Phytochemistry, Vol. 25, No. 3, pp. 703–709, 1986.
Printed in Great Britain.

0031–9422/86 $3.00 + 0.00

HEMIACETALIC THAPSANE DERIVATIVES FROM *THAPSIA VILLOSA* VAR. *MINOR*

JOAQUÍN DE PASCUAL TERESA, JOAQUÍN R. MORÁN, ALFONSO FERNÁNDEZ and MANUEL GRANDE*

Departamento de Química Orgánica, Facultad de C. Químicas, 37008 Salamanca, Spain; *Departamento de Química Orgánica, Facultad de Ciencias, Apartado 99, 03080 Alicante, Spain

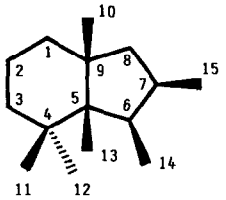
(*Revised received* 16 *July* 1985)

Key Word Index—*Thapsia villosa* var. *minor*; Umbelliferae; hemiacetalic sesquiterpenes; 14,15-epoxythapsane esters.

Abstract—The benzene extract from the roots of *Thapsia villosa* var. *minor* afforded six new sesquiterpene esters based on the thapsane skeleton for which the structure (1*R*,6*R*,8*R*,9*R*)-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane is proposed. Five of these thapsane esters were hemiacetal derivatives esterified at C-1, C-3 or C-8 and the sixth is a dimeric acetal esterified at C-8. The structures of these substances were established on the basis of their spectral data and chemical behaviour, including their transformation into the same compound, 14,15-thapsanolide.

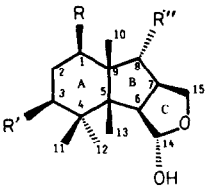
INTRODUCTION

Thapsia villosa L. var. *villosa* and *T. villosa* L. var. *minor* (Hoff. & Link) Cout. are two Mediterranean plants morphologically similar but with different chemical composition. The benzene extract from the roots of var. *villosa* contains mainly guaianolides [1, 2], phenylpropanoids [2, 3] and germacrane sesquiterpenes related to shiromodiol [4], but var. *minor*† lacks phenylpropanoids and guaianolides, containing mainly germacrane esters and thapsane esters [5], a new class of sesquiterpenoids with the carbon skeleton (1*R*,6*R*,8*R*,9*R*)-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane (**A**).

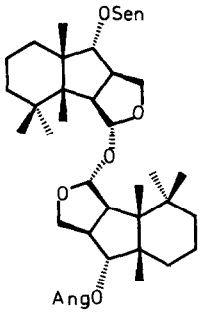


A

In a short communication [6], we reported an independent structure elucidation of the most abundant thapsane ester **1** based mainly on spectral data, including 2D-NMR spectra (COSY, NOESY, one bond and long range HCCORR). We now present a more detailed discussion of the structure elucidation and reactivity of the natural hemiacetal thapsane derivatives **1–6**.



	R	R'	R''
1	H	H	OSen
2	H	H	OCoum
3	H	H	OFer
4	H	OAng	H
5	OSen	H	H



6

RESULTS AND DISCUSSION

The benzene extract from the roots of *T. villosa minor* was fractionated into neutral and acidic portions. After chromatography and/or crystallization pure **1**, **4**, **5** and **6** were isolated from the neutral fraction, whereas **2** and **3** were isolated from the acidic portion.

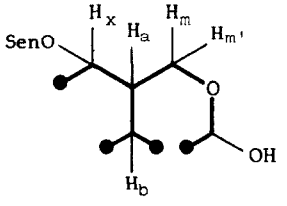
The spectral data (IR, ^{1}H NMR, MS) of the most abundant thapsane ester, **1**, established the presence of a senecioyl group [ν 1700, 1640 cm^{-1}; δ5.70 (1H, *m*), 2.20 (3H, *s*, *br*), 1.90 (3H, *s*, *br*); *m/z*: 236 [M − 100]$^+$, 83, 55] and a secondary hemiacetalic hydroxyl group‡ [ν 3400 cm^{-1}; δ5.40 (1H, *s*); *m/z*: 218 [M − 100 − H_2O]$^+$]. The mass spectral data for **1** ($C_{20}H_{32}O_4$) as well as the ^{13}C NMR spectral data (three C, four CH, four CH_2, four Me and five senecioyl carbon atoms) suggested a tricyclic system. The ^{1}H NMR spectrum of **1** showed three doublets at δ 4.80 (1H, *d*, J = 8 Hz, H_x), 4.15 (2H, *d*, J = 6 Hz, H_m, $H_{m'}$) and 3.00 (1H, *d*, J = 12 Hz, H_b), each one coupled with a multiplet centred at δ2.70 (1H, *m*, H_a), as confirmed by double irradiation experiments. These data allowed us to identify the partial structure **B**.

Oxidation of **1** with chromium trioxide–pyridine gave a

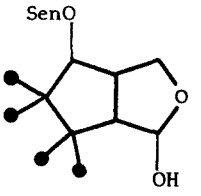
† Presented at the R. S. C. Int. Symp. Nat. Prod. I, Nottingham, U. K., July 1982.

‡ The monoacetate **7** (Ac_2O–C_5H_5N, room temp.) and the methyl acetal **8** (MeOH–*p*-TsOH) were easily prepared.

γ-lactone, **9** (ν 1770 cm^{-1}), which indicated that **1** contained a γ-lactol structure. On the other hand, hydrolysis of **1** afforded an alcohol (**10**) which on oxidation gave a cyclopentanone-γ-lactol (**11**) (PDC; ν 1740 cm^{-1}) or a cyclopentanone-γ-lactone (**12**) (Jones; ν 1745, 1780 cm^{-1}). From these data and the above mentioned coupling constants, the partial bicyclic structure **C** was deduced.



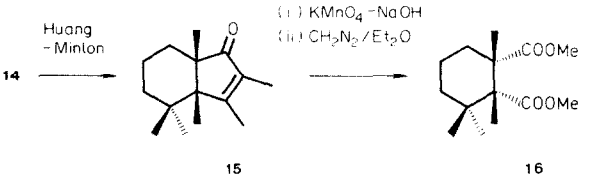
B



C

From the remaining information available (4Me, $3CH_2$, 1C), it was not possible to give a single structure, so that the following transformations were carried out.

The methyl acetal **13** prepared from **10**, was oxidized to the ketoacetal **14** and subjected to Huang–Minlon reduction conditions. The product of the reaction, **15**, $C_{15}H_{24}O$ ([M]$^+$ 220), showed signals of a conjugated ketone [ν 1700, 1650 cm^{-1}; λ_{max} 244 nm (ε 20 000)], four quaternary methyl groups [δ 1.09 (3H, *s*), 1.01 (3H, *s*), 0.80 (3H, *s*) and 0.53 (3H, *s*)] and two vinylic methyl groups [δ 1.91 (3H, *s*), 1.62 (3H, *s*)] which probably came from the lactol carbons in **C**. The proposed cyclopentenone structure can be explained by reduction of the hydrazone at C-14, dehydration and isomerization to the endocyclic enone. Oxidation of **15** with potassium permanganate–sodium hydroxide followed by esterification (CH_2N_2–Et_2O) give **16** which showed two methoxycarbonyl groups



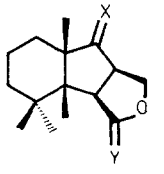
[ν 1740 cm^{-1}; δ 3.78 (3H, *s*), 3.59 (3H, *s*)], four quaternary methyl groups [δ 1.50 (3H, *s*), 1.37 (3H, *s*), 1.08 (3H, *s*), 0.97 (3H, *s*)] and three CH_2 (6H, *m*). These data, supported by the MS fragments, suggested the presence of a cyclohexane ring with a *gem*-dimethyl group and two contiguous CMe–COOMe groups. Chemical correlation of **1** with **4** and **5** (see below), also confirmed the six member ring size and the presence of three contiguous methylene groups in **1** and its derivatives (see structures **27** and **37**).

The preceding data were consistent with structure **1** and an isomeric structure with the *gem*-dimethyl group at C-1. The C-1 position for the *gem*-dimethyl group was ruled out because the benzene induced shifts on the methyl groups of **14** and **15** were all positive and a C-1 equatorial methyl group should be deshielded [7]. Also the $Eu(fod)_3$ induced shifts on the enone **15** were against the presence of a C-1 equatorial methyl group because in this case the induced shift on this methyl group should be similar to those of Me-15 [$P = 6.0 \times 10^{-2}$ ppm/mg $Eu(fod)_3$] or Me-10 [$P = 5.5 \times 10^{-2}$ ppm/mg $Eu(fod)_3$]. This was not observed. The induced shifts for the remaining methyl groups were $P(\times 10^{-2}) = 3.4$, 3.2, 2.7 and 1.8. Consequently, structure **1** is proposed for the most abundant thapsane ester. The structures shown in **2** and **3** were assigned to the phenolic substances. After alkaline hydrolysis they gave *p*-coumaric and ferulic acids respectively and the same diol (**10**).

