxy*-3-*methyl*-1-*trimethylsilylhex*-3-*ene* (**24**).—A solution of the alcohol (**22**) (2.12 g, 8.24 mmol) in methylene dichloride (20 ml) was added in one portion to a stirred suspension of PDC (12.4 g, 33.0 mmol) in methylene dichloride (40 ml), and the resulting suspension was then stirred at room temperature for 4.5 h. Florisil (35 g) and dry ether (180 ml) were added and the mixture was stirred at the same temperature for a further 20 min. The mixture was then flushed through a Celite pad with ether and the black granular residue triturated carefully with dry ether. The combined ether extracts were evaporated to give the aldehyde (**23**) as an unstable oil which was used for the next reaction without purification.

A solution of trimethylsilylmethylmagnesium chloride, prepared from trimethylsilylmethyl chloride (1.31 g, 10.7 mmol), magnesium turnings (0.28 g, 11.5 mmol), and catalytic iodine in dry ether (20 ml), was added dropwise to a stirred solution of the crude aldehyde in dry ether (60 ml) and the resulting mixture was stirred at room temperature for 1.5 h. Aqueous saturated ammonium chloride was added to the mixture which was then extracted with ethyl acetate. The combined, washed (brine) extracts were dried ($MgSO_4$) and evaporated to leave a residue which was purified by chromatography with hexane–ethyl acetate (4:1, v/v) as eluant to give the *alcohol* (**24**) (2.0 g, 71%) as an oil; $\nu_{max.}$($CHCl_3$) 3 600, 3 500, and 2 220 cm^{-1}; δ_H(90 MHz) 0.00 (9 H, s, $SiMe_3$), 0.93 (2 H, d, *J* 7.6 Hz, $SiCH_2$), 1.36—1.61 (4 H, m, one of them disappeared with D_2O, OH and Me), 2.10—2.52 (2 H, m, CH_2), 2.63—2.92 (2 H, m, CH_2), 3.82 (3 H, s, OMe), 4.20 (1 H, t, *J* 7.6 Hz, C*H*OH), 5.41 (1 H, br t, *J* 6.8 Hz, =CH), 5.92 (1 H, d, *J* 0.7 Hz, =CH*H*), 6.19 (1 H, d, *J* 0.7 Hz, =C*H*H), 6.65—6.89 (2 H, m, ArH), and 7.16 (1 H, d, *J* 9.0 Hz, ArH); *m/z* 343 (M^+) (Found: M^+, 343.1977. $C_{20}H_{29}NO_2Si$ requires *M*, 343.1968).

(4aS*)-3,4,4a,9,10,10a-*Hexahydro*-7-*methoxy*-1-*methylphenanthrene*-4aα-*carbonitrile* (**5a,b**).—Methanesulphonyl chloride (0.87 g, 7.57 mmol) was added dropwise to a stirred solution of the alcohol (**24**) (2.0 g, 5.82 mmol) and triethylamine (0.88 g, 8.73 mmol) in dry methylene dichloride (120 ml) at −78 °C. The mixture was stirred at −78 °C for 1.5 h and then at room temperature for further 2 days. It was then washed successively with 10% aqueous hydrochloric acid and brine. Evaporation of the dried ($MgSO_4$) methylene dichloride solution gave a residue which was chromatographed with hexane–ethyl acetate (9:1, v/v) as eluant to give the *tricycle* (**5a,b**) (1.27 g, 86%) as a solid. ^1H N.m.r. (90 MHz) analysis showed the presence of *trans*- and *cis*-cyanide isomers in the ratio 1:1.25. The crude tricycle was recrystallised from ether to afford the purified diastereoisomeric mixture of (**5a,b**) (the ratio is 1:1.11 from ^1H n.m.r.) as prisms, m.p. 137.5—139 °C (Found: C, 80.25; H, 7.65; N, 5.4. $C_{17}N_{19}NO$ requires C, 80.6; H, 7.55; N, 5.55%); $\nu_{max.}$($CHCl_3$) 2 220 cm^{-1}; δ_H(90 MHz) 1.36—3.12 (12 H, m, Me, CH_2 × 4, CH), 3.79 (3 H, s, OMe), 5.57 (1 H, br, =CH), 6.55—6.91 (2 H, m, ArH), 7.36 (0.47 H, d, *J* 8.5 Hz, ArH), and 7.42 (0.53 H, d, *J* 8.5 Hz, ArH); *m/z* 253 (M^+).

