Synthesis of Erivanin and 1-Epierivanin from 1-(α)-Santonin

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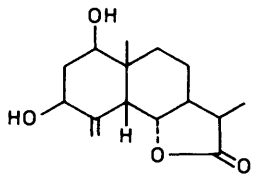
Synthesis of erivanin (**2**) along with its 1-epimer (**17**) is reported starting from 1-(α)-santonin, the crucial step in the synthesis being the successful application of Mitsunobu epimerisation procedure on a eudesmanic alcohol (**15a**) in bringing about inversion of configuration at C-1.

Erivanin was first isolated from the plant *Artemisia fragrance* WILLD, var. *erivanica* BESS by Jevstratova *et al.*,[1] and the gross structure (**1**) was proposed for this compound. Subsequently Herout and his co-workers[2] also reported its occurrence in the species *Tanacetum balsamita* L, and based on detailed ^{1}H n.m.r. data and *X*-ray crystallography they proposed the stereostructure (**2**) for erivanin. While we were



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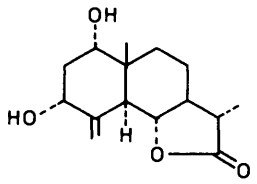

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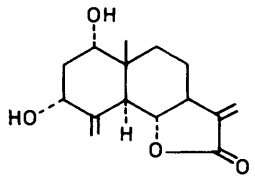

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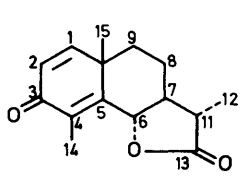
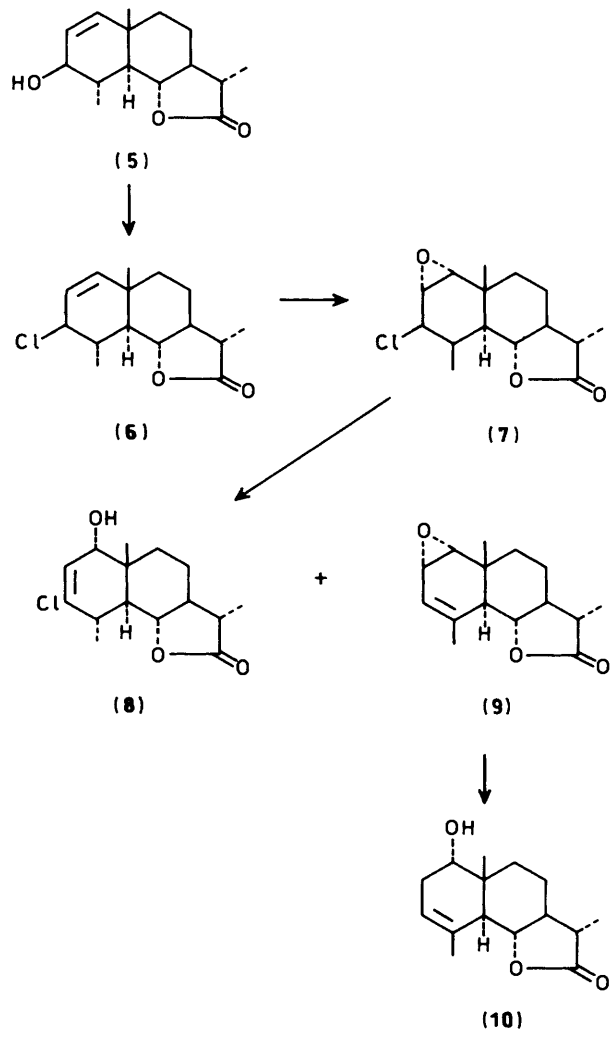


(4)

involved in transformation work on 1-(α)-santonin (**4**), we realised that some of its known intermediates could be utilised to synthesize erivanin so as to corroborate the proposed structure (**2**), since its synthesis had not then been reported. At this stage, although the synthesis of ludovicin A (**3**) had been reported by Yamakawa *et al.*,[3] no 11,12-dihydro analogues were reported by them and hence we undertook the synthesis of erivanin (**2**) despite its close resemblance to compound (**3**). The present paper hence discusses our first synthesis of erivanin (**2**) starting from 1-(α)-santonin (**4**) and is solely based on successful application of the Mitsunobu epimerisation procedure,[4] a hitherto unexplored method in terpene synthesis,[5] as a crucial step in effecting inversion of configuration at C-1.

For the transformation work on santonin (**4**) in the synthesis of erivanin (**2**), three individual approaches were devised, commencing from known intermediates.

The point of origin of the epoxide approach (Scheme 1) was the known allylic alcohol[6] (**5**) readily obtainable from santonin in six steps. It was converted into chloride (**6**), which was epoxidised further to obtain chloro epoxide (**7**) as the sole product. The ^{1}H n.m.r. spectrum of the epoxide exhibited characteristic signals at δ 2.95 (d, *J* 4 Hz, 1 H) and 3.41 (t, *J* 4 Hz, 1 H) for 1-H and 2-H, respectively, besides the 3-H signal at



Scheme 1.