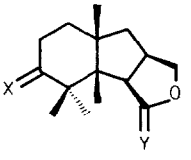
The natural sesquiterpene esters **4** and **5** showed characteristic spectral data of an angelate and a senecioate ester respectively. The remaining ^1H NMR signals were similar to those of **1**: the four methyl singlet signals were also observed and a γ-lactol group was recognized and confirmed by oxidation to the respective γ-lactones **24** and **34**, so that a thapsane skeleton was also assumed for these compounds.

The geminal protons to the ester groups appeared in **4** and **5** as broad triplets which suggested that these groups were equatorial and placed at C-1 or C-3. To establish the position of the ester group, the angelate **4** was transformed into the methyl acetal **21**, hydrolysed to **22** and oxidized to the cyclohexanone **23** (ν 1720 cm^{-1}). The $Eu(fod)_3$ induced shifts on the methyl groups of the hydroxyacetal **22** suggested that the hydroxyl group must be placed at C-3. The experimental slope of the methyl signals (P^* = 0.66, 0.59, 0.27, 0.24) fitted better with the calculated values for an equatorial C-3 hydroxyl group (P = 0.62, 0.62, 0.27, 0.25), than for a C-1 equatorial hydroxyl group (P = 0.62, 0.27, 0.25, 0.25) [8]. The C-3 hydroxylation was further supported by the presence of a RDA fragment in the mass spectrum of diol **18** at *m/z* 137 (30%).

In a similar way the senecioate **5** was transformed into the methyl acetal **31**, hydrolysed to **32** and oxidized to the cyclohexanone **33** (ν 1715 cm^{-1}). The induced benzene shifts on the methyl groups of **33** ($\Delta\delta$ 0.13, 0.14, 0.21, 0.25 ppm), can only be explained if there is no equatorial methyl group at C-1.

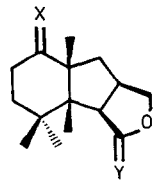


	X	Y
7	α OSen, H	α OAc, H
8	α OSen, H	α OMe, H
9	α OSen, H	=O
10	α OH, H	α OH, H
11	=O	α OH, H
12	=O	=O
13	α OH, H	α OMe, H
14	=O	α OMe, H
17	α OH,H	=O
18	α OXant, H	=O
19	Δ^7	=O
20	H_2	=O

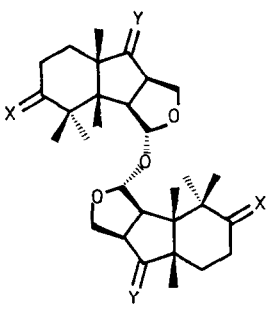


	X	Y
21	β OAng, H	α OMe, H
22	β OH, H	α OMe, H
23	=O	α OMe, H
24	β OAng, H	=O
25	β OH, H	=O
26	β OXant, H	=O
27	Δ^2	=O
28	β OH, H	α OH, H

* $P = \Delta\delta/[Eu(fod)_3]$ (**22**). Slope values relative to H-3.



	X	Y
31	βOSen, H	αOMe, H
32	βOH, H	αOMe, H
33	=O	αOMe, H
34	βOSen, H	=O
35	βOH, H	=O
36	βOXant, H	=O
37	Δ^1	=O



	X	Y
29	=O	H_2
30	βOAng, H	H_2
38	H_2	αOH, H
39	H_2	αOSen, H

The relationship between the natural thapsane esters **1**, **4** and **5**, was established by transformation into the same derivative. The thapsane **4** wás oxidized (**24**), hydrolysed (**25**), dehydrated (**27**) *via* xanthate **26** and hydrogenated to give the γ-lactone **20**. The same reaction sequence when applied to **1** and **5** also gave the lactone **20** (14,15-thapsanolide). This confirmed that the natural esters **1**–**5** have the same carbon skeleton.

Lastly, the least polar natural thapsane **6**, showed a ^{1}H NMR spectrum very similar to that of **1**. The spectrum of **6**, however, displayed signals of senecioyloxy and angeloyloxy groups but the vinylic proton signals each integrated to half that of the hemiacetalic proton signal. Because hydroxyl absorption bands were absent from its IR spectrum, we proposed for this substance the dimeric structure shown in **6**. To confirm this constitution the natural acetal **6** was hydrolysed to yield the diol **38** which could be synthesized by treatment of **1** with *p*-TsOH–C_6H_6 (dimer **39**) followed by alkaline hydrolysis.

The hemiacetals have a tendency towards dimerization, i.e. **4** gave on standing **30** and also dimer **29** was formed when diol **28** was oxidized with Jones reagent. We do not think however that **6** is an artifact because no dimeric ester **39** could be detected in the plant extract, in spite of the abundance of monomeric senecioate **1**.

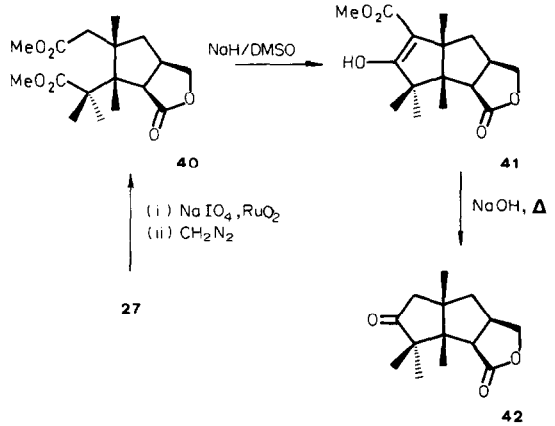
The stereochemistry of the thapsane esters was deduced as follows. The stability and easy formation of the lactol and lactone rings as well as the vicinal coupling constants observed, were indicative of a *cis* B and C ring fusion. The enone **15** showed one methyl group highly shielded (δ0.53) that must be placed above the plane of the enone function. Moreover, this methyl group was only slightly shielded by benzene (Δδ0.09 ppm), which indicated that the methyl group was held close to the reference plane perpendicular to the C=O bond [7]. These observations can only be rationalized if the six membered ring adopts the $^1C_4$ conformation and the A and B rings are *cis* fused.*

The A-B *cis* union was also deduced from the chemical behaviour of **40**, the oxidation product prepared from **27** (RuO_4; CH_2N_2). The dimethyl ester **40** gave easily the Dieckmann condensation product **41**, even with sodium hydroxide–methanol, and **41** was further transformed into the ketolactone **42** (ν 1750 cm^{-1}, *br*). A *trans* ring union could not explain the easy formation of the condensation product.

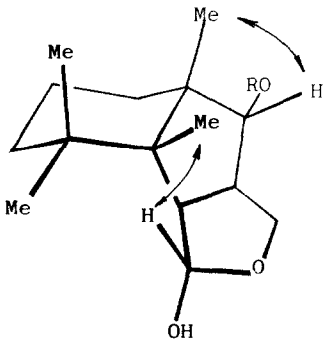
A *cis-syn-cis* configuration for the tricyclic system was rejected because it is a very puckered structure and, for instance, in the case of lactone **9** either the C-4 equatorial methyl group ($^1C_4$ A ring conformation) or the C-3 axial proton ($^4C_1$ A ring conformation) would be very shielded. However, this was not observed in the ^{1}H NMR spectrum of **9** [δ1.2–1.5 (6H, *s*, *br* 3CH_2), 1.10 (6H, *s*, *br*, 2Me), 1.00 (6H, *s*, *br*, 2Me)].

The relative configuration of the chiral centres C-8 and C-14 was deduced from the observed NOE effects. After irradiation of the methyl region of the ^{1}H NMR spectrum of **1**, NOE were observed between a methyl group (δ0.90) and the H-14 signal (24%) and between a different methyl group (δ1.05) and the H-8 signal (13%). If a $^4C_1$ conformation was assumed for the cyclohexane ring, the observed enhancements were indicative of the 8α and 14α configurations for the OR groups, whereas either the 8α,14α or the 8β,14α configurations were compatible with the observed NOE in the case of the $^1C_4$ conformation. However for the last conformation the 8-OR group in the 8α,14α isomer is nearly in contact with Me-12 and the dihedral angle of H-8 with H-7 is *ca* 100°, which is not compatible with the observed coupling constant $J_{7,8}$ = 8 Hz. In the case of the $^1C_4$ 8β,14α isomer, the proton H-15β is close to the 8β-OR substituent and an important downfield shift was expected for it when Eu(fod)$_3$ was added to the hydroxyacetal **13**. As the observed deshielding effects on both H-15 protons were small and rather similar, the $^1C_4$ conformation was discarded and consequently the 8α-OR and 14α-OH relative configurations were proposed for **1** and its derivatives.

