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ABSOLUTE CONFIGURATION OF AGERATRIOL

A GERMACRANIC SESQUITERPENE FROM *ACHILLEA AGERATUM* L.

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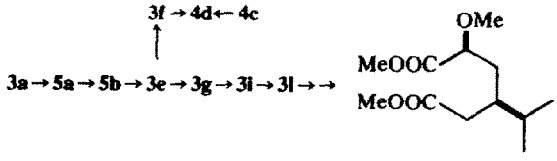
Abstract—On the basis of chemical evidence, the stereostructure 7 is proposed for ageratriol, a germacranic sesquiterpene isolated from *Achillea ageratum* L.

In a previous paper we reported the determination of the structure of ageratriol **1a**,[1] a germacranic sesquiterpene from *Achillea ageratum*. Agerol **2**[2] was subsequently isolated from the same plant and its absolute configuration determined.

We wish now to report the determination of the absolute configuration of the four asymmetric centres of **1a**. The configurations of the C atoms 7 and 9 are of particular relevance in checking the hypothesis[1] that ageratriol is biosynthesized from the (+)-germacrene A,[3] agerol **2** being an intermediate.

The key derivative in the determination of the configurations of the centres C-7 and C-9 was dihydroageratriol 9-methylether **3l**, for the dimethylester **8** of 2-methoxy-4-isopropyladipic acid, optically active,[4] was obtained from its degradation (Scheme A).



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SCHEME A.

The dihydro-derivative **3b** was obtained in good yield only by reduction of tripivaloyl–ageratriol **1c**, which shows a great steric hindrance on the C-4 and C-10 double bonds. The dihydro–ageratriol **3a**, obtained by alkaline saponification, was converted by means of transacetalisation with 2,2-dimethoxypropane into a cyclic acetal to which structure **5a** was assigned on the basis of the following transformations (Scheme A). Acetal **5a** reacted with acetic anhydride in pyridine to form an acetyl derivative **5b** from which, by means of transacetalisation with ethylene glycol, a monoacetyl–dihydroageratriol **3e** was obtained. When this compound was treated with propionyl chloride, a monoacetyl-dipropionyl-derivative **3f** was obtained, which, by partial catalytic reduction, afforded the tetrahydro-compound **4d**. The latter substance has the same chemico-physical properties as when it was derived by dipropionylation of 5-acetyl-tetrahydro-ageratriol **4c**, previously described,[1] and after selective hydrolysis of the allylic ester groups gave **4c**. It is then proved beyond doubt that the OH groups in C-1 and C-9 take part in the formation of the acetonide.

Treatment of **3e** with equimolecular quantities of acetic anhydride in pyridine yielded, after chromatographic purification, a diacetyl derivative to which, on the basis of the following transformations the structure of 1,5-diacetyl-dihyrroageratriol **3g** was assigned.

Treatment of **3g** with CH_2N_2–$BF_3 \cdot Et_2O$ afforded the diacetyl monomethylether **3i** and, after saponification, the monomethylether **3l**. When **3l** was oxidized with $KMnO_4$–$NaIO_4$,[4] a mixture of acid compounds was obtained, from which the optically active 2-methoxy-4-isopropyl-adipic acid as methylester **8**, $[\alpha]_D^{20} - 53{\cdot}2°$ (*c* 5, MeOH), was isolated. Its NMR spectrum ($CDCl_3$) is identical to that of the enantiomers 2*R*-4*S* and 2*S*-4*R* of **8** obtained† from

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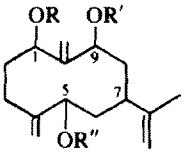
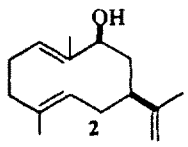
†The preparation of the four stereoisomers of **8** is the subject of a forthcoming publication.



	R	R′	R″
1a:	H	H	H
1b:	Ac	Ac	Ac
1c:	$COCMe_3$	id.	id.
1d:	Me	Me	H
1e:	H	H	Ac
1f:	Me	Me	Ac
1g:	Me	H	Me
1h:	H	H	Me
1i:	Ac	H	Me
1l:	Ac	THP	Me
1m:	H	THP	Me
1n:	Me	THP	Me
1o:	Ac	Me	Me
1p:	H	Me	Me



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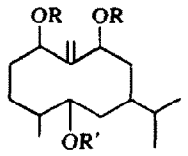
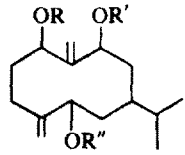
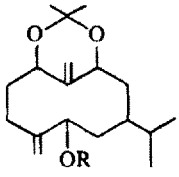


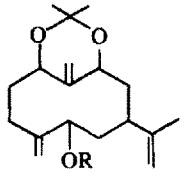
	R	R′
4a:	H	H
4b:	Ac	Ac
4c:	H	Ac
4d:	COEt	Ac
4e:	Me	Ac
4f:	Me	H



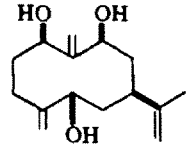
	R	R′	R″
3a:	H	H	H
3b:	Ac	Ac	Ac
3c:	$COCMe_3$	id.	id.
3d:	H	H	Me
3e:	H	H	Ac
3f:	COEt	id.	Ac
3g:	Ac	H	Ac
3h:	Ac	H	H
3i:	Ac	Me	Ac
3l:	H	Me	H
3m:	Ac	THP	THP
3n:	H	THP	THP
3o:	Me	THP	THP
3p:	Me	H	H



