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Chemistry of Zamoranic Acid. Part V* Homochiral Semisyntheses of Active Drimanes: Pereniporin B, Polygodial and Warburganal

Julio G. Urones, Isidro S. Marcos, Belen Gómez Pérez, David Díez, Anna M. Lithgow Patricio M. Gómez, Pilar Basabe and Narciso M. Garrido

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008, Salamanca, SPAIN

Abstract: Methyl 14,15-di*nor*-13-oxo-7-labden-15-oate was obtained from zamoranic acid methyl ester. The former by photochemical cleavage yielded methyl 7,9(11)-drimadien-12-oate, whose chemoselective epoxidation afforded methyl 9α,11-epoxy-7-drimen-12-oate, which is the key synthetic precursor for pereniporin B, polygodial and warburganal.

INTRODUCTION

The world needs a greater crop production to feed a continuously increasing population. With a rising productive area the number of pests have also increased considerably and thus the use of herbicides and insecticides.[1] Several insect species have developed resistance against agrochemicals causing not only a significant increase in the amount of chemicals used but also in the environmental pollutant level. The strategy used by plants to protect themselves from insect attack is the biosynthesis of secondary metabolites with antifeedant activity. These natural products are highly specific to some insect species and are completely inactive against other species useful to human beings.[2] Moreover, these compounds are biodegradable and there is no danger of accumulation or environmental pollution.[3] Among the natural antifeedants, azadirachtin isolated from *Azadirachta indica*,[4] some clerodane diterpenoids such as jodrellin A and B isolated from *Schutellaria woronowii* Juss[5] and some drimanes such as warburganal isolated from *Warburgia ugadensis*[6] and polygodial isolated from *Polygonum hydropiper*[7]should be highlighted because their specific and high antifeedant activity against *Spodoptera* species[8], which causes more than 30% crop losses in India.[9] Likewise, pereniporin A and B two natural products very similar to warburganal and polygodial have been isolated and showed strong cytotoxic and antimicrobial activity.[10]

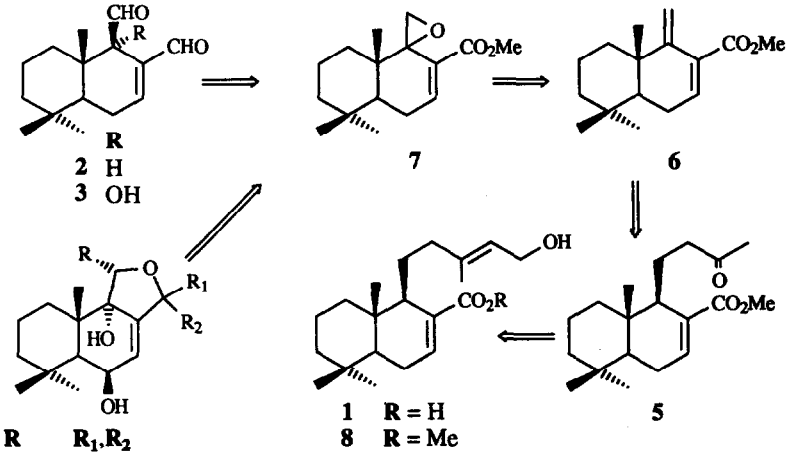
The semisyntheses of bioactive drimanes: pereniporin B, warburganal and polygodial, from zamoranic acid (**1**), one of the major acid components of *Halimium viscosum* (Valparaíso), are reported.

RESULTS AND DISCUSSION

Zamoranic acid, **1**, a bicyclic diterpene with a labdane skeleton[11] isolated from *H. viscosum* as its methyl ester **8**, has the stereochemistry and functional groups (Δ^7 conjugated to the carboxyl group in ring B at C-17 and $\Delta^{13}E$ in the side chain allylic to the primary hydroxyl at C-15) that make it a potentially good precursor[12] for the efficient semisynthesis of active drimanes. It is always accompanied by its 13,14-dihydro derivative **9**, from which can be separated by transformation in their 15-tetrahydropyranyl derivatives **10** and **11**, respectively.[13]

* For other parts see references 11, 12, 13 and 20.

Polygodial, **2**, warburganal, **3**, and pereniporin B, **4**, could be synthesized through the intermediate epoxide **7** prepared from diene **6**. The key step in the synthesis is the degradation of ketone **5** by a Norrish II type reaction.[14] The latter was prepared by oxidative cleavage of the side–chain double–bond of **8**. Finally, suitable functional group transformation will give the desired products **2**, **3** and **4** (Scheme 1).



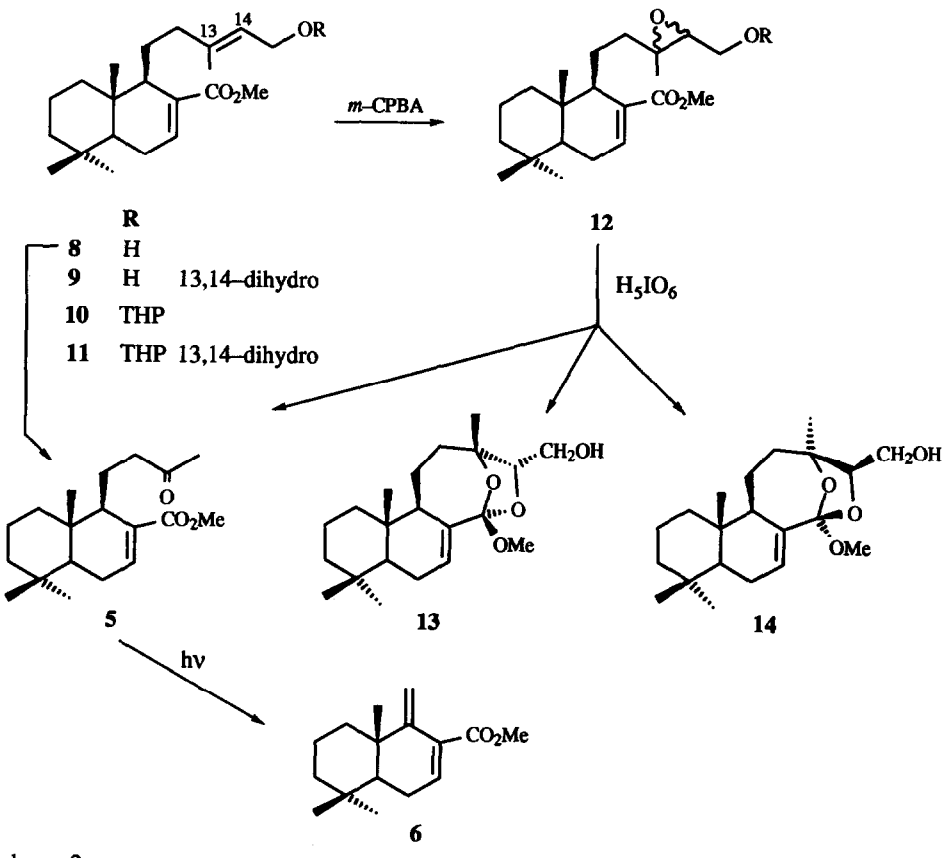
Scheme 1. Retrosynthetic analysis

Selective cleavage of the side–chain double bond of hydroxy ester **8** affords methyl ketone **5**[11] by direct oxidation methods using O_3,[15] $KMnO_4/NBu_4Br$,[16] $KMnO_4/MgSO_4$[17] or $CrO_3/HOAc$[18] with poor yields, (reaction conditions are summarized in Table 1) or by a two–step degradation that improves yields considerably. The first step requires a selective epoxidation of the side–chain double bond of compound **8** (or the natural mixture of **8** and **9**) by treatment with *m*–CPBA affording epoxides **12** quantitatively and unreacted **9** allowing an easier separation of the latter when it is present. Then, the mixture of epoxides was oxidized with H_5IO_6[19] to afford ketone **5** with more than 50% overall yield (Scheme 2). Orthoesters **13** and **14**[20] are also obtained in this oxidation step and they are being used, at present, in other interesting transformation reactions.