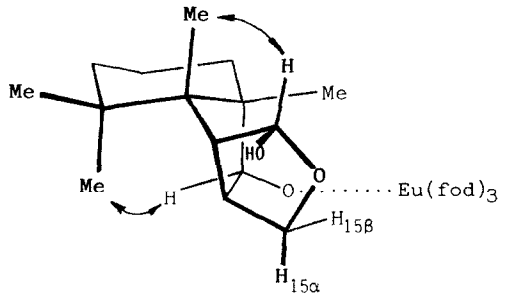
The β configuration for the ester groups in **4** and **5** was assigned in agreement with the observed coupling constants of H-1 and H-3 in **4** and **5** respectively, which are characteristic for axial protons, and also on the basis of the chemical induced shifts by Eu(fod)$_3$ on the methyl groups of the hydroxyacetal **22** and the hydroxylactone **35**. As mentioned above, the observed *P* values for the methyl groups relative to H-3 in compound **22**, fits well with the calculated values for the $^4C_1$ A ring conformation



*In the $^4C_1$ conformation the methyl groups Me-12 (equatorial at C-4) and Me-14 are almost in contact. We have adopted the ^mC_n nomenclature proposed for pyranoses [9] to represent the steroid like ($^4C_1$) and non-steroid like ($^1C_4$) conformations.



$^4C_1$



$^1C_4$

and the 3-hydroxyl equatorial group. Similarly, the observed relative P values for the methyl groups of **35** (P_{exp} = 0.52, 0.25, 0.22, 0.22) also agrees with the calculated data for the C_1 conformation and 1-hydroxyl equatorial group (P_{calc} = 0.62, 0.27, 0.25, 0.25).

The absolute configuration of the thapsane derivatives was proposed on the basis of the CD curves of the carbonyl compounds **20** ($\Delta\varepsilon_{294}$ + 1.8) and **31** ($\Delta\varepsilon_{294}$ −2.4). Once the $^4C_1$ conformation was set up and according to the octant rule [10], the observed Cotton effects correspond to the absolute configuration *5R,6R,7R,9R* for the thapsane skeleton, in agreement with that deduced previously for **10** [5].

As the relative configuration was known, the absolute configuration proposed for C-14 in all natural compounds is *S* and that of the esterified carbon atoms are 8*R* for **1**, **2**, **3** and **6**, 3*S* for **4** and 1*R* for **5**.

EXPERIMENTAL

Extraction and isolation. Plant material was collected, extracted and fractionated as previously reported [2], yielding 216 g of neutral components and 120 g of aq. NaOH soluble material. Chromatography of the neutral part was carried out on silica gel (1 kg), eluting with hexane–Et_2O of increasing polarity. Products were eluted in the following order: **6**, **1** and **4** + **5**. The less polar compounds (33 g) were chromatographed on silica gel (400 g) with hexane–EtOAc (9:1). The most polar fractions (1.0 g) were further chromatographed (silica gel H-60, 40 g, hexane–Et_2O) yielding **6** (312 mg). A 3.8 g fraction of **4** + **5** was rechromatographed on silica gel H-60 (200 g) with $CHCl_3$–EtOAc (19:1) to yield **4** (1.69 g). A mixture of **4** and **5** (3.03 g) was chromatographed on silica gel (100 g) with hexane–Me_2CO (9:1). Earlier fractions (214 mg) were further chromatographed (silica gel H-60, 40 g, hexane–Et_2O, 7:3) yielding pure compound **5** (154 mg). A 14 g fraction of the base soluble substances was chromatographed on silica gel (100 g) with C_6H_6–Et_2O (4:1), yielding 1.6 g of a mixture of **2** and **3**. A further chromatography on silica gel H-60 (40 g) of a 212 mg portion yielded pure **2** (first eluted, 47 mg) and **3** (75 mg).

7-Senecioyloxy-14,15-epoxythapsan-14-ol (**1**). A fraction containing **1** (25 g) was crystallized from hexane yielding pure **1** (5.0 g). Mp 142–143°; $[\alpha]_D$ −20.0°($CHCl_3$; *c* 3.5); IR ν_{max}^{KBr} cm^{-1}: 3400, 1700, 1640, 1210, 1150, 1100, 1000, 980, 920; ^1H NMR (60 MHz, $CDCl_3$): δ5.70 (1H, *m*, Sen), 5.40 (1H, *s*, H-14), 4.80 (1H, *d*, *J* = 8 Hz, H-8), 4.15 (2H, *d*, *J* = 6 Hz, H-15), 3.90 (1H, *s*, OH), 3.00 (1H, *d*, *J* = 12 Hz, H-6), 2.70 (1H, *m*, H-7), 2.20 (3H, *s* (*br*), Sen), 1.90 (3H, *s* (*br*), Sen), 1.50 (6H, *s* (*br*), H-1, H-2, H-3), 1.05 (3H, *s*, Me), 1.00 (3H, *s*, Me), 0.90 (6H, *s*, Me); ^{13}C NMR (20 MHz, $CDCl_3$): δ166.9 (*s*), 156.4 (*s*), 116.3 (*d*), 100.5 (*d*), 87.3 (*d*), 71.2 (*t*), 55.5 (*d*), 48.8 (*s*), 47.2 (*s*), 45.5 (*d*), 37.8 (*t*), 36.0 (*s*), 30.5 (*t*), 27.7 (*q*), 27.4 (*q*), 24.5 (*q*), 20.3 (*q*), 20.1 (*q*), 18.1 (*t*), 13.4 (*q*); EIMS (probe) *m/z* (rel. int.): 236 [M − SenOH]$^+$ (70), 218 [M − SenOH − H_2O]$^+$ (40), 207 [M − SenOH − H_2O − Me]$^+$ (40), 190 (99), 174 (60), 135 (50), 121 (100), 120 (99), 109 (80), 83 (40).

Acetate **7**. Acetylation of **1** (300 mg) with Ac_2O–C_5H_5N, room temp., yielded acetate **7** (270 mg). Oil; $[\alpha]_D$ −62.5° ($CHCl_3$; *c* 1.5); IR ν_{max}^{film} cm^{-1}: 2950, 1710, 1650, 1450, 1280, 1220, 1140, 1110, 1070, 1000; ^1H NMR (60 MHz, $CDCl_3$): δ6.10 (1H, *s*, H-14), 5.60 (1H, *s* (*br*), Sen), 4.65 (1H, *d*, *J* = 7 Hz, H-8), 4.10 (2H, *m*, H-15), 3.00 (1H, *d*, *J* = 12 Hz, H-6), 2.70 (1H, *m*, H-7), 2.10 (3H, *s* (*br*), Sen), 1.95 (3H, *s*, Ac), 1.85 (3H, *s* (*br*), Sen), 1.40 (6H, *m*, H-1, H-2, H-3), 1.00 (3H, *s*, Me), 0.95 (3H, *s*, Me), 0.90 (3H, *s*, Me), 0.80 (3H, *s*, Me). EIMS (probe) *m/z* (rel. int.): 318 (1), 218 (5), 182 (20), 122 (30), 107 (20), 105 (20), 91 (40), 83 (60), 43 (100), 29 (80).

Methylacetal **8**. Compound **1** (223 mg) was treated with MeOH (3 ml) and a trace of *p*-TsOH. Work up afforded 230 mg of **8**. Oil; $[\alpha]_D$ −55.4° ($CHCl_3$; *c* 1.7); IR ν_{max}^{film} cm^{-1}: 2900, 1705, 1640, 1440, 1360, 1220, 1140, 1090, 1050, 1000, 920, 850; ^1H NMR (60 MHz, CCl_4): δ5.58 (1H, *s* (*br*), Sen), 4.68 (1H, *s*, H-14), 4.00 (1H, *m*, H-15), 3.87 (1H, *m*, H-15), 3.15 (3H, *s*, OMe), 2.83 (1H, *d*, *J* = 12 Hz, H-6), 2.60 (1H, *m*, H-7), 2.12 (3H, *s* (*br*), Sen), 1.88 (3H, *s* (*br*), Sen), 1.48 (6H, *m*, H-1, H-2, H-3), 1.00 (6H, *s*, Me), 0.90 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 319 (3), 250 (3), 91 (20), 83 (100), 55 (50).