	R
5a:	H
5b:	Ac
5c:	Me



	R
6a:	H
6b:	Ac
6c:	Me



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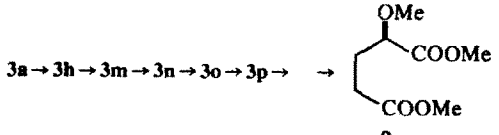
(+)- and (−)-carvone and is different from that of the enantiomers 2*S*-4*S* and 2*R*-4*R*. In particular, the isopropyl methyls of the first pair of enantiomers appear equivalent, giving rise to a single doublet at 0·87 δ (J 6·7 Hz); in the second pair, these methyls are not equivalent, giving rise to two doublets 0·88 (J 6·7 Hz) and 0·91 δ (J 6·7 Hz)). The NMR analysis and the specific optical rotation value of ester **8** obtained from ageratriol prove that both asymmetric centres C-7 and C-9 of **1a** have the *S* configuration.

The key product in the determination of the configuration of C-1 is dihydroageratriol 1-methylether **3p** from the oxidation of which one of the enantiomers of 2-methoxy-glutaric acid[5] was to be obtained (Scheme B).



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SCHEME B.

*In the NMR spectrum (C_5D_5N) the position of the signal corresponding to the MeO- group is characteristic of each individual OMe derivative, being 3·20 for 5-methoxy- **3d**, 3·34 for 1-methoxy- **3p** and 3·47 for 9-methoxy-compound 31.

Treatment of dihydroageratriol **3a** with equimolecular quantities of acetic anhydride in pyridine afforded a mixture of acetates from which a monoacetate that did not coincide with 5-acetyl-dihydro-ageratriol **3e** was obtained. To this product the structure of 1-acetyl-dihydro-ageratriol **3h** was tentatively assigned, considering that acetylation of **3e** proceeded preferably on the OH group in C-1 rather than on that in C-9 (see Scheme A).

Reaction of **3h** with dihydropyrane yielded the di(tetrahydro)pyranyl derivative **3m** in good yield. After alkaline hydrolysis, **3m** afforded dihydroageratriol-5,9-di-(tetrahydro)pyranyl-ether **3n**. Methylation of the free OH group **30** and acid hydrolysis produced the monomethylether **3p**. The position of the OMe group at C-1 was confirmed by the fact that the properties of **3p** are different from those of the 9-methoxy derivative **3l**, described above, and of the 5-methoxy derivative **3d**, obtained by methylation of the cyclic acetal **5a** and subsequent transacetalisation.*

When the compound **3p** was ozonised and the ozonide decomposed with HIO_4,[6] a mixture of acids was obtained which, after esterification with CH_2N_2, was separated by silica-gel chromatography. The dimethyl ester **9** of 2-methoxy-glutaric acid, optically active, was thus isolated. Its specific optical

rotation, $[\alpha]_D^{20}$ +36·2° (*c* 0·4 $CHCl_3$), coincided with that of the ester obtained from *R*-glutamic acid;[5] therefore the C-1 configuration of ageratriol is *R*.

Many reactions attempted in order to determine the configuration of C-5 did not produce any significant results. We therefore resorted to the method of asymmetric esterification ('partial decoupling') described by Horeau and others[7,8] and based upon the Cram–Prelog rule of asymmetric synthesis.

Ageratriol 1,9-dimethylether **1d**, which is necessary for such a determination, was obtained following the sequence of reactions reported in Scheme C.

1a → 6a → 6b → 1e → 1f → 1d
↓
6c → 1h → 1i → 1o → 1p
↓
1l → 1m → 1n → 1g

SCHEME C.

Ageratriol **1a** was transformed, by the method described for dihydroageratriol **3a** into the corresponding acetonide **6a** and subsequently into the acetyl derivative **6b**. After transacetalisation with ethylene glycol, the monoacetylageratriol **1e**† was methylated to form 5-acetylageratriol 1,9-dimethylether **1f**. Subsequent alkaline saponification produced ageratriol 1,9-dimethylether **1d**.

Working under the conditions described by Horeau for genipine,[8] *S*-(+)-phenylbutyric acid was recovered (optical yield 27%); the configuration of the C atom 5 in ageratriol is therefore *R*.

In view of the possibility[9] that, in molecules of sufficient complexity, not only the hindrance due to the substituents at α but also that due to other parts of the molecule may contribute to the asymmetric esterification, the determination of the configuration of C-5 was repeated on the C-4 saturated derivative **4f** (Scheme D), for which a modification of the molecular conformation might be suggested. *S*-(+)-phenylbutyric acid was again recovered (optical yield 18·1%), thus confirming the previous assignment.

4c → 4e → 4f

SCHEME D.

As a further check, Horeau's method was also applied to determinations of the configurations of C atoms 1 and 9. Working with ageratriol 1,5-dimethylether **1g** and ageratriol 5,9-dimethylether **1p**, obtained in accordance with the Scheme C, the conclusions reached proved to agree with the chemical determinations reported earlier; configurations were *S* (opt. yield 29·4% for C-9 and *R* (opt. yield 12·5%) for C-1.

†The position of the acetyl group was confirmed by transforming compound **1e** into 5-acetyl-dihydroageratriol **3e** (already described) by means of partial reduction.