δ 3.78 (dd, *J* 4 and 8 Hz, 1 H) and the 6-H signal at δ 3.90 (t, *J* 11 Hz, 1 H). Compound (**7**) was subsequently subjected to dehydrochlorination in an attempt to obtain the ene epoxide (**9**) for its proposed elaboration to erivanin (**2**) *via* the α-homoallylic alcohol (**10**). However, the major product formed in the reaction was undesired chloro alcohol (**8**) as a result of base-catalysed epoxide ring-opening. The structure of compound (**8**) could be inferred from its ^{1}H n.m.r. spectrum which contained a C-2 olefinic signal as a multiplet between δ 4.35—4.40 and a doublet at δ 3.80 due to 1-H. The other product, a minor ene epoxide (**9**), showed characteristic epoxy proton signals at δ 3.85 (d, *J* 8 Hz, 1 H, 1-H), and at δ 4.25 (m, 1 H, 2-H) besides a C-3 olefinic signal at δ

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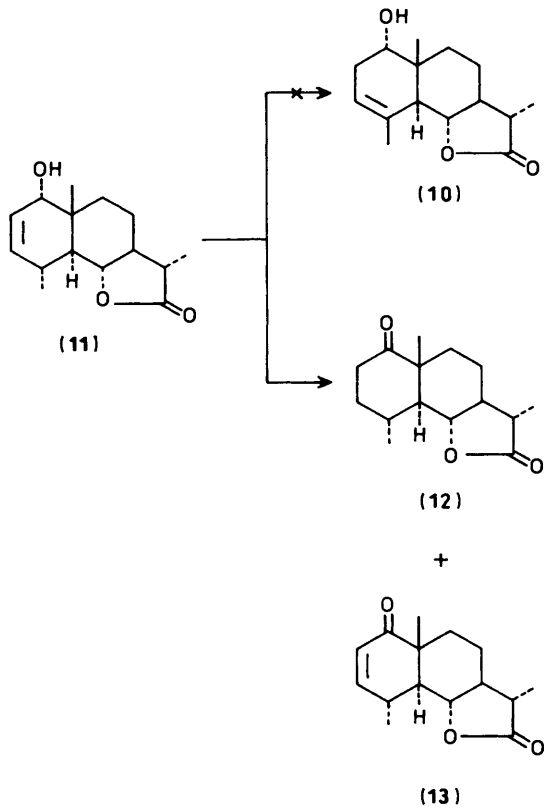
5.50 (br s, 1 H, 3-H). The amount of expected ene epoxide (**9**) was insufficient for conversion into compound (**10**).

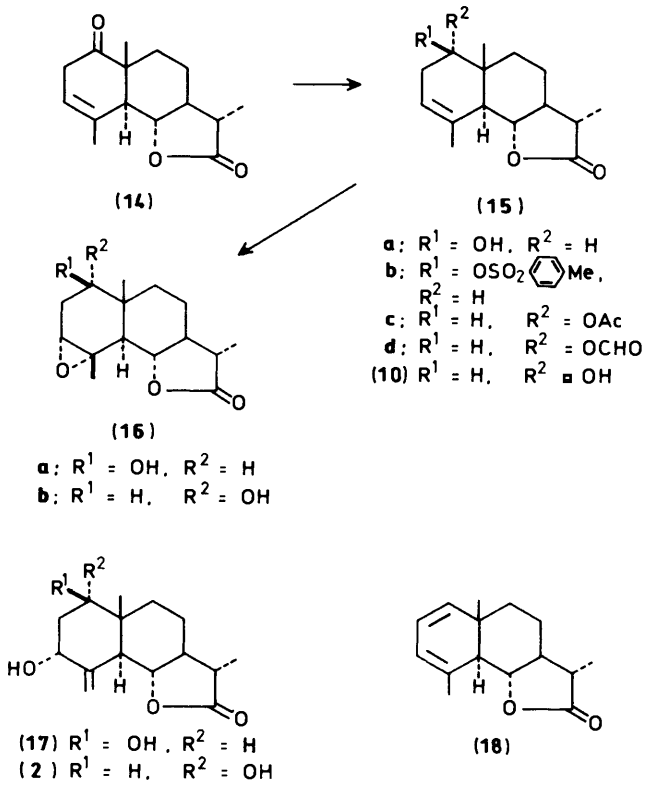
In an alternative approach (Scheme 2) to the synthesis of precursor alcohol (**10**), yet another intermediate (**11**),



Scheme 2.

obtainable from compound (**5**) by allylic rearrangement,[7] was explored. It was subjected to isomerisation in the presence of palladium chloride in an attempt to rearrange the double bond from the Δ^2 to the Δ^3 position, a thermodynamically favoured process of going from a di- to a tri-substituted system. The two products, as they turned out, were the ketones (**12**) and (**13**) with no trace of the expected ene alcohol (**10**). The saturated ketone (**12**) showed in its i.r. spectrum a ketone carbonyl band at 1 710 cm^{-1} whereas the unsaturated ketone (**13**) showed the same band at 1 670 cm^{-1} besides other bands. The saturated ketone (**12**) had arisen out of double bond migration to the Δ^1 position resulting in a highly unstable enol tautomer of the actual ketone formed, whereas the unsaturated ketone (**13**) was a product of direct allylic oxidation under the reaction conditions.

