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# STRUCTURE OF TORILIN[1]

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**Abstract**—The structure of torilin (**1**), $C_{22}H_{32}O_5$, isolated from the seeds of *Torilis japonica* DC., has been established as a sesquiterpene ester of the guaiane series.

THE seeds of *Selinum Monnieri* L. (Zyasyoosi, *Selini fructus*), indigenous to China, have been recognized as having significant medical qualities, and the recent chemical investigation of constituents revealed the presence of a coumarin derivative, edultin, $C_{21}H_{22}O_7$.[2]

In the search for active principles of the seeds of *Torilis japonica* DC. (Wazyasyoosi, *Torilis fructus*) which are used in Japan as a substitute for *Selini fructus*, cadinene and torilene (an unidentified hydrocarbon) have been reported.[3]

Since *Torilis japonica* is taxonomically very close to *Torilis scabra* (*Caucalis scabra*) from the seeds of which caucalol diacetate was isolated,[4] we reinvestigated the constituents of *Torilis fructus* and were rewarded by finding a new sesquiterpene ester, torilin (**1**), $C_{22}H_{32}O_5$, m.p. 77–78°, $[\alpha]_D$ −45·3°.

Upon refluxing with 1% methanolic potassium hydroxide for 20 min, **1** yielded acetic acid and tiglic acid together with a mixture of three isomeric keto-alcohols, $C_{15}H_{24}O_3$, torilolone (**2a**), allotorilolone (**3**), and epi-allotorilolone (**4**) in a ratio of 7:7:1. This distribution was found to vary with reaction conditions: e.g. refluxing with 5% methanolic potassium hydroxide for 2·5 hr, gave a ratio of 1:0:4.

This same equilibrium mixture could be obtained with 5% methanolic potassium hydroxide starting from **2a**, **3**, and **4** respectively, suggesting **3** as transient in the equilibrium between **2a** and **4**.

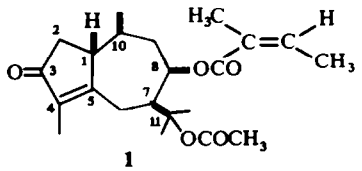
Evidence for the structural features of the most stable isomer, epi-allotorilolone (**4**), m.p. 135·5–136·5°, $[\alpha]_D$ −147·5°, was secured as follows:

LAH reduction of the keto-alcohol **4** afforded epi-allotorilolol (**7**) which was dehydrogenated by heating with 10% Pd-C. The isolation of S-guaiazulene (**8a**) from the reaction mixture strongly suggested a guaiane skeleton in the keto-alcohol **4** whose IR spectrum exhibits a band at 1735 $cm^{-1}$ characteristic of cyclopentanone.

In order to decide between the two possible locations of the keto group (C-2 or C-3) of **4**, another dehydrogenation was carried out on the glycol **9** prepared from **4** through the agency of methylmagnesium iodide. An azulene, $C_{16}H_{20}$, $\lambda_{max}$ 590 mμ, was isolated and its spectral characteristics as well as the properties of its derivative are in good agreement with those of 7-isopropyl-1,2,4-trimethyl-azulene (**8b**)[5] rather than the 3-methyl isomer **8c**.[5,6] Epi-allotorilolone (**4**) consequently has the keto group at C-3 of the guaiane skeleton.

Information concerning the position of the OH group was provided by its resistance to acetylation and its facile dehydration with phosphorous oxychloride/pyridine to

CHART 1



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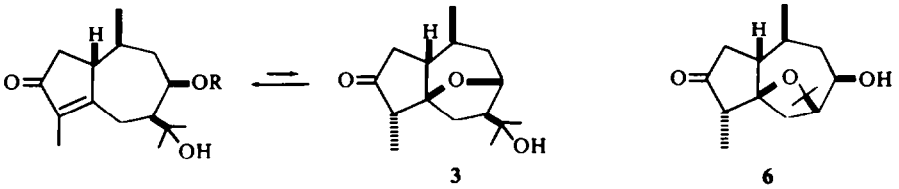
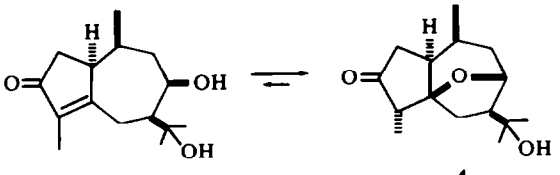