(4aS*)-4aα-(*Benzamidomethyl*)-3,4,4a,9,10,10aβ-*hexahydro*-7-*methoxy*-1-*methylphenanthrene* (**25**) *and* (4aS*)-4aα-(*Benzamidomethyl*)-3,4,4a,9,10,10aα-*hexahydro*-7-*methoxy*-1-*methylphenanthrene* (**26**).—A solution of the 1:1.25 mixture of *trans*-(**5a**) and *cis*-cyanide (**5b**) in a mixture of dry ether (4 ml) and dry THF (2 ml) was added dropwise to a suspension of lithium aluminium hydride ($LiAlH_4$) (0.28 g, 7.34 mmol) in dry ether (16 ml), and the mixture was heated under reflux for 4 h. After being cooled to 0 °C, water-saturated ether and potassium carbonate (1.22 g) were added and the resulting mixture was stirred at room temperature for 30 min. Benzoyl chloride (0.22 g, 1.59 mmol) was added to the stirred suspension and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered under suction through a pad of Celite, and the filtrate was evaporated to leave a residue which was chromatographed with hexane–ethyl acetate (4:1, v/v) as eluant to give the trans-*benzamide* (**25**) (0.2 g, 45%) as an oil; $\nu_{max.}$($CHCl_3$) 3 440 and 1 650 cm^{-1}; δ_H(90 MHz) 1.74 (3 H, br s, Me), 2.90—3.33 (3 H, m, 9-CH_2, PhCONHC*H*), 3.81 (3 H, s, OMe), 4.03 (1 H, dd, *J* 13.4 and 8.3 Hz, PhCONHC*H*H), 5.55 (1 H, br m, =CH), 5.80 (1 H, br s, PhCONH), 6.60—6.90 (2 H, m, ArH), and 7.20—7.75 (6 H, m, ArH); *m/z* 361 (M^+) (Found: M^+,

361.2031. $C_{24}H_{27}NO_2$ requires *M*, 361.2042). From the later fractions, the cis-*benzamide* (**26**) (0.23 g, 52%) was obtained as an oil; $\nu_{max.}(CHCl_3)$ 3 440 and 1 650 cm^{-1}; δ_H(90 MHz) 1.76 (3 H, br d, *J* 1.0 Hz, Me), 2.65—2.84 (2 H, m, 9-CH_2), 3.41 (1 H, dd, *J* 13.6 and 3.7 Hz, PhCONHCH*H*), 4.17 (1 H, dd, *J* 13.6 and 3.7 Hz, PhCONHC*H*H), 5.49 (1 H, br m, =CH), 5.65 (1 H, br s, PhCONH), 6.66 (1 H, d, *J* 2.7 Hz, ArH), 6.80 (1 H, dd, *J* 8.6 and 2.7 Hz, ArH), and 7.20—7.60 (6 H, m, ArH); *m/z* 361 (M^+) (Found: M^+, 361.2062. $C_{24}H_{27}NO_2$ requires *M*, 361.2042).

(4aS*)-4aα-(N-*Benzylaminomethyl*)-3,4,4a,9,10,10aβ-*hexahydro*-7-*methoxy*-1-*methylphenanthrene Hydrochloride* (**4**).—A solution of the benzoate (**25**) (0.58 g, 1.61 mmol) in dry THF (15 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.30 g, 8.02 mmol) in dry THF (10 ml). The mixture was heated under reflux for 16 h, cooled to 0 °C, and then treated dropwise with water-saturated ether to produce a white precipitate; this was flushed through a Celite pad with ether. The filtrate was dried (K_2CO_3) and evaporated to give a residue which was taken up into dry ether. The ether solution was treated with hydrogen chloride-saturated ether at 0 °C for 1 h to give the *amine hydrochloride* (**4**) (0.58 g, 94%) as needles after recrystallisation from MeOH–ether, m.p. 244—244.5 °C (Found: C, 74.8; H, 7.4; N, 3.55. $C_{24}H_{30}ClNO$ requires C, 75.05; H, 7.9; N, 3.65%); $\nu_{max.}(CHCl_3)$ 3 100—2 600 cm^{-1}; δ_H(90 MHz, $CDCl_3$ + CF_3CO_2H) 1.63 (3 H, br s, Me), 3.82 (3 H, s, OMe), 4.11 (2 H, br s, NCH_2Ph), 5.40 (1 H, br s, =CH), 6.55—6.87 (2 H, m, ArH), and 7.00—7.55 (6 H, m, ArH); *m/z* 347 (M^+ − HCl).