As a final resort, the known[3,8] intermediate enone (**14**) was explored (Scheme 3) for its conversion into erivanin (**2**). Reduction of the enone (**14**) with sodium borohydride at 0 °C over a period of 1 h furnished the β-alcohol (**15a**) as the sole product. Considering the geometry of compound (**15a**) in the vicinity of C-1, the reduction with approach of hydride anion from the less hindered α-face of the molecule was expected to furnish a more stable β-isomer as either sole product or as major product with minor amounts of α-isomer if formed. Yamakawa *et al.*,[3] on their reduction work on the same enone claimed that with sodium borohydride and lithium tri-t-butoxyaluminium hydride, the C-1α alcohol was obtained to the extent of 2.5 and 13.5%, respectively. On the basis of the above theoretical considerations, it was rather surprising to see the bulky reagent lithium tri-t-butoxyaluminium hydride furnishing more of the



Scheme 3.

α-isomer than did the simpler reagent sodium borohydride. In view of the stable β-isomer obtained exclusively by us, we made plans to use it for the synthesis of 1-epierivanin (**17**) and subsequently erivanin (**2**) after due epimerisation at C-1.

The synthesis of 1-epierivanin (**17**) from β-alcohol (**15a**) meant the chemical modification of the Δ^3 double bond into a 3α-hydroxy-$\Delta^{4,14}$ moiety, which we accomplished in a stepwise fashion *via* the epoxide (**16a**) and its rearrangement. Yamakawa *et al.*, in their synthesis of ludovicins, made use of a large excess of hydrogen peroxide in directly converting the Δ^3 group into the required moiety, and ended up with very poor yields of expected products, owing to the intervention of overoxidised products under such harsh conditions. Use of *m*-chloroperbenzoic acid (MCPBA) in the present case, however, furnished the epoxy alcohol (**16a**) in nearly quantitative yield. The crystalline epoxide, m.p. 195—200 °C, showed in its ^1H n.m.r. spectrum a doublet of doublets at δ 3.10 (*J* 2 and 4 Hz) for the C-3 epoxide proton. The observed couplings of low value revealed that the epoxide bridge was α-orientated. The 3-H in the case of a β-orientated epoxide would have coupled in nearly a *trans*-diaxial manner with the 2-H and would have given rise to a higher *J*-value. The sole formation of the α-epoxide clearly revealed that the 1β-hydroxy group exerted no effect in directing epoxidation of this homoallylic alcohol. This result is thus concurrent with Berti's generalisation[9] that a homoallylic hydroxy group can direct epoxidation only if it can be sufficiently near to the double bond, but not otherwise.

The last step in the synthesis of 1-epierivanin (**17**) was to bring about regioselective rearrangement of epoxide (**16a**) to an allylic alcohol moiety. We chose to make use of two bulky bases, namely lithium di-isopropylamide[10] (LDA) and aluminium isopropoxide[11] based on the fact that epoxide rearrangement can be made highly regioselective by proton abstraction from the least substituted carbon if the bases employed fulfil certain steric requirements. With both reagents, the required

Table. Comparison of ^{1}H n.m.r. data of natural and synthetic erivanin

Assignment	Natural erivanin[2]	Synthetic erivanin (**2**)	Synthetic 1-epierivanin (**17**)
1-H	3.36, t, *J* 3 Hz	3.40, dd, *J* 2 and 3.5 Hz	3.65, dd, *J* 7 and 11 Hz
3-H	4.39, t, *J* 2.8 Hz	4.40, t, *J* 3 Hz	4.40, m
5-H	3.01, m	2.99, m	2.90, m
6-H	4.05, dd, *J* 10.7 and 9.7 Hz	4.00, t, *J* 10 Hz	4.00, dd, *J* 10, 12 Hz
12-H_3	1.23, d, *J* 6.7 Hz	1.25, d, *J* 6 Hz	1.25, d, *J* 6 Hz
14-H	5.16, dd, *J* 1.2 and 1 Hz	5.20, m	5.20, m
14-H′	5.01, dd, *J* 1.8 and 1.0 Hz	5.05, m	5.00, m
15-H_3	0.85 s	0.90, s	0.95, s

regioselectivity was achieved and 1-epierivanin (**17**), m.p. 145—147 °C, thus synthesized showed, in its ^{1}H n.m.r. spectrum, important signals at δ 3.65 as a doublet of doublets for 1-H, δ 4.00 (a doublet of doublets for 6-H), and δ 4.40 (multiplet for 3-H). The observed coupling of high order (11 Hz) for 1-H as well as the wide difference in the m.p.s clearly ruled out the possibility of this compound being the natural erivanin.

