Tetrahedron Vol. 45, No. 5, pp. 1567 to 1576, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

A NEW AND EFFICIENT ROUTE TO OPTICALLY ACTIVE DRIMANES. SYNTHESIS OF (+)-WINTERIN, (+)-CONFERTIFOLIN, (+)-ISODRIMENIN, AND (+)-BICYCLOFARNESOL

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(*Received in UK* 13 *December* 1988)

Abstract - *The drimane sesquiterpenes (+)-winterin, (+)-confertifolin, (+)-isodrimenin, and (+)-bicyclofarnesol were synthesised starting from royleanone, an abietane diterpenoid easily available as a main constituent of the root of some Salvia species.*

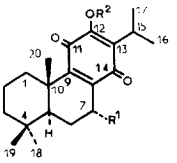
Several naturally occurring drimane sesquiterpenes show interesting biological activities, *i.e.* insect antifeedant, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties,[1-8] and a large number of syntheses of this important class of natural products have recently been published.[8-13] Among these syntheses very few led to optically active compounds, and only in the case of both the enantiomers of polygodial an enantioselective total synthesis has been achieved.[11] In all the other cases,[9,12,13] the starting material for obtaining optically active drimanes is a natural product possessing the suitable absolute configuration.

We have developed a very simple and efficient synthesis of the drimanes (+)-bicyclofarnesol[14,15] (**19**), (+)-winterin[16-19] (**4**), (+)-isodrimenin[18,19] (**18**) and (+)-confertifolin[17-19] (**17**) starting from royleanone[20] (**1**), an abietane diterpenoid easily available from natural sources. Compounds such as **4**, **17**, **18**, and **19** can provide a convenient entry to more functionalised and more biologically active members of the drimane class, for example warburganal[1,2,9,10,12,13] (**15**) and polygodial[1,7,9-11] (**16**). In fact, in this paper we also describe a formal synthesis of (-)-warburganal (**15**).

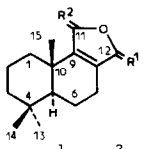
Royleanone[20] (**1**) and two related diterpenoids, namely 7α-acetoxyroyleanone[20] (**2**) and horminone[21] (**3**), have been isolated from many plants[20-23] and they are main constituents[24-26] of the root of several *Salvia* species.[27] Since it is known[20] that compounds **2** and **3** are easily and quantitatively transformed into royleanone (**1**), we selected this compound for our synthetic purposes.

Attempts for obtaining suitable degradation products of royleanone (**1**) by a variety of oxidation methods, *i.e.* potassium permanganate, ozonolysis, Jones' reagent, etc., were unsuccessful and always caused total decomposition of the diterpenoid (**1**). However, Hooker's oxidation[28] followed by treatment with periodic acid gave (+)-winterin[16-19] (**4**) although in poor yield (10%).

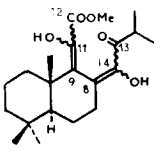
In view of the preceding results and taking into account the work of Akita and Oishi,[18,19] we attempted the ozonolysis of 12-*O*-methylroyleanone[20] (**5**) which seemed to be an adequate precursor due to the activation of its C-12 - C-13 double bond by the C-12 methoxyl substituent.[29]



	R^1	R^2
1	H	H
2	OAc	H
3	OH	H
5	H	Me



	R^1	R^2
4	O	O
17	O	H_2
18	H_2	O
21	H,OEt	H,OEt



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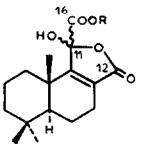
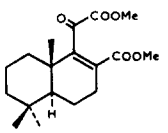


7 R = Me
8 R = H



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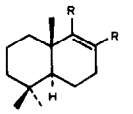
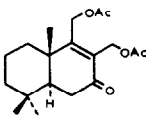
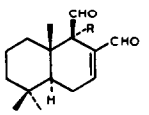


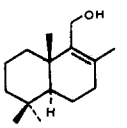
10 R = COOH
11 R = COOMe
12 R = CH_2OH
13 R = CH_2OAc



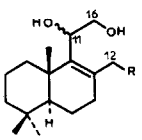
14



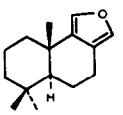
15 R = OH
16 R = H



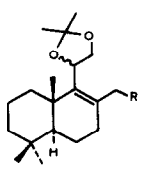
19



20 R = OH
25 R = H



22



23 R = OH
24 R = H

Effectively, reaction of **5** with ozone followed by treatment with zinc-acetic acid gave the 12,13-seco derivative **6** in 80% yield. The structure (**6**) of this compound[30] was firmly supported by its spectroscopic data (see Experimental), thus confirming the expected regioselectivity in the ozonolysis

of 12-*O*-methylroyleanone (**5**).