The stereochemistry of ageratriol, as it appears from the determinations of asymmetric centres reported in this paper, is therefore that represented in **7**. The C-7 and C-9 configurations are identical to those of corresponding C atoms of agerol **2**, supporting the hypothesis[1] that ageratriol may be the product of further biological oxidation of **2**.

EXPERIMENTAL

M.ps were determined on a Tottoli block and are uncorrected. IR spectra were determined with a Perkin Elmer 257 instrument. NMR spectra were measured on a Jeol instrument at 60 MHz, with TMS as internal standard, chemical shifts have been recorded in δ values. Optical rotations were measured in MeOH solns on a Perkin Elmer 141 instrument.

Tripivaloyl-ageratriol (**1c**). A soln of ageratriol (2 g) in pyridine (8 ml) was treated with pivaloyl chloride (4·8 ml) and allowed to stand 3 h at room temp, then hexane (60 ml) was added. The ppt was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and washed with $NaHCO_3$ aq and H_2O. Removal of the solvent gave a viscous oil which was purified by column chromatography (silica-gel) and final distillation (3·5 g), b.p. 180–182°/0·05 mm, it solidifies on standing. IR (nujol): 1720, 1150 cm^{-1}; NMR ($CDCl_3$): 1·12–1·25 (27H, CH_3–C); 1·71 (s, 3H, CH_3–C=); 4·7–5·7 (3H, m, H–C–O); 4·81 (2H, br. s, CH_2=C); 5·4 (2H, br. s, CH_2=C); 5·58 (1H, s, H–C=C); 5·7 (1H, s, H–C–=C). (Found: C 71·17; H 9·69. $C_{36}H_{68}O_6$ requires: C 71·39; H 9·59%.

Dihydroageratriol (**3a**). A soln of **1c** (2 g) in n-hexane (150 ml) was hydrogenated with PtO_2 catalyst at atmospheric pressure, until the ratio dihydro-tetrahydroderivative was *ca* 4/1, the progress of the reaction being monitored by GLC (NPGS 3% on chromosorb W, temp 215°). Usual work up gave a crude product which was treated with LAH in Et_2O, then acetylated (Ac_2O–Py). After hydrolysis with 0·1 N KOH-95% MeOH (140 ml) at room temp for 1 h, chromatography over silica gel separated **4c**[1] and **3a** m.p. 200–201°. $[\alpha]_D^{20}$ −9·2° (*c* 2); IR (nujol): 3300 cm^{-1}; NMR (C_5D_5N): 0·77 (3H, d (J 6·7), CH_3–C); 0·8 (3H, d (J 6·7 Hz), CH_3–C); 4·2–4·8 (3H, m, H–C–O); 5·2 (2H, s, CH_2=C); 5·57 and 5·91 (1H each, s, H–C=C). (Found: C, 70·59; H 10·17. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%).

Dihydroageratriol acetonide (**5a**). 2,2-dimethoxypropane (2·2 ml) was added with stirring to a soln of **3a** (4·5 g) in acetone (300 ml), containing 20 mg of *p*-toluenesulfonic acid. The mixture was stirred for 10 h at room temp, then filtrated over alumina (act III). Evaporation of the solvent, followed by chromatographic purification over alumina, afforded an oily product (4 g) which was homogeneous in TLC. The pure compound was unstable on standing; IR (film): 3400 cm^{-1}; NMR ($CDCl_3$): 0·9 (6H, d (J 6 Hz), CH_3–C); 1·43 (6H, s, CH_3–C–O); 4·0 (1H, dd, (J 3·7 and 10·8 Hz), H–C–O); 4·6–5·2 (2H, m, H–C–O); 4·8 (2H, br. s, CH_2=C) and 5·04 (2H, br. s, CH_2=C). (Found: C, 73·68; H, 10·02. $C_{18}H_{30}O_3$ requires: C, 73·42; H, 10·29%).

5-Acetyl-dihydroageratriol acetonide (**5b**). A soln of **5a** (250 mg) in pyridine (0·8 ml) and Ac_2O (0·6 ml) was allowed to stand for 2 h at room temp. After evaporation under reduced pressure, the residue, homogeneous in TLC, was distilled to yield a colourless oil (260 mg), b.p. 150°/0·1 mm, IR (film): 1730, 1250 cm^{-1}. (Found: C, 71·23; H, 9·66. $C_{20}H_{32}O_4$ requires: C, 71·39; H, 9·59%).

5-Acetyl-dihydroageratriol (**3e**). Ethylene glycol (0·5 g) and *p*-toluenesulfonic acid (5 mg) were added to a soln of **5b** (500 mg) in $CHCl_3$ (2 ml). The mixture was allowed to stand for 15 h, then evaporated to give a residue which, after chromatography over silica gel, was crystallized (350 mg) from acetone–diisopropylether, m.p. 110–111°. $[\alpha]_D^{20}$ + 10° (*c* 2); IR (nujol): 3260 cm^{-1}; NMR (C_5D_5N): 0·85 (6H, d(J 6 Hz), CH_3–C); 2·03 (3H, s, CH_3COO); 4·4–4·9 (2H, m, H–C–O); 5·3 (1H, m, H–C–O); 5·32 (2H, br. s, CH_2=C); 5·58 and 5·9 (1H each, s, H–C=C). (Found: C, 68·81; H, 9·43. $C_{17}H_{28}O_4$ requires: C, 68·89; H, 9·52%).

