

**576. The Total Synthesis of (+)-14-Isopropylpodocarpa-8,11,13-triene-13,16-diol [(+)-16-Hydroxytotarol] and (+)-Macrophylllic Acid.**

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Total syntheses of the diol (I; R = CH<sub>2</sub>·OH) and the bisditerpenoid, macrophylllic acid (II; R = CO<sub>2</sub>H), by a route which correlates them with agathenedicarboxylic acid, are described. The oxidative-coupling step in the synthesis of macrophylllic acid probably parallels the biogenesis of this compound.

14-ISOPROPYLPODOCARPA-8,11,13-TRIENE-13,16-DIOL [(+)-16-hydroxytotarol], isolated from several *Podocarpus* species,<sup>1-4</sup> has been shown to have the structure and stereochemistry contained in formula (I; R = CH<sub>2</sub>·OH).<sup>2-5</sup> The β-configuration of the 4-hydroxymethyl group is based on nuclear magnetic resonance (n.m.r.) data<sup>3,5</sup> and on the pK\*<sub>mcs</sub> value of a derived acid;<sup>4</sup> the available chemical evidence, though permissive, does not constitute classical proof of this point. Racemic hydroxytotarol has recently been synthesized by Taylor.<sup>2b</sup>

Macrophylllic acid, from *P. macrophyllus* D. Don,<sup>6,7</sup> has been correlated with the diol (I; R = CH<sub>2</sub>·OH) and assigned the structure (II; R = CO<sub>2</sub>H).<sup>7</sup> It is thus related to podototarol (II; R = Me),<sup>8</sup> which was previously the sole example of a 12,12'-bisditerpenoid.

The present communication describes total syntheses of the (+)-diol (I; R = CH<sub>2</sub>·OH) and (+)-macrophylllic acid, using as relay the tricyclic degradation product (III; R = Me)<sup>9</sup> of agathenedicarboxylic acid (IV). Barltrop and Day have already synthesized the racemic form of this intermediate,<sup>10</sup> and more recently have resolved the synthetic acid (III; R = H) *via* its cinchonine salt and converted it into the dextrorotatory ester (III; R = Me) identical with the natural material.<sup>11</sup> It was expected that this would be converted smoothly (cf. ref. 12) into the methyl ester (I; R = CO<sub>2</sub>Me), the key compound for both syntheses.

Alkylation of the (+)-ester (III; R = Me) with isopropyl bromide and potassium *t*-butoxide in *t*-butyl alcohol gave a 58% yield of the 14-isopropyl-keto-ester (V), the ultraviolet spectrum of which (λ<sub>max</sub>. 250 mμ, log ε 4.14) confirmed the position of the isopropyl group. A second crystalline product was probably the di-isopropyl compound (VI) (cf. ref. 12); but, in view of the minute yield (0.3%), the substance could not be characterized adequately.

Direct aromatization of ring c by use of 2,3-dichloro-5,6-dicyanobenzoquinone<sup>13</sup> was unsatisfactory; but the keto-ester (V) was converted by successive treatment with *N*-bromosuccinimide and collidine into the phenolic ester (I; R = CO<sub>2</sub>Me), the physical constants of which (m. p. 198.5—199.5°, [α]<sub>D</sub><sup>20</sup> +116.8° in chloroform) agree with those reported by Taylor<sup>2</sup> for methyl 13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oate from *P. mannii* Hook f. The ester was reduced with lithium aluminium hydride to the

<sup>1</sup> Brandt and Thomas, *Nature*, 1952, **170**, 1018.

<sup>2</sup> Taylor, (a) *Chem. and Ind.*, 1961, 1712; (b) *J.*, 1963, 1553.

<sup>3</sup> Cambie and Mander, (a) *Chem. and Ind.*, 1961, 1877; (b) *Tetrahedron*, 1962, **18**, 465.