For the synthesis of erivanin, the prerequisite was to epimerise C-1 in the sole borohydride-reduction product β-alcohol (**15a**). before the sequence of Δ^3-modification as established for 1-epierivanin could be employed. The tosyl derivative (**15b**) was hence prepared from alcohol (**15a**) and was subjected to acetolysis in the presence of anhydrous sodium acetate in acetic acid under varied conditions of temperature and time. At lower temperatures the reaction did not proceed and at elevated temperature, though it proceeded, it furnished an elimination product, the known[6] diene (**18**) exclusively as confirmed by comparison of its data with authentic sample; none of the inverted acetate (**15c**) was obtained. Our observations on attempted epimerisation of (**15b**) paralleled those of Yamakawa *et al.*,[3] wherein attempted epimerisation of the same tosyl ester using tetrabutylammonium formate in refluxing acetone had furnished minor amounts of the same elimination product (**18**) along with unchanged starting material.

Meanwhile, when alternatives were being tried, epimerisation studies on alcohol (**15a**) proved successful when the method reported by Mitsunobu[4] was found to be effective. Accordingly, refluxing of a solution of alcohol (**15a**), diethyl azodicarboxylate (DEAD), triphenyl phosphine, and formic acid in tetrahydrofuran (THF) furnished C-1-inverted formate ester (**15d**) whose ^{1}H n.m.r. spectrum contained prominent signals at δ 3.94 (t, *J* 10 Hz, 1 H) for 6-H, 4.99 (t, *J* 6 Hz, 1 H) for 1-H, 5.34 (br s, 1 H) for 3-H, and 8.09 (s, 1 H) for the proton on the formyloxy grouping. The triplet at δ 4.99 for 1-H with a lower *J*-value of 6 Hz clearly revealed that it is equatorially disposed so as to experience couplings of low order, namely, J_{ee} and J_{ae}, but not J_{aa}. This meant that the potential hydroxy group at C-1 is axially orientated after suffering an inversion of configuration. Careful hydrolysis of formate ester (**15d**) in aqueous methanol containing a few drops of hydrochloric acid furnished the desired inverted alcohol (**10**), m.p. 138—139 °C (lit., [3] 139—141 °C) and the m.p. differed from that of the β-isomer by at least 6 °C. The 1-*H* appeared at δ 3.65 as a triplet with *J* 4.5 Hz. The conversion of compound (**10**) into erivanin (**2**) was a mere repetition of the already established sequence for the 1β-isomer in the synthesis of 1-epierivanin. The synthetic erivanin thus prepared compared very well in all respects with the natural isomer and. as the following Table depicts, a fair comparison of ^{1}H n.m.r. data was achieved.

The synthesis of erivanin is unquestionably due to the successful Mitsunobu epimerisation reaction on the relevant β-intermediate. This forms the formal total synthesis, since the starting material of this synthesis, santonin, has already been totally synthesized.[12] A recent report by Breton and co-workers,[13] however, deals with the microbial transformation of deoxyvulgarin into erivanin and other eudesmanolides.

Experimental

All m.p.s were determined on Tempo electrothermal apparatus and are uncorrected. Dry THF was obtained by distillation from potassium. Dry dichloromethane was obtained by distillation from calcium hydride. Light petroleum refers to the fraction boiling in the range 60—80 °C. Anhydrous sodium sulphate was used for drying all organic extracts, which were evaporated at reduced pressures below 50 °C. The homogeneity of all compounds reported was checked by t.l.c. analysis. U.v. spectra were recorded on a Varian Superscan-3 instrument, with ethanol as solvent. I.r. spectra were recorded on a Perkin-Elmer 237-B grating spectrophotometer in neat form unless stated otherwise. N.m.r. data were obtained at 100 MHz from a Varian XL-100A instrument. Spectra were recorded in $CDCl_3$ solution with $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112-S instrument, with electron impact (e.i.) at 70 eV.

3β-*Hydroxy*-5α,6β,7α,11β*H*-*eudesm*-1-*en*-6,13-*olide* (**5**).—This was prepared as per the procedure of Corey and Hortmann.[6]

3β-*Chloro*-5α,6β,7α,11β*H*-*eudesm*-1-*en*-6,13-*olide* (**6**).—To a cooled (0—5 °C) and stirred solution of the allylic alcohol (**5**) (0.5 g, 2.0 mmol) in dry benzene (15 ml), protected with a guard tube, was added a solution of thionyl chloride (0.48 g, 4.0 mmol) in dry benzene (2 ml) dropwise during 30 min. The reaction mixture was stirred for a further 90 min at 0 °C and worked up after the excess of thionyl chloride had been decomposed by addition of water. Usual processing furnished compound (**6**) as a brownish solid (0.46 g, 85%), m.p. 115—118 °C (from acetone–light petroleum); $\nu_{max.}$ 2 930, 1 780, and 1 470 cm^{-1}; δ_H 1.05 (s, 3 H, 15-H_3), 1.22 (d, *J* 6 Hz, 3 H), 1.25 (d, *J* 6 Hz, 3 H) (together 14- and 12-H_3), 3.84 (t, *J* 10 Hz, 1 H, 6-H), 4.08 (dd, *J* 6 and 1.5 Hz, 1 H, 3-H), and 5.50—5.95 (m, 2 H, 1- and 2-H); *m/z* 270, 268 (1:3, M^+), 232 and 234 (1:3, $M^+ - 36$).

