Formal Total Synthesis of (+)-12-Deoxyscalarolide

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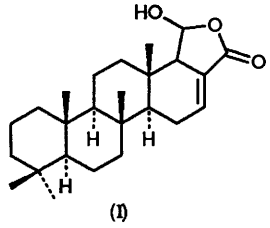
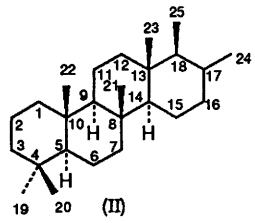
An effective formal total synthesis of (+)-12-deoxyscalarolide is described, starting from natural manool. Two alternative reaction schemes have been investigated for the synthesis of the tetracarbocyclic key intermediate (−)-methyl 17-oxo-24-norscalaran-25-oate. The unsaturated lactonic ring is then created from this ester in three steps to afford, in high yield, the (−)-scalar-16-en-25,24-olide which is easily isomerised under basic conditions to (+)-12-deoxyscalarolide.

Sesterterpenes of tetracarbocyclic structure, rare in nature, have been found in a limited range of different marine sponges. The first reported example of this group, named scalarin (I), was isolated in 1972 from the Mediterranean sponge *Cacospongia scalaris*.[1] Related compounds have been reported from *Cacospongia mollior*,[2] *Spongia officinalis*,[3] *Heteronema erecta*,[4] *Spongia nitens*,[5] and *Spongia idia*.[6] Compounds possessing the same basic ring structure as scalarin are considered to be derivatives of the hypothetical hydrocarbon scalarane[7] (II) and are referred to as scalarins. It has generally been assumed that the scalarins, which are produced as secondary metabolites by marine organisms, play an important role in their defense systems and contribute to the survival of the species.[6,8]

Several scalarins and homoscalarins (methylscalarins) isolated and identified during the last 15 years possess important biological and pharmacological activities. For example, the scalaradials[6,8,9] are cytoxic and/or inhibit fish feeding, while some methylscalarins[7,10] show anti-inflammatory activity *in vivo* and also antimicrobial and platelet aggregation inhibition activities. In recent years an intensive effort has been devoted to the isolation and structure elucidation of new members of this class of sesterterpenes in the search for pharmacologically active compounds.[7–10] In parallel the syntheses of two compounds with the basic scalarane skeleton have been published; the synthesis of methyl 12-deoxyscalar-16-en-25-oate (III) in optically active[11] and racemic[12] form and the synthesis of racemic 12-deoxyscalaradial (IV).[13]

We chose as a goal of our synthetic work the pentacyclic derivative scalarolide (V), occurring naturally in sponges of the order Dictyoceratida, and isolated from *Spongia idia* in 1980.[6] Our attention was drawn to the structural similarity of the C–D–E-ring system of scalarins with that of the drimane sesquiterpenes. In particular the upper part of the scalarolide molecule has the same structure and functional groups (except for the 12-hydroxy group) with isodrimenin (VI). Thus a synthetic scheme based on a simple and efficient synthesis of isodrimenin,[14] applied to a bicyclic substrate already possessing the necessary *trans*-fused A–B-ring system, appeared to be potentially useful. For this purpose a convenient molecule of natural origin, which can be used as the starting material, is the common labdane diterpene manool (**1**). The structure of manool was elucidated many years ago[15a] and the total synthesis of this compound has been reported.[15b,c] The success of the proposed synthesis would constitute a formal total synthesis of optically active 12-deoxyscalarolide (V; R = H) with an absolute stereochemistry induced from the stereochemistry of the natural manool. Furthermore, since isodrimenin (VI) provides a convenient entry to more functionalised members of the drimane sesquiterpenes[16] by simple chemical transformations on their C-ring, scalarolide (V) could be a valuable intermediate for the synthesis of nearly all scalarane derivatives, by similar transformations on its E-ring.


(I)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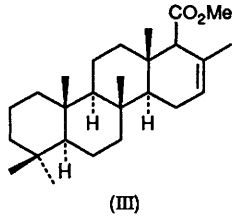
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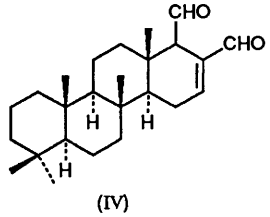
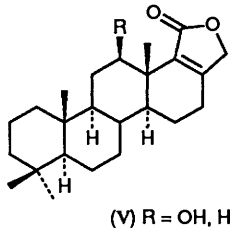
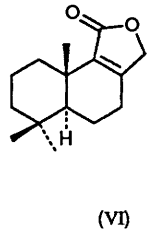

(IV)


(V) R = OH, H

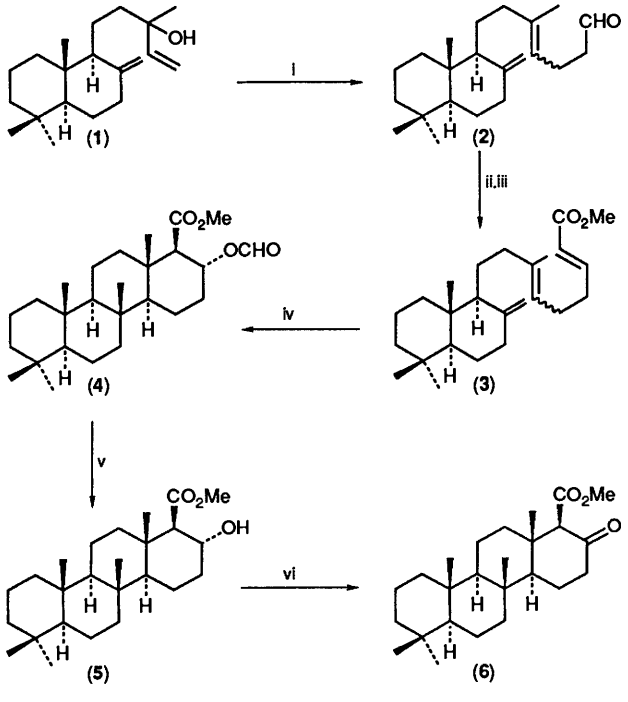

(VI)