<sup>4</sup> Cambie, Simpson, and Colebrook, *Tetrahedron*, 1963, **19**, 209.

<sup>5</sup> Wenkert and Beak, *Tetrahedron Letters*, 1961, **11**, 358.

<sup>6</sup> Takahashi, *Nippon Mokuzai Gakkaishi*, 1959, **5**, 185 (*Chem. Abs.*, 1960, **54**, 25796b).

<sup>7</sup> Bocks, Cambie, and Takahashi, *Tetrahedron*, 1963, **19**, 1109.

<sup>8</sup> Cambie, Simpson, and Colebrook, *Chem. and Ind.*, 1962, 1757; Cambie *et al.*, refs. 3b and 4.

<sup>9</sup> Ruzicka, Bernold, and Tallichet, *Helv. Chim. Acta*, 1941, **24**, 223.

<sup>10</sup> Barltrop and Day, *Chem. and Ind.*, 1958, 439; *J.*, 1959, 671.

<sup>11</sup> Barltrop and Day, unpublished work; Day, D.Phil.Thesis, Oxford, 1960.

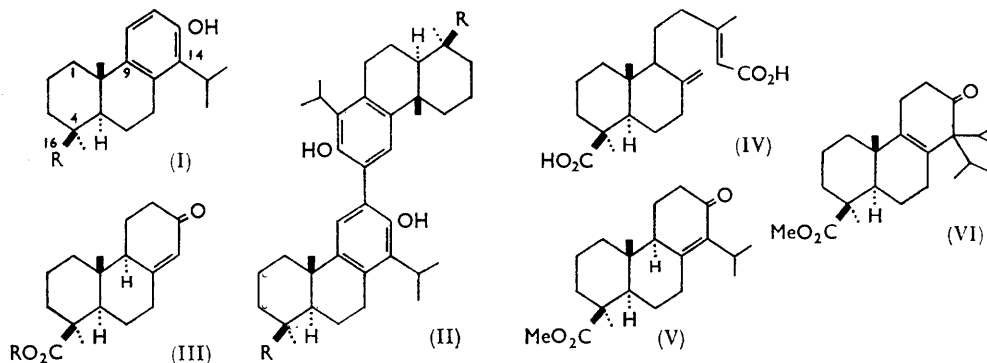
<sup>12</sup> Barltrop and Rogers, *Chem. and Ind.*, 1957, 397; *J.*, 1958, 2566.

<sup>13</sup> Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.

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(+)-13,16-diol (+)-16-hydroxytotarol],  $[\alpha]_D^{25} + 31.5^\circ$  (in chloroform),\* m. p. 227—227.5° undepressed by admixture with an authentic sample (m. p. 226—226.5°). The infrared spectra of the synthetic and the natural compound in potassium chloride were identical.

The diol (I; R = CH<sub>2</sub>OH) is accompanied in Nature by the corresponding acid (I; R = CO<sub>2</sub>H), isolated as its methyl ester,<sup>2</sup> and aldehyde (I; R = CHO),<sup>2,4</sup> both of which have been correlated with the diol. The above synthesis therefore correlates all three compounds with agathenedicarboxylic acid (IV) *via* the keto-ester (III; R = Me), and so provides proof of the configuration at C-4. Moreover, it constitutes a total synthesis of 16-oxototarol (I; R = CHO), since this compound has been prepared from the diol (I; R = CH<sub>2</sub>OH).<sup>3</sup>



In model experiments for the synthesis of macrophyllic acid (II; R = CO<sub>2</sub>H), totarol (I; R = Me) was oxidized with alkaline potassium ferricyanide to give podototarol (II; R = Me) in 56% yield (cf. ref. 15). Inferior yields (*ca.* 16%) were obtained with manganese dioxide as oxidant.