8-Senecioyloxy-14,15-thapsanolide (**9**). Product **1** (927 mg) was oxidized with Jones reagent, yielding after work up 900 mg of a crude material which on chromatography (silica gel, 60 g; hexane–Et_2O, 9:1) gave **9** (775 mg). Mp 114–116° (hexane–Et_2O); $[\alpha]_D$ + 12.8° ($CHCl_3$; *c* 6.2); IR ν_{max}^{nujol} cm^{-1}: 2900, 1780, 1720, 1660, 1460, 1380, 1350, 1280, 1230, 1190, 1150, 1080, 1020, 850; ^1H NMR (60 MHz, CCl_4): δ5.62 (1H, *s* (*br*), Sen), 4.68 (1H, *d*, *J* = 6 Hz, H-8), 4.40 (2H, *d*, *J* = 7 Hz, H-15), 3.30 (1H, *d*, *J* = 11 Hz, H-6), 3.00 (1H, *m*, H-7), 2.12 (3H, *s* (*br*), Sen), 1.90 (3H, *s* (*br*), Sen), 1.48 (6H, *m*, H-1, H-2, H-3), 1.10 (6H, *s*, Me), 1.00 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 334 [M]$^+$ (7), 234 [M − SenOH]$^+$, 119 (30), 83 (100).

14,15-Epoxythapsan-8,14-diol (**10**). Hydrolysis of **1** (700 mg) with 2 N NaOH–MeOH overnight yielded 541 mg of crystalline **10** whose physical properties were in agreement with those previously reported [5].

14-Hydroxy-14,15-epoxythapsan-8-one (**11**). Oxidation of **10** (97 mg) overnight with PDC in CH_2Cl_2 (2.5 ml) followed by chromatography (silica gel, 10 g; hexane–Et_2O, 3:2), yielded **11** (53 mg). Mp 118–120° (hexane–Et_2O); $[\alpha]_D$ −173.0° ($CHCl_3$; *c* 2.5); IR ν_{max}^{melted} cm^{-1}: 3400, 1740, 1280, 1100, 1000; ^1H NMR

(60 MHz, $CDCl_3$): δ5.50 (1H, *s*, H-14), 4.00 (2H, *m*, H-15), 3.40 (1H, *m*, H-7), 3.12 (1H, *d*, J = 12 Hz, H-6), 1.50 (6H, *m*, H-1, H-2, H-3), 1.10 (3H, *s*, Me), 1.00 (6H, *s*, Me), 0.70 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 252 $[M]^+$ (5), 234 $[M-H_2O]^+$ (8), 134 (90), 43 (100).

8-*Oxo*-14,15-*thapsanolide* (**12**). A soln of **11** (575 mg) in 50 ml Me_2CO was oxidized with Jones reagent. Work up yielded 525 mg of a syrup which crystallized from C_6H_6 (412 mg). Mp 194–196°; $[\alpha]_D$ −124° ($CHCl_3$; *c* 1.3); IR ν_{max}^{KBr} cm^{-1}: 1780, 1745, 1260, 1250, 1180, 1080, 1080, 1040, 720, 690; ^1H NMR (60 MHz, $CDCl_3$): δ4.15 (2H, *m*, H-15), 3.60 (1H, *m*, H-7), 3.38 (1H, *d*, J = 11 Hz, H-6), 1.50 (6H, *m*, H-1, H-2, H-3), 1.16 (6H, *s*, Me), 1.02 (3H, *s*, Me), 0.85 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.) 250 $[M]^+$ (2), 235 $[M-Me]^+$ (2), 83 (100).

Hydroxyacetal **13**. Product **10** (80 mg) in MeOH (1 ml) with a trace of *p*-TsOH, yielded after 10 min and usual work up an oily product (75 mg), which was crystallized from hexane (50 mg). Mp 128–130°; $[\alpha]_D$ −98.6° ($CHCl_3$; *c* 3.5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 1240, 1100, 1060, 1030, 1015, 1000; ^1H NMR (60 MHz, $CDCl_3$): δ4.71 (1H, *s*, H-14), 3.23 (3H, *s*, OMe), 1.40 (6H, *m*, H-1, H-2, H-3), 1.04 (3H, *s*, Me), 0.97 (3H, *s*, Me), 0.86 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 237 $[M-OMe]^+$ (10), 69 (100).

Ketoacetal **14**. A soln of **13** (119 mg) in 10 ml Me_2CO was oxidized with Jones reagent checking the reaction by TLC to avoid over oxidation. Work up yielded 94 mg of the ketone. Oil; $[\alpha]_D$ −150.8° ($CHCl_3$; *c* 3.7); IR ν_{max}^{film} cm^{-1}: 1740, 1260, 1190, 1100, 1090, 1070, 1040; ^1H NMR (60 MHz, CCl_4): δ4.74 (1H, *s*, H-14), 3.85 (1H, *d*, J = 5 Hz, H-8), 3.15 (3H, *s*, OMe), 1.50 (6H, *m*, H-1, H-2, H-3), 1.03 (3H, *s*, Me), 0.98 (3H, *s*, Me), 0.93 (3H, *s*, Me), 0.63 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.) 266 $[M]^+$ (2), 235 $[M-OMe]^+$ (5), 124 (100).

6-*Thapsen*-8-*one* (**15**). Product **14** (2.63 g) in $(CH_2OH)_2$ (100 ml) was reacted with KOH (15 g) and $H_2NNH_2 \cdot H_2O$ (15 ml). After refluxing 2 hr and work up 2.45 g of an oily product were obtained. Chromatography (silica gel, 60 g; hexane–Et_2O, 4:1) yielded the pure ketone (1.35 g). Oil; $[\alpha]_D$ +56.6° ($CHCl_3$; *c* 0.8); IR ν_{max}^{film} cm^{-1}: 1700, 1650; ^1H NMR (60 MHz, CCl_4): δ1.91 (3H, *s*, H-15), 1.63 (3H, *s*, H-14), 1.25 (6H, *m*, Me), 1.09 (3H, *s*, Me), 1.01 (3H, *s*, Me), 0.80 (3H, *s*, Me), 0.53 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 228 $[M]^+$ (40), 205 $[M-Me]^+$ (10), 138 (100). UV λ_{max}^{hexane} nm: 244 (ε 20 000); CD: $\Delta\varepsilon_{244}$ −1.65; $\Delta\varepsilon_{320}$ +0.49 (hexane).

Dimethyl ester **16**. A soln of **15** (213 mg) in H_2O–dioxane (1:1, 10 ml) was oxidized overnight with $KMnO_4$ (400 mg) and 10% NaOH–H_2O (0.3 ml). Work up yielded 122 mg of the starting materials and 84 mg of products, which were esterified with CH_2N_2–Et_2O and chromatographed (silica gel, 10 g; hexane–Et_2O, 4:1) to yield **16** (9 mg). Oil; $[\alpha]_D$ −33.0° ($CHCl_3$; *c* 1.9); IR ν_{max}^{film} cm^{-1}: 1740, 1280, 1200, 1090, 1030, 1010. ^1H NMR (60 MHz, $CDCl_3$): δ3.78 (3H, *s*, OMe), 3.59 (3H, *s*, OMe); EIMS (probe) *m/z* (rel. int.): 225 $[M-OMe]^+$ (25), 195 $[M-COOMe]^+$ (35), 137 $[M-H-2\times COOMe]^+$ (100).

8-*Hydroxy*-14,15-*thapsanolide* (**17**). Lactone **9** (770 mg) was hydrolysed in 2 N NaOH–MeOH overnight. After acidification and heating (90°, 5 min) lactone **17** was isolated (650 mg). Mp 240–242° (Et_2O); $[\alpha]_D$ −47.7° (MeOH; *c* 1.4); IR ν_{max}^{KBr} cm^{-1}: 3500, 1750, 1250, 1200, 1100, 1080, 1060, 1020; ^1H NMR (60 MHz, C_5D_5N): δ4.38 (*m*, 2H, H-15), 4.05 (1H, *d*, J = 7 Hz, H-8), 3.10 (2H, *m*, H-6, H-7), 1.50 (6H, *m*, H-1, H-2, H-3), 1.22 (6H, *s*, Me), 1.02 (3H, *s*, Me), 0.98 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 252 $[M]^+$ (5), 237 $[M-Me]^+$ (3), 234 $[M-H_2O]^+$ (4), 82 (100).