In this paper we describe the first formal total synthesis of (+)-12-deoxyscalarolide (**15**), which can be summarised as follows: (a) Preparation of the tetracarbocyclic key intermediate methyl 17-oxo-24-norscalaran-25-oate (**6**), starting from natural manool, by elongation of its lateral chain by four carbon atoms and subsequent acid-catalysed cyclisation of the intermediate bicyclic precursors (**3**) or (**10**) (Schemes 1 and 2); (b) Construction of the unsaturated lactonic E-ring on the

D-cycle of the intermediate (**6**), by essentially the same efficient procedure, already applied to the synthesis of drimenin and isodrimenin[14] (Scheme 3).

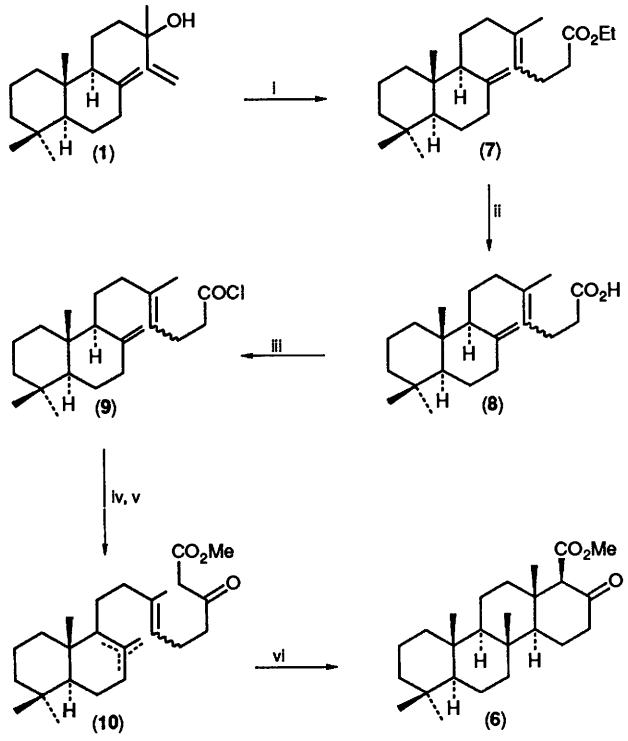
Results and Discussion

Our first attempt to assemble the tetracarbocyclic nucleus of the key intermediate (**6**), presented in Scheme 1, although successful, gave the desired product in very low overall yield. Thus, when manool (**1**) and ethyl vinyl ether were heated in an autoclave at 180 °C for 48 h in the presence of phosphoric acid as catalyst[17] a mixture of the aldehyde (**2**) and its diethyl acetal was obtained. The crude mixture was hydrolysed by dilute aq. HCl and the aldehyde (**2**) was obtained as an oil homogeneous on TLC analysis. GC-MS analysis of the obtained oil revealed the presence of two products exhibiting the same mass spectra, which are probably the two Δ^4 *Z* and *E* isomers. Several attempts to separate the two isomers by TLC or column chromatography were unsuccessful. As the stereochemistry of the Δ^4 double bond is not crucial to the final cyclisation step,[18] the product mixture was used in the next step without separation. Condensation of the aldehyde (**2**) with malonic acid in pyridine–piperidine solution,[19] followed by esterification of the acid produced gave the unsaturated ester (**3**), as a mixture of two isomers (probably the Δ^6 *Z* and *E* isomers) in 26.6% overall yield. Cyclisation of the ester (**3**) in a mixture of formic and sulphuric acids[18] gave a complex mixture of products, from which the crystalline formate (**4**) was separated with great difficulty in only 12.6% yield. Saponification of the formyl group by methanolic NaOH (where the sterically hindered 25-ester group was not attacked) followed by oxidation of the crude hydroxy ester (**5**) with pyridinium chlorochromate (PCC) in methylene dichloride gave the desired tetracarbocyclic keto ester (**6**) in 2.5% overall yield from the bicyclic precursor (**3**).



Scheme 1. *Reagents:* i, ethyl vinyl ether, H_3PO_4; ii, $CH_2(CO_2H)_2$, pyridine–piperidine; iii, CH_2N_2; iv, HCO_2H, H_2SO_4; v, aq. NaOH; vi, PCC, CH_2Cl_2.

Several attempts to ameliorate the yield in the cyclisation step by using a variety of conditions have proved unsuccesful. In view of the foregoing results and the need for a larger quantity of the tetracarbocyclic keto ester (**6**) in order to accomplish our synthesis, we were compelled to investigate other terminator units on the same substrate, which could lead, after cyclisation, to the desired keto ester (**6**) in better yield. Thus we were attracted to the olefinic β-keto esters used by White as substrates in cyclisations to form the skeleta of various diterpenoids.[20] In our case a suitable substrate for the construction of the tetracarbocyclic scalarane nucleus could be the unsaturated β-keto ester (**10**). After considerable experimentation, it was found that the more convenient procedure to prepare compound (**10**) from natural manool (**1**) is that presented in Scheme 2.

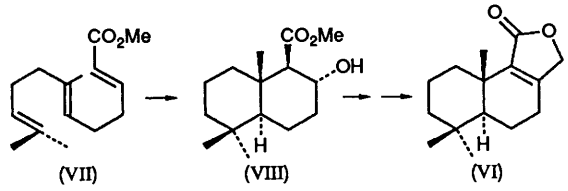


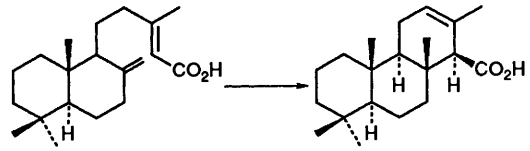
Scheme 2. *Reagents and conditions:* i, $MeC(OEt)_3$, $EtCO_2H$; ii, NaOH, EtOH; iii, $(COCl)_2$, C_6H_6; iv, Meldrum's acid, CH_2Cl_2, pyridine; v, MeOH, reflux; vi, $SnCl_4$, CH_2Cl_2.