(4aS*)-4aα-(N-*Benzylaminomethyl*)-3,4,4a,9,10,10aα-*hexahydro*-7-*methoxy*-1-*methylphenanthrene Hydrochloride* (**27**).—A solution of the benzoate (0.17 g, 0.47 mmol) in dry THF (4 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.09 g, 2.35 mmol) in dry THF (3 ml). The mixture was heated under reflux for 4 h, cooled to 0 °C, and treated dropwise with water-saturated ether to produce a white precipitate; this was flushed through a Celite pad with ether. The filtrate was dried (K_2CO_3) and evaporated to give a residue which was taken up into dry ether. The ether solution was treated with hydrogen chloride-saturated ether at 0 °C for 20 min to give the *amine hydrochloride* (**27**) (0.16 g, 87%) as needles after recrystallisation from MeOH–ether, m.p. 226—227 °C (Found: C, 74.6; H, 7.5; N, 3.6. $C_{24}H_{30}ClNO$ requires C, 75.05; H, 7.9; N, 3.65%); $\nu_{max.}(CHCl_3)$ 3 100—2 000 cm^{-1}; δ_H(90 MHz) 1.60 (3 H, br s, Me), 2.40—2.78 (2 H, m, CH_2), 2.90—3.20 (3 H, m, CH_2, CH), 3.41 (3 H, s, OMe), 3.71 (2 H, br s, NCH_2Ph), 5.23 (1 H, br s, =CH), 6.41 (1 H, d, *J* 2.7 Hz, ArH), 6.64 (1 H, dd, *J* 8.8 and 2.7 Hz, ArH), 6.95 (1 H, d, *J* 8.8 Hz, ArH), 7.30—7.60 (5 H, m, ArH), and 8.25 and 9.55 (1 H each, br s, NH_2); *m/z* 347 (M^+ − HCl).

(10S*)-17-*Benzyl*-16,17-*imino*-13-*methoxy*-5β,10α-*podocarpane*-2,8,11,13-*tetraene* (**3**).—A mixture of the amine hydrochloride (**4**) (55 mg, 0.14 mmol), 35% aqueous formaldehyde (3 ml), and acetic acid (3 ml) was degassed and heated at 150 °C for 1 h in a sealed tube. After evaporation of the solvent, aqueous ammonium hydroxide (28%) was added to the residue at 0 °C and the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated to leave a residue which was chromatographed using hexane–ethyl acetate (85:15, v/v) as eluant to give the *tetracyclic amine* (**3**) (51 mg, 98%) as an oil (Found: C, 83.25; H, 8.2; N, 3.9. $C_{25}H_{29}NO$ requires C, 83.5; H, 8.15; N, 3.9%); δ_H(500 MHz) 1.01 (3 H, s, Me), 1.71—1.74 (1 H, m), 1.77—1.81 (1 H, m), 1.91—2.04 (1 H, m), 2.08 (1 H, d, *J* 11.0 Hz, 16- or 18-CH*H*), 2.26 (1 H, d, *J* 11.0 Hz, 16- or 18-C*H*H), 2.30 (1 H, br d, *J* 18.3 Hz, 1-CH*H*), 2.40 (1 H, d, *J* 11.6 Hz, 18- or 16-CH*H*), 2.53 (1 H, d, *J* 11.6 Hz, 18- or 16-C*H*H), 2.74 (1 H, br d, *J* 18.3 Hz, 1-C*H*H), 2.80—2.86 (2 H, m, CH_2), 3.47 (1 H, d, *J* 14.0 Hz, NCH*H*Ph), 3.51 (1 H, d, *J* 14.0 Hz, NC*H*HPh), 3.75 (3 H, s, OMe), 5.51 (1 H, dt, *J* 9.2 and 2.1 Hz, 3-CH=), 5.89 (1 H, dt, *J* 9.2 and 3.4 Hz, 2-CH=), 6.56 (1 H, d, *J* 2.4 Hz, ArH), 6.67 (1 H, dd, *J* 8.6 and 2.4 Hz, ArH), 7.04 (1 H, d, *J* 8.6 Hz, ArH), and 7.25 (5 H, m, ArH); δ_C(125 MHz) 17.90(t), 24.08(q), 30.45(t), 35.93(s), 37.56(s), 41.47(t), 44.41(d), 55.21(q), 57.06(t), 62.23(t), 63.16(t), 112.37(d), 113.14(d), 126.67(d), 127.47(d), 127.81(d), 128.17(d), 128.57(d), 136.79(d), 136.95(s), 137.17(s), 139.46(s), and 157.42(s); *m/z* 359 (M^+).