When synthetic methyl 13-hydroxy-14-isopropylpodocarpatrien-16-oate (I; R = CO<sub>2</sub>Me) was oxidized with alkaline potassium ferricyanide and the product subjected to careful chromatography followed by distillation, coupled material ( $\lambda_{\max}$  290 and 252sh  $\mu$ , b. p. 200—210°/10<sup>-4</sup> mm.) was obtained in 25% yield. This resisted all attempts at crystallization, but was shown to be largely dimethyl macrophyllate (II; R = CO<sub>2</sub>Me) by thin-layer chromatography. When treated with lithium iodide in boiling collidine,<sup>16</sup> it gave (+)-macrophyllic acid (II; R = CO<sub>2</sub>H), m. p. 238—239° (decomp.), which was shown to be identical with a natural sample [m. p. 237.5—239° (decomp.)] by mixed melting point and infrared comparison in potassium chloride.

Experiments in the oxidative coupling of totarol by Falshaw, Johnson, and King,<sup>15</sup> and of totarol and the methyl 13-hydroxy-14-isopropylpodocarpatrien-16-oate, as described above, probably parallel the biogenesis of the 12,12'-bisditerpenes. However, the most decisive evidence in favour of this biosynthetic step is the enzymic oxidative

\* There is some discrepancy in the recorded optical rotation values for 14-isopropylpodocarpa-8,11,13-triene-13,16-diol. For Brandt and Thomas's sample,<sup>1</sup> Wenkert and Beak<sup>5</sup> give  $[\alpha]^{26} + 29^\circ$  (EtOH). Taylor's product<sup>2</sup> had  $[\alpha]^{22} + 44^\circ$  (MeOH). Cambie and Mander's product<sup>3</sup> ( $[\alpha]^{17} + 41.9^\circ$  in EtOH) is reported<sup>4</sup> to have been contaminated with podototarol ( $[\alpha]^{24} + 76.1^\circ$  in CHCl<sub>3</sub>); indeed, its ultraviolet spectrum suggests that it may have contained a significant quantity of this impurity. Cambie, Simpson, and Colebrook<sup>4</sup> give  $[\alpha]^{20} + 45^\circ$  (CHCl<sub>3</sub>), but this value could be in error;<sup>14</sup> and, in the present work, a sample of Cambie's diol (m. p. 226—226.5°) was found to have  $[\alpha]_D^{26} + 34.0^\circ$  (CHCl<sub>3</sub>), unchanged by further purification. This value compares satisfactorily with that of the synthetic product. In methanol, the synthetic sample had  $[\alpha]_D^{18} + 36^\circ$ .

<sup>14</sup> Cambie, personal communication.

<sup>15</sup> Falshaw, Johnson, and King, *J.*, 1963, 2422.

<sup>16</sup> Elsinger, Schreiber, and Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113; Taschner and Liberek, *Roczniki Chem.*, 1956, **30**, 323.

coupling of totarol<sup>7,17</sup> and 14-isopropylpodocarpa-8,11,13-triene-13,16-diol<sup>17</sup> by Bocks and Cambie.

A preliminary account of this work has been published.<sup>18</sup>

### EXPERIMENTAL

Ultraviolet spectra were measured for ethanol solutions, and optical rotations with an ETL-NPL automatic polarimeter for chloroform solutions. M. p.s were determined on a Kofler block. For chromatography, Peter Spence's "Grade H" alumina was used; deactivated alumina contained 5% of 10% aqueous acetic acid. "Kieselgel G" (Merck) was used for thin-layer chromatography (t.l.c.); the plates were developed with iodine vapour. Unless otherwise stated, light petroleum refers to the fraction of b. p. 60–80°. Organic extracts were dried with magnesium sulphate.