On heating manool (**1**) and triethyl orthoacetate in the presence of propionic acid[21] at 145 °C for 48 h with continuous distillation of the ethanol formed, we obtained the ethyl ester (**7**) as an oil which was homogenous by TLC. GC-MS analysis revealed the presence of two products exhibiting identical mass spectra, which are probably the Δ^4 *Z* and *E* isomers. Saponification of the ester (**7**) with ethanolic NaOH and acidification of the reaction mixture gave the corresponding acid (**8**), which was used in the next step without purification. Reaction of the acid (**8**) with oxalyl dichloride in dry benzene afforded the corresponding acid chloride (**9**) as an orange oil, which was condensed immediately with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione)[22] in methylene dichloride in presence of anhydrous pyridine. The intermediate ethylidene derivative was heated to reflux in methanol to give the olefinic β-keto ester (**10**) as a brown oil. Purification of the crude product on a silica gel column gave compound (**10**) as a viscous oil, homogeneous on TLC, in 30.5% overall yield from manool. Although the β-keto ester structure of the product was evident from its IR spectrum, detailed GC-MS analysis revealed the presence of several compounds exhibiting similar mass spectra, probably the Δ^6 *Z* and *E* isomers as well as the isomers formed by migration of the exocyclic double bond.

Cyclisation of the ester (**10**) by the method of White[20] [addition of tin(IV) chloride in a methylene dichloride solution of the ester at 5 °C] gave a complex mixture of compounds. After many unsuccesful attempts to separate the components by TLC, we were gratified to find that simple dilution of the reaction product with cold acetone caused the precipitation of a white amorphous solid, which was found to be homogeneous on TLC. Recrystallisation of this product in acetone gave the tetracyclic β-keto ester (**6**), identical in all aspects with the product obtained by the reaction sequence shown in Scheme 1, in 30% yield. Although the yield of the cyclisation of the diene (**10**) was not as high as we had hoped, the quantity of the product obtained, (**6**), was sufficient for the continuation of our synthesis.

A comparison of the cyclisation step with similar acid-catalysed cyclisations may give us useful indications for the structure of the product (**6**). As a point of reference, the drimane ring system (VIII) created by treatment of the linear compound (VII) similar to the precursor (**3**), in a mixture of formic and sulphuric acids, possesses exclusively *trans* ring fusion with the methoxycarbonyl group in the β-equatorial position.[14,18] On the other hand the bicyclic part of our precursor (**3**) is the same

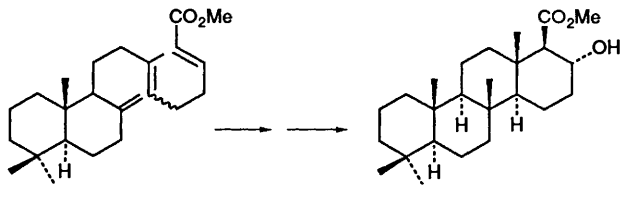




(IX) R = H
(X) R = CO_2H

(XI) R = H
(XII) R = CO_2H

as that of the labdane diterpenes agathic acid (IX) and copalic acid (X), which by the same treatment in a mixture of formic and sulphuric acids gave the tricyclic isoagathic (XI)[23] and isocopalic (XII)[24] acids, with a *trans* ring fusion and the new angular methyl group in the 8β-axial position. The same methyl 8β-axial configuration was obtained in the synthesis of a taondiol derivative[25] by an acid-catalysed cyclisation of an adequate labdane-8(17),13-diene. It is therefore reasonable to assume that the acid-catalysed cyclisation, under the above conditions, of the trienic ester (**3**), which contains both cyclisation units, should be accomplished by a similar pathway and should lead to a compound with all ring junctions *trans-anti-trans* and the angular C-21 and -23 methyl groups in axial β positions as in structure (**5**). Furthermore a Drieding model study of all other possible structures which could be formed in

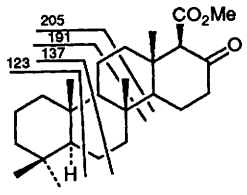


(3) (5)

the cyclisation step showed severe steric hindrance that diminishes considerably the possibility of their formation.

That the compound (**6**) obtained actually possesses the tetracarbocyclic scalarane skeleton was deduced by the following spectral data:

(*a*) the mass spectrum, except for the molecular ion peak [M^+ 388 (12%)], contained peaks [*m/z* 205 (11), 191 (59), 137 (38), and 123 (56)] which are characteristic of scalarane derivatives[1,3,11] arising by fragmentations as shown in Figure 1.



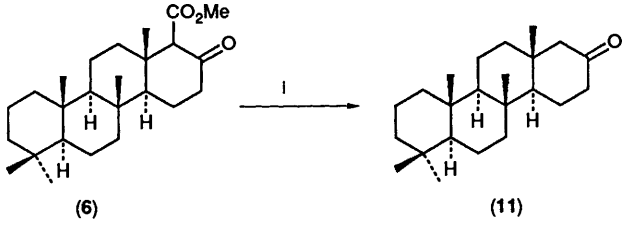
(6)

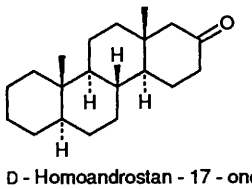
Figure 1.

(*b*) The presence, in the IR spectrum, of two absorption bands at 1 715 and 1 744 cm^{-1} which are attributed to the C-17 keto and C-25 ester groups.