3 6

2a: R = H
2b: R = CO—$C_6H_4NO_2$
2c: R = CO—$C_6H_3(NO_2)_2$



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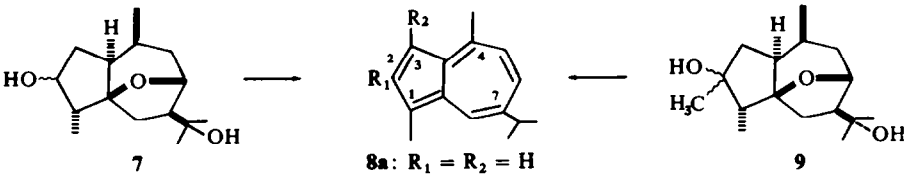
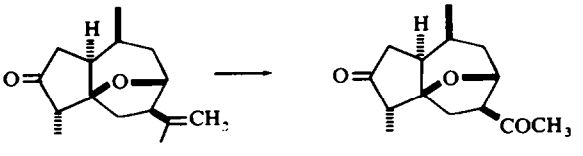


7

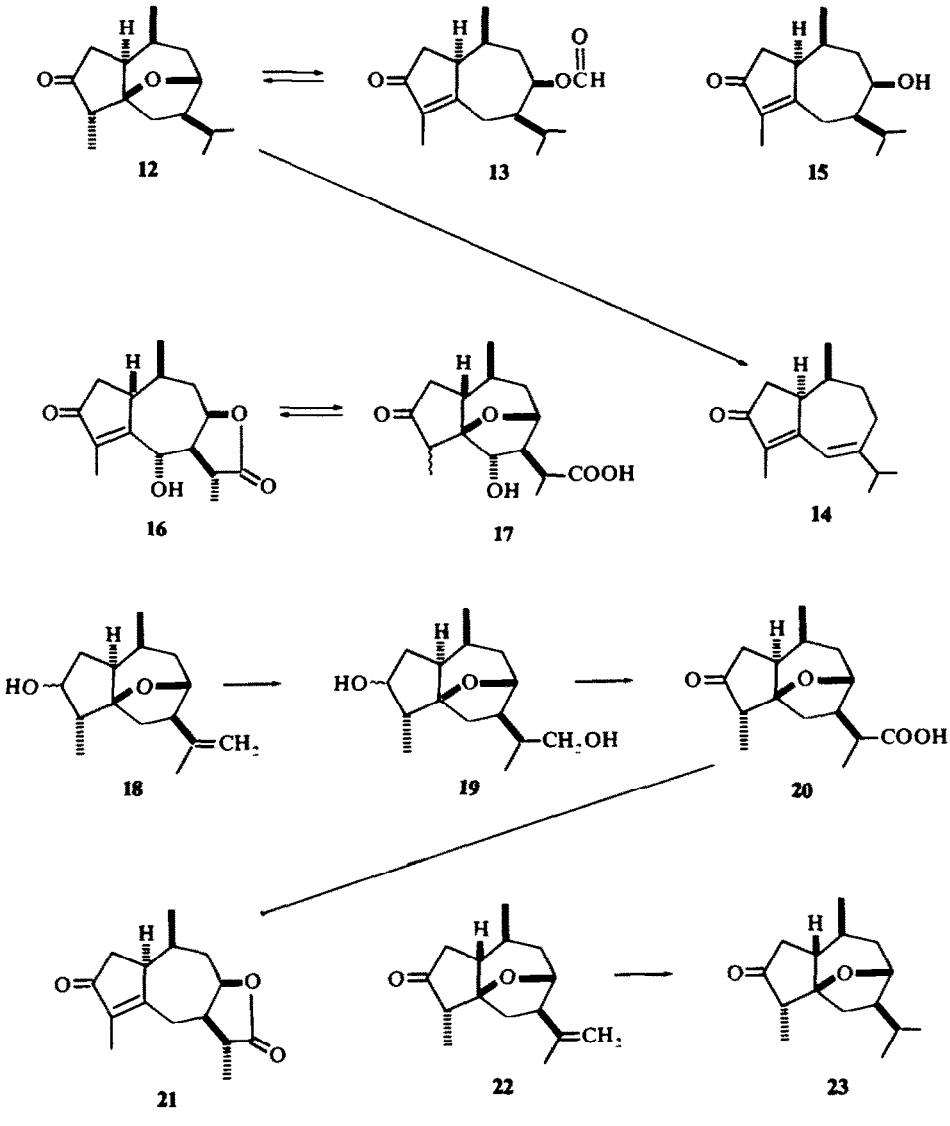
8a: $R_1 = R_2 = H$
8b: $R_1 = CH_3, R_2 = H$
8c: $R_1 = H, R_2 = CH_3$