Xanthate **18**. A soln of **17** (1.07 g) in THF (10 ml) was reacted with NaH (250 mg) for 3 hr. Afterwards, CS_2 (5 ml) and MeI (3 ml) were added and the soln was refluxed during 3 hr. Usual work up and chromatography (silica gel, 60 g; hexane–Et_2O, 9:1) yielded the xanthate **18** (635 mg). Mp 94–96° (hexane); $[\alpha]_D$ +72.6° ($CHCl_3$; *c* 7.0); IR ν_{max}^{melted} cm^{-1}: 1780, 1230, 1200, 1100, 1080, 1030; ^1H NMR (60 MHz, CCl_4): δ 5.66 (1H, *d*, J = 7 Hz, H-8), 4.38 (2H, *m*, H-15), 3.32 (1H, *d*, J = 11 Hz, H-6), 3.10 (1H, *m*, H-7), 2.53 (3H, *s*, Xant), 1.53 (6H, *s* (*br*), H-1, H-2, H-3), 1.10 (3H, *s*, Me), 1.06 (3H, *s*, Me), 1.00 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 342 $[M]^+$ (2), 235 $[M-Xant]^+$ (30), 20 (100).

7-*Thapsen*-14,15-*olide* (**19**). Product **18** (560 mg) was kept at 250° for 30 minutes. Distillation at 15 torr (420 mg) and crystallization gave **19** (310 mg). Mp 120–122° (hexane–Et_2O); $[\alpha]_D$ +22.3° ($CHCl_3$; *c* 5.9); IR ν_{max}^{nujol} cm^{-1}: 2950, 1780, 1700, 1460, 1380, 1170, 1080, 1000, 840, 800; ^1H NMR (60 MHz, $CDCl_3$): δ5.50 (1H, *m*, H-8), 4.65 (2H, *m*, H-15), 3.70 (1H, *s*, H-6), 1.45 (6H, *s* (*br*), H-1, H-2, H-3), 1.15 (3H, *s*, Me), 1.10 (3H, *s*, Me), 0.95 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 234 $[M]^+$ (4), 219 (6), 151 (30), 138 (20), 105 (85), 91 (100), 81 (20), 50 (20).

Thapsan-14,15-*olide* (**20**). Lactone **19** (115 mg) was desulphurized with Raney-Ni and afterwards hydrogenated with Adams catalyst (2 mg PtO_2) in 2 ml AcOH. Work up yielded **20** (84 mg): mp 123–125° (hexane–Et_2O); $[\alpha]_D$ −40.5° ($CHCl_3$; *c* 1.4); IR ν_{max}^{melted} cm^{-1}: 1770, 1250, 1180, 1110, 1080, 1020; ^1H NMR (60 MHz, $CDCl_3$): δ4.40 (1H, *t*, J = 9 Hz, H-15), 3.95 (1H, *dd*, J = 4 and 9 Hz, *m*, H-15), 3.25 (2H, *m*, H-7), 1.75 (2H, *d*, J = 8 Hz, *dd*, J = 4 and 9 Hz, *m*, H-15), 3.25 (2H, *m*, H-7), 1.75 (2H, *d*, J = 8 Hz, H-6), 1.20 (6H, *s*, Me), 0.98 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 234 $[M]^+$ (10), 221 $[M-Me]^+$ (4), 93 (100).

7-*Coumaroyloxy*-14,15-*epoxythapsan*-14-*ol* (**2**). Mp 210–212° (C_6H_6–Et_2O); $[\alpha]_D$ −40.6° ($CHCl_3$; *c* 1.3); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 2900, 1715, 1690, 1630, 1600, 1500, 1450, 1380, 1250, 1150, 1000; ^1H NMR (60 MHz, Me_2CO-d_6): δ7.55 (1H, *d*, J = 16 Hz, Coum), 7.45 (2H, *d*, J = 9 Hz, Coum), 6.85 (2H, *d*, J = 9 Hz, Coum), 6.33 (1H, *d*, J = 16 Hz, Coum), 5.33 (1H, *s*, H-14), 4.80 (1H, *d*, J = 6 Hz, H-8), 4.10 (2H, *d*, J = 4 Hz, H-15), 3.00 (1H, *d*, J = 12 Hz, H-6), 2.80 (1H, *m*, H-7), 1.55 (6H, *s* (*br*), H-1, H-2, H-3), 1.04 (3H, *s*, Me), 0.95 (3H, *s*, Me), 0.93 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 400 $[M]^+$ (2), 382 $[M-H_2O]^+$ (2), 218 $[M-CoumOH-H_2O]^+$ (5), 157 (90), 135 (50), 119 (60), 107 (60), 91 (100), 83 (50), 69 (90), 55 (90).

Hydrolysis of **2** (100 mg) with 2 N NaOH–MeOH (1 ml) for 10 hr at room temp. gave after usual work up **10** (60 mg) and *p*-coumaric acid (**4**, 20 mg).

7-*Feruloyloxy*-14,15-*epoxythapsan*-14-*ol* (**3**). Mp 163–165°; $[\alpha]_D$ −30.4° ($CHCl_3$; *c* 2.3); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3570, 3000, 1700, 1640, 1610, 1600, 1510, 1480, 1440, 1390, 1340, 1270, 1170, 1090, 1040, 1000; ^1H NMR (60 MHz, $CDCl_3$): δ7.60 (1H, *d*, J = 16 Hz, Fer), 7.05 (3H, *m*, Fer), 6.25 (1H, *d*, J = 16 Hz, Fer), 5.45 (1H, *s*, H-14), 4.90 (1H, *d*, J = 6 Hz, H-8), 4.25 (2H, *d*, J = 4 Hz, H-15), 3.94 (3H, *s*, Fer), 3.10 (1H, *d*, J = 12 Hz, H-6), 2.80 (1H, *m*, H-7), 1.55 (6H, *s* (*br*), H-1, H-2, H-3), 1.06 (3H, *s*, Me), 1.00 (3H, *s*, Me), 0.95 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.) 430 $[M]^+$ (5), 412 $[M-H_2O]^+$ (25), 194 (50), 177 (70), 145 (60), 119 (40), 117 (40), 107 (50), 95 (70), 83 (40), 69 (100), 55 (50).

Hydrolysis of **3** (110 mg) as above, yielded **10** (63 mg) and ferulic acid (**4**, 10 mg).

7-*Angeloyloxy*-14,15-*epoxythapsan*-14-*ol* (**4**). Mp 100–102° (hexane); $[\alpha]_D$ −24.6° ($CHCl_3$; *c* 1.2); IR ν_{max}^{melted} cm^{-1}: 3400, 2950, 1710, 1650, 1460, 1380, 1240, 1150, 1100, 1050, 1000, 930, 850, 740; ^1H NMR (60 MHz, $CDCl_3$): δ6.00 (1H, *q*, J = 6 Hz, Ang), 5.30 (1H, *s*, H-14), 5.00 (1H, *m*, H-3), 4.10 (1H, *t*, J = 7 Hz, H-15), 3.55 (1H, *d*, J = 7 Hz, H-15), 2.94 (2H, *m*, H-6, H-7), 1.95 (3H, *d*, Me); EIMS (probe) *m/z* (rel. int.): 236 $[M-AngOH]^+$ (5), 133 (50), 121 (70), 108 (70), 83 (100), 55 (80), 43 (25).

Methylacetal **21**. The natural lactol **4** (2.2 g) was kept for 5 min in MeOH (10 ml) with a trace of *p*-TsOH. Work up and chromatography on silica gel (hexane–Et_2O, 9:1) afforded pure **21** (1.24 g). $[\alpha]_D$ −39.4° ($CHCl_3$; *c* 2.6); IR ν_{max}^{film} cm^{-1}: 2900,

1700, 1650, 1450, 1380, 1225, 1150, 1100, 1060, 1040, 980, 920, 850; ^{1}H NMR (60 MHz, CCl_4): δ5.91 (1H, *q*, *J* = 6 Hz, Ang), 4.90 (1H, *t*, *J* = 8 Hz, H-3), 4.66 (1H, *s*, H-14), 3.80 (1H, *t*, *J* = 8 Hz, H-15), 3.45 (1H, *d*, *J* = 8 Hz, H-15), 3.30 (3H, *s*, OMe), 2.85 (2H, *m*, H-6, H-7), 1.95 (3H, *d*, *J* = 6 Hz, Ang), 1.90 (3H, *s* (*br*), Ang), 1.05 (3H, *s*, Me), 1.00 (3H, *s*, Me), 0.90 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 319 $[M-OMe]^+$ (3), 250 $[M-AngOH]^+$ (1), 149 (10), 109 (25), 83 (100), 69 (30), 55 (50).