Table 1. Reaction Conditions for the Selective Cleavage of **8**

Reagents	Time	Temperature °C	**5** yield (%)
O_3 (2.8 g/h)[15]	4.0 min	−78	32
O_3 (4.2 g/h)	2.0 min	−78	21
O_3 (5.2 g/h)	1.5 min	−78	31
$KMnO_4/NBu_4Br$[16]	4 h	20	8
$KMnO_4/MgSO_4$[17]	6 h	20	18
1. *m*–CPBA / 2. H_5IO_6	1 h/2.5 h	20	51
$CrO_3/HOAc$[18]	3 h	20	39

Diene **6** was obtained from the Norrish II type cleavage of **5**[21] by irradiating a hexane solution of the latter with different lamps (the results are summarized in Table 2). The best yields were achieved with a high pressure Hg vapour lamp Hanau TQ-150 (150 W).



Scheme 2.

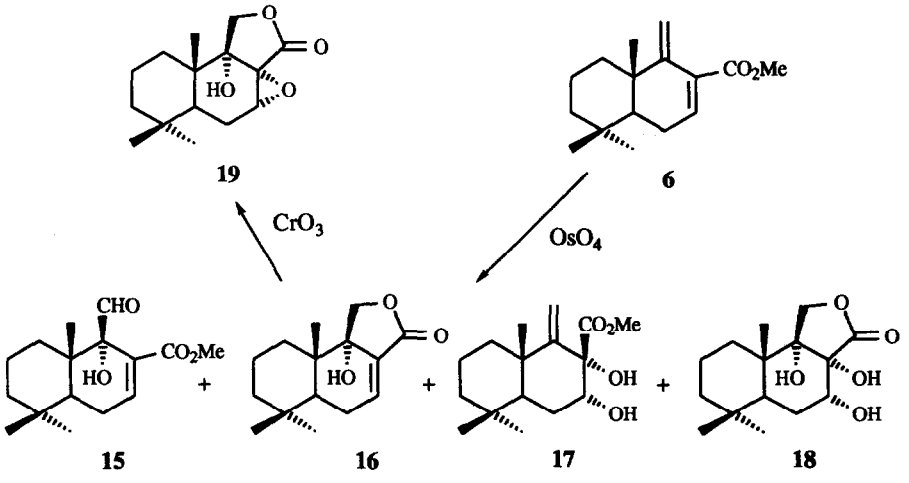
Table 2. Norrish II type Reaction Conditions

Lamp	Time (h)	6 yield (%)
Hanau Q–81*	2.5	66.0
Hanau Q–81*	3.5	84.0
Hanovia 450 W§	0.3	55.0
Hanovia 450 W§	0.5	64.0
Hanau TQ–150*	1.5	57.0
Hanau TQ–150*	2.0	86.0

*Hg vapour, high pressure; §Hg vapour, medium pressure

The first idea for the synthesis of pereniporin B, **4**, from diene **6** involved the *cis*–hydroxylation of the terminal double bond that should lead to a hydroxy lactone and later introduction of the hydroxyl group at C–6.

Treatment of **6** with OsO_4[22] under different reaction conditions, catalytic or stoichiometric (Table 3), afforded **15**, **16**, **17** and **18** that are dihydroxylated at C_9–C_{11}, C_7–C_8 or both. Compound **15** corresponds to the selective terminal double bond *cis*–hydroxylation followed by oxidation of the primary hydroxyl group. Diol **17** corresponds to the selective trisubstituted double bond *cis*–hydroxylation while **18** is a trihydroxy lactone corresponding to the *cis*–hydroxylation of the two double bonds. The desired lactone **16**[23] was obtained in a disappointing 20% yield and its allylic oxidation with CrO_3/3,5-dimethylpyrazole[24] did not lead to the α,β–unsaturated ketone but to epoxide **19**, ^1H NMR shows instead of the signal correponding to the olefinic hydrogen at C–7, a hydrogen at δ 3.94 ppm (d, J = 1.5 Hz) corresponding to H_7, where the value of the coupling constant also indicates the α–stereochemistry of the epoxide.



Scheme 3.

Table 3. *Cis*–hydroxylation Reaction Conditions from **6**

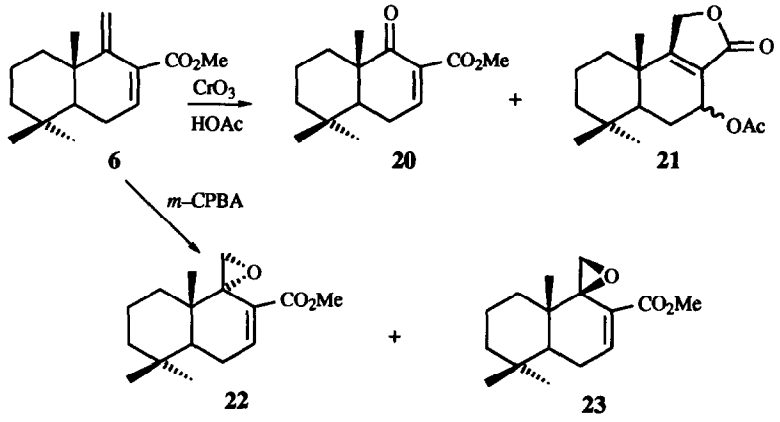
			Yield (%)			
Method*	**T/°C**	**Time**	**15**	**16**	**17**	**18**
A	20	4 days	11	10	3	13
B	20	22 h		11		
C	reflux	3h			31	52
D	20	3 days	4		12	48
E	0	9 days		19	65	

* Method A: Catalytic, OsO_4/NMO, *t*–BuOH/H_2O/THF 10:3:1; Method B: Stoichiometric, OsO_4, Pyridine; Method C: Catalytic, OsO_4/NMO, Pyridine; Method D: Catalytic, OsO_4/NMO, *t*–BuOH, Me_2CO/H_2O; Method E: Stoichiometric, OsO_4, Pyridine.

We thought, then, that pereniporin B, **4**, could be obtained by first doing the allylic oxidation followed by the *cis*–hydroxylation of the terminal double bond of diene **6**. The allylic oxidation with different oxidating chromium species afforded different products: **20**, a degradation compound ($[M]^+$ 267, $C_{15}H_{21}O_4$) was obtained

with either CrO_3/HOAc[25] or Na_2CrO_4/HOAc/NaOAc[26] as well as an acetoxy–α,β–unsaturated lactone **21**, both compounds perfectly agree with their spectroscopic properties (see experimental part); finally, oxidation with CrO_3/3,5–dimethylpirazole gave epoxide **22**.

The third approach to the synthesis of pereniporin B, **4** (Scheme 4), requires terminal double bond blocking as an epoxide before subjecting the substance to allylic oxidation of C–6. Treatment of **6** with *m*–CPBA gave the epoxide mixture **22** and **23** in a 7:3 ratio. The major compound **22** is separated by CC while the more polar **23** requires HPLC conditions for purification. However, allylic oxidation of **22** under different reaction conditions does not yield satisfactory results.



Scheme 4.

An alternative mode was designed to avoid the difficulties arising from allylic oxidation, requiring treatment of **22** with chlorosulfonyl isocyanate (CSI)[27] to afford the mixture of **24** and **25** (Scheme 5). Carbonate **24** is the major component (70 %) that shows in the ^1H NMR in addition to the peaks of the CH=C–COOMe grouping, a singlet of two hydrogens at δ 4.40 for methylene at C–11, and in its ^{13}C NMR a singlet at δ 84.4 ppm corresponding to a quaternary carbon attached to an oxygen and two carbonyls at δ 154.8 and 166.0 ppm. The minor compound **25** corresponds to a urethane according to its ^1H and ^{13}C NMR spectra.