9



10 11

CHART 2




epi-anhydroallotorilolone (**10**). Although the transformation discussed can be formulated as $(CH_3)_2C(OH) \rightarrow CH_2{=}C(CH_3)$ by mere inspection of the IR and NMR spectra (Experimental), further support was obtained from the oxonolysis of the anhydro derivative **10**. Formaldehyde and a diketone **11**, $C_{14}H_{20}O_3$, exhibiting a singlet at 2·18 $\delta$ (3H), which could be ascribed to methyl ketone, were isolated indicating the presence of the OH group at C-11.

Catalytic hydrogenation of **10** yielded epi-deoxyallotorilolone (**12**), $C_{15}H_{24}O_2$,

which according to analytical and spectroscopic evidence is a saturated tricyclic ketone with an ether linkage. Cleavage of the ether linkage in **12** by boiling with formic acid, gave the unsaturated bicyclic compound **13** having a cyclopentenone moiety, $\lambda_{max}$ 242 mμ (log ε 4·08), $\nu_{max}$ 1695, 1633 $cm^{-1}$, and a formate group, $\nu_{max}$ 1720, 1178 $cm^{-1}$.

When exposed a more drastic and acidic conditions, the keto-ether **12** gave the dienone **14**,* $\lambda_{max}$ 296 mμ (log ε 4·17), $\nu_{max}$ 1690, 1630 and 1595 $cm^{-1}$. These transformations are formulated in Chart 2, and are further supported by the NMR spectra.

Alkaline hydrolysis of the formate **13** regenerated **12** being accompanied by reformation of the ether linkage, instead of the anticipated keto-alcohol **15**.

Since this interconversion is reminiscent of the well-known equilibrium between geigerin (**16**) and allogeigeric acid (**17**),[8] our next concern was directed to secure possible route from the unsaturated keto-ether **10** to the stereoisomer of deoxygeigerin with the known absolute configuration. For this purpose, LAH reduction of **10** provided epi-anhydroallotorilolol (**18**) which upon hydroboration followed by hydrogen peroxide oxidation[9] furnished the diol **19**.

The carboxylic acid **20** obtained by further oxidation of the diol **19** with sodium dichromate was converted to the lactone **21**, m.p. 128–129°, $[\alpha]_D$ +130·8°, with sodium carbonate solution. Its identity with (+)-1-epi-deoxygeigerin (**21**), m.p. 128–130°, $[\alpha]_D$ +130°,[10] was established by direct comparison with an authentic specimen provided by Prof. D. H. R. Barton.

This successful correlation not only supported our structure assignment to epi-allotorilolone (**4**) but also established the absolute configurations of C-7, C-8, and C-10 asymmetric centers.

Before discussing the stereochemistry of the remaining asymmetric centers C-1 and C-4 in allotorilolone (**3**) and epi-allotorilolone (**4**), we had to establish that the interconversion **3** → **4**, involves only the epimerization(s) at C-1 or/and C-4 without change of their structural skeletons. (e.g. With no ether linkage rearrangement such as **3** → **6**.)†

The same kind of isomerization takes place in the series **22** and **23**, which both lack the OH group at C-11. Dehydration of the unstable isomer allotorilolone (**3**) with phosphorus oxychloride/pyridine gave the unsaturated keto-ether, anhydroallotorilolone (**22**), which was then converted into deoxyallotorilolone (**23**) by catalytic hydrogenation.

Treatment of **22** and **23** with methanolic potassium hydroxide yielded epi-anhydroallotorilolone (**10**) and epi-deoxyallotorilolone (**12**) respectively, in line with the isomerization observed in the compounds bearing OH groups at C-11 **3** → **4**.

A comparison of the optical rotatory dispersion curves of these allo and epi-allo series of compounds (Fig. 1 and Table 1, **3**, **22**, and **23**) shows that the allo series exhibit strongly positive Cotton curves while **4**, **10**, and **12** in epi-allo series show strongly negative ones, and they are virtually mirror images each other. Disregarding the stereochemistry of the Me groups at C-4 for the time being, we then have two molecular

* The synthesis of **14** with no configurational specification has been reported;[7] b.p. 128–130°/0·4 mm, $\lambda_{max}$ 296 mμ, log ε 4·35; 2,4-dinitrophenylhydrazone m.p. 217–218°.