Hydroxyacetal **22**. Usual hydrolysis of **21** (1.24 g) yielded, after crystallization, pure **22** (646 mg). Mp 155–157° (hexane–C_6H_6); $[\alpha]_D$ −63.5° ($CHCl_3$; *c* 0.8); IR ν_{max}^{film} cm^{-1}: 3600, 3500, 2950, 1450, 1380, 1270, 1110, 1080, 1010, 930; ^{1}H NMR (60 MHz, $CDCl_3$): δ4.75 (1H, *s*, H-14), 3.85 (1H, *t*, *J* = 8 Hz, H-15), 3.70 (1H, *m*, H-3), 3.60 (1H, *d*, *J* = 8 Hz, H-15), 3.25 (3H, *s*, OMe), 2.85 (2H, *m*, H-6, H-7), 1.01 (3H, *s*, Me), 1.00 (3H, *s*, Me), 0.90 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 269 (2), 237 (10), 149 (55), 121 (55), 108 (100), 93 (70), 79 (60), 69 (70).

Ketoacetal **23**. The alcohol **32** (381 mg) was oxidized as usual with Jones reagent yielding after chromatography (silica gel, hexane–Et_2O, 4:1) pure **23** (227 mg). Mp 93–95° (hexane–Et_2O); $[\alpha]_D$ −0.5° ($CHCl_3$; *c* 0.8); IR ν_{max}^{melted} cm^{-1}: 2950, 1720, 1450, 1380, 1330, 1310, 1230, 1200, 1110, 1080, 1010, 930; ^{1}H NMR (60 MHz, CCl_4): δ4.62 (1H, *s*, H-14), 3.80 (1H, *t*, *J* = 8 Hz, H-15), 3.50 (1H, *dd*, *J* = 3 and 8 Hz, H-15), 3.18 (3H, *s*, OMe), 1.25 (3H, *s*, Me), 1.10 (3H, *s*, Me), 0.94 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 266 $[M]^+$ (1), 235 $[M-OMe]^+$ (20), 206 (40), 191 (30), 109 (80), 108 (80), 107 (95), 93 (80), 69 (100).

Thapsanolides **24** *and* **34**. A mixture of the natural products **4** and **5** (0.5 g) in Me_2CO (40 ml) was oxidized with Jones reagent. Work up and chromatography (silica gel, 30 g; hexane–Et_2O, 4:1) yielded **34** (52 mg, less polar) and **24** (259 mg). *Thapsanolide* **24**: mp 95–97° (hexane–Et_2O); $[\alpha]_D$ −25.5° ($CHCl_3$; *c* 6.6); IR ν_{max}^{melted} cm^{-1}: 1770, 1720, 1650, 1240, 1160, 1090, 1040, 1000; ^{1}H NMR (60 MHz, $CDCl_3$): δ6.00 (1H, *q*, *J* = 6 Hz, Ang), 4.80 (1H, *m*, H-3), 4.40 (1H, *t*, *J* = 9 Hz, H-15), 3.90 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.30 (1H, *d*, *J* = 10 Hz, H-6), 3.10 (1H, *m*, H-7), 1.85 (3H, *s*, Ang), 1.10 (6H, *s*, Me), 1.00 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 334 $[M]^+$ (4), 234 $[M-AngOH]^+$ (15), 219 $[M-AngOH-Me]^+$ (8), 83 (100). *Thapsanolide* **34**: Mp 111–113° (hexane–Et_2O); $[\alpha]_D$ −60.2° ($CHCl_3$; *c* 0.9); IR ν_{max}^{nujol} cm^{-1}: 1780, 1720, 1660, 1230, 1150, 1080, 1020, 1000, 920; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.65 (1H, *s* (*br*), Sen), 4.85 (1H, *t*, *J* = 7 Hz, H-1), 4.40 (1H, *t*, *J* = 9 Hz, H-15), 3.90 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.25 (2H, *m*, H-6, H-7), 2.20 (3H, *s* (*br*), Sen), 1.90 (3H, *s* (*br*), Sen), 1.12 (6H, *s*, Me), 1.02 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 334 $[M]^+$ (1), 234 $[M-SenOH]^+$ (8), 219 $[M-SenOH-Me]^+$ (4), 83 (100).

3-*Hydroxythapsan*-14,15-*olide* (**25**). Thapsanolide **24** (0.85 g) was hydrolysed by refluxing in 2 N NaOH–MeOH (5 ml) for 2 hr. Work up yielded 0.63 g which crystallized from hexane–Et_2O affording 50 mg of pure **25**. Mp 132–134°; $[\alpha]_D$ −25.3° ($CHCl_3$; *c* 4.5); IR ν_{max}^{nujol} cm^{-1}: 3500, 1770, 1190, 1030, 1000; ^{1}H NMR (60 MHz, $CDCl_3$): δ4.40 (1H, *t*, *J* = 9 Hz, H-15), 3.95 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.60 (1H, *m*, H-3), 3.20 (2H, *m*, H-6, H-7), 1.20 (3H, *s*, Me), 1.00 (3H, *s*, Me), 0.92 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 252 $[M]^+$ (2), 234 $[M-H_2O]^+$ (8), 219 $[M-H_2O-Me]^+$ (3), 83 (100).

Xanthates **26** *and* **36**. A mixture of **25** and **35** (490 mg) were reacted in the same conditions as **18**, to give a crude product (411 mg) which on chromatography (silica gel, 40 g; hexane–Et_2O, 17:3) gave **36** (55 mg, less polar) and **26** (194 mg). *Xanthate* **26**: Mp 198–200° (hexane–Et_2O); $[\alpha]_D$ −0.4° ($CHCl_3$; *c* 1.8); IR ν_{max}^{KBr} cm^{-1}: 1770, 1250, 1240, 1220, 1180, 1100, 1060, 1050, 1020, 990, 950, 920, 900; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.60 (1H, *m*, H-3), 4.35 (1H, *t*, *J* = 9 Hz, H-15), 3.90 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.25 (2H, *m*, H-6, H-7), 2.50 (3H, *s*, Xant), 1.20 (6H, *s*, Me), 1.07 (3H, *s*, Me), 1.00 (3H, *s*, Me); EIMS (probe): *m/z* (rel. int.): 342 $[M]^+$ (2), 235 $[M-XantOH]^+$ (40), 91 (100). *Xanthate* **36**: Oil; $[\alpha]_D$ −101.6° ($CHCl_3$; *c* 2.6); IR ν_{max}^{film} cm^{-1}: 1770, 1230, 1170, 1050; ^{1}H NMR (60 MHz, CCl_4): δ5.60 (1H, *m*, H-1), 4.30 (1H, *t*, *J* = 9 Hz, H-15), 3.80 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.20 (2H, *m*, H-6, H-7), 2.55 (3H, *s*, Xant), 1.20 (3H, *s*, Me), 1.10 (3H, *s*, Me), 1.05 (3H, *s*, Me), 1.00 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 342 $[M]^+$ (1), 235 $[M-XantOH]^+$ (15), 83 (100).

2-*Thapsen*-14,15-*olide* (**27**). Xanthate **26** (88 mg) was kept at 200° for 30 min and the product was allowed to distil (15 torr), yielding 63 mg of an oily product which crystallized from hexane (50 mg). Mp 94–96°; $[\alpha]_D$ −79.0° ($CHCl_3$; *c* 4.3); IR ν_{max}^{nujol} cm^{-1}: 1770, 1670, 1200, 1080, 1030, 1010, 960, 920, 850, 720; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.35 (2H, *m*, H-2, H-3), 4.35 (1H, *t*, *J* = 9 Hz, H-15), 3.90 (1H, *dd*, *J* = 5 and 9 Hz, H-15), 3.05 (2H, *m*, H-6, H-7), 1.70 (2H, *d*, *J* = 8 Hz, H-1), 1.20 (3H, *s*, Me), 1.11 (3H, *s*, Me), 1.04 (3H, *s*, Me), 1.00 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 234 $[M]^+$ (10), 219 $[M-Me]^+$ (10), 82 (100).

Desulphuration and hydrogenation of **27** (51 mg) as described for **19**, led to **20** (34 mg).