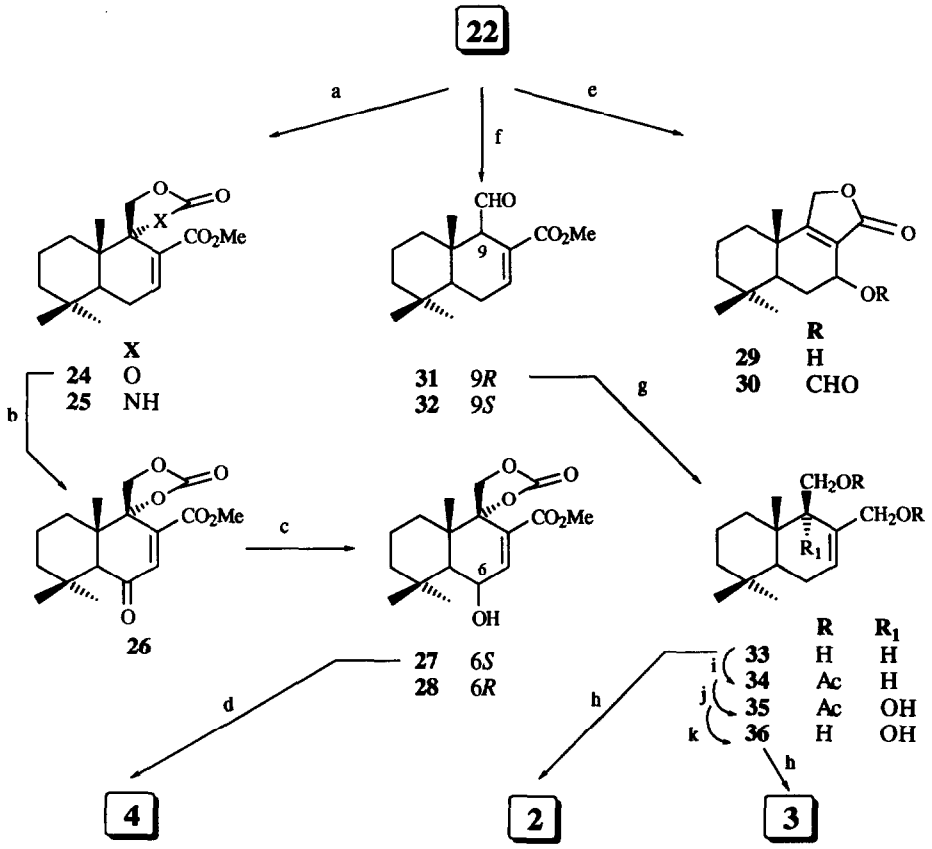
The oxidation of **24** was troublesome, obtaining the best results with CrO_3/HOAc at room temperature. Under these conditions the desired α,β–unsaturated ketone **26** was obtained in high yield. The reduction of **26** was selectively directed from the α–face by treatment with $NaBH_4/CeCl_3$[28] leading to **27** and traces of **28**. Hydrolysis of carbonate **27** with K_2CO_3[29] directly afforded pereniporin B, **4**, in an excellent overall yield (12%).

Epoxide **22** is also used to obtain polygodial and warburganal. While ring–opening of the oxiranic ring in acid medium ($HClO_4$/DMF)[30] produced allylic rearranged products **29** and **30**, treatment with Lewis acid (BF_3•Et_2O)[30,31] led to aldehydes **31** and **32** in 95:5 ratio. The stereochemistry of aldehyde **31** was confirmed by reduction with LAH to diol **33** (9*R*–7–drimen–11,12–diol)[23,32,33] a synthetic precursor of polygodial and warburganal according to the synthetic procedures already described (Scheme 5).[23]

Table . ^{13}C NMR data, 50.3 MHz, $CDCl_3$, δ (ppm).

C	2	3*	6	17	18	22	24	25	27	31	33	34	35	36
1	39.7	31.2	37.3	39.0	31.7	29.9	29.9	31.0	30.8	39.7	39.4	39.4	31.4	31.2
2	18.1	17.8	18.9	18.9	17.8	18.0	17.7	18.0	17.8	18.1	18.9	18.7	18.5	18.6
3	41.9	41.4	42.2	41.9	41.5	41.5	41.1	41.4	43.7	41.9	42.1	42.0	41.6	41.6
4	33.1	33.1	33.4	33.5	32.7	33.1	32.6	32.7	32.3	33.2	33.0	33.0	32.9	33.0
5	49.2	41.8	47.8	45.4	38.1	45.1	42.2	43.0	46.5	48.7	49.6	49.5	41.7	42.4
6	25.3	26.0	24.7	27.6	27.3	25.0	24.7	24.5	64.1	24.4	23.7	23.7	24.3	24.1
7	154.0	157.5	137.5	69.7	66.8	146.6	148.5	144.8	145.0	143.0	127.6	130.3	135.0	138.2
8	138.5	140.5	131.1	78.2	79.9	128.7	128.7	131.1	128.7	127.1	137.1	131.7	133.4	131.7
9	60.5	–	151.3	157.9	71.8	61.6	84.4	63.6	84.2	62.2	54.7	51.0	74.8	75.7
10	37.0	41.6	37.9	39.5	39.7	36.5	40.4	40.4	40.1	37.1	35.7	35.9	40.9	40.6
11	201.6	202.2	108.8	110.0	71.0	49.4	67.9	68.8	68.1	202.0	61.5	62.9	65.1	62.6
12	193.0	192.7	168.4	173.8	174.3	167.2	166.0	166.5	166.0	167.3	67.6	67.8	67.3	66.8
13	33.2	33.1	32.7	32.8	33.4	32.4	32.9	32.9	34.1	33.0	33.2	33.2	33.4	33.4
14	22.0	22.1	21.9	21.5	22.3	21.7	22.0	21.8	25.1	21.9	22.0	21.9	22.3	22.3
15	15.3	17.1	20.2	21.2	16.3	18.4	14.7	14.9	17.9	15.2	14.6	14.4	15.8	15.4
CO_2Me			51.6	52.7		51.6	52.1	51.7	52.3	51.7				
OCOMe												170.7	170.8	
OCOMe												171.0	170.6	
OCOMe												21.0	21.0	
OCOMe												21.0	21.1	
–OCOO–							154.8		154.7					
–OCONH								159.9						

* For ^{13}C NMR data in C_6D_6: see experimental part.



Scheme 5. a. CSI; b. CrO_3/HOAc; c. $NaBH_4/CeCl_3$; d. NaOH/Dioxane; e. $HClO_4$/DMF; f. $BF_3 \cdot Et_2O$; g. LAH; h. Swern oxidation; i. Ac_2O/Py; j. SeO_2; k. K_2CO_3.

EXPERIMENTAL

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively in a Bruker WP–200 SY. Chemical shifts are reported in δ ppm and coupling constants (J) are given in Hz. MS spectra were performed in a VG–TS 250 spectrometer at 70 eV ionizing voltage. Mass Spectra are presented as m/z (% rel. int.) Optical Rotations were determined in a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF, benzene were distilled from sodium, and pyridine and dichloromethane were distilled from calcium hydride under Ar atmosphere.

The raw material **8/9** was isolated from a hexane extract of *Halimium viscosum* as reported in reference 11.

TETRAHYDROPYRANYL DERIVATIVES OF **8** AND **9**: **10** AND **11**

7 ml (0.08 mol) of dihydropyrane (DHP) and 0.75 g (0.004 mol) of *p*–TsOH were added to a mixture of **8/9** (25 g, 0.07 mol) in dry benzene (35 ml). The reaction mixture was stirred at room temperature for 3.5 h, then, K_2CO_3 (0.7 g) was added and stirred for 30 min, filtered and evaporated to afford 31.0 g of crude product that was chromatographed on silica gel to give 9.0 g of **11** (29%) in the hexane/EtOAc 95:5 fractions and 21.0 g (66%) of **10** in the hexane/EtOAc 9:1 fractions.

ACID HYDROLYSIS OF **10** AND **11**: **8** AND **9**

Compound **10** (8.3 g, 0.02 mol) was dissolved in MeOH (30 ml) and *p*–TsOH (0.2 g, 0.001 mol) was added. The mixture was stirred at room temperature and monitored by TLC. After 1 h the reaction was complete, water was added and the reaction mixture extracted with ether, washed with 10% Na_2CO_3 and water until neutrality, dried, filtered and evaporated to give 6.6 g (99%) of **8** as a colourless oil.

Compound **11** (1.0 g) was dissolved in MeOH (5 ml) and treated with *p*–TsOH (0.03 g) according to the above procedure to afford 0.75 g (98%) of **9**.