(10S*)-17-*Benzyl*-16,17-*imino*-13-*methoxy*-5α,10α-*podocarpane*-2,8,11,13-*tetraene* (**30**).—A mixture of the amine hydrochloride (**27**) (70 mg, 0.18 mmol), 35% aqueous formaldehyde (4 ml), and acetic acid (4 ml) was degassed and heated at 150 °C for 1 h in a sealed tube. After evaporation of the solvent, aqueous ammonium hydroxide (28%) was added to the residue at 0 °C and the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated to leave a residue which was chromatographed using hexane–ethyl acetate (85:15, v/v) to give the *tetracyclic amine* (**30**) (60 mg, 92%) as prisms after recrystallisation from ether, m.p. 101—102 °C (Found: C, 83.25; H, 8.35; N, 3.9. $C_{25}H_{29}NO$ requires C, 83.5; H, 8.15; N, 3.9%); δ_H(500 MHz) 0.99 (3 H, s, Me), 1.30 (1 H, m), 1.43—1.50 (1 H, m), 1.83—1.86 (1 H, m), 1.86 (1 H, d, *J* 10.4 Hz, 16- or 18-C*H*H), 2.03 (1 H, br d, *J* 18.9 Hz, 1-C*H*H), 2.06 (1 H, d, *J* 10.4 Hz, 16- or 18-CH*H*), 2.26 (1 H, br d, *J* 18.9 Hz, 1-C*H*H), 2.52 (1 H, d, *J* 10.4 Hz, 16- or 18-C*H*H), 2.81—2.85 (2 H, m, CH_2), 3.32 (1 H, d, *J* 10.4 Hz, 16- or 18-CH*H*), 3.56 (1 H, d, *J* 14.0 Hz, NCH*H*Ph), 3.60 (1 H, d, *J* 14.0 Hz, NC*H*HPh), 3.76 (3 H, s, OMe), 5.36 (1 H, dd, *J* 9.8 and 1.2 Hz, 3-CH=), 5.82 (1 H, dt, *J* 9.8 and 3.4 Hz, 2-CH=), 6.60 (1 H, d, *J* 2.4 Hz, ArH), 6.65 (1 H, dd, *J* 8.5 and 2.4 Hz, ArH), 7.02 (1 H, d, *J* 8.5 Hz, ArH), and 7.32 (5 H, m, ArH); δ_C(125 MHz) 19.56(t), 23.21(q), 30.38(t), 35.87(s), 37.31(s), 39.09(t), 47.19(d), 55.05(q), 62.24(t), 65.08(t), 66.16(t), 111.94(d), 113.93(d), 125.57(d), 126.65(d), 128.11(d), 128.55(d and s), 130.98(d), 136.71(s), 139.31(s), and 157.35(s); *m/z* 359 (M^+).

Crystallographic Analysis of (**30**).—*Crystal data.* $C_{25}H_{29}NO$, *M* = 359.23. Triclinic, *a* = 8.787(2), *b* = 26.643(4), *c* = 8.699(2) Å, β = 91.67(2)°, *V* = 2 004.6(8) $Å^3$, *Z* = 4, D_c = 1.19 g/cm^3, space group P_1, Mo-K_α radiation, λ = 0.71069 Å, μ(Mo-K_α) = 0.66 cm^{-1}.