(*c*) The presence, in the ^1H NMR spectrum, of a 3 H singlet at δ_H 3.66 attributed to the methyl ester group, and a 1 H singlet at δ_H 3.2 to the 18-H show clearly the presence of only one epimer at C-18. There was also the significant disappearance of all olefinic protons of the unsaturated bicyclic precursors (**3**) and (**10**).

(*d*) Demethoxycarbonylation of compound (**6**) by refluxing it in wet dimethyl sulphoxide (DMSO) in the presence of LiCl[26] gave the saturated ketone (**11**). Inspection of the octant projection of the ketone (**11**) with all-*trans* ring junctions predicts a reasonably strong negative Cotton effect, comparable to that of D-homo-5α,14α-androctan-17-one[27] ($\Delta\varepsilon$ − 1.5 or larger), whereas a *trans-cis-trans* or *trans-trans-cis* junction of the B–C–D rings should exhibit a weak negative or a weak positive Cotton effect, respectively. In fact the ketone (**11**) obtained exhibited a strong negative Cotton effect, $[\theta]_{280}$ − 5.808 ($\Delta\varepsilon$ − 1.76), which confirms the all-*trans* structure of the molecule.





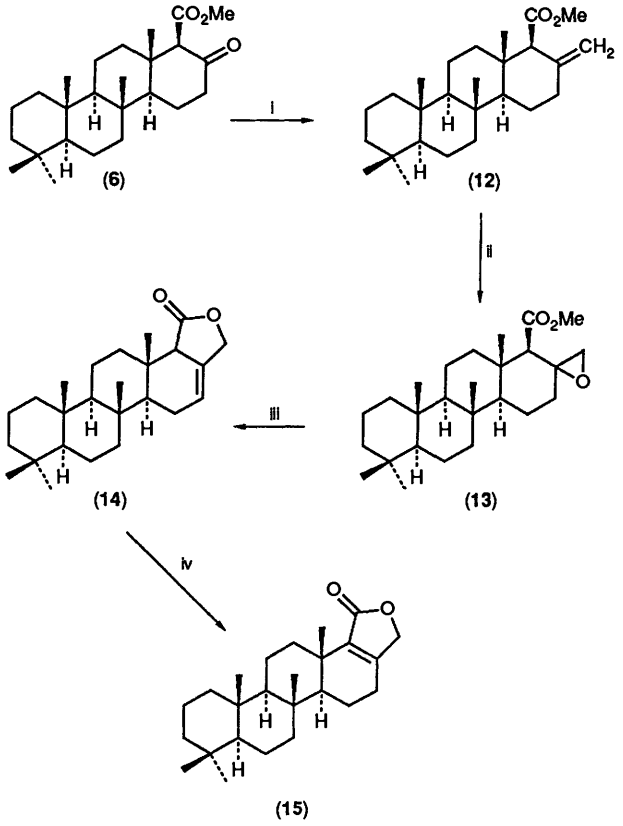
D - Homoandrostan - 17 - one

Reagents and conditions: i, DMSO, LiCl, 170 °C.

The β-keto ester moiety in compound (**6**) is significant as it can afford a convenient site for the construction of the unsaturated lactonic ring of the deoxyscalarolide, by an easily effected three-step sequence presented in Scheme 3. Wittig reaction of compound (**6**) with methylene(triphenyl)phosphorane in toluene in a salt-free reaction medium[28] at room temperature gave crystalline methylene ester (**12**) in 79% yield.

It should be noted that the β-keto ester (**6**) is insoluble in toluene and the phosphorane solution was added to a suspension of the β-keto ester (**6**) in toluene. During the addition the medium became limpid and the reaction proceeded as expected.

Epoxidation of the methylene ester (**12**) by *m*-chloroperbenzoic acid (MCPBA) in methylene dichloride at 0 °C produced the crystalline epoxy ester (**13**), which was used in the next step without purification. Many attempts to recrystallise or purify compound (**13**) were unsuccessful because it decomposes easily. Acid-catalysed treatment of the crude epoxy ester (**13**) with toluene-*p*-sulphonic acid (PTSA) in refluxing chloroform gave an amorphous solid, homogeneous on TLC, which after purification by column chromatography on silica gel and recrystallisation from diethyl ether, gave very pure (−)-scalar-16-en-25,24-olide (**14**) [(−)-12-deoxyisoscalarolide] in 88% yield from the tetracyclic β-keto ester (**6**).



Scheme 3. *Reagents:* i, $Ph_3P{=}CH_2$, toluene; ii, MCPBA, CH_2Cl_2; iii, PTSA, $CHCl_3$; iv, EtONa, EtOH.

The ^1H NMR spectrum of compound (**14**) showed striking similarity with that of drimenin[14] (broad 1 H singlet at δ_H 6.5, broad 2 H singlet at δ_H 3.5, and broad 1 H singlet at δ_H 2.1), suggesting the formation of the lactonic ring with the double bond at C-16–C-17. The IR spectrum of compound (**14**) showed a strong absorption band at 1 740 cm^{-1} due to a non-conjugated, five-membered lactonic ring. Furthermore the mass spectrum gave a correct molecular ion peak at *m/z* 370 and also peaks at *m/z* 205, 191, 137, and 123 which are characteristic for the scalarane ring system.[1,3,11]

Finally, migration of the double bond to the conjugated endocyclic position was easily realised quantitatively by reaction with sodium methoxide in methanol, giving the final product (**15**). All the spectral data of the synthetic (+)-12-deoxyscalarolide (**15**) are comparable with those of isodrimenin and are in full accord with the proposed structure.

In conclusion, the foregoing synthesis of (+)-12-deoxyscalarolide represents an efficient access to optically active scalarins. It is important to note that, in the above described synthetic approach, the relative configuration of all new asymmetric centres is controlled in the cyclisation step and therefore the absolute stereochemistry is induced by the known structure of natural manool. This synthesis is also distinguished from those already reported by a higher overall yield and by the fact that the entire sequence meets with no separation problems. Our work will continue with the aim to introduce a hydroxy group at the C-12 position in order to facilitate direct comparison of synthetic scalarin with the natural compound.