*Methyl 14-Isopropyl-13-oxopodocarp-8(14)-en-16-oate* (V).—Dry isopropyl bromide (0.65 ml.) in dry t-butyl alcohol (15 ml.) was added dropwise during 25 min. to a boiling solution of methyl (+)-13-oxopodocarp-8(14)-en-16-oate (III; R = Me)<sup>9</sup> (500 mg.) and potassium t-butoxide (from 135 mg. of metal) in dry t-butyl alcohol (15 ml.) under nitrogen. After the addition, the solution was heated under reflux for 30 min., then diluted with water and acidified with dilute hydrochloric acid. The semisolid product (540 mg.), isolated with ether, was chromatographed on deactivated alumina (50 g.). Elution with 2:1 light petroleum (b. p. 40–60°)–benzene (100 ml.) gave semisolid fraction A (51 mg.);  $\nu$  (Nujol) 1724s, 1670m, and 1712sh  $\text{cm}^{-1}$ . Further elution with the same solvent (700 ml.) gave fraction B (385 mg.) as a solid. Elution with 1:1 light petroleum (b. p. 40–60°)–benzene (100 ml.) followed by benzene (100 ml.) gave fraction C (55 mg.) as an oil.

Fraction A, recrystallized three times from light petroleum, gave laths (1.8 mg.) (probably VI), m. p. 138–144°;  $\nu$  (Nujol) 1724 and 1712sh  $\text{cm}^{-1}$ ; only weak absorption in the 240–260  $\mu$  region, which was not increased by treatment with aqueous ethanolic hydrochloric acid. Evaporation of the mother-liquors from the first recrystallization of this fraction gave solid (33 mg.),  $\nu$  (Nujol) 1725s and 1670s  $\text{cm}^{-1}$ , which was combined with fraction B. Fraction B, recrystallized from light petroleum, gave *methyl 14-isopropyl-13-oxopodocarp-8(14)-en-16-oate* (V) (258 mg.), m. p. 142–146.5°. More material (74 mg.) of comparable purity was obtained by rechromatography of the mother-liquors from this recrystallization. Recrystallized again, the compound had m. p. 146–148°,  $\lambda_{\text{max}}$  250  $\mu$  ( $\log \epsilon$  4.14),  $[\alpha]_{\text{D}}^{21} + 77.2^\circ$  ( $c$  0.97) (Found: C, 75.75; H, 9.7.  $\text{C}_{21}\text{H}_{32}\text{O}_3$  requires C, 75.9; H, 9.7%). Fraction C, which could not be crystallized, showed only weak absorption in the 240–260  $\mu$  region. When this material was treated with aqueous ethanolic hydrochloric acid, an intense, rather broad peak appeared at 246  $\mu$  [starting material (III; R = Me) has  $\lambda_{\text{max}}$  241  $\mu$ ; (V) has  $\lambda_{\text{max}}$  250  $\mu$ ].

*Methyl 13-Hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oate* (I; R =  $\text{CO}_2\text{Me}$ ).—(i) A mixture of the preceding compound (270 mg.), *N*-bromosuccinimide (161 mg.), and dry carbon tetrachloride (10 ml.) under nitrogen was heated under reflux over a 250w lamp for 30 min. After filtration, the solution was washed with water and then with saturated potassium hydrogen carbonate solution, dried, and evaporated. The residue (285 mg.) was heated under reflux under nitrogen with 2,4,6-collidine (10 ml., redistilled from potassium hydroxide) for 1 hr. The solution was poured into dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid and then with brine, dried, filtered through deactivated alumina (5 g.), and evaporated to give a glass (267 mg.) which solidified (m. p. 188–196°) when triturated with light petroleum. On recrystallization from benzene–light petroleum, the *ester* was obtained as plates, m. p. 197–199°. A sample further purified by sublimation at 160°/0.05 mm. and recrystallization from benzene–light petroleum had m. p. 198.5–199.5°,  $[\alpha]_{\text{D}}^{20} + 116.8^\circ$  ( $c$  0.79),  $\lambda_{\text{max}}$  279  $\mu$ ,  $\lambda_{\text{inf}}$  283  $\mu$  ( $\log \epsilon$  3.37 and 3.32, respectively) (Found: C, 76.0; H, 9.1.  $\text{C}_{21}\text{H}_{30}\text{O}_3$  requires C, 76.3; H, 9.15%). For the ester (I; R =  $\text{CO}_2\text{Me}$ ) from *P. mannii* Hook f., Taylor<sup>2</sup> gives m. p. 198° (from MeOH),  $[\alpha]_{\text{D}}^{20} + 124^\circ$  (in MeOH).