1,9-Dipropionyl-5-acetyl-dihydroageratriol (**3f**). A soln of **3e** (195 mg) in pyridine (1 ml) was treated with propionyl chloride (0·5 ml) and allowed to stand for 4 h at room temp, then hexane (15 ml) added. The ppt was filtered off and the filtrate evaporated *in vacuo*. Usual work up gave a colourless oil, which was purified by distillation (179 mg), b.p. 155–157°/0·02 mm (it solidifies on standing); IR (nujol): 1730, 1240, 1180 cm^{-1}; NMR ($CDCl_3$): 0·8–1·35 (12H, CH_3–C); 2·0 (3H, s, CH_3COO); 4·8–5·7 (3H, m, H–C–O); 5·36 (2H, s, CH_2=C); 5·52 and 5·62 (1H each, s, H–C=C). (Found: C, 67·46; H, 8·97. $C_{23}H_{36}O_6$ requires: C, 67·62 H, 8·88%).

Compound (**4d**) *from* (**3f**). Dehydroderivative **3f** (168 mg) in hexane (30 ml) was hydrogenated (PtO_2 catalyst) at room temp and pressure, the progress of the reaction being monitored by GLC. Usual work up gave a product which was purified by chromatography over silica gel, b.p. 167–168°/0·3 mm, (151 mg). $[\alpha]_D^{20}$ −30·4° (*c* 3); IR (film): 1728, 1240, 1190 cm^{-1}; NMR ($CDCl_3$): 0·75–1·25 (15H, CH_3–C); 2·02 (3H, s, CH_3COO); 2·34 and 2·38 (2H each, q, CH_3–CH_2–O); 4·92 (1H, m, H–C–O); 5·1–5·7 (2H, m, H–C–O); 5·45 and 5·58 (1H each, s, H–C=C). (Found: C, 67·46; H, 9·11. $C_{23}H_{38}O_6$ requires: C, 67·29; H, 9·33%).

Hydrolysis of (**4d**) **4d** (146 mg) was treated with 0·1 N KOH–95% MeOH (10 ml) for 1 h at room temp. Neutralization and solvent removal under reduced pressure afforded a viscous residue which was chromatographed over silica gel. The C_6H_6-acetone (6:4) eluate yielded a pure crystalline (acetone) compound **4c** (52 mg), m.p. 164° (164° in admixture with 5-acetyl-tetrahydroageratriol (m.p. 165°) from triacetyl-tetrahydroageratriol), $[\alpha]_D^{20}$ −58·9° (*c* 1). IR (nujol): 3360, 3300, 1730, 1240 cm^{-1}. NMR (C_5D_5N): 0·8–1·1 (9H, CH_3–C); 2·15 (3H, s, CH_3COO); 4·5–5·5 (3H, m, H–C–O); 5·81 (2H, s, CH_2=C).

Compound (**4d**) *from* *5-acetyl-tetrahydroageratriol* (**4c**).[1] Using the conditions employed for **3e**, the acetyl derivative **4c** (200 mg), obtained from **4b**,[1] was propionylated to give a colourless oil, which was purified by distillation (180 mg), b.p. 169–170°/0·3 mm. $[\alpha]_D^{20}$ −31° (*c* 3). The IR and NMR spectra were identical with those of the compound obtained by hydrogenation of **3f**.

1,5-Diacetyl-dihydroageratriol (**3g**). To a soln of **3e** (2·6 g) in pyridine (9 ml), cooled to 0°, Ac_2O (0·9 ml) was added over a period of 2 h. The mixture was allowed to stand for 15 h at room temp, then worked up. Chromatography over silica gel of the crude product (2·8 g) gave **3b**, **3g**, and **3e**. **3g** (1·3 g) was purified by distillation, b.p. 168–170°/0·1 mm. $[\alpha]_D^{20}$ +49·4° (*c* 2); IR (film): 3440, 1720, 1240 cm^{-1}; NMR ($CDCl_3$): 0·86 (3H, d (J 6·7 Hz), CH_3–C); 0·93 (3H, d (J 6·7 Hz), CH_3–C); 2·0 (3H, s, CH_3COO); 2·07 (3H, s, CH_3COO); 3·96 (1H, m, H–C–O); 5·0–5·5 (2H, m, H–C–O); 5·3 (2H, s, CH_2=C); 5·51 and 5·76 (1H each, s, H–C=C). (Found: C, 67·64; H, 8·77. $C_{19}H_{30}O_5$ requires: C, 67·43; H, 8·94%).

1,5-Diacetylageratriol 9-methylether (**3l**). A soln of **3g** (1·38 g) in $CHCl_3$ (5 ml) was treated with an excess of CH_2N_2 in Et_2O in the presence of $BF_3 . Et_2O$. The product was isolated by chromatography over silica gel, b.p. 129–130°/0·2 mm (1·23 g); IR (film): 1730, 1235 cm^{-1}; NMR ($CDCl_3$): 0·85 (3H, d (J 6·6 Hz), CH_3–C); 0·91 (3H, d (J 6·7 Hz), CH_3–C); 1·98 (3H, s, CH_3COO); 2·04 (3H, s, CH_3COO); 3·14 (3H, s, CH_3–O); 3·35 (1H, m, H–C–O); 5·0–5·6 (2H, m, H–C–O). 5·34 (2H, 5·56 and 5·64 (1H each, s, H–C=C). (Found: C, 68·33; H, 9·01. $C_{20}H_{32}O_5$ requires: C, 68·15; H, 9·15%).