Experimental

M.p.s were determined with a Buchi 510 apparatus and are uncorrected. IR spectra were obtained for CCl_4 5% solutions unless otherwise stated and were recorded on a Perkin-Elmer 1750 IR Fourier transform spectrophotometer. ^1H NMR spectra were obtained for solutions in CCl_4 unless otherwise stated and were recorded on a Varian EM360 instrument (60 MHz) at room temperature. Chemical shifts (δ) are reported in ppm downfield from internal $SiMe_4$. Mass spectra of compounds (**2**)–(**5**), (**7**), (**8**), and (**10**) were recorded on a Hewlett-Packard 5970 mass spectrometer, interfaced on a Hewlett-Packard 5890A gas chromatograph, equipped with an SE-30 capillary column (12 m × 0.25 mm i.d.). Mass spectra of all other compounds were recorded by direct inlet on a VG 2000 instrument. Optical rotations were determined in $CHCl_3$ solutions at 20–25 °C on a Perkin-Elmer 141 polarimeter. Analytical TLC was carried out on Merck silica gel 60 F_{254} precoated aluminium sheets with mixtures of diethyl ether–light petroleum and spots were visualised with 5% methanolic H_2SO_4. Preparative TLC (PLC) was performed with Merck precoated silica gel 60 F_{254} plates (2 mm; 20 × 20 cm). Column chromatography was carried out on Merck silica gel (0.05–10.2 mm), or on Florisil Serva (60–100 mesh). Light petroleum refers to that fraction boiling in the range 40–60 °C. All solvents used were either spectroscopic grade or distilled prior to use. Extracts were dried over Na_2SO_4 unless otherwise stated.

Methyl 17-Oxo-24-norscalaran-25-oate (**6**) (Scheme 1).—*7-(5,5,8a-Trimethyl-2-methylenedecahydronaphthyl)-5-methylhept-4-enal* (**2**). Natural manool (**1**) (43.5 g, 0.15 mol), ethyl vinyl ether (36 g, 0.5 mol), and H_3PO_4 (0.5 ml) were heated in an autoclave at 120 °C for 24 h. The homogeneous solution was treated with triethylamine (0.7 ml) and the volatile by-products were removed under reduced pressure. The dark, oily residue obtained (59 g) consisted of a mixture of the aldehyde (**2**) and its diethyl acetal. A solution of the crude product in tetrahydrofuran (THF) (100 ml) and 10% HCl (10 ml) was heated to reflux for 2 h to effect hydrolysis of the diethyl acetal. After usual work-up the crude oily product was purified by chromatography on silica, and eluted with a mixture of diethyl ether–light petroleum to give compound (**2**) as a viscous, oily mixture of two isomers exhibiting the same mass spectra (probably Δ^4 *cis* and *trans*) in a 1:1 ratio, as was determined by gas chromatography (23 g, 48.5%); ν_{max} 3 081, 3 000, 2 715, 1 730, 1 640, and 890 cm^{-1}; δ 0.60 (3 H, s), 0.74 (3 H, s), 0.81 (3 H, s), 1.62 and 1.67 (total 3 H, 2 s), 4.45 (1 H, br s), 4.75 (1 H, br s), 5.0 (1 H, br s), and 9.75 (1 H, t, *J* 2 Hz); *m/z* 316 (M^+, 4%), 301 (68), 205 (45), 191 (14), 137 (33), 109 (87), 95 (87), and 41 (100).

Methyl 9-(5,5,8a-Trimethyl-2-methylenedecahydronaphthyl)-7-methylnona-2,6-dienoate. (**3**). A solution of the aldehyde (**2**) (4.4 g, 13.9 mmol) in pyridine (10 ml) containing piperidine (0.5 ml) was added to a solution of malonic acid (4.5 g, 43 mmol) in pyridine (10 ml) containing piperidine (1.5 ml). The mixture was

stirred at room temperature for 30 min and was then heated on a water-bath for *ca.* 2 h until no more CO_2 was evolved. The reaction mixture was cooled to room temperature, poured into 10% HCl (50 ml), and extracted with diethyl ether. The organic phase was washed with water, dried, and evaporated under reduced pressure to give an orange, viscous oil. Purification by column chromatography was performed on silica, with diethyl ether–light petroleum (1:3) as eluant, to give a viscous oil, homogeneous by TLC; ν_{max} 1 695, 1 650, and 890 cm^{-1}.

An ethereal solution of the above product was treated with an excess of diazomethane in diethyl ether. After usual work-up, the triene methyl ester (**3**) was obtained as a viscous oil, homogeneous by TLC (2.85 g, 55%). GC-MS analysis revealed the presence of two compounds exhibiting the same mass spectra (Δ^6 *cis* and *trans* isomers) in a 1:1 ratio; ν_{max} 3 080, 1 725, 1 660, 1 645, and 890 cm^{-1}; δ 0.60 (3 H, s), 0.75 (3 H, s), 0.82 (3 H, s), 1.54 and 1.57 (total 3 H, 2 s), 3.55 (3 H, s), 4.45 (1 H, s), 4.75 (1 H, s), 4.95 (1 H, br s), 5.60 (1 H, d, *J* 14 Hz), and 6.8 (1 H, dt, J_1 5, J_2 14 Hz); *m/z* 372 (M^+ 5%), 357 (64), 298 (5), 205 (5), 191 (7), 137 (48), 95 (72), and 81 (100).