MS of **8**: 334 ($[M]^+$, 3), 316 (13), 284 (10), 248 (23), 235 (10), 175 (11), 153 (9), 124 (17), 109 (54), 91 (21), 85 (100), 69 (48).

MS of **9**: 336 ($[M]^+$, 11), 304 (98), 235 (79), 181 (70), 124 (100), 107 (29),85 (97), 61 (91).

All other spectroscopic properties for **8**, **9**, **10** and **11** were reported in previous papers: refs. 11 and 13.

OXIDATION OF **8**: SYNTHESIS OF *Methyl 14,15–dinor–13–oxo–7–labden–17–oate*, **5**

Method A: To a solution of **8** (200 mg, 0.6 mmol) in reagent acetone (10 ml) $KMnO_4$ (311 mg, 2.0 mmol) and $MgSO_4$ (266 mg, 2.2 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, then filtered through a plug of Celite, solvent removal and chromatography gave 33 mg (18%) of **5** and 20 mg (20 %) of starting material.

Method B: To a stirred solution of $KMnO_4$ (474 mg, 2.96 mmol) and NBu_4Br (20 mg) in water (10 ml) was added a solution of **8** (330 mg, 0.99 mmol) in benzene (4 ml). After four hours at room temperatures the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (10 ml), filtered and extracted with ether. After usual work–up, the residue was chromatographed on silica gel affording 22 mg (7.7%) of **5** in the hexane/EtOAc 4:1 fractions and 17 mg (5.1%) of **8** in the hexane/EtOAc 7:3 fractions.

Method C: To 1.3 ml of 90% acetic acid CrO_3 (145mg, 1.4 mmol) was added. After stirring for 15 min, **8** (250 mg, 0.7 mmol) in CH_2Cl_2 (2ml) and glacial acetic acid (6 ml) were added and stirring was continued at room temperature for 3 h. MeOH was added and the solvent removed in vacuo. Work–up afforded 235 mg of crude product that after chromatography on silica gel gave 89 mg (40%) of **5** in the hexane:EtOAc 4:1 fractions.

Method D: A solution of **8** (978 mg, 2.9 mmol), in 15 ml of CH_2Cl_2, was cooled to –78° C with acetone/Dry Ice. Ozone (about 5.2 g of O_3/h) was bubbled through this solution for 1.5 min. To the cooled reaction mixture Ph_3P (1.53 g, 5.8 mmol) in 6 ml of CH_2Cl_2 was added and gradually allowed to reach room

temperature. The solvent was then removed at reduced pressure and the residue chromatographed on silica gel to give 116 mg (31%) of **5** with hexane/EtOAc 85:15 and 572 mg (56%) of starting material with hexane/EtOAc 7:3.

Compound **5**: MS: 306 ([M]$^+$, 4), 275 (98), 215 (19), 190 (43), 133 (17), 119 (36), 109 (100), 73 (84), 61 (61).

All other physical and spectral properties of **5** were previously reported in reference 11.

EPOXIDATION OF **8** WITH *m*–CPBA: SYNTHESIS OF *Methyl 13,14–epoxy–15–hydroxy–7–labden–17–oate*, **12**

To a solution of **8** (7.2 g, 0.02 mol) in dry CH_2Cl_2 (25 ml), *m*–CPBA (3.8 g, 0.02 mol) was added and stirred at room temperature. After 1 h, the solvent was removed and ether was added, washed with 40% $Na_2S_2O_3$, 10% Na_2CO_3 and water until neutrality, dried over Na_2SO_4, filtered and evaporated to give **12** (7.1 g, 94%).

Compound **12**. MS: 350 ([M]$^+$, 1), 304 (16), 248 (9), 205 (28), 181 (10), 149 (8), 124 (39), 109 (74), 99 (36), 69 (50), 61 (100). IR: ν_{max} (film) cm^{-1}: 3450, 1730, 1655, 1470, 1440, 1280, 1250, 1150, 1070, 790. ^{1}H NMR: 6.68 (1H, m, H–7), 3.74 (2H, m, H–15), 3.71 (3H, s, COOMe), 2.95 (1H, m, H–14),1.27 (3H, s, Me–16), 0.90, 0.86, 0.82 (3H, s ea, Me–18, Me–19, Me–20).

REACTION OF **12** WITH PERIODIC ACID: SYNTHESIS OF **5**, **13** AND **14**

To a solution of **12** (6.9 g, 0.02 mol) in THF (20 ml) a solution of H_5IO_6 (4.6 g, 0.02 mol) in H_2O (15 ml) was added and stirred for 2.5 h. The mixture was extracted with ether and washed with 5% $Na_2S_2O_3$, 10% Na_2CO_3 and water to afford after solvent removal 6.5 g of yellow oil that was chromatographed on silica gel affording 2.9 g of **5** (51%) with hexane/EtOAc 4:1 and 1.7 g (25%) of **13** and 1.4 g (20%) of **14** with hexane/EtOAc 7:3.

Compound **13**: MS: 350 ([M]$^+$, 2), 319 (8), 304 (41), 247 (6), 213 (23), 181 (23), 124 (86), 109 (100), 91 (48), 69 (78), 55 (98).

Compound **14**: MS: 350 ([M]$^+$, 6), 319 (7), 304 (31), 247 (6), 213 (32), 181 (23), 124 (73), 109 (100), 91 (48), 81 (57), 69 (78), 55 (98).

All other physical and spectral properties of **13** and **14** were previously reported in reference 20.

NORRISH II TYPE REACTION OF **5**: SYNTHESIS OF *Methyl 7,9(11)–drimadien–12–oate*, **6**

A solution of **5** (114 mg, 0.37 mmol) in dry hexane (250 ml) was poured in a quartz flask and a stream of dry N_2 was bubbled through. The solution was irradiated with UV light (Hanau Hg vapour lamp, 150 W, high pressure) for 2 h. Removal of solvent afforded a yellow oil which was purified by chromatography on silica gel with hexane/EtOAc 9:1, yielding 49 mg (53%) of **6** and 44 mg (39%) of starting material **5**.

Compound 6: $[\alpha]_D$= –75.2° ($CHCl_3$; c= 2.8%).UV (EtOH), λ_{max} (nm): 219 (ε=21000). MS: 248 ([M]$^+$, 41), 233 (15), 217 (13), 205 (14), 179 (18), 163 (16), 149 (25), 133 (15), 119 (28), 105 (33), 91 (41), 81

(49), 69 (100). IR: ν_{max} (film) cm^{-1}: 3080, 1725, 1645, 1240, 1160, 905, 790. ^1H NMR: 6.69 (1H, m, H-7); 5.32 (1H, s, H-11); 5.09 (1H, s, H-11); 3.77 (3H, s, –COOMe); 2.31 (1H, dt, J_{AB}=20.0, $J_{6,7}$=$J_{6,5}$=5.4, H_A–6); 2.14 (1H, ddd, J_{AB}=20.0, $J_{6,5}$=11.7, $J_{6,7}$=2.9, H_B–6); 0.98, 0.93, 0.87 (3H, s ea, Me–15, Me–14, Me–13). ^{13}C NMR: see Table.

REACTION OF **6** WITH OsO_4: SYNTHESIS OF **15**, **16**, **17** AND **18**

Method A: A solution of OsO_4 (2.5 % by weight in *t*–BuOH, 0.24 ml, 0.023 mmol) was added to a stirred solution of **6** (300 mg, 1.2 mmol) and N–Methylmorpholine–N–oxide (NMO, 163 mg, 1.2 mmol) in *t*–BuOH/THF/H_2O (10:3:1, 20 ml) at room temperature. After 4 days, the reaction was cooled to 0°C and 5 ml of 40% aqueous $NaHSO_3$ added and the mixture stirred for 4 h. The mixture was then filtered through a plug of celite eluting with CH_2Cl_2. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic phases dried, filtered and evaporated affording a residue which after chromatography yielded 36 mg (11%, H/EtOAc 9:1) of **15**, 31 mg (10%, H/EtOAc 4:1) of **16**, 9 mg (3%, H/EtOAc 4:1) of **17**, 43 mg (13%, H/EtOAc 65:35) of **18**.

