Erythrophleum Alkaloids. Synthesis of (−)-4-*epi*-Cassamine

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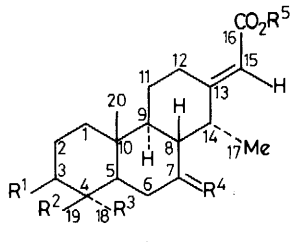
A route for the transformation of the tricyclic podocarpenone (**3**) into the 4-*epi*-cassamine (**1**; R^1 = H, R^2 = Me, R^3 = CO_2Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$), is reported. Elaboration of the cassane skeleton starts with the stereoselective introduction of a C-7 oxygen functionality by γ-oxidation of the dienyl acetate (**4**). Catalytic hydrogenation of the hydroxy enone (**5a**) led to a mixture of tricyclic ketones (**6a**) (*trans-anti-cis*) and (**7a**) (*trans-anti-trans*), which could be easily separated by column chromatography. They were transformed, through a route based on the regio- and stereospecific introduction of the 14-methyl group and stereoselective introduction of the methoxycarbonylmethylene group at C-13, into the epimers of methyl cassamate (**18**) (at C-4) and (**23**) (at C-4 and C-14). Transesterification of the former gave the corresponding 2-dimethylaminoethyl ester, an epimer at C-4 of the natural alkaloid cassamine.

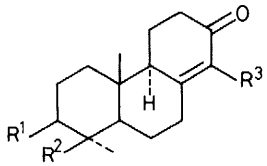
A large number of alkaloids with the cassane skeleton (**1**) have been isolated from several *Erythrophleum* species.[1a–c] Considerable attention has been paid to the pharmacological activity of these alkaloids,[2a,b,3a] and a large amount of information is available regarding structure-activity relationships.[2a,3a–f] However, their synthesis has attracted little attention to date, only the formal total synthesis of cassaine (**1**; R^1 = β-OH, R^2 = R^3 = Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$) and cassaidine[4] (**1**; R^1 = R^4 = β-OH, R^2 = R^3 = Me, R^5 = $CH_2CH_2NMe_2$) as well as the synthesis of several cassaic (**1**; R^1 = β-OH, R^2 = R^3 = Me, R^4 = O, R^5 = H) and cassamic acid (**1**; R^1 = R^5 = H, R^2 = CO_2Me, R^3 = Me, R^4 = O) analogues[5a–f] having been reported.

The common intermediate in all these approaches towards the cassane skeleton is a tricyclic ketone (**2**) in which the A-ring is appropriately functionalised. While several alternative routes to the key tricyclic ketone (**2**) are available, a good route for its transformation into *Erythrophleum* alkaloids has not yet been developed, probably due to problems associated with the oxidation of C-7 and the introduction of the axial 14-methyl group.

Here[6] we report the synthesis of (−)-4-*epi*-cassamine (**1**; R^1 = H, R^2 = Me, R^3 = CO_2Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$) from methyl 13-oxopodocarp-8(14)-en-18-oate (**3**),[7] *via* a route based on the oxidation of C-7, stereospecific introduction of the 14-methyl group and stereoselective formation of the 13-methoxycarbonylmethylene group, which eventually enables the preparation of the cassane skeleton and may be adapted to the synthesis of several naturally occurring *Erythrophleum* alkaloids when starting from the appropriate ketone (**2**).



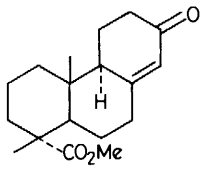
(**1**)



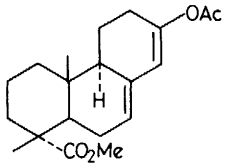
(**2**)

R^1 = H, OH, OAc, CO_2Me; R^2 = Me, CO_2Me, CHO
R^3 = Me; R^4 = β-OH, O
R^5 = $CH_2CH_2NMe_2$, CH_2CH_2NHMe

R^1 = OAc
R^2 = Me
R^3 = H, Me



(**3**)



(**4**)

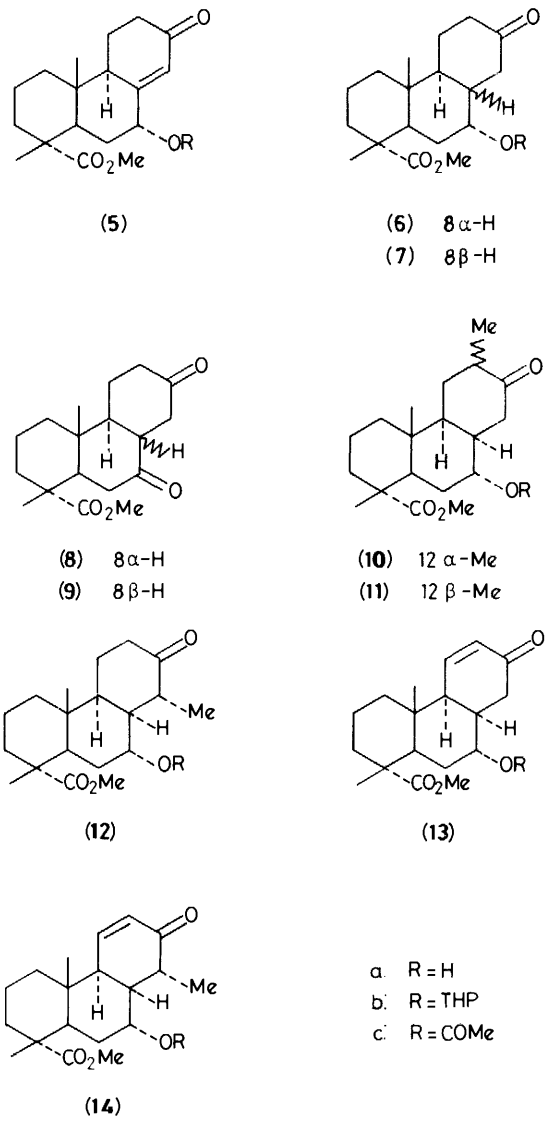
Results and Discussion

This approach begins with the oxidation of C-7 through the transformation of the enone (**3**) into the corresponding 7,13-dienyl acetate (**4**) under standard conditions.[8] Its oxidation with *m*-chloroperoxybenzoic acid[9a,b] gave the known hydroxy enone (**5a**) in 75% yield from the enone (**3**). With the hydroxy enone (**5a**) in hand we focused our efforts on the elaboration of the *cis*-arrangement of the B and C rings. This strategy was based on the expectation that, after methylation of C-14 to obtain (**12**) (see below), the equatorially orientated 14-methyl group would enable the stereoselective introduction of the 13-methoxycarbonylmethylene group to give the desired *E*-configuration of the double bond present in the *Erythrophleum* alkaloids. Subsequent oxidation of the 7-hydroxy group and epimerization of the *cis*-junction of the B and C rings to the more stable *trans*-ring junction would then lead to the axially-oriented 14-methyl group present in the desired cassane skeleton. Towards this end, a solution of the hydroxy enone (**5a**) in ethyl acetate was chemoselectively hydrogenated using 5% rhodium on alumina as catalyst to avoid hydrogenolysis of the C(7)–O bond, giving a 4.5:5.5 mixture of diastereoisomers (**6a**) and (**7a**) in 98% yield, easily separated by column chromatography on silica gel. The stereochemistry of C-8 in both isomers was indicated by the spectral data and was later confirmed by subsequent chemical transformations. The α-orientation of 8-H in (**6a**) may be inferred from the chemical shift of the 10-Me which is deshielded by 0.18 p.p.m. with respect to the 10-Me in (**7a**). In addition, the initial B/C-*cis*-diketone (**8**) obtained by oxidation of (**6a**) with pyridinium chlorochromate (PCC)[10] was epimerized when

treated with sodium methoxide in methanol to the thermodynamically more stable B/C-*trans*-diketone (**9**), which was also obtained by direct oxidation of (**7a**), thus confirming the stereochemical assignment. The lack of α-stereoselectivity in the hydrogenation reaction of (**5a**) compared with the known β-stereoselectivity observed in the hydrogenation reaction of related structures[11] may be attributed to the presence of the axially-oriented C(7)–OH; in fact, hydrogenation of acetylated hydroxy enone (**5c**), with a more bulky group at C-7, gave exclusively (**7c**). We tried to invert the axial hydroxy group in the hydroxy enone (**5a**) in an attempt to obtain a greater degree of α-stereoselectivity in the hydrogenation reaction but, unfortunately, all attempts gave rise to complex reaction mixtures or to the formation of dehydrated products.[12]

The next step in the synthetic plan involved the regiospecific introduction of the 14-methyl group. Firstly the hydroxy group in (**6a**) was protected as the tetrahydropyranyl ether by treatment with 3,4-dihydro-2*H*-pyran in the presence of pyridinium toluene-*p*-sulphonate (PTPS) to afford (**6b**) in almost quantitative yield. Naturally, (**6b**) and all products containing the tetrahydropyranyl (THP) group exist as diastereoisomeric mixtures and were best characterized as the free alcohol after removal of the THP group (see Experimental section).