Diol **28**. Usual hydrolysis of **4** (1.02 g) afforded diol **28** (670 mg). Mp 205–207° (Et_2O); $[\alpha]_D$ −26.9° (MeOH; *c* 0.5); IR ν_{max}^{nujol} cm^{-1}: 3400, 2950, 1450, 1380, 1370, 1320, 1300, 1120, 1090, 1040, 1020, 970, 920, 850, 760; ^{1}H NMR (60 MHz, C_5D_5N): δ5.70 (1H, *s*, H-14), 4.30 (1H, *t*, *J* = 7 Hz, H-15), 3.90 (1H, *m*, H-3), 3.65 (1H, *dd*, *J* = 3 and 7 Hz, H-15), 3.02 (1H, *d*, *J* = 11 Hz, H-6), 2.90 (1H, *m*, H-7), 1.75 (2H, *d*, *J* = 7 Hz, H-8), 1.32 (3H, *s*, Me), 1.10 (3H, *s*, Me), 1.00 (6H, *s*, 2Me); EIMS (probe) *m/z* (rel. int.): 237 $[M-OH]^+$ (50), 175 (20), 149 (30), 137 (30), 121 (60), 108 (100), 95 (85), 81 (50), 69 (90).

Acetal **29**. Usual Sarret oxidation of **28** (779 mg) yielded after 3 hr the acetal **29** (580 mg). Mp 219–221° (hexane); $[\alpha]_D$ −50.9° ($CHCl_3$; *c* 2.0); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1705, 1480, 1460, 1400, 1380, 1230, 1120, 1100, 1080, 1060, 980, 940; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.05 (1H, *s*, H-14), 3.90 (1H, *t*, *J* = 7 Hz, H-15), 3.55 (1H, *dd*, *J* = 2 and 7 Hz, H-15), 1.25 (3H, *s*, Me), 1.15 (3H, *s*, Me), 0.97 (3H, *s*, Me), 0.96 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 486 $[M]^+$ (6), 388 (8), 235 (100), 217 (15), 133 (40), 69 (45).

Acetal **30**. A soln of **4** (1.34 g) in C_6H_6 (10 ml) was treated for 30 min. with a trace of *p*-TsOH. After usual work up and chromatography (silica gel, hexane–Et_2O, 93:7), **23** (1.03 g) was isolated. This substance was also obtained when oily **4** was left to stand for a long period at room temp. *Acetal* **30**: Oil; $[\alpha]_D$ −105.7° ($CHCl_3$; *c* 4.5); IR ν_{max}^{film} cm^{-1}: 2900, 1715, 1650, 1450, 1380, 1230, 1150, 1050, 970, 930, 830; ^{1}H NMR (60 MHz, CCl_4): δ5.90 (2H, *q*, *J* = 6 Hz, Ang), 5.05 (2H, *s*, H-14), 4.85 (2H, *m*, H-3), 3.75 (2H, *m*, H-15), 3.40 (2H, *d*, *J* = 11 Hz, H-15), 2.85 (4H, *m*, H-6, H-7), 1.90 (6H, *s* (*br*), Ang), 1.05 (6H, *s*, Me), 1.00 (6H, *s*, Me), 0.90 (12H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 335 (1), 319 (15), 137 (10), 83 (100), 69 (40), 55 (80).

3-*Senecioyloxy*-14,15-*epoxythapsan*-14-*ol* (**5**). Oil; $[\alpha]_D$ −35.7° ($CHCl_3$; *c* 4.7); IR ν_{max}^{film} cm^{-1}: 3400, 2950, 1700, 1670, 1460, 1380, 1230, 1150, 1100, 1000, 940, 850; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.60 (1H, *s* (*br*), Sen), 5.30 (1H, *s*, H-14), 4.95 (1H, *m*, H-1), 4.10 (1H, *t*, *J* = 7 Hz, H-15), 3.50 (1H, *d*, *J* = 7 Hz, H-15), 2.90 (2H, *m*, H-6, H-7), 2.17 (3H, *s* (*br*), Sen), 1.90 (3H, *s* (*br*), Sen), 1.00 (3H, *s*, Me), 0.99 (3H, *s*, Me), 0.95 (3H, *s*, Me), 0.90 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 319 $[M-OH]^+$ (35), 219 $[M-OH-SenOH]^+$ (10), 137 (35), 95 (35), 83 (100), 69 (60), 55 (40).

Methylacetal **31**. The natural hemiacetal **5** (210 mg) was kept at room temp. for 10 min in MeOH (10 ml) and a trace of *p*-TsOH. Usual work up yielded **31**. Mp 114–116° (hexane–Et_2O); $[\alpha]_D$ −37.0° ($CHCl_3$; *c* 1.0); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1950, 1710, 1660, 1460, 1380, 1220, 1160, 1110, 1080, 1000, 930; ^{1}H NMR (60 MHz, $CDCl_3$): δ5.55 (1H, *s* (*br*), Sen), 4.85 (1H, *t*, *J* = 8 Hz, H-1), 4.65 (1H, *s*, H-14), 3.75 (1H, *t*, *J* = 7 Hz, H-15), 3.45 (1H, *d*, *J* = 7 Hz,

H-15), 3.13 (3H, *s*, OMe), 2.85 (2H, *m*, H-6, H-7), 2.15 (3H, *s* (*br*), Sen), 1.86 (3H, *s* (*br*), Sen), 1.05 (3H, *s*, Me), 0.96 (3H, *s*, Me), 0.87 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 319 (6), 290 (6), 190 (6), 108 (20), 83 (100), 69 (30), 55 (90).

Hydroxyacetal **32**. Hydrolysis of **31** (94 mg) by refluxing 2 N NaOH–MeOH yielded after work up pure **32** (51 mg). Mp 112–114° (hexane); $[\alpha]_D$ −67.5° ($CHCl_3$; *c* 2.4); IR ν_{max}^{melted} cm^{-1}: 3400, 2950, 1460, 1380, 1200, 1100, 1080, 1030, 1000, 990, 930; ^1H NMR (60 MHz, CCl_4): δ4.70 (1H, *s*, H-14), 3.50 (3H, *m*, H-15, H-1), 3.20 (3H, *s*, OMe), 0.96 (3H, *s*, Me), 0.92 (3H, *s*, Me), 0.88 (6H, *s*, 2Me); EIMS (probe) *m/z* (rel. int.): 268 $[M]^+$ (1), 237 $[M-Me]^+$ (10), 208 (20), 121 (50), 108 (100), 93 (95), 81(80), 69 (85).

Ketoacetal **33**. Compound **32** (51 mg) was oxidized with PDC in CH_2Cl_2 over night yielding the compound **33** (34 mg). Mp 88–90° (MeOH); $[\alpha]_D$ −101.3° ($CHCl_3$; *c* 7.9); IR ν_{max}^{film} cm^{-1}: 2950, 1750, 1460, 2380, 1310, 1280, 1200, 1105, 1080, 1010, 940; ^1H NMR (60 MHz, CCl_4): δ4.65 (1H, *s*, H-14), 3.70 (1H, *m*, H-15), 3.50 (1H, *m*, H-15), 3.17 (3H, *s*, OMe), 1.20 (3H, *s*, Me), 1.15 (3H, *s*, Me), 1.00 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 266 $[M]^+$ (2), 235 $[M-OMe]^+$ (20), 206 (30), 191 (35), 108 (100), 93 (95), 69 (50).

1-*Hydroxythapsan*-14,15-*olide* (**35**). Thapsanolide **34** (87 mg) was hydrolysed under the same conditions as **31**, yielding after chromatography (silica gel, 10 g; hexane–Et_2O, 3:2) 58 mg of the hydroxylactone **35**. Mp 184–186°; $[\alpha]_D$ −71.6° ($CHCl_3$; *c* 0.85); IR ν_{max}^{nujol} cm^{-1}: 3400, 1760, 1170, 1070, 1020, 1000, 980; ^1H NMR (60 MHz, $CDCl_3$): δ4.40 (1H, *t*, *J* = 9 Hz, H-15), 3.95 (1H, *dd*, *J* = 4 and 9 Hz, H-15), 3.45 (1H, *t*, *J* = 7 Hz, H-1), 3.15 (2H, *m*, H-6, H-7), 1.11 (3H, *s*, Me), 1.05 (3H, *s*, Me), 1.02 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 252 $[M]^+$ (10), 237 $[M-Me]^+$ (2), 234 $[M-H_2O]^+$ (5), 41 (100).

1-*Thapsen*-14,15-*olide* (**37**). Xanthate **36** (386 mg) was kept at 250° for 5 min and then distilled (15 torr), yielding 309 mg which were chromatographed (silica gel, 20 g; hexane–Et_2O, 19:1) to afford pure **37** (212 mg). Mp 157–159°; $[\alpha]_D$ +37.6° ($CHCl_3$; *c* 1.7); IR ν_{max}^{nujol} cm^{-1}: 1770, 1660, 1260, 1190, 1080, 1010, 930, 730; ^1H NMR (60 MHz, $CDCl_3$): δ5.50 (1H, *m*, H-2), 5.20 (1H, *d*, *J* = 7 Hz, H-1), 4.20 (1H, *t*, *J* = 8 Hz, H-15), 3.90 (1H, *dd*, *J* = 3 and 9 Hz, H-15), 3.00 (2H, *m*, H-6, H-7), 1.20 (9H, *s*, Me), 1.00 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 234 $[M]^+$ (10), 219 $[M-Me]^+$ (8), 91 (100).