(ii) A solution of the keto-ester (V) (48 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (50 mg.) in benzene (2 ml.) was heated under reflux for 48 hr., then chromatographed on

<sup>17</sup> Bocks and Cambie, *Proc. Chem. Soc.*, 1963, 143.

<sup>18</sup> Day, *Chem. and Ind.*, 1963, 1760.

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deactivated alumina (10 g.). Elution with 1 : 1 light petroleum–benzene (50 ml.) gave an oil (7 mg.), then (with 75 ml. of solvent) starting material (9 mg.). Elution with benzene (50 ml.) and 4 : 1 benzene–ether (50 ml.) gave an uncrystallizable gum (9.6 mg.), which closely resembled the product of the preceding experiment in its infrared spectrum. On reduction with lithium aluminium hydride in tetrahydrofuran, this material gave an intractable gum.

**14-Isopropylpodocarpa-8,11,13-triene-13,16-diol** [16-Hydroxytotarol] (I; R = CH<sub>2</sub>·OH).—The synthetic ester (I; R = CO<sub>2</sub>Me) (23 mg.) in tetrahydrofuran (2 ml.; redistilled from lithium aluminium hydride) was treated with an excess of lithium aluminium hydride, then kept at room temperature for 1 hr. Excess of reagent was destroyed by addition of moist ether, and the acidified mixture was extracted with ether to give the *diol* (21 mg.) as needles, m. p. 221–224°. Sublimed at 170–180°/0.2 mm. and twice recrystallized from benzene–light petroleum, it had m. p. 227–227.5°,  $[\alpha]_D^{25} + 31.5^\circ$  (c 0.38),  $\lambda_{\max}$  279 m $\mu$ ,  $\lambda_{\text{infl}}$  283 m $\mu$  (log  $\epsilon$  3.33 and 3.31, respectively) (Found: C, 79.2; H, 9.8. C<sub>20</sub>H<sub>30</sub>O<sub>2</sub> requires C, 79.4; H, 10.0%). A sample of the diol from *P. hallii* Kirk<sup>4</sup> had m. p. 226–226.5°,  $[\alpha]_D^{25} + 34.0^\circ$  (c 0.46), these physical constants being unchanged by sublimation and recrystallization. The identity of the synthetic and the natural material was shown by mixed m. p. (undepressed) and comparison of infrared spectra in potassium chloride discs. Both samples gave a single spot ( $R_F$  0.53) on t.l.c. in 1 : 1 benzene–ether.

**Oxidative coupling of Totarol** (I; R = Me).—(i) A solution of totarol (100 mg.) in benzene (15 ml.) was filtered during 1 hr. through a column of manganese dioxide (1 g.) mixed with Celite (1 g.). The column was washed with benzene (4 ml.), and the combined solutions were evaporated to give an orange glass (103 mg.). This was shown by t.l.c. in 2 : 1 light petroleum–benzene and by its ultraviolet spectrum to contain both totarol ( $R_F$  0.13;  $\lambda_{\max}$  278 m $\mu$ ) and podototarol (II; R = Me) ( $R_F$  0.64;  $\lambda_{\max}$  254 and 290 m $\mu$ ). Chromatography on deactivated alumina (10 g.) and elution with light petroleum (b. p. 40–60°) (100 ml.), followed by sublimation at 210°/0.1 mm., gave a glass (16 mg.) which crystallized with methanol. Recrystallization from ethanol gave needles, m. p. 221–225° undepressed by admixture with authentic podototarol (m. p. 222–225°).