Direct regioselective C-14 methylation of the THP-protected ketone (**6b**) was first attempted. Thus, treatment of (**6b**) successively with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, hexamethylphosphoric triamide (HMPA), and methyl iodide afforded a mixture of isomeric methylated products (**10b**) and (**12b**) in a ratio of 3:2, in 80% yield. The ratio of isomeric methyl ketones (**10b**):(**12b**) was essentially the same when lithium hexamethyldisilazide (LiHMDS) was used as base. However, when a very hindered base such as triphenylmethyl-lithium was used under kinetically controlled conditions, to promote the enolization of (**6b**), only regioisomer (**10b**) was obtained in high yield; The ^{1}H n.m.r. spectrum of the crude reaction mixture showed less than 1% of (**12b**). In contrast, the proportion of isomeric methylated products changed to *ca.* 1:1 under thermodynamically controlled conditions using slightly less than 1 equiv. of LDA at 0 °C. Several interesting conformational features of the unusual *cis-anti-trans*-2-perhydrophenanthrenone system, which are indicated by spectroscopic data of the above-mentioned methylated compounds, are worthy of comment. Distinction between regioisomers (**10b**) and (**12b**) was easily realized by selective homonuclear decoupling experiments on deprotected methylated ketones (**10a**) and (**12a**). Thus, irradiation of 12-Me at δ_H 0.98 in the spectrum of the methyl ketone (**10a**) led to a doublet of doublets at δ_H 2.63 with *J* 12.4 and 6.5 Hz for the 12-H signal due to coupling with 11-hydrogens. However, in the case of (**12a**) irradiation of 14-Me at δ_H 1.10 collapsed the 14-H signal at δ_H 2.26 to a doublet with *J* 13.5 Hz due to coupling with 8-H. The orientation of the introduced methyl group in both regioisomers was assumed to be α on the basis of mechanistic considerations;[13] Dreiding models of the respective enolates clearly show that attack of the electrophile (MeI) from the β-face is impeded by the angular methyl group present at C-10. This α-configuration for 12-Me in (**10a**) seems compatible only with an equatorially oriented methyl group and a chair-like conformation for ring C. Supporting this conformation is, in addition to the deshielding of 10-Me at δ_H 1.23, the distinctive double doublet of doublets centred at δ_H 1.39 corresponding to 11α-H, indicating coupling to three protons (*J* 14.7, 12.6, and 6.8). The presence of the geminal 11β-proton, the *trans*-diaxial relationship of the 11α- and 12β-hydrogens, and a small dihedral angle between 11α-H and 9α-H, respectively, give rise to such coupling. The unusually large vicinal coupling constant



(15.3 Hz) between 14β-H and 8α-H is also in agreement with the J_{vic} observed in related systems.[14,15]

Interestingly, compound (**10a**) was epimerised to (**11a**) (*ca.* a 1:1 mixture at equilibrium) when treated with methanolic sodium methoxide at room temperature. In compound (**11a**) the C-ring is forced to adapt a non-chair conformation due to the large 1,4-interaction of 10- and 12-methyl groups which would be introduced in the chair-like form.* An examination of models shows that the conformation which appears most favourable is the twist-boat form that results when C-13 is moved upward toward the plane defined by carbons 11, 12, and 14. Evidence for the twist-boat conformation of ring C can be obtained from the ^{1}H n.m.r. spectrum of (**11a**) which shows that the 10-Me group at δ_H 0.75 is situated within the shielding cone of the carbonyl group, thus inducing a diamagnetic shift[16] of 0.48 p.p.m. for the 10-Me of (**11a**) with respect to the signal for (**10**).†

Owing to the time-scale of the n.m.r. experiments, the fact that the 10-Me signal appears in the ^{1}H n.m.r. spectrum of methyl

* Nonchair forms of ring B in both (**10a**) and (**11a**) are clearly ruled out. The half-band widths of 7β-H (8—9 Hz) and the signal of axial methine proton at C-5 (dd, *J* 12.6 and 2.5 Hz) are only compatible with a chair-like conformation for ring B.

† A similar nonchair form of ring C has also been invoked to explain the inversion of the Cotton effect in a related system see ref. 17.

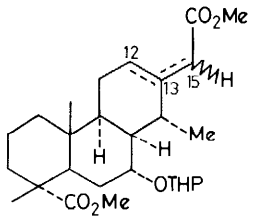
ketone (**12a**) at δ_H 0.91, roughly the average of the values corresponding to that of (**10a**) and (**11a**), may be interpreted as (**12a**) existing in solution as a mixture of the chair and twist-boat conformations in fast conformational interconversion with very low barriers.[15,18] Probably such an equilibrium also takes place in the case of compound (**6a**) in which the resonance of the Me group attached to C-10 appears at δ_H 1.0.

As preliminary experiments had made it clear that direct regioselective alkylation at C-14 was not possible we decided to explore an alternative approach involving introduction of a blocking group at C-12 that would prevent the formation of the corresponding enolate at this position. With this prospect in mind and on the basis of the previous results obtained in the alkylation of (**6b**) under kinetically controlled conditions (see above) we investigated the possibility of blocking C-12 in (**6b**) by introducing an 11(12)-olefinic bond, through a kinetically-controlled regiospecific deprotonation at C-12, by employing selenium-based methodology. Thus, treatment of THP-protected ketone (**6b**) with triphenylmethyl-lithium at −78 °C followed by selenylation with benzeneselenenyl bromide and subsequent oxidation with 30% hydrogen peroxide in aqueous methylene dichloride containing pyridine at room temperature provided, after column chromatography, the enone (**13b**) in 85% yield. With the C-12 position conveniently blocked, regio- and stereo-selective introduction of the methyl group at C-14 was readily achieved by treatment of (**13b**) with LDA at −30 °C followed by addition of an excess of methyl iodide and HMPA, which gave the methyl enone (**14b**) in 75% yield. The stereochemistry of (**14b**) follows, as before, from the considerable hindrance to approach by the alkylating agent at the β-face of the enolate by the 10-Me group. Methylation thus occurred on the α-face, and this was confirmed by the ^{1}H n.m.r. spectrum of deprotected methyl enone (**14a**) in which 14-H is observed as sextet at δ_H 2.32. This signal collapsed to a doublet with J 13.8 Hz when 14-Me was irradiated; this large vicinal coupling constant is consistent with a diaxial orientation of 8α- and 14β-hydrogens that establishes the α-orientation of 14-Me.

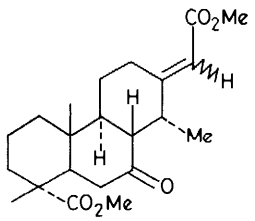
Once the double bond had served its purpose as a blocking group for the C-12 methylene function during the methylation of C-14 it was removed. Thus, catalytic hydrogenation of enone (**14b**) in the presence of 5% palladium–charcoal led in essentially quantitative yield to the ketone (**12b**), which was identical in all respects with that derived from the direct alkylation of (**6b**) (see above).