1α,2α-*Epoxy*-3β-*chloro*-5α,6β,7α,11β*H*-*eudesman*-6,13-*olide* (**7**).—To a stirred solution of the allylic chloride (**6**) (0.3 g, 1.11 mmol) in dry dichloromethane at ambient temperature was added MCPBA (0.52 g, 3.0 mmol) and the solution was stirred for 36 h, with intermittent addition of more MCPBA (0.1 g each, twice). The solution was worked up by dilution with dichloromethane (20 ml) and washing successively with aqueous potassium iodide (10%), aqueous sodium thiosulphate (10%), and aqueous sodium hydrogen carbonate (1M). The usual work-up thus furnished the *epoxide* (**7**) as a yellow amorphous mass (0.25 g, 79%), m.p. 125—128 °C (Found: C, 63.1; H, 7.1; Cl, 12.2. $C_{15}H_{21}ClO_3$ requires C, 63.27; H, 7.38. Cl, 12.48%); $\nu_{max.}$ 3 010, 1 770, and 1 460 cm^{-1}; δ_H 1.16 (s, 3 H, 15-H_3), 1.18—1.30 (dd, *J* 6 Hz, 6 H, 12- and 14-H_3), 2.95 (d, *J* 4 Hz, 1 H, 1-H), 3.41 (d, *J* 4 Hz, 1 H, 2-H), 3.78 (d, *J* 8 Hz, 1 H, 3-H), and 3.90 (t, *J* 11 Hz, 1 H, 6-H); *m/z* 284 and 286 (3:1, M^+), 278 and 270 (3:1, $M^+ - 16$).

3-*Chloro*-1α-*hydroxy*-5α,6β,7α,11β*H*-*eudesm*-2-*en*-6,13-*olide* (**8**) *and* 1α,2α-*Epoxy*-5α,6β,7α,11β*H*-*eudesm*-3-*en*-6,13-*olide* (**9**).—The epoxy chloride (**7**) (0.2 g, 0.70 mmol) was dissolved in a mixture of 15% pyridine in dimethylformamide and the solution was heated under mild reflux in nitrogen for 1.5 h, and

then worked up by dilution with water, extraction with dichloromethane, and successive washing of the organic extract with water, hydrochloric acid (10%), aqueous sodium hydrogen carbonate (10%), and brine. Usual work-up and chromatography over silica gel furnished two components. Elution with 20% ethyl acetate in light petroleum furnished *epoxide* (**9**) (0.035 g, 20%), m.p. 120—122 °C (Found: C, 72.25; H, 7.85. $C_{15}H_{20}O_3$ requires C, 72.58; H, 8.06%); $\nu_{max.}$ 2 990, 1 770, and 1 460 cm^{-1}; δ_H 1.05 (s, 3 H, 15-H_3), 1.30 (d, *J* 4 Hz, 3 H, 12-H_3), 1.90 (s, 3 H, 14-H_3), 3.85 (d, *J* 8 Hz, 1 H, 1-H), 3.90 (t, *J* 11 Hz, 1 H, 6-H), 4.25 (m, 1 H, 2-H), and 5.50 (s, 1 H, 3-H).

Elution with 25% ethyl acetate in light petroleum furnished *allylic alcohol* (**8**) (0.1 g, 50%), m.p. 128—130 °C (Found: C, 63.05; H, 7.15; Cl, 12.35. $C_{15}H_{21}ClO_3$ requires C, 63.27; H, 7.38; Cl, 12.48%); $\nu_{max.}$ 3 500, 1 780, and 1 610 cm^{-1}; δ_H 0.95 (s, 3 H, 15-H_3), 0.96—1.15 (m, 6 H, 12- and 14-H_3), 3.80 (d, *J* 2 Hz, 1 H, 1-H), 3.95 (dd, *J* 10 and 12 Hz, 1 H, 6-H), and 4.35—4.40 (m, 1 H, 2-H); *m/z* 286 and 284 (1:3, M^+).

Palladium Chloride-catalysed Rearrangement of Compound (**11**). *Formation of* 1-*Oxo*-5α,6β,7α,11β*H*-*eudesman*-6,13-*olide* (**12**) *and* 1-*Oxo*-5α,6β,7α,11β*H*-*eudesm*-2-*en*-6,13-*olide* (**13**).—To a solution of allylic alcohol (**11**) (0.1 g, 0.4 mmol) in dry benzene or absolute ethanol (30 ml) was added palladium chloride (0.09 g, 0.5 mmol) and the reaction mixture was refluxed under N_2 for 5 h. T.l.c. analysis revealed near complete depletion of starting material. After the mixture had been cooled and filtered, the solvent was distilled off and the crude product was chromatographed over silica gel. Elution with 15% ethyl acetate in light petroleum furnished *crystalline compound* (**12**) (0.041 g, 41%), m.p. 145—149 °C (Found: C, 71.8; H, 8.2. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.30%); $\nu_{max.}$ 3 020, 1 780, and 1 710 cm^{-1}; δ_H 1.15 (s, 3 H, 15-H_3), 1.18—1.30 (m, 6 H, 12- and 14-H_3), and 4.00 (t, *J* 10 Hz, 1 H, 6-H); *m/z* 250 (M^+) and 194 ($M^+ - 56$).