Ozonolysis of **5** and subsequent treatment with periodic acid in ethanol gave the 11-homodrimane derivative **7** in 80% yield.[31] The presence of a C-11 hydroxylactonic carbon in this compound was clearly revealed by its ^{13}C nmr chemical shift at δ 100.2, s. When the ozonolysis of **5** was followed by treatment with hydrogen peroxide in presence of base, compound **8** was obtained[31] in 90% yield. In both cases, small quantities (about 5%) of the drimane (+)-winterin[16-19] (**4**) were also obtained. This is in agreement with structures such as **7** and **8**, since the formation of these compounds blocks further degradation towards winterin (**4**).

Reaction of compounds **7** and **8** with diazomethane quantitatively yielded the same derivative (**9**), whereas treatment of **8** with lead tetraacetate in benzene solution at 0°C gave the drimane derivative **10** in 80% yield (72% overall yield from **5** and **1**). Methylation of **10** with diazomethane quantitatively produced **11**, identical in all respects with a sample obtained from (+)-winterin (**4**) by successive treatments with boiling methanol-pyridine and diazomethane. Further reduction of **11** with lithium aluminium hydride yielded the diol **12**, which was quantitatively transformed into its diacetyl derivative **13** by acetic anhydride-pyridine treatment. Compounds **12** and **13** have previously been obtained as transformation products of some natural terpenoids.[12,32,33]

Compounds such as **11**, **12**, and **13** have already been used as intermediates in the synthesis of some naturally occurring drimanes of biological interest.[9,12,33]

The above described easy and efficient preparation of compound **10** starting from royleanone (**1**) in three steps and 72% overall yield, provides an alternative route for the availability of drimane-related sesquiterpenes in enantiomerically pure form. In fact, oxidation of compound **13** with chromium trioxide in acetic acid[34] gave the derivative **14** (65% yield), previously used[34,35] as intermediate in a synthesis of (±)-warburganal (**15**).

We next turned our attention to compound **9** as a suitable intermediate for obtaining some other drimanes, because its functionality provides a wide range of possibilities for this purpose. In the present work we demonstrate how it can also be used as a precursor for other compounds, *i.e.* the natural drimanes (+)-confertifolin[17-19,36] (**17**) and (+)-isodrimenin[18,19] (**18**), and the (+)-enantiomer of bicyclofarnesol[14,15] (**19**).

Compound **9**, obtainable (90% yield) in three steps from royleanone (**1**) (see above), was reduced with lithium aluminium hydride giving the triol **20** (60% yield) as a mixture of C-11 epimers. Reaction of **20** with periodic acid in ethanol led to the formation of the diacetal **21**, in 75% yield, as a mixture of all stereoisomers. This result must be explained as follows. Initial cleavage of the glycol function of **20** produces 12-hydroxydrim-8-en-11-al which, in the presence of acid, is transformed into euryfuran[9,12] (**22**). Subsequently, compound **22** reacts with the solvent due to the presence of iodine[36] giving the diacetal **21**.

When compound **21** was treated with 10% hydrochloric acid in acetone following the method of Ley and Mahon,[36] a 70% yield of a mixture of (+)-confertifolin (**17**) and its regioisomer, (+)-isodrimenin (**18**), (in a 24:1 ratio, respectively) was obtained. The predominant formation of (+)-confertifolin (**17**) from **21** is rationalised[36] as an easy 1,4-elimination of ethanol by loss of the more accessible proton and the sterically more congested ethoxyl group to afford 12-ethoxyeuryfuran which would undoubtedly hydrolyse rapidly to give compound **17**.

On the other hand, treatment of **20** with acetone-copper sulphate gave the acetonide **23** (90% yield, a mixture of C-11 epimers). Further reaction with mesyl chloride in triethylamine at -78°C, followed by reduction of the mesylate with lithium aluminium hydride at -20°C, produced the derivative **24** (75% yield) which was transformed into compound **25** with 80% aqueous acetic acid (85% yield). Finally, cleavage of the diol **25** with lead tetraacetate and subsequent reaction with lithium aluminium hydride at 0°C produced (+)-bicyclofarnesol (**19**, 70% yield), previously synthesised in its racemic form.[14,15]

In summary, starting from an easily available natural diterpenoid we believe we have described a versatile route to the synthesis of a wide range of enantiomerically pure drimane sesquiterpenoids.

EXPERIMENTAL

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 657 spectrometer as neat oils or KBr disk. Mass spectra were obtained on a VG 12-250 (MassLab) instrument at 70 eV. Uv spectra were recorded on a Perkin-Elmer 402 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^{1}H Nmr spectra were recorded on a Varian EM-390 or XL-300 instrument in $CDCl_3$ solution with TMS as internal standard. ^{13}C Nmr spectra were recorded at 20.1 MHz (Bruker WP-80) or at 75.4 MHz (Varian XL-300), also in $CDCl_3$ with TMS as internal reference. All solvents were purified and dried by standard techniques. Column chromatography was performed on silica gel (Merck No. 7729) and run under low pressure. All organic extracts were dried with anhydrous Na_2SO_4.