With the 14α-methyl ketone (**12**) in hand we were ready to introduce the methoxycarbonylmethylene group at C-13. It had been found previously in similar systems that this goal could be accomplished in a stereoselective manner by the Wadsworth-Emmons olefination procedure.[5b,19] In our hands treatment of the THP-protected ketone (**12b**) with trimethylphosphonoacetate and sodium hydride in THF or *N*,*N*-dimethylformamide (DMF) as solvent provided after 48 h at room temperature a 7:3 mixture of (*E*)- and (*Z*)-α,β-unsaturated methyl esters (**15**) and (**16**), respectively, in very poor yield (25—30%), together with 75—70% of unchanged (**12b**). Much higher conversion (nearly 50%) was obtained when the reaction was conducted using sodium methoxide as base in 1,2-dimethoxyethane during 3 days at 80 °C; however, substantial isomerisation of the *exo*-13(15)-olefinic bond of (**15**) and (**16**) to the *endo*-12(13)-double bond [compound (**17**)] occurred under these conditions as deduced from the ^{1}H n.m.r. spectrum of the reaction mixture which showed a characteristic AB system [δ_H 2.85 (d, J 15 Hz) and 3.14 (d, J 15 Hz)] for diastereotopic 15-hydrogens of (**17**). It is worth noting here that the β,γ-unsaturated ester (**17**) was the only identifiable product after prolonged basic treatment of α,β-unsaturated esters (**15**) and (**16**) (sodium methoxide in methanol, sealed tube at 80 °C, 24 h). As has been invoked for related systems,[3a] the low percentage of conversion exhibited by (**12b**) in the above attempted conditions might result from partial enolization of the carbonyl group followed by formation of an enol phosphate which would regenerate starting material during work-up. It was hoped that the use of much more nucleophilic silicon reagents[20] would circumvent this problem. Peterson olefination of THP-protected hydroxy methyl ketone (**12b**) using methyl 2-lithio-2-(trimethylsilyl)acetate furnished an 8:2 mixture of isomeric (**15**) and (**16**), respectively, in 95% yield. The mixture of (*E*)- and (*Z*)-stereoisomers could not be easily separated by routine chromatographic methods. However, cleavage of protecting tetrahydropyran group by treatment with PTPS in ethanol at 55 °C followed by oxidation of the free hydroxy groups using PCC in dichloromethane and isomerization of the (8α,9α)-*cis*-ring junction of B/C rings to the thermodynamically more stable (8β,9α)-*trans*-isomers with sodium methoxide in methanol gave a mixture of methyl 4-*epi*-cassamate (**18**) and its (*Z*)-isomer (**19**), which were readily separable by chromatography on silica gel. The less polar (*E*)-α,β-unsaturated ester (**18**), was obtained in 75% yield, and the more polar, (*Z*)-α,β-unsaturated ester (**19**), was obtained in 16% yield from the mixture of (**15**) and (**16**). The ^{1}H n.m.r. spectra of both isomers showed that the 12β-H and 14β-H resonances of the major isomer (**18**) occur at 1.8 p.p.m. downfield and 1.5 p.p.m. upfield, respectively, relative to the minor isomer (**19**) indicating a *cis*-vicinal relationship of 12β- and 14β-hydrogens of (**18**) and (**19**), respectively, with the electron-withdrawing ester function.[19,21] In addition, a 20% n.O.e. between 14β-H and the vinylic hydrogen of the predominant isomer conclusively proved the *E*-stereochemistry of the 13(15)-olefinic bond of (**18**). Irradiation of 14-Me at δ_H 1.06 collapsed the multiplet at δ_H 3.03 (14β-H) to a doublet with J 4 Hz, in agreement with the *trans*-ring junction of B/C rings and an axially-oriented methyl group at C-14.

With the α,β-unsaturated methyl ester (**18**) in hand we turned our attention to its transformation to the corresponding α,β-unsaturated 2-(*N*,*N*-dimethylamino)ethyl ester (**1**; R^1 = H, R^2 = Me, R^3 = CO_2Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$). This transformation has been accomplished in related systems[3a,5f,22,23] *via* reaction of the corresponding acid chloride with *N*,*N*-dimethylaminoethanol; however, only moderate yields of the (*E*)-α,β-unsaturated basic ester, usually contaminated by substantial amounts of the (*Z*)-isomer, were obtained with this procedure. A more attractive method of generating the basic ester was sought and it was eventually found that the use of the ester exchange technique in the



(**15**) (*E*)-$\Delta^{13,15}$
(**16**) (*Z*)-$\Delta^{13,15}$
(**17**) $\Delta^{12,13}$



(**18**) (*E*)-$\Delta^{13,15}$
(**19**) (*Z*)-$\Delta^{13,15}$

presence of molecular sieves[24] gave the best results. Thus, when a mixture of ester (**18**), *N*,*N*-dimethylaminoethanol, 3 Å molecular sieves, and catalytic sodium *N*,*N*-dimethylaminoethoxide was stirred at 3—5 °C, almost complete chemoselective transesterification took place during 22 h, affording, after column chromatography, 4-*epi*-cassamine (**1**; R^1 = H, R^2 = Me, R^3 = CO_2Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$) in

90% yield and 8% of unchanged methyl ester (**18**). ^{1}H N.m.r. spectra of the chromatographed alkaloid showed that partial isomerization (*ca.* 10%) of the (*E*)-13(15)-*exo*- to the 12(13)-*endo*-double bond had occurred during the transesterification reaction [signals at δ_H 5.50 (t, *J* 3.9 Hz, 12-H) and at δ_H 0.90 (d, *J* 6.9 Hz, 14-Me)]. The use of precise reaction conditions were essential to obtain a good yield of the desired product, and the use of alternative conditions produced larger amounts of the β,γ-unsaturated 2-(dimethylamino)ethyl ester. Pure (−)-4-*epi*-cassamine was obtained by selective precipitation of the corresponding hydrochloride from acetone followed by liberation of the free alkaloid. Its ^{1}H n.m.r. spectrum showed the presence of the signals due to dimethylaminoethanol moiety [a singlet at δ_H 2.29 (NMe_2) and two triplets at δ 2.59 (*J* 5.8 Hz, CH_2N) and δ_H 4.17 (*J* 5.8 Hz, OCH_2)]. That neither *E*–*Z*-isomerization of the 13(15)-double bond nor epimerization at C-14 occurred during the transesterification reaction was evident from the 20% n.O.e. observed between 14β-H at δ_H 3.01 and the olefinic hydrogen at δ_H 5.73.

Concurrently with the transformation of the hydroxy ketone (**6a**) into the cassane skeleton and in order to compare the chemical behaviour and spectroscopic data of *cis-anti-trans*- and *trans-anti-trans*-2-perhydrophenanthrenone systems, we carried out the sequence described above on the 8β-isomeric hydroxy ketone (**7a**). Firstly we examined the preparation of the methyl ketone (**22**) by means of methylation of enone (**20**). As before, blocking of the C-12 position was initially achieved by treatment of THP-protected hydroxy ketone (**7b**) with triphenylmethyl-lithium at −78 °C, followed by selenylation and subsequent oxidation–elimination. The overall yield of this conversion was only 40% in contrast with the much higher yield obtained for the conversion of ketone (**6b**) into enone (**13b**). Competitive nucleophilic addition of triphenylmethyl anion to the carbonyl group of (**7b**) favoured by much slower deprotonation at C-12 accounted for this poor result. As in the case of the B/C-*cis* fused ketone (**6**) the use of less hindered bases resulted in no regiospecific deprotonation at C-12 with mixtures of enones (**20b**) and (**5b**) being obtained. In spite of this, a higher yield (55%) of enone (**20b**) was obtained by using LDA to effect deprotonation. Much better results were obtained following the Saegusa[25] method for the conversion of a ketone into an α,β-unsaturated ketone. Thus, silyl enol ether formation of (**7b**) using trimethylsilyl triflate and triethylamine in dichloromethane at −78 °C followed by treatment with palladium(II) acetate in acetonitrile afforded almost exclusively the enone (**20b**) in 94% yield after chromatographic purification. Of critical importance was the regioselective silyl enol ether formation in the initial step. In view of this result this appears to be the procedure of choice for the regioselective functionalization of the C-12 position of this system.

Unexpectedly, the enone (**20b**), when subjected to methylation employing the same conditions described above for (**13b**), gave rise to methyl enone (**21b**). Evidence to assign the axial (α) orientation of the methyl group at C-14 was obtained from the ^{1}H n.m.r. spectrum of methyl enone (**21a**) (with the deprotected hydroxy group), which showed the 8β-H signal at δ_H 2.01 as an apparent double triplet (due to similar coupling constants between 7β- and 14β-hydrogens with 8β-H) from which a value of 3.4—3.1 Hz was deduced for the coupling constants between 14β- and 8β-hydrogens. This small coupling constant was confirmed by selective decoupling experiments; thus, irradiation of 14α-Me at δ_H 1.26 collapsed the 14β-H signal at δ_H 2.51 to a narrow doublet (*J* 3.4 Hz). Additional evidence that the 14-methyl group was axial was found in the same ^{1}H n.m.r. spectrum of (**21a**). The 7α-OH eclipses and thereby deshields[26] the 14α-Me causing the resulting doublet to be shifted to δ_H 1.26 (compare this value with the chemical shifts of this methyl resonances in the other compounds described in this paper which always appear in the range 0.9—1.1). We do not know if the methyl enone (**21b**) was formed directly in the methylation reaction of (**20b**), or if isomerization occurred at C-14 during its isolation or even in the same methylation process. In any case, the methyl enone (**21a**) was recovered unchanged on exposure to the action of sodium methoxide in methanol. The conclusion is, therefore, that the α-orientation of the methyl group in (**21a**) is thermodynamically preferred to the alternative β-orientation.*

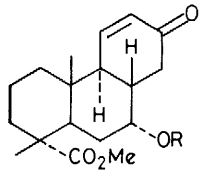
Hydrogenation of methyl enone (**21b**) in the presence of 5% palladium-charcoal furnished the saturated methyl ketone (**22b**) as the sole product in 92% yield. Evidence for the β-orientation of 14-Me was obtained by homonuclear decoupling experiments after hydrolysis of the THP moiety. Irradiation of 14-Me of the deprotected hydroxy ketone (**22a**) at δ_H 1.03 collapsed the normal 14-H multiplet at δ_H 2.66 to a doublet with a coupling constant of 10.7 Hz, which established the α-orientation of 14-H (a *trans*-relationship between 8β- and 14α-hydrogens) and hence an equatorial position for 14-Me. The formation of (**22b**) indicates that epimerization at C-14 occurs under these conditions of hydrogenation[27] and that, as expected,[19] the equatorial arrangement of 14-Me is thermodynamically preferred.