Desulphuration and hydrogenation of **37** (117 mg) as above, led to **20** (87 mg).

Acetal **6**. Mp 182–184° (MeOH); $[\alpha]_D$ −65.5° ($CHCl_3$; *c* 2.5); IR ν_{max}^{KBr} cm^{-1}: 2900, 1700, 1650, 1460, 1390, 1230, 1150, 1100, 1060, 980, 950, 840; ^1H NMR (60 MHz, CCl_4): δ5.95 (1H, *m*, *J* = 6 Hz, Ang), 5.50 (1H, *m*, Sen), 5.07 (2H, *s*, H-14), 4.65 (2H, *d*, *J* = 6 Hz, H-8), 3.70 (4H, *m*, H-15), 2.70 (4H, *m*, H-6, H-7), 2.10 (3H, *s* (*br*), Sen), 1.95 (3H, *d*, *J* = 6 Hz, Ang), 1.87 (6H, *s* (*br*), Ang, Sen), 1.50 (12H, *s* (*br*), H-1, H-2, H-3), 0.95 (24H, Me); EIMS (probe) *m/z* (rel. int.): 610 $[M-CO_2]^+$ (1), 554 $[M-SenOH]^+$ (2), 319 (18), 235 (4), 219 (5), 151 (10), 137 (15), 107 (15), 95 (20), 83 (100).

Acetal **38**. Usual hydrolysis of **6** or **39** produced **38**. Mp 260–262° (C_6H_6); $[\alpha]_D$ −150.0°; IR ν_{max}^{nujol} cm^{-1}: 3500, 2950, 1460, 1380, 1330, 1280, 1130, 1100, 1060, 970, 960, 940, 920, 860, 800; ^1H NMR (60 MHz, $CDCl_3$): δ5.10 (2H, *s*, H-14), 3.80 (4H, *m*, H-15), 3.55 (2H, *d*, *J* = 7 Hz, H-8), 2.70 (4H, *m*, H-6, H-7), 1.40 (12H, *s* (*br*), H-1, H-2, H-3), 1.04 (6H, *s*, Me), 0.98 (6H, *s*, Me), 0.85 (12H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 262 (15), 253 (17), 237 (40), 214 (5), 83 (35), 69 (100).

Acetal **39**. To a soln of the natural compound **1** (948 mg) in C_6H_6 (10 ml) a trace of *p*-TsOH was added. After 20 min, work up and chromatography (silica gel, hexane–Et_2O, 9:1) gave **39** (712 mg). Mp 153–155° (hexane–Et_2O); $[\alpha]_D$ −48.8° ($CHCl_3$; *c* 7.0); IR ν_{max}^{melted} cm^{-1}: 2900, 1710, 1650, 1450, 1380, 1220, 1140, 1100, 970, 940, 840, 800, 760, 740, 710; ^1H NMR (60 MHz, $CDCl_3$): δ5.70 (2H, *s* (*br*), Sen), 5.28 (2H, *s*, H-14), 4.80 (2H, *d*, *J* = 6 Hz, H-8), 4.10 (4H, *m*, H-15), 2.80 (4H, *m*, H-6, H-7), 2.18 (6H, *s* (*br*), Sen), 1.90 (6H, *s* (*br*), Sen), 1.50 (12H, *s* (*br*), H-1, H-2, H-3), 1.00 (6H, *s*, Me), 0.96 (6H, *s*, Me), 0.90 (12H, *m*, Me); EIMS (probe) *m/z* (rel. int.): 319 (1), 290 (2), 250 (3), 221 (3), 190 (5), 175 (4), 85 (50), 83 (100), 69 (20), 55 (25).

RuO_2 *oxidation of* **27** *to give* **40**. A soln of **27** (649 mg) in CCl_4 (7 ml) and MeCN (7 ml) was stirred with H_2O (9 ml), $NaIO_4$ (3 g) and RuO_2 (17 mg) at room temp. for 2 hr. Usual work up afforded 661 mg of a crude product which was esterified with CH_2N_2–Et_2O and chromatographed (silica gel, 40 g; hexane–Et_2O, 1:1) to yield **40** (420 mg). Oil; $[\alpha]_D$ −46.4° ($CHCl_3$; *c* 4.7); IR ν_{max}^{film} cm^{-1}: 1760, 1720, 1250, 1180, 1140, 1080, 1000; ^1H NMR (60 MHz, $CDCl_3$): δ4.30 (1H, *d*, *J* = 9 Hz, H-15), 3.95 (1H, *dd*, *J* = 3 and 9 Hz, H-15), 3.65 (3H, *s*, OMe), 3.60 (3H, *s*, OMe), 2.40 (2H, *s*, H-1), 1.40 (3H, *s*, Me), 1.35 (3H, *s*, Me), 1.21 (3H, *s*, Me), 1.15 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 326 $[M]^+$ (2), 311 $[M-Me]^+$ (2), 294 $[M-MeOH]^+$ (10), 107 (100).

Dieckmann cyclization of **40** *to give* **41**. A dispersion of NaH (60 mg) was stirred in DMSO (2 ml) for 2 hr. Afterwards product **40** (186 mg) in DMSO (1 ml) was added. After 1 hr the reaction was worked up affording 282 mg of a crude product which was chromatographed (silica gel, 10 g; hexane–Et_2O, 3:2) to yield crystalline **41** (90 mg). $FeCl_3$ positive test; mp 139–141° (hexane–Et_2O); $[\alpha]_D$ −11.0° ($CHCl_3$; *c* 1.8); IR ν_{max}^{KBr} cm^{-1}: 3400, 1780, 1720, 1650, 1620, 1310, 1080, 1020, 830, 710, 690; ^1H NMR (60 MHz, $CDCl_3$): δ3.76 (3H, *s*, OMe), 1.30 (3H, *s*, Me), 1.25 (3H, *s*, Me), 1.15 (3H, *s*, Me), 1.02 (3H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 294 $[M]^+$ (3), 277 $[M-OH]^+$ (10), 29 (100).

Decarboxylation of **41** *to give compound* **42**. Hydrolysis of **41** (30 mg) by refluxing in 2 N NaOH–MeOH (1 ml), work up and distillation (170°, 15 mm) yielded ketolactone **42** (17 mg). Oil; $[\alpha]_D$ −71° ($CHCl_3$; *c* 1.1); IR ν_{max}^{film} cm^{-1}: 1750, 1180, 1070, 1020, 920; ^1H NMR (60 MHz, $CDCl_3$): 4.35 (1H, *t*, *J* = 9 Hz, H-15), 3.95 (1H, *dd*, *J* = 3 and 9 Hz, H-15), 3.00 (2H, *m*, H-6, H-7), 2.30 (2H, *s*, H-1), 1.27 (6H, *s*, Me), 1.09 (6H, *s*, Me); EIMS (probe) *m/z* (rel. int.): 236 $[M]^+$ (15), 29 (100).

REFERENCES

1. Christensen, S. B., Norup, E., Rasmussen, U. and Madsen, J. O. (1984) *Phytochemistry* **23**, 1659.
2. Pascual Teresa, J. de, Morán, J. R., Hernández, J. M. and Grande, M. (1985) *Phytochemistry* **24**, 2071.
3. Pascual Teresa, J. de, Pascual, M. de, Arias, A., Hernández, J. M., Morán, J. R. and Grande, M. (1985) *Phytochemistry* **24**, 1773.
4. Pascual Teresa, J. de, Morán, J. R., Hernández, J. M. and Grande, M. (1985) *Phytochemistry* **24**, 1779.
5. Lemmich, E., Jensen, B. and Rasmussen, U. (1984) *Phytochemistry* **23**, 809.
6. Pascual Teresa, J., Morán, J. R. and Grande, M. (1985) *Chem. Letters* 865.
7. Connolly, J. D. and McCrindle, R. (1965) *Chem. Ind.* 379.
8. Cockerill, A. F., Davies, G. L. O., Harden, R. C. and Rackham, O. M. (1973) *Chem. Rev.* **73**, 553.
9. Schwarz, J. C. P. (1973) *J. Chem. Soc. Chem. Commun.* 505.
10. Moffitt, W., Woodward, R. B., Moscowitz, A., Klyne, W. and Djerassi, C. (1961) *J. Am. Chem. Soc.* **83**, 4013.