† Acetate of **6** derivated from guaioxide was easily converted to torilolone acetate (**2**, R = Ac) during chromatography on alumina.[11]

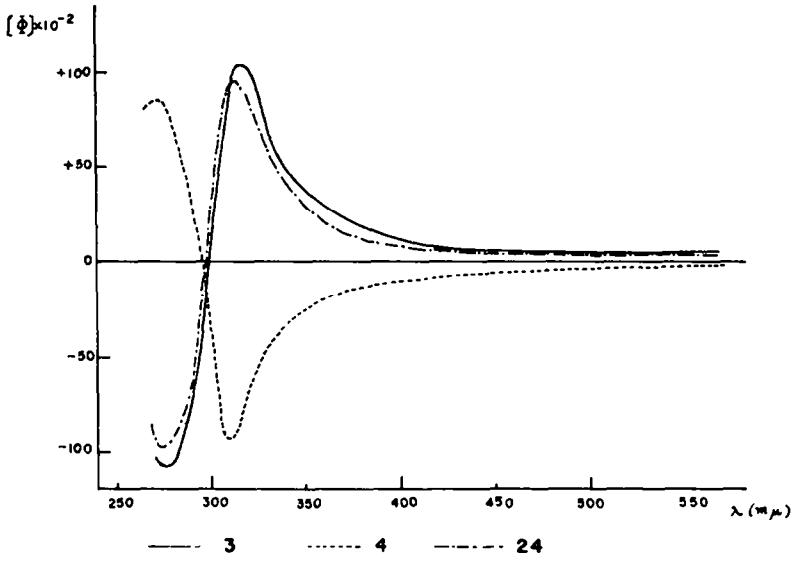



FIG. 1 Methanol.

TABLE 1. ORD CONSTANT

| Compound | Cotton effect extrema (MeOH) | | | | Amplitude |
|---|---|---|---|---|---|
| | $[\phi] \times 10^{-2}$ | mμ | $[\phi] \times 10^{-2}$ | mμ | a[a] |
| **3** | +104 | 314 | −106 | 278 | +210 |
| **4** | − 95 | 311 | + 85 | 272 | −180 |
| **22** | +113 | 313 | −103 | 274 | +216 |
| **10** | − 92 | 313 | + 85 | 273 | −177 |
| **23** | +119 | 313 | − 97 | 272 | +216 |
| **12** | − 90 | 313 | + 85 | 272 | −175 |
| **17**[b] | +100 | 310 | − 95 | 271 | +195 |
| **24** | + 96 | 313 | − 99 | 273 | +195 |
| **29**[c] | + 68 | 320 | − 65 | 278 | +133 |

[a] For the definition of the molecular amplitude a, see C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962).
[b] Methyl ester.
[c] In THF.

models which differ only in the configuration of C-1 asymmetric center, and Fig. 2 and Fig. 3 represent their octant projections. According to Djerassi-Klyne's rule,[12] the molecules corresponding to Fig. 2 and Fig. 3 are supposed to show strongly positive and strongly negative Cotton effects respectively. Thus we arrive, disregarding the stereochemistry of C-4 asymmetric center, at the structure **3** for allotorilolone and the structure **4** for 1-epi-allotorilolone.*

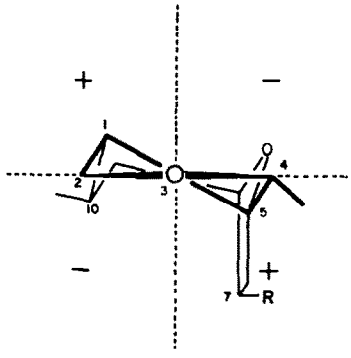



FIG. 2 Octant projection of allo series.

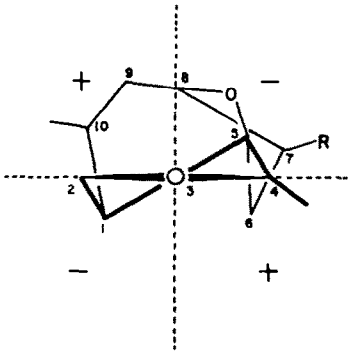



FIG. 3 Octant projection of 1-epi-allo series.

The amplitudes of the allo series are always larger than that of 1-epi-allo series, and this amplitude difference can be explained by assuming that both series of compounds have (4*R*)-configuration; i.e. C-4 Me group resides in the positive octant in both series.