Further elution with 20% ethyl acetate in light petroleum furnished compound (**13**), m.p. 109—112 °C (lit.,[7] 110—112 °C) (Found: C, 72.0; H, 7.9. Calc. for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06%); $\nu_{max.}$ 3 020, 1 780, and 1 670 cm^{-1}; δ_H 1.19 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 1.35 (d, *J* 6 Hz, 3 H, 14-H_3), 4.05 (t, *J* 11 Hz, 1 H, 6-H), 5.90 (dd, *J* 3 and 10 Hz, 1 H, 2-H), and 6.65 (dd, *J* 3 and 10 Hz, 1 H, 3-H); *m/z* 248 (M^+) and 166 ($M^+ - 82$).

1-*Oxo*-5α,6α,7β,11β*H*-*eudesm*-3-*en*-6,13-*olide* (**14**).—Enone (**14**) was synthesized from santonin (**4**) in ten steps, by following Corey's procedure[6] to afford compound (**5**), and its further conversion into the desired compound by the procedure of Ando *et al.*[8]

1β-*Hydroxy*-5α,6β,7α,11β*H*-*eudesm*-3-*en*-6,13-*olide* (**15a**).—To a stirred solution of enone (**14**) (0.5 g, 2.016 mmol) in absolute ethanol (30 ml) at 0 °C was added powdered sodium borohydride (0.077 g, 2.016 mmol) during 5 min. The resulting solution was stirred for 1 h, when t.l.c. analysis clearly revealed completion of the reaction. The excess of borohydride was slowly decomposed by addition of aqueous acetic acid (50%). Most of the alcohol was evaporated off under reduced pressure, and the crude reaction mixture was extracted with ethyl acetate (3 × 20 ml) after dilution with water (30 ml). The organic layer was washed successively with water, aqueous sodium hydrogen carbonate (5%), and brine, and dried. Evaporation of the solvent furnished a pale yellow gum, which upon crystallization in acetone–water yielded crystalline compound (**15a**) (0.26 g, 51.6%), m.p. 133—135 °C (lit.,[3] 135.5—137 °C); $\nu_{max.}$ 3 500, 2 900, 1 755, and 1 460 cm^{-1}; δ_H 0.89 (s, 3 H, 15-H_3), 1.22 (d, *J* 7.5 Hz, 3 H, 12-H_3), 1.81 (s, 3 H, 14-H_3), 3.60 (dd, *J* 7 and 10 Hz, 1 H, 1-H), and 3.94 (t, *J* 10 Hz, 1 H, 6-H); *m/z* 250 (M^+), 232 ($M^+ - 18$), 194 ($M^+ - 56$), and 108 ($M^+ - 142$).

3α,4α-*Epoxy*-1β-*hydroxy*-5α,6β,7α,11β*H*-*eudesman*-6,13-*olide* (**16a**).—The alcohol (**15a**) (0.2 g, 0.8 mmol) was dissolved in dry dichloromethane (20 ml) and to the solution was added MCPBA (0.250 g, 1.379 mmol) in one go. The solution was stirred at ambient temperature for 48 h, by which time t.l.c. analysis showed completion of the reaction. The mixture was worked up by dilution with dichloromethane (20 ml), and washing successively with aqueous potassium iodide (10%), aqueous sodium thiosulphate (10%), water, aqueous sodium hydrogen carbonate (10%), and brine. Further processing in the usual way furnished the amorphous epoxide (**16a**) (0.17 g, 80%). A small portion upon crystallisation from acetone–light petroleum furnished a *crystalline material*, m.p. 198—200 °C (Found: C, 67.1; H, 8.05. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.27%); $\nu_{max.}$ 3 500, 2 920, and 1 170 cm^{-1}; δ_H 0.95 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 1.50 (s, 3 H, 14-H_3), 3.10 (dd, *J* 4 and 2 Hz, 1 H, 3-H), 3.45 (dd, *J* 6 and 10 Hz, 1 H, 1-H), and 3.95 (dd, *J* 8 and 10 Hz, 1 H, 6-H); *m/z* 266 (M^+), 250 ($M^+ - 16$), and 210 ($M^+ - 56$).