Dihydroageratriol 9-methylether (**3l**). **3l** (1·21 g) was hydrolysed with 0·1 N KOH–95% MeOH (80 ml), at room temp for 90'. The soln was evaporated under vacuum and the residue crystallized from acetone-diisopropyl ether, m.p. 125–126°, (953 mg). $[\alpha]_D^{20}$ −47·6° (*c* 1·6); IR (nujol): 3300 cm^{-1}; NMR (C_5D_5N): 0·77 (3H, d (J 6·7 Hz), CH_3–C); 0·85 (3H, d (J 6·7 Hz), CH_3–C); 3·47 (3H, s, CH_3–O); 3·87 (1H, m, H–C–O); 4·4 (2H, m, H–C–O); 5·25 (2H, s, CH_2=C); 5·6 and 5·66 (1H each, s, H–C=C). (Found: C, 71·66; H, 10·45. $C_{16}H_{28}O_3$ requires: C, 71·60; H, 10·52%).

Oxidative cleavage of (**3l**). $NaIO_4$ (10·25 g) dissolved in H_2O (49 ml) was added dropwise to a soln of **3l** (910 mg) in acetone (39 ml). $NaHCO_3$ (3·5 g) was then added. The stirred soln was cooled in an ice bath to 5° and then $KMnO_4$ (0·354 g) in H_2O (13·6 ml) was added simultaneously with acetone (13·6 ml) at 5–10° over a 30' period under N_2. Stirring was continued for 4 h at 5°, then for 12 h at room temp, at which time the blue-violet reaction media was decanted from the residue, which was further extracted twice with H_2O (10 ml). The aqueous phases were combined, washed with Et_2O and acidified, then $NaHSO_3$ was added. Extraction with Et_2O in a soxhlet apparatus and evaporation afforded a light yellow oil (640 mg) which, after methylation with CH_2N_2 in Et_2O, was chromatographed over silica gel. In addition to the methyl esters of succinic (110 mg) and 3-isopropylglutaric* (125 mg) acid, the methyl ester **8'** of 2*S*-methoxy-4*R*-isopropyladipic acid (125 mg) was thus isolated, b.p. 169–170°/16 mm; $[\alpha]_D^{20}$ −53·2° (*c* 5); IR (film): 1735 cm^{-1}; NMR ($CDCl_3$): 0·87 (6H, d (J 6·7 Hz), CH_3–C); 3·38 (3H, s, CH_3–O); 3·68 (3H, s, CH_3OCO); 3·77 (3H, s, CH_3OCO); 3·7–4·0 (1H, m, H–C–O).

1-Acetyl-dihydroageratriol (**3h**). Ac_2O (1·1 ml) was added dropwise (5 h) under constant stirring to a soln of **3a** (1·5 g) in dry pyridine (4·8 ml), cooled to 0°. The mixture was allowed to stand for 24 h at r.t., then evaporated *in vacuo* to give a pale yellow oil (1·7 g), which was chromatographed over silica gel. In addition to triacetyl- and diacetyl–dihydroageratriols (200 and 625 mg, respectively), **3h** (505 mg) was thus isolated, b.p. 150–155°/0·004 mm. $[\alpha]_D^{20}$ +39·8° (*c* 1·5); IR (film): 3380, 1710, 1250 cm^{-1}; NMR (C_5D_5N): 0·82 (3H, d (J 6·7 Hz), CH_3–C); 0·9 (3H, d (J 6·7 Hz), CH_3–C); 1·83 (3H, s, CH_3COO); 4·2–4·7 (2H, m, H–C–O); 5·30 (2H, m, CH_2=C); 5·62, 6·03 (1H each, s, H–C=C); 5·5–6·0 (1H, m, H–C–O). (Found: C, 68·94; H 9·38. $C_{17}H_{28}O_4$ requires: C, 68·89; H, 9·52%).

Dihydroageratriol 1-methylether (**3p**). A soln of **3h** (900 mg), dihydropyrane (1·5 ml) and *p*-toluenesulfonic acid (2 mg) in CH_2Cl_2 (5 ml) was allowed to stand for 2 h, then filtered over alumina. The filtrate was evaporated *in vacuo* to give **3m** as an yellow oil, which was homogeneous in TLC and unstable on keeping. IR (film): 1728, 1235 cm^{-1}. This compound (1·1 g) was treated with 0·1 N KOH–95%

*It was shown experimentally that, under these reaction conditions, 2-methoxy-4-isopropyladipic acid is partially transformed to 3-isopropylglutaric acid.