Finally, Peterson olefination of (THP-protected hydroxy) methyl ketone (**22b**) followed by hydrolysis of the tetrahydropyranyl group and oxidation of the free hydroxy group in the same manner as described for (**12b**) gave an approximately 8:2 mixture of α,β-unsaturated esters (**23**) and (**24**), respectively, easily separated by chromatography. As in the case of 14-*epi*-analogues, the less polar isomer was the (*E*)-α,β-unsaturated ester (**23**) (72% yield), which was followed by the slightly more polar (*Z*)-isomer (**24**) (18% yield). Assignment of structure (**23**) was made by ^{1}H n.m.r. spectroscopy in strict analogy to the (*E*)-α,β-unsaturated ester (**18**). The structure of the (*Z*)-isomer (**24**) was also determined on the basis of its ^{1}H n.m.r. spectrum, which showed the presence of the 14α-H signal as a multiplet at δ_H 4.01 which collapsed to a doublet with *J* 8.7 Hz when 14-Me was irradiated. Such strong deshielding of 14α-H and the coupling constant observed between 14α- and 8β-hydrogens are only compatible with the C-ring adopting a boat-form in which 14α-H is positioned in close proximity to carbonyl groups at C-7 and C-16. This conformation clearly reduces the severe non-bonded interaction between the equatorial Me group and the carbonyl group of the ester that would exist in the normal chair form of ring C. In this respect, it is also interesting to note that the 14β-Me isomer has never been isolated when the Wadsorth–Emmons olefination procedure has been used for introducing the methoxycarbonylmethylene group in related systems.[19,5b,d]

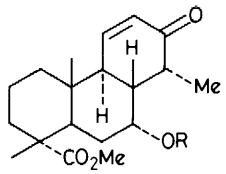
Experimental

All m.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter using a 10-cm path length cell. I.r. spectra were measured as KBr pellets or liquid films on a Perkin-Elmer 281 spectrophotometer. ^{1}H N.m.r. spectra were measured at 200.13 MHz (Bruker AC-200 model) in $CDCl_3$ solution. The proton chemical shifts are reported in p.p.m. from TMS with the small amount of residual $CHCl_3$ as an internal reference (7.24 p.p.m.). Complete assignments of most of the products were obtained by COSY n.m.r. correlated spectroscopy. Mass spectra were run on a Varian MAT-311A

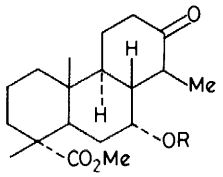
* A Dreiding model of (**21a**) shows that the conformation of ring C which appears most favourable is the twist-boat form. However, no definitive conformational conclusion may be drawn from the available spectroscopic data of (**21a**).



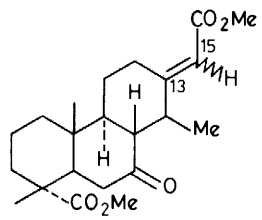
(20)



(21)



(22)



(23) (*E*)-$\Delta^{13,15}$
(24) (*Z*)-$\Delta^{13,15}$

a; R = H
b; R = THP

spectrometer using electron impact (70 eV) ionization. Elemental analyses were performed by Servicio de semi-microanálisis del CSIC (Barcelona). Analytical t.l.c. was carried out on Merck pre-coated 0.2 mm thick plates of silica gel 60 F_{254}. Chromatography refers to flash chromatography and was performed on Merck silica gel 60 (230—400 mesh). All reactions involving organometallic reagents or other moisture-sensitive reactants were executed under an atmosphere of dry argon using oven-dried glassware. Commercially available chemicals were used as obtained without further purification, except for solvents, which were purified and dried before use by standard methods. The tricyclic enone (**3**) was obtained from abietic acid or commercial colophony following the procedure previously described by us.[7]

General Procedure for the Hydrolysis of Tetrahydropyranyl Ethers.—A solution of the tetrahydropyranyl ether (10 mmol) and pyridinium toluene-*p*-sulphonate (3 mmol) in 95% ethanol (40 ml) was stirred at 55 °C for 24 h. The mixture was poured into water and extracted with ether. The combined organic layers were washed with brine and dried (Na_2SO_4). The residue left after evaporation of the solvent was purified by chromatography on silica gel to give the corresponding free alcohol. Yields were in all cases better than 95%.

Methyl (−)-13-*Acetylpodocarpa*-7,13-*dien*-18-*oate* (**4**).—To a solution of the enone (**3**) (8.34 g, 28.7 mmol) in acetic anhydride (153 ml) and acetyl chloride (61 ml) was added pyridine (6.9 ml). The mixture was heated at reflux for 3 h. The acetic anhydride and acetyl chloride were removed by distillation *in vacuo* and the dark brown residue was filtered through a pad of silica gel with hexane–ether (8:2) as eluant to give the *dienyl acetate* (**4**) (9.5 g, 99%) as a colourless oil which crystallised on standing, m.p. 94—96 °C (from methanol) (Found: M^+, 332.1995. $C_{20}H_{28}O_4$ requires *M*, 332.1988); $[\alpha]_D$ −71° (*c* 1.3 in $CHCl_3$); $\nu_{max.}$(KBr) 3 010, 1 740, 1 655, and 1 625 cm^{-1}; δ_H 5.65 (1 H, d, *J* 2.2 Hz, 14-H), 5.37 (1 H, d, *J* 5.2 Hz, 7β-H), 3.58 (3 H, s, CO_2Me), 2.07 (3 H, s, OCOMe), 1.20 (3 H, s, 4-Me), and 0.78 (3 H, s, 10-Me); *m/z* 332 (M^+, 9%), 290 (100), 230 (31), and 215 (17).

Methyl (−)-7α-*Hydroxy*-13-*oxopodocarp*-8(14)-*en*-18-*oate* (**5a**).—A solution of 85% *m*-chloroperoxybenzoic acid (9.0 g, 44.5 mmol) in 96% ethanol (160 ml) was added dropwise during 30 min to a stirred solution of the above prepared dienol acetate (**4**) (9.5 g, 28.7 mmol) in 96% ethanol (50 ml) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, treated with a solution of sodium thiosulphate (7.9 g) and sodium hydrogen carbonate (4.7 g) in the minimum amount of water and the stirring was continued for a further hour. The solution was poured into cold water and extracted with dichloromethane. The extracts were washed with aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and then evaporated to dryness to give a yellow solid. Recrystallisation from hexane–ether gave the *hydroxy enone* (**5a**) (5.36 g, 61%). Evaporation of the filtrate gave a yellow oil which after column chromatography on silica gel using hexane–ethyl acetate (1:1) as eluant, gave an additional amount of (**5a**) (1.24 g, 15%), m.p. 154—155 °C (from hexane–ether) (lit.,[28] 154 °C); $[\alpha]_D$ −95° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(KBr) 3 450, 3 010, 1 700, and 1 620 cm^{-1}; δ_H 5.86 (1 H, d, *J* 1.8 Hz, 14-H), 4.25 (1 H, br s, $W_{\frac{1}{2}}$ 6.8 Hz, 7β-H), 3.60 (3 H, s, CO_2Me), 2.54 (1 H, m, 9α-H), 2.45 (1 H, dd, *J* 13, 5, and 2.4 Hz, 5α-H), 2.4—2.1 (2 H, m, 12-H), 1.14 (3 H, s, 4-Me), and 0.76 (3 H, s, 10-Me).