Winterin (**4**) *from royleanone* (**1**). To a mixture of **1** (1 g) and Na_2CO_3 (1 g) in dioxane-water (3:1, 40 ml), heated at 75°C under N_2 atmosphere, 3 ml of 30% H_2O_2 were added. After 30 min the reaction was cooled, acidified (5% HCl), diluted with water and extracted with $CHCl_3$. The extract, without characterization, was treated with an EtOH solution of H_5IO_6 (20% w/v, 25 ml) at room temperature for 60 h; then diluted with an aqueous solution of Na_2SO_3 (10% w/v), stirred for 30 min and extracted with $CHCl_3$. Work-up in the usual manner yielded a residue which was chromatographed with $CHCl_3$-MeOH (32:1) as eluant, giving (+)-winterin (**4**, 78 mg, 10% yield), mp 151-153°C (*n*-hexane); $[\alpha]_D^{26}$ +97.8° (c 0.61, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 1840, 1770, 1670; uv MeOH) λ_{max} nm (log ε): 256 (3.75); ^{1}H nmr (90 MHz): δ 1.25 (3H, *s*, Me-15), 0.97 and 0.91 (3H, each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 248 $[M]^+$ (6), 233 (15), 220 (79), 203 (100), 166 (67), 123 (49), 91 (42), 69 (36), 41 (73). (Found: C, 72.72; H, 8.31. $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%). Identical in all respects with the previously described compound.[16-19]

Preparation of 12-methoxy-8,12-abietadiene-11,14-dione (**5**) *from royleanone* (**1**). To a solution of royleanone (**1**, 4.7 g) in acetone (100 ml) were added dimethyl sulphate (10 ml) and K_2CO_3 (9 g), and the mixture was refluxed under N_2 atmosphere for 4 h. The reaction mixture was cooled (0°C), treated dropwise with diluted NH_4OH (10%) and acidified (10% HCl). Extraction with $CHCl_3$ and evaporation of the solvent gave **5** (4.9 g, 100%), mp 100-102°C (MeOH); ^{1}H nmr (90 MHz): δ 3.90 (3H, *s*, OMe), 3.17 (1H, *septet*, J = 7.2 Hz, H-15), 1.30 (3H, *s*, Me-20), 1.20 and

1.18 (3H each, *d*, J = 7.2 Hz, Me-16 and Me-17), 0.93 and 0.90 (3H each, *s*, Me-18 and Me-19). (Found: C, 76.21; H, 9.29. $C_{21}H_{30}O_3$ requires: C, 76.32; H, 9.15%). Identical to previously prepared 12-*O*-methylroyleanone.[20]

Ozonolysis of 12-O-methylroyleanone (**5**) *to give compounds* **6**, **7**, *and* **8**. Ozone was bubbled through a solution of **5** (1 g) in CH_2Cl_2 (200 ml) at -78°C until disappearance of the initial orange-coloured of the solution. Then, Zn dust (9 g) and cooled AcOH (40 ml) were added and the reaction mixture was stirred for 2 h at room temperature, filtered, diluted with water and extracted with $CHCl_3$. Drying and removal of solvent gave a crude of reaction which was chromatographed on silica gel (*n*-hexane-EtOAc 4:1 as eluant) yielding 880 mg of **6** (80%).