Compound **15**: *Methyl 9α–hydroxy–11–al–7–drimen–12–oate*. MS: 280 ($[M]^+$, 4), 262 (4), 251 (76), 219 (100), 163 (11), 149 (13), 124 (29), 109 (61), 95 (20), 81 (28), 69 (48). IR: ν_{max} (film) cm^{-1}: 3465, 2860, 1720, 1445, 1275, 1255, 1135, 1045, 765. ^1H NMR: 9.74 (1H, s, –CHO, H-11); 7.42 (1H, dd, J=2.7 and 5.4, H-7); 4.03 (1H, s, -OH); 3.72 (3H, s, –COOMe); 1.10, 0.97, 0.92 (3H, s, ea).

Compound **16**: *9α–hydroxy–7–drimen–12,11–olide*. MS: 250 ($[M]^+$, 25), 217 (6), 149 (10), 127 (59), 109 (100), 91 (19), 81 (31), 69 (42). IR: ν_{max} (film) cm^{-1}: 3440, 2980, 2840, 1745, 1680, 1460, 1230, 1100, 760. ^1H NMR: 7.04 (1H, dd, J=3.5 and 5.0, H-7); 4.37 (1H, d, J=10, H_A-11); 4.23 (1H, d, J=10, H_B-11); 0.99, 0.96, 0.90 (3H, s, ea).

Compound **17**: *Methyl 7α,8α–dihydroxy–9(11)–drimen–12–oate*. MS: 282 ($[M]^+$, 4), 264 (8), 249 (6), 223 (100), 205 (27), 189 (11), 177 (38), 163 (21), 149 (15), 130 (77), 123 (33), 109 (52), 91 (32), 81 (38), 69 (57). IR: ν_{max} (film) cm^{-1}: 3440, 1730, 1635, 1245, 1020, 910, 760. ^1H NMR: 5.20 (1H, s, H_A-11), 5.12 (1H, s, H_B-11), 4.41 (1H, m, H-7), 3.77 (3H, s, –COOMe), 3.38 (1H, bs, –OH); 0.99, 0.89, 0.88 (3H, s, ea). ^{13}C NMR: see Table.

Compound **18**: *Methyl 7α,8α,9α–trihydroxy–driman–12,11–olide*. MS: 284 ($[M]^+$, 5), 248 (11), 213 (10), 167 (9), 149 (11), 124 (35), 109 (72), 97 (29), 81 (42), 69 (79), 55 (100).IR: ν_{max} (film) cm^{-1}: 3440, 1760, 1645, 1460, 1375. ^1H NMR: 4.31 (1H, m, H-7); 4.24 (1H, d, J=9.2, H_A-11); 3.98 (1H, d, J=9.2, H_B-11); 2.92 (1H, bs, -OH); 0.95, 0.94, 0.87 (3H, s, ea). ^{13}C NMR: see Table.

Method B: A solution of OsO_4 (40 mg, 0.16 mmol) in dry pyridine (2 ml) was added to a stirred solution of **6** (47 mg, 0.19 mmol) in dry pyridine (2 ml). The deep yellow solution was stirred at room temperature for 22 h and 1.2 ml of 40% aqueous $NaHSO_3$ added. The mixture was stirred for 1.5 h, diluted with water and extracted with $CHCl_3$ (3 x 15 ml) and EtOAc (3 x 15 ml). The combined organic phases were washed with 6N HCl and water, dried, filtered and evaporated affording a residue which was chromatographed yielding 5 mg (11%, H/EtOAc 4:1) of **16**.

Method C: A solution of OsO_4 (2.5 % by weight in *t*–BuOH, 0.05 ml) was added to a stirred solution of **6** (37 mg, 0.15 mmol) and NMO (28 mg, 20 mmol) in pyridine (0.05 ml), water (2 ml) and *t*–BuOH (4 ml) and refluxed for 3 h, after cooling to room temperature 2 ml of 40% aqueous $NaHSO_3$ was added and the mixture stirred for 1 h. *t*–BuOH was evaporated at reduced pressure, brine was added and the mixture extracted with ether, usual work–up afforded a residue which was chromatographed yielding 13 mg (31%, H/EtOAc 4:1) of **17** and 22 mg (52%, H/EtOAc 7:3) of **18**.

Method D: NMO (48 mg, 0.35 mmol) and a solution of OsO_4 (2.5 % by weight in *t*–BuOH, 0.08 ml) was added to a stirred solution of **6** (44 mg, 0.17 mmol) in a mixture of acetone/water 8:1 (4 ml) at room temperature and stirred at room temperature for 3 days. After that time 5 ml of 40% aqueous $NaHSO_3$ was added and the mixture stirred for 20 min, extracted with EtOAc (3 x 15 ml) and washed with brine, dried, filtered and evaporated to afford a residue which was chromatographed yielding 2 mg (4%, H/EtOAc 9:1) of **15**, 6 mg (12%, H/EtOAc 75:25) of **17** and 24 mg (49%, H/EtOAc 7:3) of **18**.

Method E: A solution of OsO_4 (38 mg, 0.15 mmol) in dry pyridine (1.5 ml) was added to a stirred solution of **6** (42 mg, 0.17 mmol) in dry pyridine (1.5 ml) at –10°C. The deep solution is stirred at 0 °C for 9 days and 4 ml of 40% aqueous $NaHSO_3$ added. The mixture was stirred for 1.5 h diluted with water and extracted with ether (3 x 15 ml) and EtOAc (3 x 15 ml). The combined organic phases were washed with 6N HCl and water, dried, filtered and evaporated affording a residue which was chromatographed yielding 8 mg (19%, H/EtOAc 4:1) of **16** and 31 mg (65%, H/EtOAc 4:1) of **17**.

REACTION OF **16** WITH CrO_3/3,5–DMP: SYNTHESIS OF *9α–hydroxy–7α,8α–epoxy–driman–12,11–olide*, **19**

To a solution of CrO_3 (64 mg, 0.64 mmol) in CH_2Cl_2 (0.65 ml) at –20 °C 62 mg (0.68 mmol) of 3,5–dimethylpyrazole (3,5–DMP) was added in one portion. After stirring for 15 min, a solution of **16** (8 mg, 0.032 mmol) in CH_2Cl_2 (0.65 ml) was added. The reaction mixture was stirred at –20 °C for 18 h, warmed to 0 °C and 1 ml of 1M NaOH solution was added. The organic phase was separated and washed with 5 % HCl, water, 5% $NaHCO_3$ and brine, dried and evaporated affording after chromatography on silica gel (hexane/EtOAc 75:25) 6 mg of **19** (71%). IR: ν_{max} (film) cm^{-1}: 3450, 1770, 1275, 1120, 1070, 1035, 960. ^1H NMR: 4.67 (1H, d, J =11.2, H_A-11); 4.41 (1H, d, J=11.2, H_B-11); 3.94 (1H, d, J=1.5, H-7); 2.61 (1H, s, –OH); 0.96, 0.94, 0.90 (3H, s, ea, Me–13, Me–14 and Me–15).

OXIDATION OF **6** WITH CrO_3/HOAc: SYNTHESIS OF **20** AND **21**

To a stirred solution of diene **6** (50 mg., 0.20 mmol.) in acetic acid (2 ml.) CrO_3 (187 mg., 1.87 mmol.) was added at room temperature and stirred for 6.5 h, then it was diluted with water (50 ml.) extracted with ether (x3) and washed with 5% $Na_2S_2O_3$, saturated $NaHCO_3$ and brine, dried and evaporated to yield, after CC on silica gel with H/EtOAc 4:1, 9 mg (16.1%) of **20** and 7 mg (12.6%) of **21**.

Compound **20**: *Methyl 11–nor–9–oxo–7α,8α–epoxy–driman–12–oate*. MS: 250 ($[M]^+ - C_2H_2O$, 17), 232 ($[M]^+$ – HOAc, 65), 217 (24), 189 (11), 173 (16), 161 (16), 147 (19), 133 (18), 119 (30), 105 (44), 91 (70),

77 (51), 69 (63), 55 (100). IR: ν_{max} (film) cm^{-1}: 1760, 1750, 1720, 1460, 1440, 1280, 1240, 990, 760. ^1H NMR: 3.81 (3H, s, –COOMe), 3.66 (1H, t, J = 2.2, H-7); 2.37 (1H, ddd, J = 14, 4.3 and 2.2, H_A-6); 1.96 (1H, ddd, J = 14, 10 and 2.2, H_B-6); 1.15, 0.96, 0.91 (3H, s, ea, Me–13, Me–14 and Me–15).