Methyl 17-*Formyloxy*-24-*norscalaran*-25-*oate* (**4**). A solution of the triene methyl ester (**3**) (8 g, 21.5 mmol) in diethyl ether (20 ml) was added slowly to a stirred, cold (0 °C) solution of formic acid (100 ml) and H_2SO_4 (10 ml). The ice-bath was removed and the reaction mixture was allowed to reach room temperature. The mixture was stirred for 3 h at ambient temperature. The dark brown mixture was then poured into ice-cold water (400 ml) and extracted with diethyl ether. The organic phase was washed with aq. $NaHCO_3$ (5%), dried, and evaporated under reduced pressure to give a viscous residue (6.3 g). Upon storage in a refrigerator for a week, crystals were deposited on the bottom of the container. Dilution with light petroleum and filtration gave a crystalline product, homogeneous by TLC (1.1 g, 12%), m.p. 180–182 °C, which was used in the next step without further purification. Two recrystallisations from diethyl ether–light petroleum gave an analytically pure sample of the *diester* (**4**), m.p. 190–192 °C (Found: C, 74.5; H, 9.95. $C_{26}H_{42}O_4$ requires C, 74.6; H, 10.1%); $[\alpha]_D^{20}$ +27° (*c* 1, $CHCl_3$); ν_{max}(KBr) 2 986, 2 957, 2 890, 2 843, 1 736, 1 728, and 1 187 cm^{-1}; δ($CDCl_3$) 0.80 (15 H, s) 1.0 (3 H, s), 3.62 (3 H, s), 5.1 (1 H, br s), and 7.9 (1 H, s); *m/z* 418 (3%), 403 (12), 372 (34), 357 (42), 259 (27), 191 (100), 137 (24), 123 (47), 109 (40), 95 (63), 81 (68), and 41 (65).

Methyl 17-*Hydroxy*-24-*norscalaran*-25-*oate* (**5**). A suspension of the formate (**4**) (204 mg, 0.5 mmol) in methanol (20 ml) was refluxed with 10% aq. NaOH (2 ml) overnight. After acidification with acetic acid, the mixture was poured into water (50 ml) and extracted with methylene dichloride. The organic phase was washed successively with saturated aq. $NaHCO_3$ and water, dried, and evaporated to dryness. The white solid (167 mg) was recrystallised from diethyl ether to give pure *hydroxy ester* (**5**) as needles (150 mg, 77%), m.p. 199–200 °C (Found: C, 76.7; H, 10.55. $C_{25}H_{42}O_3$ requires C, 76.9; H, 10.8%); $[\alpha]_D^{20}$ + 38° (*c* 1.1, $CHCl_3$); ν_{max}(KBr) 3 625, 2 935, 1 735, and 1 030 cm^{-1}; δ($CDCl_3$) 0.80 (15 H, s), 0.98 (3 H, s), 3.60 (3 H, s), and 4.6 (1 H, br s); *m/z* 390 (8%), 375 (14), 372 (28), 357 (30), 191 (100), 137 (28), 129 (42), 81 (71), and 69 (82).

Methyl 17-*Oxo*-24-*norscalaran*-25-*oate* (**6**). A solution of the hydroxy ester (**5**) (100 mg, 0.25 mmol) in methylene dichloride (5 ml) was added to a suspension of PCC (90.5 mg, 0.42 mmol) and sodium acetate (6.7 mg, 0.087 mmol) in methylene dichloride (5 ml) at 25 °C and the mixture was stirred at room temperature for 3 h. The supernatant liquid was poured into diethyl ether (30 ml), and the solution was washed successively with aq. $NaHCO_3$, HCl (5%), and water, dried, and evaporated to give a brown oil (70 mg), which was purified by PLC to afford pure β-*keto ester* (**6**) (24 mg, 25%), m.p. 219–221 °C (from acetone) (Found: C, 77.35; H, 10.5. $C_{25}H_{40}O_3$ requires C, 77.3; H, 10.4%); $[\alpha]_D^{20}$ − 27° (*c* 0.8, $CHCl_3$); ν_{max}(KBr) 2 925, 2 845, 1 744, 1 715, 1 435, 1 380, 1 195, 1 170, and 1 125 cm^{-1}; δ($CDCl_3$) 0.85 (9 H, s) 0.89 (3 H, s), 1.14 (3 H, s), 3.2 (1 H, br s), and 3.66 (3 H, s); *m/z* 388 (M^+, 12%), 373 (17), 370 (9), 357 (13), 341 66), 272 (87), 205 (11), 191 (59), 178 (35), 137 (38), 123 (56), 81 (70), and 69 (100).

Methyl 17-*Oxo*-24-*norscalaran*-25-*oate* (**6**) (Scheme 2).—*Methyl* 9-(5,5,8a-*Trimethyl*-2-*methylenedecahydronaphthyl*)-7-*methyl*-3-*oxonon*-6-*enoate* (**10**). (*a*) A mixture of manool (**1**) (23.2 g, 80 mmol), triethyl orthoacetate (50 g, 0.3 mol), and propionic acid (5 ml) was heated in an oil-bath at 120 °C for 48 h with continuous removal of the ethanol formed during the reaction. After cooling, the solution was poured into an excess of 10% aq. $NaHCO_3$ and extracted twice with diethyl ether. The organic phase was washed with water, dried, and evaporated under reduced pressure, leaving the unsaturated ester (**7**) as a yellow oil (32 g). A sample (0.5 g) of the crude product was purified by PLC to give a viscous oil, homogeneous by TLC. GC-MS analysis revealed the presence of two compounds in a 1:1 ratio (probably the Δ^4 *cis* and *trans* isomers) and exhibiting identical mass spectra; ν_{max}3 085, 2 943, 1 737, 1 640, and 890 cm^{-1}; δ 0.60 (3 H, s), 0.75 (3 H, s), 0.85 (3 H, s), 2.20 and 2.25 (total 3 H, 2 s), 4.00 (2 H, q), 4.45 (1 H, br s), 4.75 (1 H, br s), and 5.00 (1 H, br s); *m/z* 360 (M^+, 8%), 345 (91), 245 (44), 137 (63), 109 (52), 95 (82), 81 (100), and 41 (77). The crude product was used in the next step, without further purification.