Methyl 11,14-dihydroxy-13-oxo-12,13-seco-8(14),9(11)-abietadien-12-oate (**6**). Mp 121-123°C (*n*-hexane); $[\alpha]_D^{20}$ +202.5° (*c* 0.121, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 3460, 3430, 1740, 1720; uv (MeOH + NaOMe) λ_{max} nm (log ε): 213 (3.96), 361 *sh* (3.81), 375 (3.88); ^{1}H nmr (300 MHz): δ 4.98 and 4.86 (1H each, *s*; interchangeable with D_2O, *OH*), 3.90 (3H, *s*, COOMe), 3.38 (1H, *septet*, J = 6.8 Hz, H-15), 2.17 (1H, *ddd*, J_1 = 18.6 Hz, J_2 = 11.1 Hz, J_3 = 7.3 Hz, H-7α), 1.26 (3H, *s*, Me-20), 1.15 and 1.06 (3H each, *d*, J = 6.8 Hz, Me-16 and Me-17), 0.91 and 0.88 (3H each, *s*, Me-18 and Me-19); ^{13}C nmr (75.4 MHz): δ SFORD and DEPT *multiplicity* (assignment): 211.9 *s* (C-13), 172.1 *s* (C-12), 146.8 *s* (C-11), 137.3 *s* (C-14), 107.7 *s* (C-9), 105.6 *s* (C-8), 54.0 *q* ($COOCH_3$), 51.0 *d* (C-5), 41.8 *t* (C-3), 36.3 *s* (C-10), 34.0 *t* (C-1), 33.4 *q* (C-18), 33.2 *s* (C-4), 32.5 *d* (C-15), 21.9 *t* (C-7), 21.6 *q* (C-19), 20.6 *q* and 20.0 *q* (C-16 and C-17), 19.1 *q* (C-20), 18.3 *t* (C-2), 18.0 *t* (C-6); eims (direct inlet) *m/z* (rel. int.): 364 $[M]^+$ (2), 310 (28), 263 (85), 249 (29), 175 (17), 105 (12), 91 (14), 71 (92), 55 (15), 43 (100). (Found: C, 69.32; H, 8.91. $C_{21}H_{32}O_5$ requires: C, 69.20; H, 8.85%).

Compound **5** (1.5 g) was treated with ozone as above and the reaction mixture was transferred to a cooled solution of H_5IO_6 (900 mg) in EtOH-H_2O (1:1, 100 ml). After 12 h at room temperature, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extracts were washed with a solution of Na_2SO_3, dried and evaporated giving a residue which was chromatographed on silica gel (*n*-hexane-EtOAc 3:1) yielding (+)-winterin (**4**, 40 mg, <5%) and compound **7** (1.02 g, 80%).

11ζ-Hydroxy-11-homo-(carboxymethyl)-drim-8-en-12,11ζ-olide (**7**).[31] Mp 92-94°C (spontaneously on cooling); $[\alpha]_D^{18}$ +84.9° (*c* 0.277, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 3420, 1760, 1745, 1680; uv (MeOH) λ_{max} nm (log ε): 223 (3.84); ^{1}H nmr (90 MHz): δ 5.33 (1H, *br* signal, disappeared, after addition of D_2O, OH), 3.83 (3H, *s*, COOMe), 2.30 (2H, *m*, 2H-7), 1.27 (3H, *s*, Me-15), 0.93 and 0.90 (3H, each, *s*, Me-13 and Me-14); ^{13}C nmr (75.4 MHz) δ SFORD *multiplicity* (assignment): 170.5 *s* and 169.3 *s* (C-16 and C-12, these assignments may be interchanged), 165.2 *s* (C-9), 129.8 *s* (C-8), 100.2 *s* (C-11), 54.2 *q* ($COOCH_3$), 51.0 *d* (C-5), 41.6 *t* (C-3), 37.5 *s* (C-10), 33.8 *t* (C-1), 33.4 *q* (C-13), 33.3 *s* (C-4), 21.6 *q* (C-14), 21.2 *t* (C-7), 20.0 *q* (C-15), 18.1 *t* (C-2), 17.7 *t* (C-6); eims (direct inlet) *m/z* (rel. int.): 308 $[M]^+$ (1), 249 (100), 203 (30), 175 (12), 91 (8), 69 (9), 55 (9), 41 (16). (Found: C, 66.39; H, 8.01. $C_{17}H_{24}O_5$ requires: C, 66.21; H, 7.85%).

12-*O*-Methylroyleanone (**5**, 1.5 g) was treated with ozone as above and the reaction mixture was transferred to a cooled (0°C) solution of NaOH (10% w/v, 50 ml) and H_2O_2 (30%, 13 ml). After 12 h at room temperature, the reaction was cooled at 0°C, acidified (2N HCl) and

extracted with Et_2O. The extracts were washed with brine, dried and evaporated. The crude of reaction was subjected to flash chromatography (silica gel, *n*-hexane-EtOAc 3:1) yielding (+)-winterin (**4**, 50 mg, <5%) and compound **8** (1.09 g, 90%).

11ζ-Hydroxy-11-homo-(carboxy)-drim-8-en-12,11ζ-olide (**8**).[31] Mp 100-102°C (EtOAc-*n*-hexane); $[\alpha]_D^{18}$ +91.6° (c 0.203, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 3565, 3330-3000, 1765, 1715, 1668; uv (MeOH) λ_{max} nm (log ε): 227 (3.72); ^1H nmr (90 MHz, pyridine-d_5): δ 2.45-2.15 (2H, *m*, 2H-7), 1.46 (3H, *s*, Me-15), 0.81 (6H, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 294 $[M]^+$ (0.1), 276 (0.2), 250 (18), 217 (28), 205 (53), 203 (47), 135 (40), 123 (74), 91 (55), 55 (50), 41 (100). (Found: C, 65.12; H, 7.47. $C_{16}H_{22}O_5$ requires: C, 65.29; H, 7.53%).