21: *7ξ–acetoxy–8–drimen–12,11–olide*. MS: 250 ($[M]^+$–H_2O, 17), 232 ($[M]^+$–HOAc, 65), 217 (24), 189 (11), 173 (16), 161 (16), 147 (19), 133 (18), 119 (30), 105 (44), 91 (70), 77 (51), 69 (63), 55 (100). IR: ν_{max} (film) cm^{-1}: 1770, 1750, 1240, 1040, 950. ^1H NMR: 5.65 (1H, m, H-7); 4.75 (2H, s, H-11); 2.05 (3H, s, –OCOMe); 1.14 (3H, s); 0.90 (6H, s). ^{13}C NMR: 35.65 (1), 18.35 (2), 41.44 (3), 29.74 (4), 46.63 (5), 26.06 (6), 62.64 (7), 122.31 (8), 130.85 (9), 37.17 (10), 66.07 (11), 176.94 (12), 32.88 (13), 21.06 (14), 19.56 (15), 169.99 (OCOMe), 21.43 (OCOMe).

OXIDATION OF **6** WITH Na_2CrO_4: SYNTHESIS OF **21**

To a solution of **6** (53 mg, 0.21 mmol) in benzene (0.4 ml) at 0°C anhydrous Na_2CrO_4 (60 mg, 0.37 mmol.), acetic acid (0.3 ml), acetic anhydride (0.54 ml) and anhydrous sodium acetate (46 mg) were added. The mixture was stirred for 7 days at 0 °C. The mixture was then poured in ice–water for 1 hour and extracted with ether (3x20 ml.). The organic phase was washed with 5% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and evaporated affording a residue that was chromatographed (H/EtOAc, 4:1) yielding 19 mg (30.0%) of **21**. MS: 292 ($[M]^+$, 1), 250 (17), 232 (65), 217 (24), 189 (11), 173 (16), 161 (16), 147 (19), 133 (18), 119 (30), 105 (44), 91 (70), 77 (51), 69 (63), 55 (100). IR: ν_{max} (film) cm^{-1}: 1770, 1750, 1240, 1040, 950. ^1H NMR: 5.65 (1H, m, H-7), 4.75 (2H, s, H-11), 2.05 (3H, s, –OCOMe), 1.14 (3H, s), 0.90 (6H, s). ^{13}C NMR: 35.7 (1), 18.4 (2), 41.4 (3), 29.7 (4), 46.6 (5), 26.1 (6), 62.6 (7), 122.3 (8), 130.9 (9), 37.2 (10), 66.1 (11), 176.9 (12), 32.9 (13), 21.1 (14), 19.6 (15), 170.0 (–OCOMe), 21.4 (–OCOMe).

OXIDATION OF **6** WITH CrO_3/3,5–DMP

To a solution of CrO_3 (454 mg, 4.54 mmol) in dry CH_2Cl_2 (4.5 ml) at – 20 °C, was added 453 mg (4.71 mmol) of DMP in one portion. After stirring for 15 min at – 20 °C a solution of **6** (56 mg, 0.22 mmol.) in CH_2Cl_2 (4.5 ml) was added and stirred for 8 days, then the solvent was removed at reduced pressure and the residue chromatographed yielding with hexane/EtOAc 85:15, 39 mg (65.2%) of **22**.

EPOXIDATION OF **6** WITH *m*–CPBA: SYNTHESIS OF **22** AND **23**

To a solution of **6** (44 mg, 0.2 mmol) in dry CH_2Cl_2 (2 ml) was added *m* –CPBA (34 mg, 0.2 mmol) and stirred at room temperature for 50 min. The solvent was evaporated and the residue dissolved in ether, washed with 40 % $Na_2S_2O_3$, 10% aqueous Na_2CO_3 and H_2O, dried over anhydrous Na_2SO_4, filtered and evaporated yielding 40 mg of yellow oil that was purified by HPLC affording 25 mg (70%) of **22** and 12 mg (30%) of **23**.

Compound **22**: *Methyl 9α(11)–epoxy–7–drimen–12–oate*.

MS: 264 ($[M]^+$, 72), 249 (10), 219 (100), 109 (32), 91 (38), 69 (33), 55 (40). IR: ν_{max} (film) cm^{-1}: 1730, 1650, 1450, 1250, 1160, 1050, 825. ^1H NMR: 7.20 (1H, m, H-7), 3.75 (1H, d, J = 4.4, H_A-11), 3.70 (3H, s, –COOMe), 2.94 (1H, d, J = 4.4, H_B-11), 1.00, 0.93, 0.91 (3H, s, ea, Me–13, Me–14 and Me–15). ^{13}C NMR: see Table .

Compound **23**: *Methyl 9β(11)–epoxy-7-drimen-12-oate.*

MS: 264 ([M]$^+$, 72), 249 (52), 219 (100), 109 (53), 91 (40), 69 (39), 55 (68). IR: ν_{max} (film) cm^{-1}: 1730, 1650, 1450, 1250, 1160, 1050, 825. ^{1}H NMR: 6.88 (1H, dd, J = 2.9 and 4.9, H-7), 3.88 (3H, s, –COOMe), 3.42 (1H, d, J = 4.9, H_A-11), 3.18 (1H, d, J = 4.9, H_B-11), 1.07, 0.96, 0.91 (3H, s, ea, Me–13, Me–14 and Me–15).

REACTION OF **22** WITH CSI: SYNTHESIS OF **24** AND **25**

To a stirred solution of **22** (680 mg, 2.57 mmol) in benzene/CH_2Cl_2 (5:1, 8.5 ml) at -10°C, was added a solution of CSI (chlorosulfonylisocyanate, 0.23 ml., 2.59 mmol) in the same solvent mixture (17ml). After stirring for 10 min the solvent was evaporated at reduced pressure. The residue was dissolved in 20 ml of acetone/water 95:5 and the resulting acid solution was carefully neutralized by adding 5% aqueous KOH dropwise. The solution was stirred for 30 min at room temperature and diluted with water, extracted with ether (3 x 20 ml), washed with water, dried, filtered and evaporated. The residue was chromatographed (SiO_2) affording 539 mg (68%) of **24** (H/EtOAc 4:1) and 198 mg (25%) of **25** (H/EtOAc 3:2).

Compound **24**. MS: 308 ([M]$^+$, 6), 264 (7), 232 (9), 163 (7), 124 (100), 81 (54), 69 (36). IR: ν_{max} (film) cm^{-1}: 1780, 1710, 1280, 1075, 1000, 760.^{1}H NMR: 7.36 (1H, dd, J=3.0 and 6.0, H-7); 4.40 (2H, s, H-11); 3.79 (3H, s, –COOMe); 0.96, 0.93, 0.86 (3H, s, ea, Me–13, Me–14 and Me–15). ^{13}C NMR: see Table.

Compound **25**. MS: 307 ([M]$^+$, 5), 233 (4), 183 (100), 151 (46), 124 (21), 109 (65), 91 (18), 81 (23), 69 (36), 55 (31).IR: ν_{max} (film) cm^{-1}: 3270, 1745, 1720, 1260, 1240, 1130, 1040, 760.^{1}H NMR: 7.14 (1H, dd, J = 2.4 and 5.4, H-7); 6.02 (1H, bs, –NH); 4.38 (1H, d, J = 9.3, H_A-11); 4.32 (1H, d, J = 9.3, H_B-11); 3.76 (3H, s, –COOMe); 0.94, 0.93, 0.82 (3H, s, ea, Me–13, Me–14 and Me–15). ^{13}C NMR: see Table.

