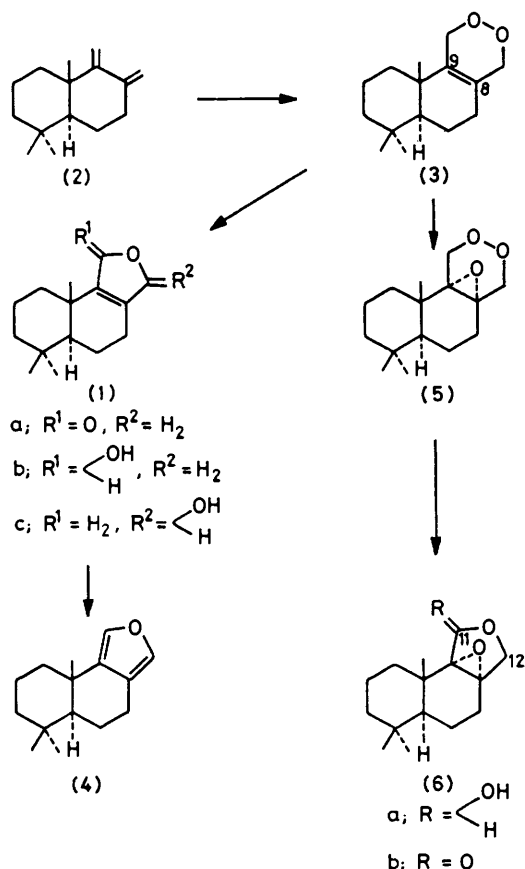


## A New, Efficient Synthesis of (+)-Isodrimenin

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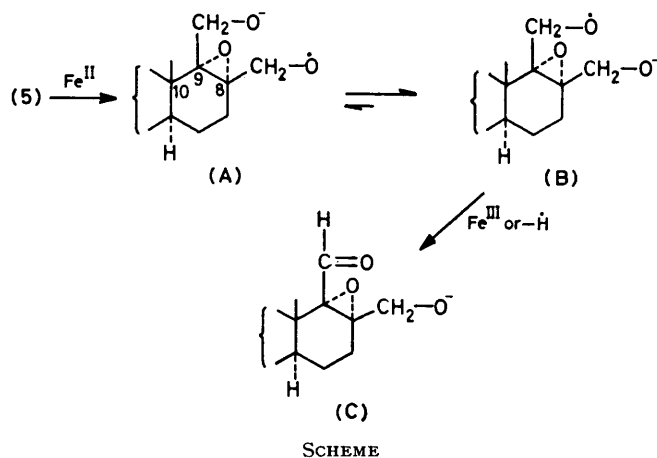
A new, efficient synthesis of natural (+)-isodrimenin (1a) from manool is reported. This synthesis consists of the following key steps. The cyclic peroxide (3), obtained from the diene (2) by photo-oxygenation in *meso*-tetraphenylporphine in carbon tetrachloride, was epoxidised to protect the  $\Delta^{8,9}$ -double bond. The epoxy-peroxide (5) thus obtained smoothly underwent ferrous sulphate-catalysed rearrangement to the epoxy-lactol (6a), which on oxidation with Sarett reagent led to the epoxy-lactone (6b). Deoxygenation of (6b) with pentacarbonyliron in *N,N*-dimethylacetamide afforded the  $\alpha,\beta$ -unsaturated lactone (1a).

ISODRIMENIN (1a) is one of the drimanic sesquiterpenes isolated from the stem barks of the South American *Drimys* species.<sup>1</sup> Recently interesting biological activities of the sesubstances have been reported.<sup>2</sup> The objective of our present work is to explore a new convenient route to the synthesis of these naturally occurring substances.<sup>3</sup> Our recent three-step synthesis<sup>4</sup> of natural confertifolin from commercially available manool<sup>5</sup> made the conversion of the latter into another related sesquiterpene an intriguing problem of organic synthesis. Here we describe a short, highly efficient synthesis of natural (+)-isodrimenin (1a).