Methyl 11-oxo-11-homo-(carboxymethyl)-drim-8-en-12-oate (**9**) *from compounds* **7** *and* **8**. Treatment of compounds **7** and **8** with ethereal diazomethane in the usual manner, quantitatively yielded the same derivative (**9**), mp 110-112°C (MeOH); $[\alpha]_D^{19}$ +145.5° (c 0.088, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 1740, 1718, 1697, 1630; ^1H nmr (90 MHz): δ 3.87 and 3.69 (3H each, *s*, two $COOCH_3$), 2.55-2.30 (2H, *m*, 2H-7), 1.28 (3H, *s*, Me-15), 0.96 and 0.89 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 263 $[M-59]^+$ (100), 175 (9), 105 (8), 91 (6), 69 (6), 55 (6), 41 (13). (Found: C, 66.89; H, 8.14. $C_{18}H_{26}O_5$ requires: C, 67.06; H, 8.13%).

Drim-8-ene-11,12-dioic acid (**10**) *and its dimethyl ester* (**11**) *from compound* **8**. A solution of **8** (1 g) in benzene-MeOH (1:1, 20 ml) was treated with $Pb(OAc)_4$ (4.52 g, 3 equiv.) at 0°C under stirring. After 1.5 h, the reaction mixture was diluted with Et_2O, then filtered through a Celite pad, washed with diluted HCl (5%) and brine, and solvents removed. The residue (724 mg, 80%, 72% overall yield from **5** and **1**) was pure **10** (TLC). Methylation of this residue with diazomethane in the usual manner quantitatively yielded the diester **11**.

Dimethyl drim-8-ene-11,12-dioate (**11**). A colourless oil, $[\alpha]_D^{18}$ +66.1° (c 0.28, $CHCl_3$); ir (NaCl) ν_{max} cm^{-1}: 1750, 1730, 1640; ^1H nmr (90 MHz): δ 3.75 and 3.67 (3H each, *s*, two COOMe), 2.5-2.3 (2H, *m*, 2H-7), 1.22 (3H, *s*, Me-15), 0.90 and 0.85 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 294 $[M]^+$ (4), 263 (20), 234 (100), 219 (34), 203 (39), 185 (28), 105 (27), 91 (30), 41 (25). (Found: C, 69.48; H, 8.70. $C_{17}H_{26}O_4$ requires: C, 69.36; H, 8.90%).

Preparation of compound **11** *from (+)-winterin* (**4**). A solution of (+)-winterin (200 mg) in MeOH (5 ml) and pyridine (2 ml) was refluxed for 4 h and the solvents removed under reduced pressure. The residue was treated with diazomethane to give compound **11** (230 mg, 97%), identical with the previously prepared material (see above).

11,12-Dihydroxydrim-8-ene (**12**) *from compound* **11**. A solution of the diester **11** (138 mg) in ether (10 ml) was added dropwise to a suspension of $LiAlH_4$ (113 mg) in ether (12 ml) at 0°C under N_2. After a further 45 min, the reaction was worked up as usual to provide compound **12** (100 mg, 90%), mp 118-120°C (*n*-hexane); $[\alpha]_D^{20}$ +175.0° (c 0.116, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 3350; ^1H nmr (90 MHz): δ 4.2-4.1 (4H, *m*, 2H-11 and 2H-12), 2.6 (2H, *br* signal, interchangeable with D_2O, two OH), 2.3-2.2 (2H, *m*, 2H-7), 1.00 (3H, *s*, Me-15), 0.90 and 0.85 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 221 $[M-17]^+$ (48), 208 (24), 189 (70), 137 (33), 121

(39), 107 (54), 95 (70), 82 (62), 69 (82), 41 (100). (Found: C, 75.31; H, 10.79. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%). Identical in all respects with the previously described compound.[12,32,33]

11,12-Diacetoxydrim-8-ene (**13**) *from compound* **12**. Ac_2O-pyridine (1:2, 6 ml) treatment of compound **12** (382 mg) 48 h at room temperature gave **13** (515 mg, 100%), a colourless thick oil, $[\alpha]_D^{20}$ +81.9° (c 1.009, $CHCl_3$); ir (NaCl) ν_{max} cm^{-1}: 1745 strong; ^1H nmr (90 MHz): δ 4.6-4.4 (4H, *m*, 2H-11 and 2H-12), 2.05 and 2.01 (3H each, *s*, two OAc), 1.01 (3H, *s*, Me-15), 0.91 and 0.85 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 262 $[M-60]^+$ (18), 220 (50), 189 (44), 119 (35), 91 (27), 69 (27), 43 (100). (Found: C, 70.50; H, 9.13. $C_{19}H_{30}O_4$ requires: C, 70.77; H, 9.38%).