ALLYLIC OXIDATION OF **24**: SYNTHESIS OF **26**

To a stirred solution of **24** (53 mg, 0.17 mmol) in acetic acid (1.6 ml) was added CrO_3 (161 mg, 1.6 mmol) at room temperature and stirring was continued for 9 h, then it was diluted with water (30 ml) and extracted with ether (3x20 ml). The combined organic phases were washed with 5% $Na_2S_2O_3$ solution, saturated $NaHCO_3$ and brine, dried, filtered and evaporated. The residue was chromatographed yielding 39 mg (70%) of **26**. MS: 322 ([M]$^+$, 7), 279 (7), 235 (16), 198 (16), 154 (62), 109 (46), 81 (51), 69 (100). IR: ν_{max} (film) cm^{-1}: 1790, 1725, 1690, 1260, 1075, 760. ^{1}H NMR: 6.78 (1H, s, H-7); 4.51 (1H, d, J = 9.0, H_A-11); 4.41 (1H, d, J = 9.0, H_B-11); 3.87 (3H, s, –COOMe); 2.70 (1H, s, H-5); 1.18, 1.17, 0.99 (3H, s, ea, Me–13, Me–14 and Me–15).

REDUCTION OF **26**: SYNTHESIS OF **27** AND **28**

To a solution of **26** (18mg, 0.056 mmol) and $CeCl_3$ (25 mg, 0.068 mmol) in methanol (0.3 ml) and THF (0.3 ml) at –10 °C, was added $NaBH_4$ (3 mg, 0.074 mmol), the mixture was stirred for 40 min at –10 °C, diluted with saturated NH_4Cl (15 ml.) and extracted with ether, washed with brine, dried filtered and evaporated. The residue was chromatographed (SiO_2, H/EtOAc 7:3) yielding 10 mg(56%) of **27** and 1 mg (5.5%) of **28**.

Compound **27**. MS: 324 ([M]$^+$, 3), 279 (8), 256 (8), 199 (30), 156 (37), 124 (42), 109 (46), 95 (25), 81 (48), 69 (100). IR: ν_{max} (film) cm^{-1}: 3460, 1780, 1720, 1260, 1080, 765. ^{1}H NMR: 7.14 (1H, d, J = 5.4, H-7); 4.67 (1H, dd, J = 5.4 and 4.8, H-6); 4.43 (1H, d, J = 9.1, H_A-11); 4.37 (1H, d, J = 9.1, H_B-11); 3.82 (3H, s, –COOMe); 1.32, 1.12, 1.11 (3H, s, ea, Me–13, Me–14 and Me–15). ^{13}C NMR: see Table.

Compound **28**. IR: ν_{max} (film) cm^{-1}: 3460, 1780, 1720, 1260, 1080, 765. ^{1}H NMR: 7.16 (1H, d, J = 2.5, H-7); 4.8–4.2 (1H, m, H-6); 4.40 (2H, s, H-11); 3.82 (3H, s, –COOMe); 1.32, 1.10, 0.95 (3H, s, ea, Me–13, Me–14 and Me–15).

HYDROLYSIS OF **27**: **Pereniporin B, 4.**

To a solution of **27** (16 mg, 0.050 mmol) in 4% NaOH/Dioxane (1:1, 1 ml), stirred for 1h at room temperature, 1N NaOH (30 ml) was added and extracted with ether. The ethereal phase was washed with 1N NaOH. The combined aqueous phases were acidified at 5°C with 2N HCl (pH 3-4) and extracted with CH_2Cl_2. The organic phase was washed with brine, dried, filtered and evaporated to afford a residue which was chromatographed yielding 9 mg (70%) of Pereniporin B. IR: ν_{max} (film) cm^{-1}: 3430, 1750, 1660, 1465, 1120, 930. ^{1}H NMR: 6.81 (1H, d, J = 3.8, H-7); 4.66 (1H, m, H-6); 4.48 (1H, d, J = 9.7, H_A-11); 4.25 (1H, d, J = 9.7, H_B-11); 1.35, 1.16, 1.13 (3H, s, ea, Me–13, Me–14 and Me–15).

ACID RING–OPENING OF **22/23**: SYNTHESIS OF **29** AND **30**.

To a solution of the mixture of **22/23** (358 mg, 1.5 mmol) in DMF (3 ml) was added an aqueous solution of perchloric acid (70%, 0.1 ml, 1.6 mmol) and stirred at room temperature for 7 h. Water was added (30 ml) the mixture extracted with ether; washed with 10% Na_2CO_3 and water, dried, filtered and evaporated yielding 350 mg of a crude reaction product which was chromatographed affording with H/EtOAc 55 mg (16%) of **30** and with EtOAc 260 mg (80%) of **29**.

Compound **29**. IR: ν_{max} (film) cm^{-1}: 3460, 1750, 1220, 1060, 910. ^{1}H NMR: 4.75 (2H, m, H-11), 4.55 (1H, m, H-7), 1.13, 0.98, 0.92 (3H, s, ea, Me–13, Me–14 and Me–15). ^{13}C NMR: 35.7 (1), 18.4 (2), 41.6 (3), 33.0 (4), 46.0 (5), 27.8 (6), 60.2/65.1 (7), 131.0 (8), 125.1(9), 37.2 (10), 68.4 (11), 174.2 (12), 33.2 (13), 21.5 (14), 19.6 (15).

Compound **30**. IR: ν_{max} (film) cm^{-1}: 1760, 1730, 1170, 1020, 980. ^{1}H NMR: 8.10 (1H, s, –OCHO), 5.65 (1H, m, H-7), 4.76 (2H, m), 1.15 (3H, s), 0.91 (6H, s).

ACETYLATION OF **29**: **21**.

To **29** (25 mg, 0.1 mmol) was added pyridine (1 ml) and Ac_2O (0.5 ml) and left at room temperature for 12 h. Following the usual work–up 25 mg (97%) of **21** was obtained.

REACTION OF **22** WITH BF_3•Et_2O: SYNTHESIS OF *Methyl 9R–11–oxo–7–drimen–12–oate*, **31** AND *Methyl 9S–11–oxo–7–drimen–12–oate*, **32**

To a solution of **22** (160 mg, 0.6 mmol) in dry benzene (5 ml) was added a drop of freshly distilled BF_3•Et_2O, and stirred for 5 min. Water was added, extracted with ether and washed with 10% Na_2CO_3 and

water, dried, filtered and evaporated to afford 158 mg of **31/32** (99%) as a colourless oil. MS: 264 ([M]$^+$, 2), 236 (70), 221 (20), 177 (10), 124 (68), 109 (100), 91 (55), 81 (38), 69 (58), 55 (57). IR: ν_{max} (film) cm^{-1}: 2710, 1720, 1710, 1660, 1250, 1150, 860. ^{1}H NMR: 9.82 (1H, d, J = 3.9, H-11′), 9.53 (1H, d, J = 3.9, H-11), 7.23 (1H, m, H-7), 3.70 (3H, s, -COOMe), 2.92 (1H, m, H-9), 0.92 (6H, s), 0.88 (3H, s). ^{13}C NMR: see Table.

The integral of the peaks corresponding to H-11 and H-11′ showed that **31** and **32** are in 95:5 ratio.

REDUCTION OF **31**: SYNTHESIS OF *9R–7–drimen–11,12–diol*, **33**.

To a solution of **31** (65 mg, 0.25 mmol) in dry ether (3 ml) was added 8 mg (0.2 mmol) of $LiAlH_4$ and stirred at room temperature for 1 h. Then, wet ether was added, filtered, dried and evaporated to afford 41 mg (80%) of **33**. $[\alpha]_D$ –6.4 ($CHCl_3$, c 1.0). MS: ([M]$^+$-18, 21), 190 (17), 137 (10), 123 (50), 109 (83), 95 (30), 81 (41), 69 (70), 55 (74), 41 (100). IR: ν_{max} (film) cm^{-1}: 3340, 1465, 1390, 1365, 1036. ^{1}H NMR: 5.81 (1H, m, H-7), 4.38 (1H, d, J = 12.1, H_A-12), 3.99 (1H, d, J = 12.1, H_B-12), 3.92 (1H, dd, J=11.9 and 2.1, H_A-11), 3.69 (1H, dd, J=11.9 and 7.5, H_B-11), 0.89, 0.87, 0.77 (3H, s,ea, Me–13, Me–14 and Me–15). ^{13}C NMR: see Table.