(*b*) A stirred solution of the ester (**7**) (28 g, 80 mmol) in ethanol (60 ml) was treated with a solution of NaOH (14 g, 0.35 mol) in 50% aq. ethanol (60 ml). The mixture was stirred at room temperature for 4 h. The resulting solution was poured into 10% aq. HCl (150 ml) and extracted with diethyl ether. The organic phase was washed with water, dried, and evaporated under reduced pressure to give the unsaturated acid (**8**) as a yellow, viscous oil (25 g). A sample (0.5 g) of the product was purified by PLC to give a viscous oil, homogeneous by TLC. GC-MS analysis showed the presence of two isomers with identical mass spectra; ν_{max} 3 080, 1 715, 1 645, and 890 cm^{-1}; δ 0.60 (3 H, s), 0.75 (3 H, s), 0.82 (3 H, s), 2.25 and 2.27 (total 3 H, 2 s), 4.45 (1 H, br s), 4.75 (1 H, br s), and 5.00 (1 H, br s); *m/z* 332 (M^+, 5%), 317 (84), 221 (9), 149 (33), 137 (74), 109 (67), 95 (81), and 81 (100).

The crude product was used in the next step without further purification.

(*c*) A solution of the acid (**8**) (24 g, 72 mmol) in dry benzene (200 ml) was cooled at 0–5 °C and oxalyl dichloride (23 g, 0.18 mol) was slowly added. The mixture was stirred at 5 °C for 1 h and then at room temperature for 2 h. The solvent and the excess of the reagent were removed at reduced pressure at a temperature not exceeding 30 °C. Further benzene (50 ml) was added and removed under the same conditions, leaving the chloride (**9**) as a dark brown oil (27 g), which was used immediately in the next step without purification; ν_{max} 3 090, 3 035, 2 950, 1 800, 1 645, and 890 cm^{-1}.

(*d*) To a vigorously stirred solution of Meldrum's acid (14.4 g, 0.1 mol) in dry methylene dichloride (60 ml) cooled in an ice-bath was added dry pyridine (16 ml) under nitrogen, followed by dropwise addition of a solution of the chloride (**9**) (25 g, 71 mmol) in methylene dichloride (50 ml). After completion of addition, the mixture was stirred for 1 h at 0 °C and was then left at room temperature overnight. The mixture was poured into 10% HCl (100 ml). The organic phase was separated and the aqueous phase was extracted by methylene dichloride. The combined organic phases were washed with water, dried, and evaporated under reduced pressure at a temperature not exceeding 30 °C. The solid, dark residue thus obtained (28 g) was heated to reflux with methanol (200 ml) for 3 h and the mixture was left overnight at room temperature. Methanol was

removed under reduced pressure to leave a dark, viscous oil (27 g), which was purified by chromatography on silica. Elution with diethyl ether–light petroleum afforded the β-keto ester (**10**) as a viscous liquid homogeneous by TLC (9.5 g, overall yield from manool 30.5%); ν_{max} 3 080, 2 920, 1 750, 1 722, 1 656, 1 630, 1 446, 1 236, and 890 cm^{-1}; δ 0.85 (3 H, s), 3.20 (2 H, s), 3.85 (3 H, s), 4.40 (1 H, br s), 4.73 (1 H, br s), and 4.90 (1 H, br s); GC-MS analysis showed the presence of several isomers with similar mass spectra, from which the main peak exhibited the following spectrum; *m/z* 315 (12%), 272 (3), 245 (9), 205 (11), 149 (21), 137 (17), 95 (34), 81 (28), and 43 (100).

Methyl 17-Oxo-24-norscalaran-25-oate (**6**). To a solution of tin(IV) chloride (8.2 ml, 0.07 mol) in dry methylene dichloride cooled at −10 °C in an ice–salt-bath was added dropwise a solution of the β-keto ester (**10**) (3.1 g, 8 mmol) in methylene dichloride (5 ml) under nitrogen. The reaction mixture was stirred for 1 h at 0 °C and was then left for 24 h at room temperature before being poured into vigorously stirred 10% HCl (100 ml). The organic phase was separated and the aqueous phase was extracted with methylene dichloride. The combined organic phases were washed successively with brine and water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give a thick, orange oil (3.2 g). This was diluted with acetone (30 ml) and, after 1 h at 4 °C, a white solid had precipitated. The solution was filtered and the remaining solid was washed with cold acetone to give the tetracyclic β-keto ester (**6**) as an amorphous but very pure white solid (0.76 g). The mother liquors were concentrated and treated again with acetone to give a second crop of the β-keto ester (**6**), also of high purity (0.15 g). The overall yield of the cyclisation product was 30%. An analytical sample of the product was obtained by two recrystallisations from acetone, m.p. 219–221 °C. All physical and spectroscopic data of this compound are identical with those of the compound obtained from the reactions presented in Scheme 1.

24,25-*Dinorscalaran-17-one* (**11**).—A solution of β-keto ester (**6**) (80 mg, 0.2 mmol) and LiCl (42 mg, 1 mmol) in DMSO (5 ml) containing water (1 drop) was refluxed under nitrogen for 6 h. After cooling, the reaction mixture was poured into water (50 ml) and extracted with diethyl ether (3 × 100 ml). The organic phase was washed with water, dried, and concentrated under reduced pressure to afford a yellowish solid, homogeneous by TLC. Recrystallisation from acetone gave the *ketone* (**11**) as lustrous plates (50 mg, 79%), m.p. 251–252 °C (Found: C, 83.65; H, 11.5. $C_{23}H_{38}O$ requires C, 83.6; H, 11.6%); $[\alpha]_D^{20}$ − 54° (*c* 1, $CHCl_3$); ν_{max} 1 717 cm^{-1}; δ($CDCl_3$) 0.85–0.90 (15 H, s); *m/z* 330 (M^+, 43%), 315 (32), 245 (11), 217 (38), 191 (100), 177 (47), 137 (30), 123 (60), 69 (60), and 55 (75).