11,12-Diacetoxydrim-8-en-7-one (**14**) *from compound* **13**. CrO_3 (145 mg) was added to a solution of **13** (160 mg) in AcOH (4 ml) and the mixture was stirred overnight at room temperature. After addition of water, the reaction was extracted with Et_2O. Work-up in the usual manner followed by chromatrography (silica gel, *n*-hexane-EtOAc 7:3) gave compound **14** (107 mg, 65%), mp 87-88°C (*n*-hexane); $[\alpha]_D^{20}$ +62.3° (c 0.755, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 1750, 1745, 1680; ^1H nmr (90 MHz): δ 4.83 (4H, *m*, 2H-11 and 2H-12), 2.05 and 2.00 (3H each, *s*, two OAc), 1.15 (3H, *s*, Me-15), 0.92 and 0.88 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 336 $[M]^+$ (0.1), 234 (46), 124 (24), 109 (18), 65 (15), 55 (17), 43 (100). (Found: C, 67.69; H, 8.27. $C_{19}H_{28}O_5$ requires: C, 67.83; H, 8.39%). Identical with the previously described compound (racemic form).[34,35]

11,12-Dihydroxy-11-homo-(hydroxymethyl)-drim-8-ene (**20**) *from compound* **9**. A solution of the cetodiester **9** (1.6 g) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (1.2 g) in THF (20 ml) at 0°C under N_2. After a further 13 h, the reaction was worked up as usual to provide a crude product which was purified by chromatography (silica gel, $CHCl_3$-MeOH 9:1) yielding 798 mg of **20** as a mixture of C-11 epimers. An amorphous solid, ir (KBr) ν_{max} cm^{-1}: 3350, 2940, 1070, 1035; ^1H nmr (300 MHz, pyridine-d_5): δ (major C-11 epimer) 5.85-5.68 (3H, *br* signal, interchangeable with D_2O, three OH), 5.07 (1H, *dd*, J_1 = 9.2 Hz, J_2 = 3.9 Hz, H-11), 4.89 and 4.67 (1H each, *d*, an AB system, J = 11.7 Hz, 2H-12), 4.56 (1H, *dd*, J_1 = 11.3 Hz, J_2 = 9.2 Hz, H_B-16), 4.07 (1H, *dd*, J_1 = 11.3 Hz, J_2 = 3.9 Hz, H_A-16), 2.60 and 2.36 (1H each, *m*, 2H-7), 1.14 (3H, *s*, Me-15), 0.84 and 0.81 (3H each, *s*, Me-13 and Me-14), small signals (20%) of the H-11, 2H-16 and Me-15 protons corresponding to the minor C-11 epimer were also observed; ^{13}C nmr (20.1 MHz, pyridine-d_5) δ SFORD *multiplicity* (assignment): 144.1 *s* (C-9)*, 135.9 *s* (C-8)*, 71.9 *d* (C-11), 68.2 *t* (C-16), 63.3 *t* (C-12), 52.2 *d* (C-5), 41.8 *t* (C-3), 39.3 *s* (C-10), 36.9 *t* (C-1), 33.4 *s*+*q* (C-4 and C-13, respectively), 31.4 *t* (C-7), 21.9 *q* (C-14), 20.7 *q* (C-15), 19.4 *t* (C-6), 19.1 *t* (C-2), (*these assignments may be interchanged), these chemical shifts are those of the major C-11 epimer (small signals corresponding to the C-5, C-8, C-9, C-10, C-11, C-12, and C-16 carbons of the minor epimer were also observed); eims (direct inlet) *m/z* (rel. int.): 250 $[M-18]^+$ (0.6), 237 (15), 220 (12), 219 (42), 191 (69), 121 (51), 109 (56), 95 (87), 81 (52), 69 (88), 55 (74), 43 (77), 41 (100). (Found: C, 71.70; H, 10.61. $C_{16}H_{28}O_3$ requires: C, 71.60; H, 10.52%).

11,12-Diethoxy-11,12-epoxydrim-8-ene (**21**) *from compound* **20**. A solution of **20** (300 mg) in EtOH (4 ml) was added to a solution of H_5IO_6 (230 mg) in EtOH (3 ml). After 13 h at room temperature the reaction mixture was diluted with water and extracted with $CHCl_3$ to give compound **21** (an oil, 256 mg, 75%) as a mixture of all stereoisomers, ir (NaCl) ν_{max} cm^{-1}: 2930, 1100, 1040, 1000; ^1H nmr (90 MHz): δ 3.65 (4H, *m*, OCH_2Me), 1.19 (3H, *s*, Me-15), 1.18 (6H, *t*, *J* = 6 Hz, OCH_2Me), 0.88 (6H, *s*, Me-13 and Me-14). (Found: C, 74.19; H, 10.69. $C_{19}H_{32}O_3$ requires: C, 73.98; H, 10.46%).