Methyl (−)-7α-*Hydroxy*-13-*oxo*-(8αH)-*podocarpan*-18-*oate* (**6a**) *and Methyl* (−)-7α-*Hydroxy*-13-*oxopodocarpan*-18-*oate* (**7a**).—Rhodium on alumina (5%, 2.0 g) was added to a solution of the hydroxy enone (**5a**) (6.0 g, 19.6 mmol) in dry ethyl acetate (200 ml), and the heterogeneous mixture was stirred under an atmosphere of hydrogen at room temperature until approximately 440 ml (19.6 mmol) of hydrogen had been consumed (1—2 h). The mixture was filtered, and the filtrate was concentrated to a residue which showed two differentiated spots by t.l.c. [hexane–ethyl acetate (1:1)]. On occasions, a variable amount of two more polar products, formed by reduction of the carbonyl groups of initially obtained saturated ketones, was observed. However, the formation of these polar compounds could be prevented by careful monitoring (t.l.c.) of the reaction. Chromatography of the residue (gradient elution: 20% to 60% ethyl acetate–hexane) gave, in order of elution, *saturated hydroxy ketone* (**7a**) (3.2 g, 53%) as a solid, m.p. 130—132 °C (from hexane–ether) (Found: C, 69.9; H, 9.3. $C_{18}H_{28}O_4$ requires C, 70.1; H, 9.15%; $M^+ - H_2O$, 290.1874. $C_{18}H_{26}O_3$ requires 290.1882); $[\alpha]_D$ −19° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(KBr) 3 480, 1 720, and 1 700 cm^{-1}; δ_H 3.67 (1 H, q, *J* 2.7 Hz, 7β-H), 3.61 (3 H, s, CO_2Me), 2.63 (1 H, dd, *J* 13.7 and 12.6 Hz, 14α-H), 2.30 (1 H, dd, *J* 13.5 and 2.1 Hz, 5α-H), 1.14 (3 H, s, 4-Me), and 0.82 (3 H, s, 10-Me); *m/z* 308 (M^+, 1%), 290 (27), 275 (25), 232 (22), 231 (46), 230 (27), 123 (32), 121 (49), 109 (47), and 55 (100) and 8H-*epimeric hydroxy ketone* (**6a**) (2.7 g, 46%) also a solid, m.p. 95—97 °C (from hexane–ether) (Found: C, 70.05; H, 9.25%; M^+, 308.1988. $C_{18}H_{28}O_4$ requires C, 70.1; H, 9.15%; *M*, 308.1988); $[\alpha]_D$ −95° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(KBr) 3 560 and 1 710 cm^{-1}; δ_H 3.79 (1 H, m, $W_{\frac{1}{2}}$ 8.2 Hz, 7β-H), 3.65 (3 H, s, CO_2Me), 2.4—2.2 (6 H, m, 5α-, 8α-, 9α-, 12-H, 14-hydrogens), 1.19 (3 H, s, 4-Me), and 1.00 (3 H, s, 10-Me); *m/z* 308 (M^+, 2%), 290 (19), 275 (32), 232 (46), 231 (61), 230 (49), 123 (96), and 109 (100).

Methyl 13-*Oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)-(8αH)-*podocarpan*-18-*oate* (**6b**).—To a solution of the hydroxy ketone (**6a**) (3.0 g, 9.7 mmol) in dry dichloromethane (40 ml) was added 3,4-dihydro-2*H*-pyran (1.64 g, 19.5 mmol) and pyridinium toluene-*p*-sulphonate (0.48 g, 1.9 mmol). The mixture was stirred at room temperature for 2 h, then diluted with dichloromethane and washed with aqueous sodium hydrogen-carbonate and brine. After drying (Na_2SO_4), the solvent was evaporated and the crude product purified by chromatography on silica gel with hexane–ether (7:3) as eluant to give the tetrahydropyranyl ether (**6b**). The ^1H n.m.r. spectrum of this compound showed doubling of a number of peaks, and,

specifically, resonances at 4.53 and 4.62 (each 0.5 H, t, *J* 3.5 Hz, OCHO) indicated that (**6b**) was an approximately 1:1 mixture of diastereomeric tetrahydropyranyl ethers.

Methyl (−)-7α-*Hydroxy*-12α-*methyl*-13-*oxo*-(8αH)-*podocarpan*-18-*oate* (**10a**) *and* 12β-*Epimer* (**11a**).—(*a*) To a stirred solution of the THF-protected hydroxy ketone (**6b**) (200 mg, 0.51 mmol) in dry THF (4 ml) was added dropwise a 1M solution of triphenylmethyl-lithium in THF (prepared from triphenylmethane and butyl-lithium at room temperature)[29] at −78 °C until the colour of the reaction mixture changed to the characteristic wine red colour of triphenylmethyl-lithium and the stirring was continued at −78 °C for 2 min. An excess of methyl iodide (0.31 ml, 5.1 mmol) was added and the mixture was then allowed to warm to room temperature. The mixture was quenched with saturated ammonium chloride solution and the product was isolated by extraction with ether. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane–ether (7:3) as eluant to give the (*THP-protected hydroxy*)*methyl ketone* (**10b**) (172 mg, 83%). Hydrolysis of the tetrahydropyranyl ether moiety of this compound (130 mg, 0.32 mmol) was realised by treatment with pyridinium toluene-*p*-sulphonate (25 mg, 0.1 mmol) in 95% ethanol (1.5 ml) following the general procedure previously described. The *methyl ketone* (**10a**) (88 mg, 85%) was obtained as a solid, m.p. 146—147 °C (from hexane–ethyl acetate) (Found: C, 70.5; H, 9.25%; M^+, 322.2142. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%; *M*, 322.2144); $[\alpha]_D$ −31° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(KBr) 3 570 and 1 720 cm^{-1}; δ_H 3.76 (1 H, q, *J* 2.6 Hz, 7β-H), 3.66 (3 H, s, CO_2Me), 2.63 (1 H, m, 12β-H), 2.50 (1 H, dd, *J* 15.5 and 15.3 Hz, 14β-H), 2.38 (1 H, dd, *J* 12.8 and 2.2 Hz, 5α-H), 2.35—2.1 (3 H, m, 8α-, 11β- and 14α-hydrogens), 2.0—1.75 (3 H, m, 1β-, 9α-, and 6β-hydrogens), 1.39 (1 H, ddd, *J* 14.7, 12.6, and 6.8 Hz, 11α-H), 1.23 (3 H, s, 10-Me), 1.22 (3 H, s, 4-Me), and 0.98 (3 H, d, *J* 6.5 Hz, 12α-Me); *m/z* 322 (M^+, 6%), 304 (31), 289 (12), 272 (5), 262 (11), 245 (33), 244 (25), 232 (15), and 41 (100).

(*b*) The above prepared hydroxy methyl ketone (**10a**) (79 mg, 0.24 mmol) was added with stirring to 0.25M sodium methoxide in methanol (5 ml) at room temperature. After being stirred for 1 h the mixture was poured into water and extracted with ether. The ethereal extracts were washed with water and brine. Drying (Na_2SO_4) and evaporation of the ether afforded a solid residue which was purified by chromatography on silica gel using hexane–ethyl acetate (7:3) as eluant. The first eluted compound was the unchanged 12α-methyl ketone (**10a**) (36 mg, 46%) followed by the isomerised 12β-*methyl ketone* (**11a**) (38 mg, 48%), *m.p. 163—164* °C (from hexane–ethyl acetate) (Found: C, 70.7; H, 9.2%; M^+, 332.2137. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%; *M*, 322.2144); $[\alpha]_D$ −96° (*c* 0.6 in $CHCl_3$); $\nu_{max.}$(KBr) 3 420, 1 730, and 1 710 cm^{-1}; δ_H 3.83 (1 H, q, *J* 2.9 Hz, 7β-H), 3.65 (3 H, s, CO_2Me), 2.67—2.42 (2 H, m, 12α-H partially overlapped with 8α-H), 2.29 (1 H, dd, *J* 12.6 and 2.5 Hz, 5α-H), 2.35—1.95 (4 H, m, 9α-, 11β-, and 14-hydrogens), 1.76 (1 H, ddd, *J* 14.5, 12.8, and 3.0 Hz, 6β-H), 1.25—1.15 (2 H, m, 11α-H and 6α-H), 1.15 (3 H, s, 4-Me), 1.0 (3 H, d, *J* 6.4 Hz, 12β-Me), and 0.75 (3 H, s, 10-Me); Irradiation of 12β-Me collapsed the 12α-H signal to a double doublet with *J* 10.5 and 7.0 Hz; *m/z* 322 (M^+, 3%), 304 (29), 289 (23), 245 (49), 244 (35), 232 (41), and 198 (100).

Methyl 13-*Oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)-(8αH)-*podocarp*-11-*en*-18-*oate* (**13b**).—A solution of the lithium 12-enolate of the THP-protected hydroxy ketone (**6b**) (3.0 g, 7.65 mmol) in THF (20 ml) was prepared as described above using an 1M triphenylmethyl-lithium solution in THF at −78 °C to effect regioselective enolisation of the C-12 position (see text). A solution of phenylselenyl bromide (2.17 g, 9.20 mmol) in dry THF (4 ml) was added, and the reaction mixture was stirred for 30 min, poured into cold dilute hydrochloric acid, and extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate and brine. Drying (Na_2SO_4) and removal of the solvent gave a yellowish residue which was dissolved in dichloromethane (25 ml). This solution was chilled to 0 °C and mixed with pyridine (1.25 ml), water (2 ml), and 30% hydrogen peroxide (2.1 ml). After 30 min the vigorously stirred mixture was allowed to warm to room temperature and was stirred for a further hour. The layers were separated, the aqueous layer was extracted with dichloromethane (×3), and the combined organic layers were washed with aqueous hydrogen carbonate, dilute hydrochloric acid, and brine. Drying (Na_2SO_4) and removal of the solvent gave the crude product which was purified by chromatography with hexane–ethyl acetate (8:2) as eluant to afford the *enone* (**13b**) (2.55 g, 85%). Data for the free *alcohol* (**13a**), m.p. 165—167 °C (from hexane–ether) (Found: C, 70.8; H, 8.4%; M^+, 306.1838. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.55%; *M*, 306.1831); $[\alpha]_D$ +69° (*c* 0.54 in $CHCl_3$); $\nu_{max.}$(KBr) 3 410, 3 030, 3 005, 1 720, 1 660, and 1 605 cm^{-1}; δ_H 6.93 (1 H, dd, *J* 10.2 and 5.9 Hz, 11-H), 6.16 (1 H, d, *J* 10.2 Hz, 12-H), 3.78 (1 H, br s, $W_{\frac{1}{2}}$ 8.0 Hz, 7β-H), 3.65 (3 H, s, CO_2Me), 2.57 (1 H, t, *J* 4.2 Hz, 9α-H), 2.51 (1 H, dd, *J* 12.8 and 2.0 Hz, 5α-H), 1.16 (3 H, s, 4-Me), and 0.91 (3 H, s, 10-Me); *m/z* 306 (M^+, 1%), 288 (5), 273 (2), 229 (7), 211 (28), and 151 (100).