MeOH (50 ml) at r.t. for 1 h. The solvent was removed under reduced pressure and the oily residue taken up in Et_2O (50 ml). After filtration over alumina, the solvent was evaporated to give a colourless oil, **3n** (980 mg), homogeneous in TLC. IR (film): 3440 cm^{-1}. A soln of **3n** (950 mg) in Et_2O (15 ml) containing 2 drops of BF_3. Et_2O was treated at 0° with an Et_2O soln of CH_2N_2, concentrated *in vacuo*, and the product (890 mg) isolated by chromatography over alumina. A homogeneous (TLC), oily material was obtained which proved unstable on distillation. IR: no OH group. A soln of this product **30** (830 mg) in CH_3OH–H_2O (5:1) (25 ml) containing a few mg of *p*-toluenesulfonic acid was allowed to stand for 48 h at r.t., then concentrated *in vacuo* and extracted with CH_2Cl_2. Chromatography (silica gel) of the CH_2Cl_2 extractable material (720 mg) gave the pure **3p** (320 mg), which was crystallized from isopropyl ether, (290 mg), m.p. 137–8°. $[\alpha]_D^{20}$ +6·6° (*c* 1); IR (nujol): 3360, 3420 cm^{-1}; NMR (C_5D_5N): 0·8 (3H, d (J 6·7 Hz), CH_3–C); 0·87 (3H. d (J 6·7 Hz), CH_3–C); 3·34 (3H, s, CH_3–O); 3·9–4·6 (3H. m, H–C–O); 5·2 (2H, br. s, CH_2=C); 5·45 and 5·92 (1H each, s, H–C=C). (Found: C, 71·63; H, 10·46. $C_{16}H_{28}O_3$ requires: C, 71·60; H, 10·52%).

Dihydroageratriol 5-methylether (**3d**). A soln of **5a** (600 mg) in Et_2O was treated with an Et_2O soln of CH_2N_2 in the presence of a few drops of BF_3. Et_2O, concentrated, and the product **5c** purified by chromatography over alumina (act II). The acetonide group was then split off under the same conditions as for **5b**. The product was purified by distillation (273 mg), b.p. 160–162°/0·08 mm. IR (film): 3350 cm^{-1}; NMR (C_5D_5N): 0·77 (3H, d (J 6·7 Hz), CH_3–C); 0·82 (3H, d (J 6·7 Hz), CH_3–C); 3·2 (3H, s, CH_3–O); 3·65 (1H, dd (J 9·7 and 5·2 Hz), H–C–O); 4·4–4·9 (2H, m, H–C–O); 5·13, 5·30, 5·52 and 5·88 (1H each, s, H–C=C). (Found: C, 71·73; H, 10·40. $C_{16}H_{28}O_3$ requires: C, 71·60; H, 10·52%).

Ozonolysis of dihydroageratriol 1-methylether (**3p**). The **3p** (250 mg) in CH_2Cl_2 (10 ml) was cooled with an acetone-solid CO_2 freezing mixture (−70°) and a slow stream of ozonized O_2 was passed through. The blue mixture was then treated for 24 h at room temp, under constant stirring, with HIO_4[5] (2 g) in H_2O (15 ml). CH_2Cl_2 was removed under reduced pressure and the remaining soln alkalinized with 0·1 N NaOH before being extracted with Et_2O (3 × 20 ml). The Et_2O layers were combined and evaporated to give a yellow residue (60 mg). The aqueous layer was acidified with dil H_2SO_4 and extracted again with Et_2O (4 × 20 ml). The extracts were combined, the solvent distilled off and the residue (90 mg) esterified with CH_2N_2. Chromatography over silica gel gave **9**, (314mg), which was purified by distillation (25 mg), b.p. 120/15 mm, $[\alpha]_D^{20}$ + 36·2° (*c* 0·4 $CHCl_3$)[5]; IR (film): 1730 cm^{-1}; NMR (CCl_4): 1·7–2·6 (4H, m, CH_2–CH_2); 3·32 (3H, s, CH_3–O); 3·62 (3H, s, CH_3OCO); 3·7 (3H, s, CH_3OCO); 3·6–3·9 (1H, m, H–C–O).

5-Acetyl-ageratriol (**1e**). Ageratriol (4g) was treated with 2,2-dimethoxypropane (2 ml) under the same conditions as for **3a**. Filtration on alumina, followed by evaporation *in vacuo* of the solvent, afforded the oily **6a** (3·8 g), which was homogeneous (TLC) and unstable on keeping. IR (film): 3450 cm^{-1}; NMR ($CDCl_3$): 1·45 (6H, s, CH_3–C–O); 1·73 (3H, s, CH_3–C=); 3·98 (1H, dd (J_{AX} + J_{BX} 15 Hz), H–C–O); 4·77 (2H, br. s, CH_2=C); 4·86 (2H, br. s, CH_2=C); 5·1 (2H, br. s, CH_2=C), 4·7–5·2 (2H, m, H–C–O). The acetonide **6a** (930 mg) was acetylated in the manner described for **5a**. The crude acetate **6b** was chromatographed over alumina and a homogeneous (TLC) compound was obtained (670 mg), which could not be distilled. IR (film): 1730, 1240 cm^{-1}; NMR ($CDCl_3$): 1·45 (6H, s, CH_3–C–O); 1·73 (3H, s, CH_3–C=); 2·02 (3H, s, CH_3COO); 4·6–5·3 (6H, m, CH_2=C); 4·6–5·3 (3H, m, H–C–O). **6b** (640 mg) was hydrolysed in the manner described for **5b**. Chromatography over silica gel afforded a pure acetate (415 mg), $[\alpha]_D^{20}$ +47·5° (*c* 2); IR (film): 3400, 1730, 1240 cm^{-1}; NMR ($CDCl_3$): 1·68 (3H, s, CH_3–C=); 1·97 (3H, s, CH_3COO); 3·9–4·3 (2H, m, H–C–O); 4·7 (2H, s, CH_2=C); 4·7–5·2 (1H, m, H–C–O); 5·16, 5·21, 5·33, 5·47 (1H each, s, H–C=C). (Found: C, 69·48; H, 8·76. $C_{17}H_{26}O_4$ requires: C, 69·36; H, 8·90%).