SWERN OXIDATION OF **33**: **Polygodial, 2**

Oxalyl chloride (0.03 ml, 0.37 mmol) in CH_2Cl_2 (1.5 ml) was cooled at –60 °C. A solution of DMSO (0.06 ml, 0.7 mmol) in CH_2Cl_2 (1 ml) was slowly added in a 5 min period. A solution of **33** (43 mg, 0.18 mmol) in CH_2Cl_2 (2 ml) was added dropwise and stirred for 1 h at –60 °C. Triethylamine (0.36 ml, 1.8 mmol) was added and the reaction kept at –60 °C for 5 min, warmed to room temperature and quenched with water, extracted with ether and washed successively with 0.5N HCl, 5% $NaHCO_3$ and water, dried, filtered and evaporated yielding 41 mg (98%) of a solid **2** that was recrystallized from hexane. mp 58-60 °C. $[\alpha]_D$ -112 (EtOH, c 0.2). UV (EtOH) λ_{max} (nm) 223 (ε 4500). MS: 234 ([M]$^+$, 4), 206 (100), 191 (48), 163 (15), 121 (70), 124 (30), 109 (98), 91 (65), 77 (50), 69 (58), 55 (68). IR: ν_{max} (film) cm^{-1}: 2740, 1725, 1680, 1645, 1460, 1260, 1070, 800, 760. ^{1}H NMR: 9.52 (1H, d, J=5.2 Hz, H-11), 9.44 (1H, s, H-12), 7.12 (1H, m, H-7), 2.81 (1H, m, H-9), 0.95, 0.94, 0.91 (3H, s, c/u). ^{13}C NMR: see Table.

ACETYLATION OF **33**: SYNTHESIS OF *9R–11,12–diacetoxy–7–drimene*, **34**.

Pyridine (1 ml) and Ac_2O (0.5 ml) were added to **33** (140 mg, 0.6 mmol) and left at room temperature for 12 h. Following the usual work–up 25 mg (97%) of **34** was obtained. $[\alpha]_D$ –1.2 ($CHCl_3$, c 0.5). MS: 322 ([M]$^+$, 3), 278 (10), 262 (96), 247 (11), 234 (31), 220 (99), 202 (45), 159 (30), 133 (39), 119 (40), 109 (100), 91 (44), 69 (53), 55 (57). IR: ν_{max} (film) cm^{-1}: 2910, 1745, 1465, 1390, 1370, 1240. ^{1}H NMR: 5.87 (1H, m, H-7), 4.52 (1H, d, J = 12.3, H_A-12), 4.47 (1H, d, J = 12.3, H_B-12), 4.30 (1H, dd, J = 11.7 and 2.9, H_A-11), 4.25 (1H, dd, J = 11.7 and 7.0, H_B-11), 2.01, 1.98 (3H, s, ea, –OCOMe), 0.88, 0.85, 0.80 (3H, s, ea). ^{13}C NMR: see Table.

HYDROXYLATION OF **34**: SYNTHESIS OF *11,12-diacetoxy-7-drimen-9α-ol*, **35**.

To a solution of **34** (127 mg, 0.4 mmol) in dioxane (10 ml) was added SeO_2 (26 mg, 0.2 mmol) and the mixture refluxed for 1 h monitoring the reaction by TLC. The reaction mixture was filtered and washed with a mixture of CH_2Cl_2/MeOH 20:1. The solvent was removed and a yellow oil (130 mg) was obtained which was chromatographed on SiO_2 (hexane/EtOAc 9:1)yielding 84 mg (80%) of **35**. $[\alpha]_D$ -37.5 ($CHCl_3$, c 4). MS: ($[M]^+$, 2), 278 (13), 265 (48), 214 (42), 205 (29), 154 (100), 109 (85), 81 (72), 69 (71), 55 (65). IR: ν_{max} (film) cm^{-1}: 3340, 1750, 1470, 1380, 1240, 1100. ^1H NMR: 6.04 (1H, dd, J = 5.4 and 2.4, H-7), 4.60 (1H, d, J = 11.6, H_A-12), 4.59 (1H, d, J = 11.6, H_B-12), 4.28 (1H, d, J = 11.7, H_A-11), 4.19 (1H, d, J = 11.7, H_B-11), 2.05, 2.04 (3H, s, ea, –OCOMe), 0.93 (3H, s), 0.90 (6H, s). ^{13}C NMR: see Table .

HYDROLYSIS OF **35**: SYNTHESIS OF *7-drimen-9α,11,12-triol*, **36**.

To a solution of **35** (58 mg,0.17 mmol) in methanol (3 ml) was added K_2CO_3 (150 mg).The reaction mixture was stirred at room temperature for 30 min, water was added and the mixture extracted with ether washed with 2N HCl and H_2O, dried, filtered and evaporated yielding 47 mg (93%) of **36**. $[\alpha]_D$ –83.0 ($CHCl_3$, c 0.3). MS: 254 ($[M]^+$, 3), 236 (3), 223 (60), 219 (6), 205 (38), 149 (28), 130 (68), 112 (57), 109 (80), 91 (34), 81 (63), 69 (83), 55 (79), 41 (100). IR: ν_{max} (film) cm^{-1}: 3380, 2920, 1460, 1380, 1360, 1150, 1070. ^1H NMR: 5.91 (1H, dd, J = 4.7 and 2.3, H-7), 4.32 (1H, d, J = 12.2, H_A-12), 4.14 (1H, d, J = 12.2, H_B-12), 3.76 (1H, d, J = 11.5, H_A-11), 3.75 (1H, d, J = 11.5, H_B-11), 0.93, 0.91, 0.82 (3H, s, ea). ^{13}C NMR: see Table .

SWERN OXIDATION OF **36**: **Warburganal, 3**

Oxalyl chloride (0.04 ml, 0.38 mmol) in CH_2Cl_2 (1.5 ml) was cooled at –60 °C. A solution of DMSO (0.06 ml, 0.77 mmol) in CH_2Cl_2 (1 ml) was slowly added in a 5 min period. A solution of **36** (49 mg, 0.19 mmol) in CH_2Cl_2 (2 ml) was added dropwise and stirred for 50 min at –60 °C. Triethylamine (0.37 ml, 1.9 mmol) was added and the reaction kept at –60 °C for 5 min, warmed to room temperature and quenched with water, extracted with ether and washed successively with 0.5N HCl, 5% $NaHCO_3$ and water, dried, filtered and evaporated yielding 40 mg (96%) of a solid **3** that was recrystallized from hexane. mp 106-107°C. $[\alpha]_D$ -262 ($CHCl_3$; c 0.3). UV (EtOH) λ_{max} (nm) 237 (ε 3300). MS: 250 ($[M]^+$, 6), 233 (4), 221 (70), 204 (7), 203 (5), 189 (15), 177 (3), 150 (24), 124 (40), 109 (100), 95 (33), 81 (44), 69 (81), 55 (85). IR ν_{max} cm^{-1} 3440, 3400, 1715, 1680, 1645, 1120, 1045. ^1H NMR ($CDCl_3$): 9.73 (1H, s, H-11), 9.41 (1H, s, H-12), 7.24 (1H, dd, J = 4.8 and 2.7, H-7), 4.07 (1H, bs, –OH), 2.59 (1H, dt, J = 20.4 and 4.8, H_α-6), 2.33 (1H, ddd, J = 20.4, 11.3 and 2.7, H_β-6), 1.89 (1H, dd, J = 11.3 and 4.8, H-5), 1.09, 0.99, 0.95 (3H, s, ea). ^1H NMR (C_6D_6): 9.61 (1H, s, H-11), 8.99 (1H, s, H-12), 6.18 (1H, m, H-7), 4.17 (1H, d, J = 1.0, –OH), 0.68 (6H, s), 0.59 (3H, s). ^{13}C NMR (C_6D_6): 31.4 (1), 18.0 (2), 41.5 (3), 32.9 (4), 41.7 (5), 25.7 (6), 155.5 (7), 140.9 (8), 77.8 (9), 41.4 (10), 201.5 (11), 192.0 (12), 33.0 (13), 22.0 (14), 16.7 (15). ^{13}C NMR ($CDCl_3$): see Table .

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