Methyl 14α-*Methyl*-13-*oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)-(8αH)-*podocarp*-11-*en*-18-*oate* (**14b**).—A stirred solution of the THP-protected hydroxy enone (**13b**) (2.2 g, 5.64 mmol) in anhydrous THF (45 ml) containing a few crystals of anhydrous phenanthroline was treated dropwise with a stock solution of lithium di-isopropylamide[30] in THF at −30 to −40 °C until persistence of the characteristic rust colour of LDA-phenanthroline (approximately 7.1 ml, 0.8M, 5.7 mmol). The stirring was continued at the same temperature for an additional 2 min. Hexamethylphosphoric triamide (3 ml, 16.9 mmol), followed by methyl iodide (3.5 ml, 56.4 mmol), was added and the resulting solution was allowed to warm to room temperature. After 30 min, water was added and the mixture was extracted with ether. The combined organic extracts were washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and brine. Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by chromatography on silica gel with hexane–ethyl acetate (8:2) as eluant to give the *methyl enone* (**14b**) (1.71 g, 75%) as a solid. Data for the free *alcohol* (**14a**), m.p. 115–116 °C (from hexane–ether) (Found: C, 71.0; H, 9.1%; M^+, 320.1978. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%; *M*, 320.1988); $[\alpha]_D$ +73° (*c* 0.63 in $CHCl_3$); $\nu_{max.}$(KBr) 3 470, 3 030, 1 725, and 1 670 cm^{-1}; δ_H 6.90 (1 H, dd, *J* 10.2 and 6.1 Hz, 11-H), 6.14 (1 H, d, *J* 10.2 Hz, 12-H), 4.07 (1 H, br s, $W_{\frac{1}{2}}$ 8 Hz, 7β-H), 3.65 (3 H, s, CO_2Me), 2.61 (1 H, t, *J* 5.7 Hz, 9α-H), 2.52 (1 H, dd, *J* 12.8 and 1.9 Hz, 5α-H), 2.32 (1 H, sextet, *J* 6.7 Hz, 14β-H), 1.94 (1 H, dd, *J* 13.8 and 5.7 Hz, 8α-H), 1.14 (3 H, s, 4-Me), 1.14 (3 H, d, *J* 6.7 Hz, 14α-Me), and 0.86 (3 H, s, 10-Me); *m/z* 320 (M^+, 0.5%), 302 (0.5), 279 (2), 243 (2), 211 (16), 167 (14), and 151 (100).

Methyl 14α-*Methyl*-13-*oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)-(8αH)-*podocarpan*-18-*oate* (**12b**).—A mixture of the THP-protected hydroxy methyl enone (**14b**) (1.6 g, 3.96 mmol) and 5% palladium on carbon (0.65 g) in dry ethyl acetate (50 ml) was stirred at room temperature under an atmosphere of hydrogen for 40 min. After filtration, evaporation of the solvent from the filtrate at reduced pressure afforded a semisolid which was chromatographed on silica gel using hexane–ethyl acetate (8:2) as eluant to give the *saturated methyl ketone* (**12b**) (1.56 g, 97%). Data for the free *alcohol* (**12a**), m.p. 154—155 °C (from

hexane–ethyl acetate) (Found: C, 70.5; H, 9.1%; M^+, 322.2134. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%; M, 322.2144); $[\alpha]_D$ −91° (*c* 0.16 in $CHCl_3$); $\nu_{max.}$(KBr) 3 420, 1 710, and 1 675 cm^{-1}; δ_H 4.01 (1 H, q, *J* 2.7 Hz, 7β-H), 3.66 (3 H, s, CO_2Me), 2.46 (1 H, ddd, *J* 14.4, 9.4, and 8.2 Hz, 12α-H), 2.35 (1 H, dd, *J* 12.8 and 1.8 Hz, 5α-H), 2.35—2.15 (2 H, m, 12β-H and 14β-H), 1.96 (1 H, br d, *J* 13.5 Hz, this signal collapses to a dd with *J* 13.2 and 2 Hz upon irradiation at 4.01, 8α-H), 1.74 (1 H, ddd, *J* 14.4, 12.8, and 2.7 Hz, 6β-H), 1.16 (3 H, s, 4-Me), 1.10 (3 H, d, *J* 6.7 Hz, 14α-Me), and 0.91 (3 H, s, 10-Me); *m/z* 322 (M^+, 14%), 304 (27), 289 (20), 245 (45), 244 (43), 232 (33), 229 (22), and 109 (100).

(E)-*Dimethyl* (−)-7-*Oxocass*-13(15)-*ene*-16,18-*dioate* (**18**) *and* (**Z**)-*Isomer* (**19**).—To a mixture of di-isopropylamine (1.46 g, 14.5 mmol) and THF (9 ml) was added with stirring butyllithium (9.0 ml of a 1.6M solution in hexane, 14.4 mmol). The mixture was cooled to −78 °C and a solution of methyl trimethylsilylacetate (2.56 ml, 15.7 mmol) in THF (3 ml) was added dropwise. The resulting solution was stirred at the same temperature for 15 min. A solution of the THP-protected hydroxy methyl ketone (**12b**) (1.45 g, 3.57 mmol) in THF (18 ml) was then added dropwise at −78 °C. After stirring for 2 h the reaction mixture was allowed to warm to room temperature and the stirring was continued for a further hour. Sodium hydrogen sulphate monohydrate (2.8 g) was then added, the mixture was stirred for 15 min and poured into water. The mixture was extracted with ether and the combined organic phases were washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give a mixture of stereoisomeric α,β-*unsaturated methyl esters* (**15**) and (**16**) as a semisolid (1.58 g) which showed only one spot by t.l.c. Hydrolysis of the THP–ether moiety of the above α,β-unsaturated methyl esters following the general procedure previously described gave a mixture of alcohols (1.26 g) which were dissolved in dry dichloromethane (30 ml) and treated with pyridinium chlorochromate (4.0 g, 18.6 mmol). After being stirred at room temperature for an hour the mixture was filtered through a pad of silica gel. The solvent was removed under reduced pressure and the residue was treated with methanolic sodium methoxide (28 ml of a 0.25M solution of sodium methoxide in anhydrous methanol). After 1 h the reaction mixture was poured into water and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel with hexane–ethyl acetate (8:2) as eluant to afford the (E)-α,β-*unsaturated ester* (**18**) (900 mg, 74%) as a colourless solid, m.p. 127—128 °C (from hexane–ether) (Found: C, 70.3; H, 8.4%; M^+, 376.2239. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.6%; M, 376.2249); $[\alpha]_D$ −118° (*c* 4.5 in $CHCl_3$); $\nu_{max.}$(KBr) 1 720, 1 700, and 1 645 cm^{-1}; δ_H 5.67 (1 H, d, *J* 1.0 Hz, 15-H), 3.75 (1 H, dt, *J* 15.2 and 4.3 Hz, 12β-H), 3.65 and 3.62 (each 3 H, each s, 2 × CO_2Me), 3.01 (1 H, m, 14β-H), 1.18 (3 H, s, 4-Me), 1.03 (3 H, d, *J* 6.9 Hz, 14α-Me), and 0.96 (3 H, s, 10-Me); *m/z* 376 (M^+, 21%), 361 (2), 345 (28), 344 (100), 316 (6), 301 (3), 284 (9), and 267 (2). Further elution gave the (**Z**)-*isomer* (**19**) (190 mg, 16%) as a semisolid (Found: M^+, 376.2235. $C_{22}H_{32}O_5$ requires M, 376.2249); $[\alpha]_D$ −74° (*c* 1.9 in $CHCl_3$); $\nu_{max.}$(film) 1 720 and 1 650 cm^{-1}; δ_H 5.57 (1 H, d, 1.0 Hz, 15-H), 4.56 (1 H, m, that collapses to a d with *J* 3.6 Hz on irradiation at 1.02, 14β-H), 3.66 and 3.64 (each 3 H, each s, 2 × CO_2Me), 1.18 (3 H, s, 4-Me), 1.02 (3 H, d, *J* 6.9 Hz, 14α-Me), and 0.95 (3 H, s, 10-Me); *m/z* 376 (M^+, 2%), 361 (0.4), 345 (27), 344 (100), 326 (10), 317 (3), 285 (4), and 267 (4).