5-Acetyl-ageratriol 1,9-dimethylether (**1f**). Treatment of **1e** (380 mg) with CH_2N_2 in Et_2O in the presence of BF_3. Et_2O, followed by chromatography over silica gel, afforded an oily compound **1f**, (310 mg), which was purified by distillation, b.p. 150–152°/0·2 mm. $[\alpha]_D^{20}$ +4·2° (*c* 2); IR (film): 1730, 1240 cm^{-1}; NMR ($CDCl_3$): 1·7 (3H, s, CH_3–C=); 1·98 (3H, s, CH_3COO); 3·22 (3H, s, CH_3–O); 3·33 (3H, s, CH_3–O); 3·4–3·9 (2H, m, H–C–O); 4·68 (2H, s, CH_2=C); 4·8–5·2 (1H, m, H–C–O); 5·25 (2H, s, CH_2=C); 5·36, 5·49 (1H each, s, H–C=C). (Found: C, 70·59; H, 9·43. $C_{19}H_{30}O_4$ requires: C, 70·77; H, 9·38%).

Ageratriol 1,9-dimethylether (**1d**). Using the same conditions as for **3m**, the acetate **1f** (290 mg) was submitted to alkaline hydrolysis, to afford the oily **1d** (230 mg), which was purified by chromatography over silica gel and distillation, b.p. 135–137°/0·2 mm. $[\alpha]_D^{20}$ −11·5° (*c* 2); IR (film): 3400 cm^{-1}; NMR ($CDCl_3$): 1·7 (3H, s, CH_3–C=); 3·22 (3H, s, CH_3O); 3·33 (3H, s, CH_3O); 3·4–4·1 (3H, m, H–C–O); 4·67 (2H, s, CH_2=C); 5·13 (2H, s, CH_2=C); 5·36 (1H, s, H–C=C); 5·5 (1H, s, H–C=C). (Found: C, 72·74; H, 9·89. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%).

5-Acetyl-tetrahydroageratriol 1,9-dimethylether (**4e**). A soln of **4c** (305 mg) in Et_2O (5 ml) containing some BF_3. Et_2O was treated with excess CH_2N_2 in Et_2O soln and concentrated. The product, isolated by chromatography over silica gel, was distilled to give a colourless oil (261 mg), b.p. 150–2°/1 mm. $[\alpha]_D^{20}$ −33·4° (*c* 1·5); IR (film): 1730, 1245 cm^{-1}; NMR ($CDCl_3$): 0·84 (9H, d (J 6·7 Hz), CH_3–C); 2·01 (3H, s, CH_3COO); 3·24, 3·32 (3H each, s, CH_3O); 3·52 (1H, br. t, H–C–O); 3·8 (1H, t, H–C–O); 4·7 (1H, br. t, H–C–O); 5·31 and 5·43 (1H each, s, H–C=C). (Found: C, 69·97; H, 10·34. $C_{19}H_{34}O_4$ requires: C, 69·90; H, 10·50%).

Tetrahydroageratriol 1,9-dimethylether (**4f**). The acetate **4e** (800 mg) was treated with alkali in the manner described for **3m**. The mixture afforded **4f**, which was then purified by chromatography (silica gel) and distillation (650 mg), b.p. 160–2°/0·4 mm; IR (film): 3420 cm^{-1}; NMR ($CDCl_3$): 0·85, 0·9, 1·0 (3H each, d (J 6·7 Hz), CH_3–C); 3·22 (3H, s, CH_3O); 3·31 (3H, s, CH_3O); 3·0–3·9 (3H, m, H–C–O); 5·31 (1H, s, H–C=C); 5·42 (1H, s, H–C=C). (Found: C, 71·90; H, 11·51. $C_{17}H_{32}O_3$ requires: C, 71·78; H 11·34%).

Ageratriol 5-methylether (**1h**). NaH (80% oily dispersion) (1·2 g) was added at intervals, over a period of 1 h, to a soln of **6a** (2·5 g) in dry THF (100 ml), under constant stirring. MeI (15 g) was then added dropwise and stirring continued overnight at 40°. The mixture was then filtered over alumina and the filtrate concentrated *in vacuo*, diluted with H_2O (100 ml) and extracted with Et_2O (5 × 30 ml). The Et_2O layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil, which was rapidly chromatographed over silica gel. The **6c** (2·3 g) was thus obtained, as an oil homogeneous in TLC. NMR ($CDCl_3$): 1·45 (6H, s, CH_3C–O); 1·74 (3H, s, CH_3–C=); 3·16 (3H, s, CH_3O); 3·38 (1H, dd (J_{AX} + J_{BX} 15

Hz), H–C–O); 4·7–5·3 (6H, m, CH_2=C); 4·7–5·3 (2H, m, H–C–O). Using the same conditions as for **5b**, **6c** (2·2 g) was treated with ethylene glycol and *p*-toluenesulfonic acid and then worked up. Chromatography over silica gel afforded a pure compound which was crystallized from diisopropyl ether (1·8 g), m.p. 69–70°. $[\alpha]_D^{20}$ +58·7° (*c* 1·9); IR (nujol): 3350 cm^{-1}; NMR ($CDCl_3$): 1·68 (3H, s, CH_3–C=); 3·08 (3H, s, CH_3O); 3·32 (1H, t (J 7·5 Hz), H–C–O); 4·0 (2H, m, H–C–O); 4·6 (2H, br. s, CH_2=C); 5·07, 5·20, 5·25 and 5·44 (1H each, br. s, H–C=C). (Found: C, 72·03; H, 9·88. $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%).