Similar results were obtained with chloroform as solvent.

(ii) Totarol (100 mg.) was oxidized with alkaline potassium ferricyanide under essentially the conditions described by Falshaw, Johnson, and King.<sup>15</sup> The yellow gum (100 mg.) was chromatographed on deactivated alumina (10 g.) and eluted with light petroleum (b. p. 40–60°) (100 ml.) to give podototarol (56 mg.), m. p. 215–222°, identified by t.l.c. Recrystallization from ethanol raised the m. p. to 218–225°. Elution with 1 : 1 light petroleum–benzene (50 ml.) gave totarol (28 mg.).

**Dimethyl Macrophyllate** (II; R = CO<sub>2</sub>Me).—Synthetic methyl 13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-16-oate (I; R = CO<sub>2</sub>Me) (71 mg.) in benzene (2 ml.) was stirred under nitrogen at room temperature with potassium hydroxide (65 mg.) in water (1.5 ml.) during the dropwise addition of potassium ferricyanide (125 mg.) in water (4 ml.). Stirring was continued under nitrogen for 2 hr. at room temperature, and finally for 15 min. on a steam-bath. After acidification with 2N-hydrochloric acid, the product (78 mg.) was isolated with ether. By chromatography on "Grade H" alumina (15 g.) and successive elution with benzene (150 ml.), 19 : 1 benzene–ether (180 ml.), and 9 : 1 benzene–ether (150 ml.), the product was divided into 18 fractions. By t.l.c. in 19 : 1 benzene–ether, fractions 1–9 (30 mg.) were shown to be predominantly dimethyl macrophyllate ( $R_F$  0.69), fractions 10–18 (24 mg.) to be starting material ( $R_F$  0.56). Fractions 1–9 were combined and distilled at 10<sup>-4</sup> mm. Material (4 mg.) distilling below 190° was identified by t.l.c. as starting material. The less volatile fraction (18 mg.; b. p. 200–210°/10<sup>-4</sup> mm.;  $\lambda_{\max}$  290 and 252sh m $\mu$ ) was identified by t.l.c. as dimethyl macrophyllate, but it could not be induced to crystallize.

**Macrophylllic Acid** (II; R = CO<sub>2</sub>H).—The crude ester (10 mg.) from the preceding experiment, anhydrous lithium iodide (100 mg.; dried at 70°/0.1 mm. for 6 hr.), and 2,4,6-collidine (3 ml.; redistilled from potassium hydroxide) were heated under reflux under nitrogen for 8 hr. After addition of 2N-hydrochloric acid and ether, the product was separated into acidic and neutral fractions with 10% sodium carbonate solution in the usual way. No dimethyl macrophyllate could be detected in the neutral fraction (2.0 mg.) by t.l.c. The acidic fraction (5.3 mg.), m. p. 226–228°, when treated with charcoal and filtered in ether through "Florosil," gave macrophylllic acid (2.6 mg.) as fine needles, m. p. 231–235°. After three recrystallizations from ether–hexane, the acid had m. p. 238–239° (decomp.) undepressed by admixture

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with an authentic sample [m. p. 237.5—239° (decomp.)]. The infrared spectra of the synthetic and the natural material, measured in potassium chloride discs, were identical. Both samples gave a single spot ( $R_F$  0.53) on t.l.c. in 19:1 chloroform-ethanol. The ultraviolet spectrum of synthetic macrophylic acid had  $\lambda_{max}$ . 218, 253, and 290 m $\mu$  ( $\log \epsilon$  4.62, 4.12, and 3.84, respectively);  $\lambda_{max}$ . (in ethanolic sodium hydroxide) 318 m $\mu$ ,  $\lambda_{inf}$ . 255 m $\mu$  ( $\log \epsilon$  3.99 and 4.17, respectively) (cf. ref. 7).

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