1β,3α-*Dihydroxy*-5α,6β,7α,11β*H*-*eudesm*-4(14)-*en*-6,13-*olide*, *1-Epierivanin* (**17**).—*Reaction in refluxing LDA/THF.* LDA Was prepared in dry THF by addition of butyl-lithium (1.54M solution in hexane; 1.6 ml, 2.6 mmol) to a solution of di-isopropylamine (0.42 ml, 3.0 mmol) in dry THF (10 ml) under totally anhydrous conditions under nitrogen. To this stirred turbid solution was added the epoxide (**16a**) (0.150 g, 0.56 mmol) in one lot and the resulting solution was gently refluxed under nitrogen for 2.5 h and worked up after t.l.c. analysis. The work-up involved cooling the reaction mixture, decomposing excess of LDA with 10% aqueous ammonium chloride, distilling off THF, dilution with water, and extraction with ethyl acetate (3 × 20 ml). The extract was washed with hydrochloric acid (2M) and the usual processing yielded a yellow gum, which was passed through a silica gel column (20 gm, 1 × 30 cm) packed in light petroleum. Elution with ethyl acetate–light petroleum (40:60) furnished the crystalline *allylic alcohol* (**17**) (0.078 g, 52%), m.p. 145—147 °C (Found: C, 67.3; H, 8.1. $C_{15}H_{22}O_4$ requires C, 67.67; H, 8.27%); $\nu_{max.}$ 3 300, 3 200, and 1 760 cm^{-1}; δ_H 0.95 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 2.90 (m, 1 H, 5-H), 3.65 (dd, *J* 7 and 11 Hz, 1 H, 1-H), 4.00 (dd, *J* 10 and 12 Hz, 1 H, 6-H), 4.40 (m, 1 H, 3-H), and 5.0—5.20 (m, 2 H, 14-H_2); *m/z* 266 (M^+), 248 ($M^+ - 18$), 230 ($M^+ - 36$), and 210 ($M^+ - 56$).

Epoxide Cleavage in Refluxing Toluene containing Aluminium Isopropoxide.—A solution of epoxide (**16a**) (0.1 g, 0.3759 mmol) in anhydrous sulphur-free toluene (25 ml) was refluxed, after the addition of aluminium isopropoxide (0.204 g, 1.0 mmol) under dry nitrogen, for 13 h. After further addition of the reagent (0.1 g, 0.5 mmol) the mixture was refluxed for a further 5 h. The solvent was removed under reduced pressure and the crude material was stirred after addition of a mixture of ethyl acetate (20 ml) and hydrochloric acid (2M; 20 ml) until the residue had dissolved. The organic layer, obtained after the usual work-up, furnished the crude product as a pale solid (0.048 g, 48%), which upon crystallisation yielded the same compound (**17**) as obtained by the LDA method.

1β-(p-*Tolylsulphonyloxy*)-5α,6β,7α,11β*H*-*eudesm*-3-*en*-6,13-*olide* (**15b**).—The alcohol (**15a**) (0.2 g, 0.8 mmol) was dissolved in dry pyridine (10 ml) and to the solution was added toluene-*p*-sulphonyl chloride (0.19 g, 1.0 mmol). The reaction mixture was swirled till complete dissolution, and the flask was stoppered and kept at ambient temperature overnight. The appearance of needles of pyridinium hydrochloride confirmed the progess of reaction. Water (20 ml) was added and the material was extracted with dichloromethane (2 × 15 ml). The organic layer,

after being washed with hydrochloric acid (2M) and worked up in the usual way, afforded a gum, to which light petroleum (10 ml) was added, and the mixture was kept in a deep freeze for 4 h to give needle-like crystals of the *tosyl derivative* (**15b**) (0.29 g, 90%), m.p. 153—154 °C (Found: C, 65.0; H, 6.75; S, 7.8. $C_{22}H_{28}O_5S$ requires C, 65.35; H, 6.93; S, 7.92%); $\nu_{max.}$ 1 775 and 1 600 cm^{-1}; δ_H 0.98 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 1.80 (br s, 3 H, 14-H_3), 2.50 (s, 3 H, Ar*Me*), 3.92 (t, *J* 9 Hz, 1 H, 6-H), 4.55 (t, *J* 8 Hz, 1 H, 1-H), 5.25 (br s, 1 H, 3-H), 7.40 (d, *J* 8 Hz, 2 H, *m*-ArH). and 7.5 (d, *J* 8 Hz, 2 H, *o*-ArH); *m/z* 404 (M^+) and 231 (M^+ − OTs).

Acetolysis of Tosyl Ester (**15b**). *Formation of* 5α,6β,7α,11β*H-Eudesma*-1,3-*dien*-6,13-*olide* (**18**).—The tosyl ester (**15b**) (0.1 g, 0.24 mmol) was dissolved in a solution of acetic acid (5 ml) and anhydrous sodium acetate (0.082 g, 1.0 mmol) and the whole reaction mixture was stirred at 65—70 °C for 12 h, when t.l.c. of the reaction mixture revealed formation of a minor, new non-polar compound. Hence the temperature was raised to 95 °C and the mixture was stirred overnight, till completion of the reaction. Water (25 ml) was added and the product was extracted with dichloromethane (2 × 20 ml). The extract was washed with 10% aqueous sodium hydrogen carbonate and worked up to afford a crude gum, which was chromatographed on silica gel, eluting with 5% ethyl acetate in light petroleum, to give pure non-polar product (**18**) (0.03 g), m.p. 96—97 °C (lit.,[6] 98—99 °C); $\lambda_{max.}$(EtOH) 269 nm (ε 4 795); $\nu_{max.}$ 3 040, 1 770, and 1 600 cm^{-1}; δ_H 0.95 (s, 3 H, 15-H_3), 1.24 (d, *J* 6 Hz, 3 H, 12-H_3), 1.95 (br s. 3 H, 14-H_3), 4.04 (dd, *J* 8 and 10 Hz, 1 H, 6-H), and 5.41—5.90 (m, 3 H, 1-, 2-, and 3-H).