1-*Acetyl-ageratriol 5-methylether* (**1i**). **1h** (1·7 g) was acetylated as described for **3e** to give an oily monoacetate **1i** (1·6 g), b.p. 150–2°/0·5 mm. $[\alpha]_D^{20}$ + 107° (*c* 2). IR (film): 1730, 1240 cm^{-1}. NMR ($CDCl_3$): 1·67 (3H, s, CH_3–C=); 2·03 (3H, s, CH_3COO); 3·09 (3H, s, CH_3O); 3·32 (1H, m, H–C–O); 4·0 (1H, dd, H–C–O); 4·62 (2H, s, CH_2=C); 5·13, 5·30, 5·42 and 5·65 (1H each, s, H–C=C); 5·0–5·4 (1H, m, H–C–O). (Found: C, 70·32; H, 9·01. $C_{18}H_{28}O_4$ requires: C, 70·10; H, 9·15%).

Ageratriol 1,5-*dimethylether* (**1g**). Using the conditions for **3h**, **1i** (1·1 g) was treated with dihydropyrane. Chromatography over alumina (act II) afforded a pure compound (950 mg), **1l**. IR (film): 1730, 1235 cm^{-1}, which was treated with 0·1 N KOH– 95% MeOH (40 ml). An alcoholic compound **1m** was recovered from the mixture and purified by chromatography over alumina, (780 mg). IR (film): 3380 cm^{-1}. After methylation with NaH–MeI as described for **6a**, followed by chromatography over alumina, **1n** (560 mg) was obtained. Finally, acid hydrolysis using the conditions employed for **3o**, afforded **1g**, isolated by chromatography (silica gel) and purified by distillation (370 mg), b.p. 143–5°/0·6 mm. $[\alpha]_D^{20}$ +51·2° (*c* 2). IR (film): 3400 cm^{-1}; NMR ($CDCl_3$): 1·67 (3H, s, CH_3–C=); 3·1 (3H, s, CH_3O); 3·31 (3H, s, CH_3O); 3·2–3·5 (1H, m, H–C–O); 3·6–4·2 (2H, m, H–C–O); 4·63 (2H, s, CH_2=C); 5·11, 5·21, 5·27 and 5·53 (1H each, s, H–C=C). (Found: C, 72·98; H, 10·24. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%).

1-*Acetyl-ageratriol* 5,9-*dimethylether* (**1o**). A soln of **1i** (420 mg) in Et_2O was treated with an Et_2O soln of CH_2N_2 in the presence of BF_3. Et_2O, concentrated and the product isolated by chromatography over silica gel and purified (390 mg) by distillation, b.p. 130–2°/0·5 mm. $[\alpha]_D^{20}$ +42·5° (*c* 2·4). IR (film): 1730, 1240 cm^{-1}; NMR ($CDCl_3$): 1·67 (3H, s, CH_3–C=); 2·02 (3H, s, CH_3COO); 3·1 (6H, s, CH_3O); 3·2–3·6 (2H, m, H–C–O); 4·61 (2H, s, CH_2=C); 4·8–5·2 (1H, m, H–C–O); 5·16, 5·35 (1H each, br. s, H–C=C); 5·47, 5·53 (1H each, s, H–C=C). (Found: C, 70·91; H, 9·22. $C_{19}H_{30}O_4$ requires: C, 70·77; H, 9·38%).

Ageratriol 5,9-*dimethylether* (**1p**). Using the conditions for **3m**, **1o** (372 mg) was treated with alkali to afford **1p**, which was purified by chromatography (silica gel) and distillation (270 mg), b.p. 132–4°/0·2 mm. $[\alpha]_D^{20}$ +15·1° (*c* 1) IR (film): 3400 cm^{-1}; NMR ($CDCl_3$): 1·69 (3H, s, CH_3–C=); 3·13 (3H, s, CH_3O); 3·23 (3H, s, CH_3O); 3·2–4·4 (3H, m, H–C–O); 4·64 (2H, s, CH_2=C); 5·13, 5·29, 5·36 and 5·39 (1H each, s, H–C=C). (Found: C, 72·90; H, 10·14. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%).

Asymmetric esterification.[8] A soln A (4 ml) M/5 alcohol and 2M/5 α-phenylbutyric-anhydride in pyridine was prepared and allowed to stand at room temp for 7 h. H_2O (0·15 ml) was then added to 3 ml of soln A to form soln B, which was allowed to stand for 30 min. The optical rotation α_1 of B was then measured under 1 dm. Triethylamine (0·2 ml) was added to soln B (2 ml) and the optical rotation α_2 immediately measured.

alcohol	**1d**	**4f**	**1p**	**1g**
$\alpha_1 - 1{\cdot}1\ \alpha_2$	+0·702	+0·471	+0·320	−0·764
acid recovered	*S*(+)	*S*(+)	*S*(+)	*R*(−)
alcohol configuration	*R*	*R*	*R*	*S*
optical yield $(\alpha_1 - 1{\cdot}1\ \alpha_2)/2{\cdot}6$	27·0	18·1	12·5	29·4

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