Methyl Scalar-17(24)-en-25-oate (**12**) (Scheme 3).—A solution of methylene(triphenyl)phosphorane in toluene was prepared by refluxing a suspension of methyl triphenylphosphonium bromide (2 g, 5.5 mmol) and sodium amide (0.8 g, 20 mmol) in dry toluene (40 ml) for 3 h under nitrogen. The reaction mixture was left to settle for 15 min and the clear, yellow supernatant liquid was removed by a syringe and added dropwise to a suspension of the tetracyclic β-keto ester (**6**) (0.2 g, 0.5 mmol) in dry toluene (10 ml) until the yellow colour of the ylide persisted. The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. When the starting material was consumed (*ca.* 1 h) the reaction mixture was decolourised by a few drops of acetic acid, washed with water, and dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure. The residue was triturated with diethyl ether–light petroleum (1:1) (50 ml) and most of the Ph_3PO was removed by filtration. The remaining crude product (0.5 g) was purified by column chromatography on Florisil with diethyl ether–light petroleum (8:1) as eluant. Thus, pure *methylene ester* (**12**) (0.185 mg) was obtained as a crystalline product. Recrystallisation from diethyl ether–light petroleum gave very pure *needles* (153 mg, 79%), m.p. 209–210 °C (Found: C, 80.9; H, 11.05. $C_{26}H_{42}O_2$ requires C, 80.8; H, 10.95%); $[\alpha]_D^{20}$ + 7° (*c* 1, $CHCl_3$); ν_{max} 3 080, 2 965, 1 740, and 1 645 cm^{-1}; δ 0.82 (12 H, s), 0.9 (3 H, s), 2.8 (1 H, s), 3.60 (3 H, s), and 4.70–4.80 (2 H, br d); *m/z* 386 (M^+, 28%), 371 (27), 312 (13), 273 (13), 260 (27), 259 (68), 205 (11), 191 (100), 163 (26), 81 (56), 69 (53), and 55 (47).

(−)-*Scalar-16-en-25,24-olide* [(−)-12-*Deoxyisoscalarolide*] (**14**).—(*a*) A solution of MCPBA (85%; 0.41 g, 2 mmol) in dry methylene dichloride (10 ml) was added dropwise to a stirred, cold (0–5 °C) solution of methylene ester (**12**) (0.3 g, 0.78 mmol) in methylene dichloride (20 ml). The mixture was stirred for 24 h at 0 °C and was then washed successively with dil. aq. Na_2SO_3, 5% aq. Na_2CO_3, and water (until neutral). The solution was dried over anhydrous sodium sulphate and the solvent was evaporated off under reduced pressure to afford the epoxy ester (**13**) (0.32 g) as a solid, which was used immediately in the next step without further purification; m.p. 236–241 °C; ν_{max} 2 970, 1 735, and 1 130 cm^{-1}.

(*b*) The epoxy ester (**13**) obtained previously was dissolved in chloroform (100 ml). PTSA (0.5 g) was added and the mixture was refluxed. The progress of the reaction was monitored by TLC. After consumption of the starting material (3 h) the solution was washed twice with water then dried, and the solvent was evaporated off under reduced pressure to afford a solid (0.32 g), which was purified by column chromatography on silica with diethyl ether–light petroleum (5:1) as eluant to afford pure crystalline *lactone* (**14**) (254 mg, 88%). Recrystallisation from ethanol gave an analytical sample, m.p. 230–232 °C (Found: C, 81.1; H, 10.1. $C_{25}H_{38}O_2$ requires C, 81.0; H, 10.3%); $[\alpha]_D^{25}$ − 4° (*c* 1.1, $CHCl_3$); ν_{max}($CHCl_3$) 2 940, 1 770, 1 470, 1 390, 1 370, 1 130 and 1 010 cm^{-1}; (KBr) 1 770, 1 465, 1 435, 1 385, 1 370, 1 145, and 1 005 cm^{-1}; δ($CDCl_3$) 0.85–0.9 (15 H, s), 2.8 (1 H, br s), 4.75 (2 H, s), and 5.85 (1 H, br s); *m/z* 370 (M^+, 61%), 355 (22), 260 (29), 245 (17), 205 (20), 191 (100), 163 (24), 149 (42), 123 (61), 81 (78), 69 (84), and 55 (89).

(+)-*Scalar-17-en-25,24-olide* [(+)-12-*Deoxyscalarolide*)] (**15**).—A solution of pure scalar-16-en-25,24-olide (**14**) (34 mg, 0.09 mmol) in ethanol (5 ml) was treated with a solution of EtONa in EtOH [prepared from Na (0.05 g) in 2 ml] at room temperature. The initially clear solution became cloudy after 5 min. The mixture was stirred for 1 h and acetic acid was then added to neutralise the medium. The majority of the ethanol was removed under reduced pressure and the residue was treated with methylene dichloride. The organic phase was washed with water, and dried over anhydrous sodium sulphate, and the solvent was evaporated off under reduced pressure to give a solid (30 mg). This product was suspended in absolute ethanol (10 ml) and then filtered off. The solid was washed with cold ethanol and dried, to afford pure 12-*deoxyscalarolide* (**15**) (30 mg, 88%), m.p. >300 °C (Found: C, 81.25; H, 10.25. $C_{25}H_{38}O_2$ requires C, 81.0; H, 10.3%); $[\alpha]_D^{25}$ + 65° (*c* 1, $CHCl_3$); ν_{max}($CHCl_3$) 2 935, 1 743, 1 665, 1 450, 1 390, 1 345, 1 130, 1 026, 1 010, and 993 cm^{-1}; (KBr) 1 740, 1 720, 1 666, 1 440, 1 380, 1 035, 1 020, and 785 cm^{-1}; δ($CDCl_3$) 0.9 (12 H, s), 1.1 (3 H, s), 2.25 (2 H, br s), and 4.6 (2 H, s).

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