(−)-4-epi-*cassamine* (**1**; R^1 = H, R^2 = Me, R^3 = CO_2Me, R^4 = O, R^5 = $CH_2CH_2NMe_2$).—Molecular sieves (3 Å) were added to a solution of the α,β-unsaturated methyl ester (**18**) (274 mg, 0.66 mmol) in dry benzene (5.5 ml), followed by a solution of sodium 2-(*N*,*N*-dimethylamino)ethoxide in 2-(*N*,*N*-dimethylamino)ethanol [prepared from 55% sodium hydride in oil (23 mg, 0.53 mmol) and 2-(*N*,*N*-dimethylamino)ethanol (1.3 ml, 13 mmol)]. The mixture was stirred at 3 to 5 °C during 22 h and then diluted with ethyl acetate and filtered to remove the molecular sieves. The ethyl acetate solution was washed with aqueous sodium carbonate and then was extracted with 2M hydrochloric acid (×3). The organic layer was washed with aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and evaporated to dryness to give unchanged α,β-unsaturated methyl ester (**18**) (22 mg, 8%). The acid extracts were made alkaline with concentrated aqueous sodium carbonate, extracted with ethyl acetate and the extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a viscous oil which after chromatography on silica gel with ethyl acetate–methanol (7:3) as eluant yielded (−)-4-*epi*-cassamine (284 mg, 90%) of 90% purity (see text).

Pure (−)-4-*epi*-cassamine was obtained through its hydrochloride salt in the following way: the above oil (150 mg) dissolved in anhydrous ether was treated with dry hydrogen chloride at 0 °C. The precipitated hydrochloride salt was recrystallised from aqueous acetone. Thus were obtained 126 mg of the *hydrochloride salt* of 4-epi-*cassamine* melting at 200—204 °C (decomp.) (Found: C, 61.25; H, 8.4; N, 2.8. $C_{25}H_{39}NO_5 \cdot HCl \cdot H_2O$ requires C, 61.5; H, 8.7; N, 2.9%). The recrystallised salt was shaken with water (20 ml), 2M sodium hydroxide (5 ml), and ether (70 ml). The ether layer was separated and washed with brine, dried (Na_2SO_4), and concentrated to give pure (−)-4-epi-*cassamine* (115 mg) as an oil (Found: M^+, 433.2833. $C_{25}H_{39}NO_5$ requires 433.2828); $[\alpha]_D$ −99° (*c* 0.46 in $CHCl_3$); $\nu_{max.}$(film) 1 725, 1 705, and 1 625 cm^{-1}; δ_H 5.73 (1 H, s, 15-H), 4.17 (2 H, t, *J* 5.8 Hz, CO_2CH_2), 3.78 (1 H, dt, *J* 14.7 and 4.3 Hz, 12β-H), 3.65 (3 H, s, CO_2Me), 3.01 (1 H, m that collapses to a d with *J* 3.6 Hz upon irradiation at 1.04, 14β-H), 2.59 (2 H, t, *J* 5.8 Hz, CH_2N), 2.29 (6 H, s, 2 × NMe), 1.20 (3 H, s, 4-Me), 1.04 (3 H, d, *J* 6.9 Hz, 14α-Me), and 0.97 (3 H, s, 10-Me); *m/z* 433 (M^+, 1%), 374 (2), 345 (1), 285 (1), 286 (0.5), 71 (74), and 58 (100).

Methyl 13-*Oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)*podocarp*-11-*en*-18-*oate* (**20b**).—The hydroxy ketone (**7a**) (1.0 g, 3.2 mmol) in dry dichloromethane (14 ml) was treated with 3,4-dihydro-2*H*-pyran (0.54 g, 6.4 mmol) and pyridinium toluene-*p*-sulphonate (32 mg, 1.3 mmol) in the same way as described for the hydroxy ketone (**6a**). The *tetrahydropyranyl ether* (**7b**) was obtained as a solid (1.22 g, 96%).

To a stirred solution of the above tetrahydropyranyl ether (**7b**) (250 mg, 0.64 mmol) in dry dichloromethane (5 ml) at −78 °C was added, dropwise, triethylamine (0.265 ml, 193 mg, 1.9 mmol) followed by trimethylsilyl triflate (0.245 ml, 282 mg, 1.28 mmol). After being stirred at −78 °C for 1.5 h the reaction mixture was poured into cold hexane. The organic layer was washed with water and brine and dried (Na_2SO_4). The residue left after evaporation of the solvent was dissolved in acetonitrile (5 ml) and added to a solution of palladium(II) acetate (145 mg, 0.64 mmol) in acetonitrile (2.5 ml) at room temperature. The resultant mixture was stirred for 4 h, filtered, and the filtrate concentrated to a residue which was chromatographed on silica gel using hexane–ethyl acetate (8:2) as eluant to give the THP-protected hydroxy enone (**20b**) (234 mg, 94%). Data for the free *alcohol* (**20a**), m.p. 167—170 °C (from hexane–ether) (Found: C, 70.9; H, 8.5. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.55%; $M^+ - H_2O$, 288.1700. $C_{18}H_{24}O_3$ requires 288.1725); $[\alpha]_D$ −1° (*c* 0.9 in $CHCl_3$); $\nu_{max.}$(KBr) 3 500, 3 010, 1 700, and 1 665 cm^{-1}; δ_H 6.90 (1 H, dd, *J* 10.4 and 0.9 Hz, 11-H), 5.95 (1 H, dd, *J* 10.4 and 2.8 Hz, 12-H), 3.78 (1 H, br s, $W_{\frac{1}{2}}$ 8.1 Hz, 7β-H), 3.61 (3 H, s,

CO_2Me), 2.57 (1 H, dd, *J* 16.3 and 14.0 Hz, 14α-H), 2.41 (1 H, br d, *J* 11.3 Hz, 9α-H), 2.35 (1 H, dd, *J* 12.9 and 2.4 Hz, 5α-H), 2.21 (1 H, dd, *J* 16.3 and 3.2 Hz, 14β-H), 2.02 (1 H, dtd, *J* 14.0, 11.3, and 3.0 Hz, 8β-H), 1.11 (3 H, s, 4-Me), and 0.81 (3 H, s, 10-Me); *m/z* 306 (M^+, 1%), 288 (43), 275 (14), 273 (20), 229 (22), 228 (17), 159 (28), and 151 (100).

Methyl 14α-*Methyl*-13-*oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)*podocarp*-11-*en*-18-*oate* (**21b**).—Methylation of enone (**20b**) (280 mg, 0.91 mmol) in the same way described for (**13b**) afforded, after purification by chromatography on silica gel using hexane–ethyl acetate (7:3) as eluant, the methyl enone (**21b**) (234 mg, 80%). Data for the free *alcohol* (**21a**), m.p. 187—189 °C (from hexane–ethyl acetate) (Found: C, 71.1; H, 9.0%; M^+, 320.1962. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%; *M*, 320.1988); $[\alpha]_D$ −7.6° (*c* 0.1 in $CHCl_3$); $\nu_{max.}$ 3 440, 3 020, 1 715, and 1 660 cm^{-1}; δ_H 6.84 (1 H, dd, 10.4 and 1.7 Hz, 11-H), 5.92 (1 H, dd, *J* 10.4 and 2.8 Hz, 12-H), 4.02 (1 H, br s, $W_{\frac{1}{2}}$ 8.3 Hz, 7β-H), 3.65 (3 H, s, CO_2Me), 2.56 (1 H, dt, *J* 11.2 and 2.2 Hz, 9α-H), 2.51 (1 H, m, 14β-H), 2.46 (1 H, dd, *J* 13.1 and 2.4 Hz, 5α-H), 2.01 (1 H, dt, *J* 11.2 and 3.1 Hz, 8β-H), 1.26 (3 H, d, *J* 7.2 Hz, 14α-Me), 1.14 (3 H, s, 4-Me), and 0.83 (3 H, s, 10-Me); *m/z* 320 (M^+, 0.4%), 302 (15), 287 (5), 243 (5), 242 (5), 211 (7), 173 (6), and 151 (100).