A colourless crystal with dimensions of *ca.* 0.2 × 0.3 × 0.4 mm was used for the data collection on a Rigaku automated four-circle diffractometer with a rotating anode (40 KV, 200 mA). A total of 4 197 independent reflections within 2θ = 52° were collected by the θ—2θ scan mode at a w-scan speed of 4° min^{-1}. The structure was solved by the direct methods using the RANTAN 81 program[21] with some modifications. After the block-diagonal least-squares refinement for non-hydrogen atoms with anisotropic temperature factors, the positions of hydrogen atoms, geometrically calculated and some verified by the difference Fourier map, were included in the refinement with the isotropic temperature factors. The final *R* factor was 0.073 (R_w = 0.069) for 2 553 reflections with $F_o > 3\sigma F_o$.

Atomic scattering factors from International Tables for *X*-Ray Crystallography were used.[22] All the computations were carried out by a ACOS 2000 computer using the applied library program of UNICS III system.[23]

There are two independent molecules in the crystalline state; the molecular structure of one is shown in the Figure. Final atomic co-ordinates, bond lengths, and angles are collected in the Tables. The two molecules have almost identical conformations even including the methyl groups. There are no abnormal

bond lengths and angles in these structures, indicating a reasonably stable conformation. Thermal parameters and hydrogen atom co-ordinates are available on request from the Cambridge Crystallographic Data Centre.*

(10S*)-16,17-*Iminio*-13-*methoxy*-5β,10α-*podocarpane*-8,11,13-*triene Hydrochloride* (**2**).—A solution of the amine hydrochloride (27 mg, 0.07 mmol), prepared from the amine (**3**) by treatment with hydrogen chloride-saturated ether at 0 °C, in dry MeOH (1 ml) was hydrogenated over 10% palladium on carbon (10 mg) under a hydrogen pressure of 6 kg/cm^2 at room temperature for 6 days. The reaction mixture was filtered under suction through a pad of Celite, and the filtrate was evaporated to leave a solid which was recrystallised from ether to give the amine hydrochloride (**2**) (21 mg, 100%) as needles, m.p. 274—276 °C (lit.,[1c,1g] 274—276 °C); $\nu_{max.}$(Nujol) 3 100—2 400 cm^{-1}; δ_H(90MHz) 1.00 (3 H, s, Me), 3.77 (3 H, s, OMe), 6.55—6.90 (2 H, m, ArH), and 7.15 (1 H, d, *J* 8.6 Hz, ArH); *m/z* 271 (M^+ − HCl) (Found: M^+ − HCl, 271.1949. $C_{18}H_{25}NO$ requires *M*, 271.1936).

(10aS*)-16,17-*Iminio*-13-*methoxy*-5a,10α-*podocarpane*-8,11,13-*triene Hydrochloride* (**31**).—A solution of the amine hydrochloride (12.4 mg, 0.031 mmol), prepared from the amine (**30**), in dry MeOH (1.5 ml) was hydrogenated over 10% palladium on carbon (10 mg) under a hydrogen pressure of 6.4 kg/cm^2 at room temperature for 4 days. The reaction mixture was filtered under suction through a pad of Celite, and the filtrate was evaporated to leave a solid which was recrystallised from MeOH to give the amine hydrochloride (**31**) (8.8 mg, 91%) as colourless prisms, m.p. 268 °C; δ_H(90 MHz) 1.00 (3 H, s, Me), 1.39—2.26 (9 H, m, CH_2 × 4, CH), 2.60—3.32 (6 H, m, NCH_2 × 2, $ArCH_2$), 3.79 (3 H, s, OMe), and 6.50—7.20 (3 H, m, ArH); *m/z* 271 (M^+ − HCl) (Found: M^+ − HCl, 271.1915. $C_{18}H_{25}NO$ requires *M*, 271.1936).

Acknowledgements

We thank Miss K. Mushiake, Miss K. Koike, Mrs. E. Niwa, Mrs. H. Nagai, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University for microanalyses and spectral measurements.

* For details, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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Received 26*th September* 1988; *Paper* 8/03762K