(+)-Confertifolin (**17**) *and (+)-isodrimenin* (**18**) *from compound* **21**. A solution of compound **21** (240 mg) in acetone (5 ml) was added to a vigorously stirred mixture of 10% HCl in acetone (5 ml). After 30 min at room temperature the reaction mixture was transferred to a mixture of aqueous $NaHCO_3$ and Et_2O. The ethereal extract was dried and evaporated to give a crude oil. Column chromatography (silica gel, *n*-hexane-EtOAc 6:1) successively gave (+)-isodrimenin (**18**, 5 mg) and (+)-confertifolin (**17**, 123 mg), (combined yield 70%).

Drim-8-en-12,11-olide (confertifolin) (**17**). Mp 153-154°C (*n*-hexane); $[\alpha]_D^{25}$ +68.3° (c 0.404, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 1765, 1740, 1680; ^1H nmr (90 MHz): δ 4.74 (2H, *m*, 2H-11), 2.42-2.22 (2H, *m*, 2H-7), 1.21 (3H, *s*, Me-15), 0.95 and 0.91 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 234 $[M]^+$ (7), 219 (15), 188 (38), 123 (34), 91 (42), 69 (34), 55 (38), 41 (100). (Found: C, 76.94; H, 9.37. $C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%). Identical with the previously described compound.[17]

Drim-8-en-11,12-olide (isodrimenin) (**18**). Mp 103-105°C (*n*-hexane); $[\alpha]_D^{20}$ +86.3° (c 0.256, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 1745, 1670; ^1H nmr (90 MHz): δ 4.54 (2H, *s*, 2H-12), 1.23 (3H, *s*, Me-15), 0.90 and 0.88 (3H each, *s*, Me-13 and Me-14); eims (direct inlet) *m/z* (rel. int.): 234 $[M]^+$ (48), 219 (100), 189 (43), 151 (50), 123 (47), 112 (30), 91 (40), 69 (35), 41 (58). (Found: C, 76.71; H, 9.31. $C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%). Identical with the natural sesquiterpenoid.[32]

(+)-Confertifolin (**17**) and (+)-isodrimenin (**18**) were also obtained by us by reduction ($LiAlH_4$) of (+)-winterin (**4**). In this case, compound **18** was the major product of the reaction in a 9:1 ratio.

Preparation of the acetonide **23** *from compound* **20**. To an acetone solution (40 ml) of compound **20** (270 mg) 2 g of anhydrous $CuSO_4$ were added and the reaction mixture refluxed for 10 h. Then it was cooled, filtered and the solvent removed. The residue (277 mg, 90%) was the acetonide **23** as a mixture of C-11 epimers; colourless thick oil, ir (NaCl) ν_{max} cm^{-1}: 3430, 2940, 1210, 1160; ^1H nmr (90 MHz): δ 4.83 (1H, *t*, *J* = 7.5 Hz, H-11), 4.15-3.55 (4H, *m*, 2H-12 and 2H-16), 1.23 (6H, *s*, acetonide), 0.90, 0.88 and 0.83 (3H each, *s*, Me-13, Me-14 and Me-15). (Found: C, 73.76; H, 10.30. $C_{19}H_{32}O_3$ requires: C, 73.98; H, 10.46%).

Preparation of the derivative **24** *from compound* **23**. To a solution of the acetonide **23** (525 mg) in CH_2Cl_2 (10 ml) at -20°C under N_2 was added Et_3N (5.9 ml) and subsequently, a solution of MsCl (6 ml) in CH_2Cl_2 (6 ml) was dropwise added during 10 min under stirring. After a further 40 min, the reaction mixture was transferred to an aqueous solution of $NaHCO_3$ at 0°C,