The starting material for this synthesis was the diene (2), obtained from manool by the two-step manipulation reported previously.<sup>4</sup>

On photo-oxygenation in *meso*-tetraphenylporphine in carbon tetrachloride the diene (2) provided in 65% yield the cyclic peroxide (3), as reported earlier.<sup>4</sup> Our previous work<sup>4</sup> has shown that attempts to rearrange it to the  $\Delta^{8,9}$ -unsaturated lactol (1b) or/and (1c) with a variety of reagents, including basic alumina,<sup>6</sup> ferrous sulphate,<sup>7</sup> tetracarbonyl-di- $\mu$ -chloro-dirhodium,<sup>8</sup> or palladium,<sup>9</sup> were not successful. The possible intermediate lactols (1b, c) apparently were unstable and readily dehydrated to the furanoid (4).<sup>†</sup> We attributed this failure to the presence of the  $\Delta^{8,9}$ -double bond and considered it necessary to mask it by epoxidation before rearrangement. Treatment of the peroxide (3) with *m*-chloro-perbenzoic acid gave the epoxy-peroxide (5) in 97% yield. On treatment with ferrous sulphate<sup>7</sup> compound (5) afforded solely the epoxy-lactol (6a) in 93% yield. It is surprising to note that in this case no detectable amount of an isomeric  $C_{12}$ -lactol was formed. Turner and Herz<sup>7</sup> suggested earlier that the  $Fe^{II}$ -induced isomerisation may involve the  $Fe^{II}$ - $Fe^{III}$  redox system. As depicted in the



Scheme, the epoxy-peroxide (5) would undergo cleavage and reduction with ferrous ion to a radical anion (A) or/and (B). A molecular model indicates that the  $C_8$ -substituent is far more distant from the  $C_{10}$ -angular methyl than the  $C_9$ -substituent. Therefore, as a result

<sup>†</sup> It is interesting to note that a new oxygenated derivative of this compound has recently been isolated from the Mediterranean nudibranch *Dendrodoris limbata* (G. Cimino, S. de Rosa, S. de Stefano, and G. Sodano, *Tetrahedron Lett.*, 1981, 1271).

of the greatly reduced interaction between the anion and the C<sub>10</sub>-methyl group, the radical anion (B) is apparently more stable than (A) and may exist in predominant amount. It would further oxidise with ferric ion or with loss of a hydrogen radical to the anion (C) which would then cyclise to the lactol (6a).

Subsequent oxidation of compound (6a) with Sarett reagent<sup>10</sup> led to the epoxy-lactone (6b) in 78% yield. Deoxygenation of compound (6b) with either zinc dust<sup>11</sup> or copper-zinc couple<sup>12</sup> failed. On refluxing with pentacarbonyliron<sup>13</sup> in *N,N*-dimethylacetamide, however, compound (6b) afforded in nearly 100% yield (+)-isodrimenin (1a). Identity of this compound was established by direct comparison (m.p., mixed m.p., optical rotation, i.r., and n.m.r. spectra) with an authentic sample.

#### EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, i.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 spectrometer. N.m.r. spectra were obtained on a Varian EM 3940. Chemical shifts are reported in p.p.m. downfield from internal SiMe<sub>4</sub>. Mass spectra were determined on a DuPont 21-492B (Data System 21-094B) on 70 eV using a direct-inlet system. Rotations were measured in chloroform solutions at 23 °C with a Zeiss polarimeter (0.01°). For column chromatography silica gel 60 (70–230 mesh) was used. Thin layer chromatograms were prepared on silica gel G or silica gel GF<sub>254</sub>60 (Merck) and the spots were observed by exposure to iodine vapour or u.v. light. All organic extracts were dried over anhydrous sodium sulphate or magnesium sulphate and evaporated under reduced pressure below 60 °C. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

*Epoxidation of the Peroxide (3) with m-Chloroperbenzoic Acid.*—The peroxide (3) (800 mg) in chloroform (10 ml) was treated with *m*-chloroperbenzoic acid (1.20 g) at room temperature for 45 min. The solution was then passed through Merck standardised alumina (activity II–III) and elution with benzene yielded the epoxy-peroxide (5) as an oil (813 mg);  $\delta$  (CDCl<sub>3</sub>) 0.83 (3 H, s, Me), 1.12 (3 H, s, Me), 1.23 (3 H, s, Me), and 4.20 (4 H, ABq, *J* 15 Hz, CH<sub>2</sub>O·OCH<sub>2</sub>); *m/e* 252 (*M*<sup>+</sup>) (Found: C, 71.0; H, 9.2. C<sub>15</sub>H<sub>24</sub>O<sub>3</sub> requires C, 71.39; H, 9.59%).