1α-*Formyloxy*-5α,6β,7α,11β*H-eudesm*-3-*en*-6,13-*olide* (**15d**).—A solution of the alcohol (**15a**) (0.625 g, 2.5 mmol), triphenylphosphine (1.31 g, 5.00 mmol), and formic acid (0.23 g, 5.00 mmol) in dry THF (25 ml) was stirred at room temperature whilst a solution of DEAD (0.87 g, 5.00 mmol) in THF (10 ml) was added dropwise. A mild exothermic reaction ensued. The mixture was mildly refluxed for 6 h, then evaporated, and the residue was eluted through a column of silica gel with 15% ethyl acetate in light petroleum as eluant to furnish the *inverted formate ester* (**15d**) as a crystalline solid (0.59 g, 85%), m.p. 152—153 °C (Found: C, 68.75; H, 7.4. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.91%); $\nu_{max.}$ 2 920, 1 770, 1 720, and 1 460 cm^{-1}; δ_H 1.00 (s. 3 H, 15-H_3), 1.22 (d, *J* 6.5 Hz, 3 H, 12-H_3), 1.82 (s, 3 H, 14-H_3), 3.94 (t, *J* 10 Hz, 1 H, 6-H), 4.99 (t, *J* 7 Hz, 1 H, 1-H), 5.34 (br s, 1 H, 3-H), and 8.09 (s, 1 H, OCHO); *m/z* 278 (M^+) and 232 (M^+ − HCO_2H).

1α-*Hydroxy*-5α,6β,7α-11β*H-eudesm*-3-*en*-6,13-*olide* (**10**).—The formate ester (**15d**) (0.1 g, 0.36 mmol) was added to a solution of 3% conc. hydrochloric acid in methanol, and the mixture was stirred for 1 h and was then worked up by evaporation of methanol and extraction with dichloromethane (2 × 25 ml). Further work-up and concentration furnished the hydrolysed product (**10**) (0.074 g, 82%), m.p. 138—139 °C (lit.,[3] 139—141 °C); $\nu_{max.}$ 3 500, 1 775, and 1 610 cm^{-1}; δ_H 0.89 (s, 3 H, 15-H_3), 1.22 (d, *J* 6.5 Hz, 3 H, 12-H_3), 1.81 (br s, 3 H, 14-H_3), 3.65 (t, *J* 4.5 Hz, 1 H, 1-H), 3.95 (t, *J* 11 Hz, 1 H, 6-H), and 5.33 (br s, 1 H, 3-H).

1α-*Hydroxy*-3α,4α-*epoxy*-5α,6β,7α,11β*H-eudesman*-6,13-*olide* (**16b**).—The procedure discussed for reaction of (**15a**) was followed by its 1-epimer (**10**) (0.08 g, 0.32 mmol) to give the *epoxide* (**16b**) (0.05 g, 62%), m.p. 140—143 °C (Found: C, 67.2; H, 8.0. $C_{15}H_{22}O_4$ requires C, 67.67; H, 8.27%); $\nu_{max.}$ 3 500, 1 780, and 1 450 cm^{-1}; δ_H 0.95 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 1.50 (s, 3 H, 14-H_3), 2.30 (ddd, *J* 16, 6, and 1 Hz, 1 H, 2-H_β), 2.50 (ddd, *J* 16, 6, and 1 Hz, 1 H, 2-H_α), 3.05 (dd, *J* 2 and 1 Hz, 1 H, 3-H), 3.45 (dd, *J* 9 and 7 Hz, 1 H, 1-H), and 3.95 (dd, 1 H, *J* 10 and 9 Hz, 6-H).

1α,3α-*Dihydroxy*-5α,6β,7α,11β*H-eudesm*-4(14)-*en*-6,13-*olide*, *Erivanin* (**2**).—The procedure discussed for isomerisation of (**16a**) was followed for its 1-epimer (**16b**) (0.05 g, 0.18 mmol) to afford erivanin (**2**) (0.023 g, 50%), m.p. 198—200 °C (lit.,[1,2] 200—202 °C) (Found: C, 67.4; H, 8.1. Calc. for $C_{15}H_{22}O_4$: C, 67.69; H, 8.27%); $\nu_{max.}$ 3 500, 2 940, 1 770, and 1 460 cm^{-1}; δ_H 0.90 (s, 3 H, 15-H_3), 1.25 (d, *J* 6 Hz, 3 H, 12-H_3), 2.99 (m, 1 H, 5-H), 3.40 (dd, *J* 2 and 3.5 Hz, 1 H, 1-H), 4.00 (t, *J* 10 Hz, 1 H, 6-H), 4.40 (t, *J* 3 Hz, 1 H, 3-H), and 5.05—5.20 (m, 2 H, 14-H_2); *m/z* 266 (M^+), 248 (M^+ − 18), 230 (M^+ − 36), and 210 (M^+ − 56).

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