then stirred for 5 min and extracted with cold CH_2Cl_2. The extract was successively washed with water, diluted HCl (5%) and brine, and the solvent removed at 5°C under reduced pressure. The residue, without purification, was treated with a suspension of $LiAlH_4$ (350 mg) in THF (88 ml) at -20°C for 40 min. Then, 2 ml of saturated aqueous solution of Na_2SO_4 were added to the reaction mixture. After a further 4 h, the reaction mixture was filtered through a Celite pad and the solvent removed yielding a crude residue from which, after chromatography (silica gel, *n*-hexane-EtOAc 3:1), 346 mg (70%) of compound **24** were isolated as a mixture of C-11 epimers; colourless thick oil, ^{1}H nmr (90 MHz): δ 4.80 (1H, *t*, J = 7 Hz, H-11), 4.0-3.7 (2H, *m*, 2H-16), 1.73 (3H, *s*, Me-12), 1.50 and 1.30 (3 each, *s*, acetonide), 0.90, 0.84 and 0.80 (3H each, *s*, Me-13, Me-14 and Me-15); ^{13}C nmr (20.1 MHz) δ SFORD *multiplicity* (assignment): 136.6 *s* (C-9), 133.7 *s* (C-8), 108.4 *s* (acetonide), 72.8 *d* (C-11), 69.4 *t* (C-16), 51.9 *d* (C-5), 41.5 *t* (C-3), 38.8 *s* (C-10), 36.4 *t* (C-1), 35.3 *t* (C-7), 33.3 *s* + *q* (C-4 and C-13, respectively), 26.6 *q* (acetonide), 24.3 *q* (acetonide), 21.6 *q* (C-14), 20.8 *q* (C-15),* 19.9 *q* (C-12),* 19.1 *t* (C-2),** 18.9 *t* (C-6),** (*,** these assignments may be interchanged, but those given here are considered to be the most likely). (Found: C, 78.14; H, 10.87. $C_{19}H_{32}O_2$ requires: C, 78.03; H, 11.03%).

The ^{1}H and ^{13}C nmr spectra of **24** showed some small signals of the minor C-11 epimer.

11-Hydroxy-11-homo-(hydroxymethyl)-drim-8-ene (**25**) *from compound* **24**. A solution of the acetonide **24** (290 mg) in THF (5 ml) was added to aqueous AcOH (80%, 20 ml) at room temperature under stirring. After a further 4.5 h, the solvents were removed and the residue chromatographed (silica gel, $CHCl_3$-MeOH 9:1) giving 214 mg (85%) of the diol **25** as a mixture of C-11 epimers; colourless amorphous powder; ^{1}H nmr (90 MHz): δ 4.50 (1H, *m*, H-11), 4.10-3.40 (2H, *m*, 2H-16), 1.80 (3H, *s*, Me-12), 0.98, 0.91 and 0.87 (3H each, *s*, Me-13, Me-14 and Me-15). (Found: C, 75.97; H, 11.07. $C_{16}H_{28}O_2$ requires: C, 76.14; H, 11.18%).

(+)-11-Hydroxydrim-8-ene (bicyclofarnesol) (**19**) *from compound* **25**. A solution of the diol **25** (250 mg) in benzene-MeOH (1:1, 30 ml) was treated with $Pb(OAc)_4$ (400 mg) at room temperature for 2 h. Work-up in the usual way gave a residue which, without characterization, was treated with a suspension of $LiAlH_4$ (100 mg) in ether (10 ml) at 0°C for 45 min and then worked in the usual manner. The crude product was crystallised from *n*-hexane yielding (+)-bicyclofarnesol (**19**, 155 mg, 70%), mp 89-90°C; $[\alpha]_D^{15}$ +105.4° (*c* 0.13, $CHCl_3$); ir (KBr) ν_{max} cm^{-1}: 3380, 2940, 1435, 1375, 1000; ^{1}H nmr (90 MHz): an AB system centered at δ 4.10 (J_{gem} ≈ 10.5 Hz, 2H-11), 1.70 (3H, *s*, Me-12), 0.98, 0.90 and 0.85 (3H each, *s*, Me-13, Me-14 and Me-15); eims (direct inlet) *m/z* (rel. int.): 222 $[M]^+$ (10), 207 (12), 204 (7), 191 (100), 189 (78), 121 (63), 95 (98), 69 (61), 41 (83). (Found: C, 81.17; H, 11.63. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%). Identical with the previously described compound (racemic form).[14,15]

Acknowledgements

We thank the Spanish Ministry of Education and Science for a research studentship (to J. A. H.-R.). This work was supported in part by the "Comisión Interministerial de Ciencia y Tecnología" (Grant SEUI No. PB0418).

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27. The root of *Salvia pratensis* L. contains a mixture of compounds **1**, **2**, and **3** in 3% yield on dry plant material, 25-30% on the acetone extract. (Unpublished results from our laboratory).
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30. It is of interest to note that **6** was the only tautomeric form of this compound detected by spectroscopic means. This can be attributed to the presence in **6** of a completely extended chromophore and intramolecular hydrogen bonding of the enolic protons (at δ 4.98 and 4.86, both sharp singlets in the ^{1}H nmr spectrum of **6**).
31. The derivatives **7** and **8** are one of the two possible epimers at C-11. Although this configuguration was not ascertained, it is reasonable to assume that both compounds are the 11 β-hydroxy epimer, since a 11 β configuration for the carbomethoxyl or carboxyl group causes strong steric interactions with the 15 methyl group.
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