*Rearrangement of the Epoxy-peroxide (5) with Ferrous Sulphate.*—A solution of ferrous sulphate heptahydrate (1.51 g) in water (33 ml) was added in one portion to the epoxy-peroxide (5) (831 mg) in tetrahydrofuran (25 ml). The mixture was stirred at room temperature for 1.5 h after which water was added. The product was then extracted with chloroform and isolated in the usual way. Chromatography over silica gel and elution with 20% ether in hexane yielded a mixture of the two C<sub>11</sub>-isomeric epoxy-lactols (6a) as an oil (769 mg). The n.m.r. spectrum in CCl<sub>4</sub> showed, besides an AB quartet at  $\delta$  3.70 (2 H, *J* 12 Hz, 12-H), two singlets at  $\delta$  5.06 and 5.20 whose integral ratio is 1 : 2, respectively, attributable to 11-H; *m/e* 252 (*M*<sup>+</sup>) (Found: C, 71.2; H, 9.4. C<sub>15</sub>H<sub>24</sub>O<sub>3</sub> requires C, 71.39; H, 9.59%).

*Oxidation of the Epoxy-lactol (6a) with Chromium Trioxide-Pyridine Complex.*—A solution of the epoxy-lactol (6a) (280 mg) in dry pyridine (4 ml) was added to the Sarett

reagent prepared from chromium trioxide (300 mg) and dry pyridine (12 ml) at 0–5 °C. The mixture was then stirred at room temperature for 72 h, after which it was diluted with water and extracted with ether. The ether extract was washed with water and evaporated. The crude product was then chromatographed over silica gel with 30% ether in hexane as eluant to yield the epoxy-lactone (6b) (225 mg), m.p. 90–92 °C;  $\delta$  (CCl<sub>4</sub>) 0.83 (3 H, s, Me), 0.86 (3 H, s, Me), 1.16 (3 H, s, Me), and 4.06 (2 H, ABq, *J* 11 Hz, 12-H);  $\nu_{\max}$ . 1770 cm<sup>-1</sup> ( $\gamma$ -lactone CO); *m/e* 250 (*M*<sup>+</sup>) (Found: C, 71.7; H, 8.7. C<sub>15</sub>H<sub>22</sub>O<sub>3</sub> requires C, 71.79; H, 8.86%).

*Deoxygenation of the Epoxy-lactone (6b).*—(a) *With zinc dust in acetic acid.* The epoxy-lactone (6b) (50 mg) in glacial acetic acid (3 ml) was stirred with zinc dust (30 mg) at room temperature for 72 h. Work-up resulted in the recovery of starting material (50 mg). A 24 h period of reflux gave the same result.

(b) *With copper-zinc couple.* The epoxy-lactone (6b) (70 mg) in ethanol (27 ml) was heated under reflux with copper-zinc couple (2.5 g) for 72 h. Work-up resulted in recovery of starting material.

(c) *With pentacarbonyliron.* The epoxy-lactone (6b) (94 mg) in *N,N*-dimethylacetamide (5 ml) was heated under reflux with pentacarbonyliron (0.5 ml) for 4.5 h in an atmosphere of nitrogen. Water was then added and the product was extracted with chloroform. The chloroform extract was washed several times with water and the product was isolated in the usual way. (+)-Isodrimenin (1a) (86 mg) crystallised from ether-hexane and had m.p. 131–132 °C (lit.,<sup>1</sup> 131–132 °C),  $[\alpha]_D +93^\circ$  (*c*, 1.1) (lit.,<sup>1</sup> +87°);  $\delta$  (CDCl<sub>3</sub>) 0.86 (3 H, s, Me), 0.91 (3 H, s, Me), 1.13 (3 H, s, Me), 2.60 (1 H, dm, *J* 13 Hz, 1 $\beta$ -H), and 4.53 (2 H, s, 12-H);  $\nu_{\max}$ . 1770 ( $\alpha,\beta$ -unsaturated  $\gamma$ -lactone CO) and 1670 cm<sup>-1</sup> (conjugated C=C);  $\nu_{\max}$ . (CCl<sub>4</sub>) 1763 ( $\alpha,\beta$ -unsaturated  $\gamma$ -lactone CO) and 1671 cm<sup>-1</sup> (conjugated C=C); *m/e* 234 (*M*<sup>+</sup>) (Found: C, 76.55; H, 9.25. C<sub>15</sub>H<sub>22</sub>O<sub>2</sub> requires C, 76.88; H, 9.46%).

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