Methyl 14β-*Methyl*-13-*oxo*-7α-(*tetrahydro*-2H-*pyran*-2-*yloxy*)*podocarpan*-18-*oate* (**22b**).—The methyl enone (**21b**) (214 mg, 0.53 mmol) was hydrogenated in the same manner described for (**14b**). The residue obtained after removal of catalyst was purified by chromatography with hexane–ethyl acetate (8:2) as eluant to afford the *saturated methyl ketone* (**22b**) (202 mg, 94%). Data for the free alcohol (**22a**), m.p. 109—110 °C (from hexane–ether) (Found: C, 70.5; H, 9.7. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%; $M^+ - H_2O$, 304.2031. $C_{19}H_{28}O_3$ requires 304.2038); $[\alpha]_D$ −37° (*c* 0.4 in $CHCl_3$); $\nu_{max.}$(KBr) 3 530, 1 720, and 1 695 cm^{-1}; δ_H 4.02 (1 H, q, *J* 2.9 Hz, 7β-H), 3.67 (3 H, s, CO_2Me), 2.66 (1 H, sextet, *J* 6.4 Hz, 14α-H), 1.18 (3 H, s, 4-Me), 1.03 (3 H, d, *J* 6.4 Hz, 14β-Me), and 0.84 (3 H, s, 10-Me); *m/z* 304 ($M^+ - H_2O$, 4%), 289 (5), 245 (8), 244 (6), 232 (4), 229 (4), 109 (16), and 43 (100).

(E)-*Dimethyl*(−)-7-*Oxo*-(14αH)-*cass*-13(15)-*ene*-16,18-*dioate* (**23**) *and* (Z)-*Isomer* (**24**).—The procedure followed to transform the methyl ketone (**22b**) (100 mg, 0.25 mmol) into the α,β-unsaturated esters (**23**) and (**24**) was identical with that used to transform the methyl ketone (**12b**) into the α,β-unsaturated esters (**18**) and (**19**). Obviously, basic treatment with methanolic sodium methoxide was unnecessary in this case. The mixture of (E)- and (Z)-isomers was chromatographed on silica gel using hexane–ethyl acetate (8:2) as eluant to give the (E)-α,β-*unsaturated ester* (**23**) (67 mg, 72%) as a semisolid (Found: C, 70.5; H, 8.3%; M^+, 376.2243. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.6%; *M*, 376.2249); $[\alpha]_D$ −127° (*c* 0.26 in $CHCl_3$); $\nu_{max.}$ 1 720, 1 710, 1 650, and 1 640 cm^{-1}; δ_H 5.63 (1 H, br s, 15-H), 3.87 (1 H, dt, *J* 13.1 and 3.6 Hz, 12β-H), 3.67 and 3.65 (3 H each, each s, 2 × CO_2Me), 2.56 (1 H, m, that collapses to a dd with *J* 10.0 and 1.4 Hz upon irradiation at 1.05, 14α-H), 2.42 (1 H, dd, *J* 14.0 and 11.8 Hz, 6β-H), 2.18 (1 H, dd, *J* 10.0 and 11.8 Hz, 8β-H), 2.09 (1 H, dd, *J* 14.0 and 2.6 Hz, 5α-H), 1.92 (1 H, dd, *J* 11.8 and 2.6 Hz, 6α-H), 1.41 (1 H, td, *J* 11.8 and 3.4 Hz, 9α-H), 1.18 (3 H, 4-Me), 1.05 (3 H, d, *J* 6.2 Hz, 14β-Me), and 1.04 (3 H, s, 10-Me); *m/z* 376 (M^+, 1%), 361 (0.5), 346 (4), 345 (27), 344 (100), 326 (10), 316 (2), and 285 (7).

Further elution gave the (Z)-*isomer* (**24**) (17 mg, 18%) as a solid, m.p. 138—140 °C (from hexane–ethyl acetate) (Found: M^+, 376.2238. $C_{22}H_{32}O_5$ requires *M*, 376.2249); $\nu_{max.}$ 1 720, 1 702, 1 650, and 1 640 cm^{-1}; δ_H 5.58 (1 H, br s, 15-H), 4.01 (1 H, m that collapses to a d with *J* 8.7 Hz upon irradiation at 1.15, 14α-H), 3.68 and 3.63 (3 H each, each s, 2 × CO_2Me), 1.19 (3 H, s, 4-Me), 1.15 (3 H, d, *J* 6.7 Hz, 14β-Me), and 1.06 (3 H, s, 10-Me); *m/z* 376 (M^+, 1%), 346 (4.5), 361 (0.5), 345 (28), 344 (100), 326 (12), and 285 (8).

Acknowledgements

Financial support from CAICYT (Grant No. 2071/83) is gratefully acknowledged. One of us (R. J. Z.) wishes to thank the Ministerio Español de Educatión y Ciencia for a grant. We also thank Dr. D. Craig for manuscript revision.

References

1 (*a*) G. Dalma, 'The Alkaloids,' R. H. F. Manske and H. L. Holmes, Academic Press Inc., New York, vol. IV, 1954, ch. 36; (*b*) E. L. McCawley, *ibid.*, vol. V, 1955, p. 101; (*c*) R. B. Morin, *ibid.*, vol. X, 1968, ch. 3.
2 (*a*) A. Cronlund and F. Sandberg, *Acta Pharm. Suec.*, 1976, **13**, 35; (*b*) F. Sandberg, *J. Ethnopharmacol.*, 1980, **2**, 105.
3 (*a*) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Connor, *J. Med. Chem.*, 1967, **10**, 582; (*b*) H. Hauth, *Planta Med.*, 1971, 40; (*c*) A. Cronlund, *Sven. Farm. Tidskr.*, 1975, **79**, 666; (*d*) *Acta Pharm. Suec.*, 1976, **13**, 27; (*e*) *ibid.*, p. 175; (*f*) H. Hauth, *Pharm. Unserer Zeit*, 1977, **6**, 179.
4 R. B. Turner, O. Buchardt, E. Herzog, and R. B. Morin, *J. Am. Chem. Soc.*, 1966, **88**, 1766.
5 (*a*) G. Traverso, G. P. Pollini, F. Fringuelli, and A. Taticchi, *Farmaco Ed. Sci.*, 1966, **21**, 728; (*b*) K. Mori and M. Matsui, *Tetrahedron*, 1966, **22**, 2883; (*c*) S. J. Daum, M. M. Riano, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, 1967, **32**, 1435; (*d*) A. Taticchi, F. Fringuelli, and V. Mancini, *Tetrahedron*, 1969, **25**, 5341; (*e*) H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, 1971, **54**, 1278; (*f*) *ibid.*, 1972, **55**, 1532.
6 For preliminary publication of some of this work, see: A. Abad, C. Agullò, M. Arnò, L. R. Domingo, and R. J. Zaragozà, *Tetrahedron Lett.*, 1986, **27**, 3289.
7 A. Abad, M. Arnò, L. R. Domingo, and R. J. Zaragozà, *Tetrahedron*, 1985, **41**, 4937.
8 K. Mori, I. Takemoto, and M. Matsui, *Tetrahedron*, 1976, **32**, 1497.
9 (*a*) D. Caine and H. Deutsch, *J. Am. Chem. Soc.*, 1978, **100**, 8030; (*b*) S. N. Suryawanshi and P. L. Fuchs, *Tetrahedron Lett.*, 1981, **22**, 4201.
10 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **16**, 2647.
11 A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, 1969, **34**, 1550.
12 R. J. Zaragozá, Ph.D. Thesis, Universidad de Valencia, October 1986.
13 H. O. House, 'Modern synthetic reactions,' W. A. Benjamin, Inc., Menlo Park, 1972, p. 586.
14 D. Loganathan, G. K. Trivedi, and K. V. R. Chari, *J. Org. Chem.*, 1986, **51**, 3366.
15 V. Burkert and N. L. Allinger, *Tetrahedron*, 1977, **34**, 807.
16 B. B. Dewhurst, J. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pete, *Bull. Soc. Chim. Fr.*, 1964, 3259.
17 W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, 1965, **30**, 3190.
18 G. Aranda, M. Fetizon, and N. Tayeb, *Tetrahedron*, 1987, **43**, 4159.
19 R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *J. Am. Chem. Soc.*, 1966, **88**, 5865.
20 H. Taguchi, K. Shimoji, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 2529.
21 H. Hauth, P. Niklaus, and D. Stauffacher, *Helv. Chim. Acta*, 1971, **54**, 1289.
22 R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Connor, *J. Med. Chem.*, 1967, **10**, 593.
23 R. L. Clarke and S. J. Daum, *J. Med. Chem.*, 1970, **13**, 320.
24 D. P. Roelofsen, J. A. Hagendoorn, and H. van Bekkum, *Chem. Ind. (London)*, 1966, 1622.
25 Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011.
26 N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field,' Holden-Day: San Francisco, 1964, p. 30.

27 There are cases in the literature of this phenomenon, see: (*a*) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, 1958, **80**, 5220; (*b*) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, 1952, **74**, 4223.
28 S. W. Pelletier, K. N. Iyer, and C. W. J. Chang, *J. Org. Chem.*, 1970, **35**, 3535.
29 H. Gilman and B. J. Gaj, *J. Org. Chem.*, 1963, **28**, 1725.
30 E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.*, 1978, **43**, 188.

Received 16*th February* 1989; *Paper* 9/00740G