We can now proceed to discuss the structure of torilolone (**2a**), whose spectroscopic evidence ($\lambda_{max}$ 241 mμ, log ε 4·0; $\nu_{max}$ 1690 and 1630 $cm^{-1}$) suggests a cyclopentenone. The facile interconversion with 1-epi-allotorilolone (**4**) reminiscent of the relationship

* Allogeigeric acid methyl ester whose ORD curve shows a strongly positive Cotton effect (Table 1), can be assigned as **17** (methyl ester).

of geigerin (**16**) with allogeigeric acid (**17**), is also in good agreement with the structure **2a**.*

The assignment of the absolute configuration at C-8 and C-1 is based on the following observations. (a) Since the molecular rotations of *p*-nitrobenzoate **2b** and 3,5-dinitrobenzoate **2c** show large negative increments in comparison with that of

TABLE 2. MOLECULAR ROTATIONS OF TORILOLONE AND ITS DERIVATIVES (in $CHCl_3$)

| | $[M]_D^8$ | $\Delta[M]_D^{8*}$ |
|---|---|---|
| **2a** | − 65 | |
| **2b** | −353 | −288 |
| **2c** | −383 | −318 |

* $\Delta[M]_D^8 = [M]_{D\,(PNB)}^8 - [M]_{D\,(OH)}^8$
(DNB)

torilolone (**2a**) (see Table 2), the (8*R*)-configuration can be assigned according to the "benzoate rule"[13] and this confirms the stereochemistry at C-8 already made in allo and epi-allo series of compounds. (b) Comparison of the strongly positive Cotton effect (a +195) exhibited by dihydrotorilolone (**24**) obtained by catalytic hydrogenation of torilolone, with that of (+)-*trans*-1β-methyl-bicyclo-[5,3,0]-9-decanone (**25**) (a +159)[14] and (+)-dihydrogeigerin (**26**) (a +147)[15] suggests the (1*R*, 5*R*)-configuration as shown in **24**. (See Fig. 1 and Table 1).

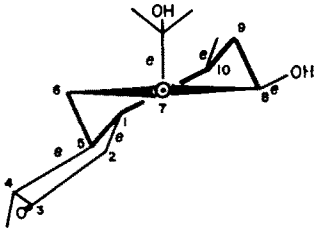



FIG. 4

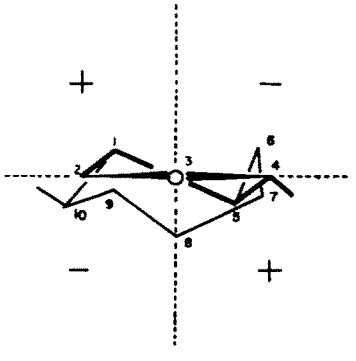
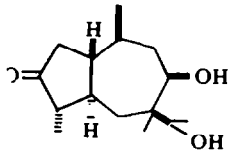



FIG. 5

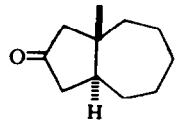
* 1-Epi-torilolone (**5**) which could not be detected even by GLC, may be an intermediate in the isomerization between **2a** and **4**.

These conclusions are further confirmed by inspection of a scale model of dihydrotorilolone (**24**) in the most favourable conformation according to Hendrickson's analysis.[16] (Fig. 4) When we look at the model from the carbonyl side of the cyclopentanone, we have the octant projection shown in Fig. 5 and the twist conformation of the cyclopentanone moiety is supposed to exhibit a positive Cotton curve with a large amplitude. These facts support the structure **24** for dihydrotorilolone and, consequently, the structure **2a** for torilolone itself.

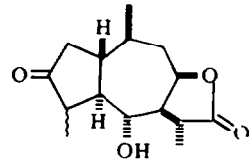
CHART 3



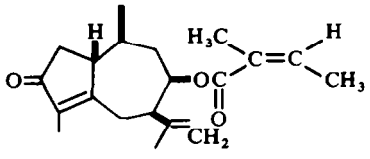
**24**



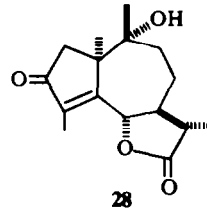
**25**



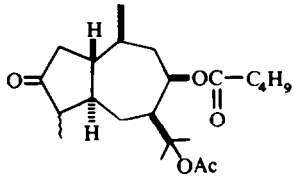
**26**



**27**



**28**

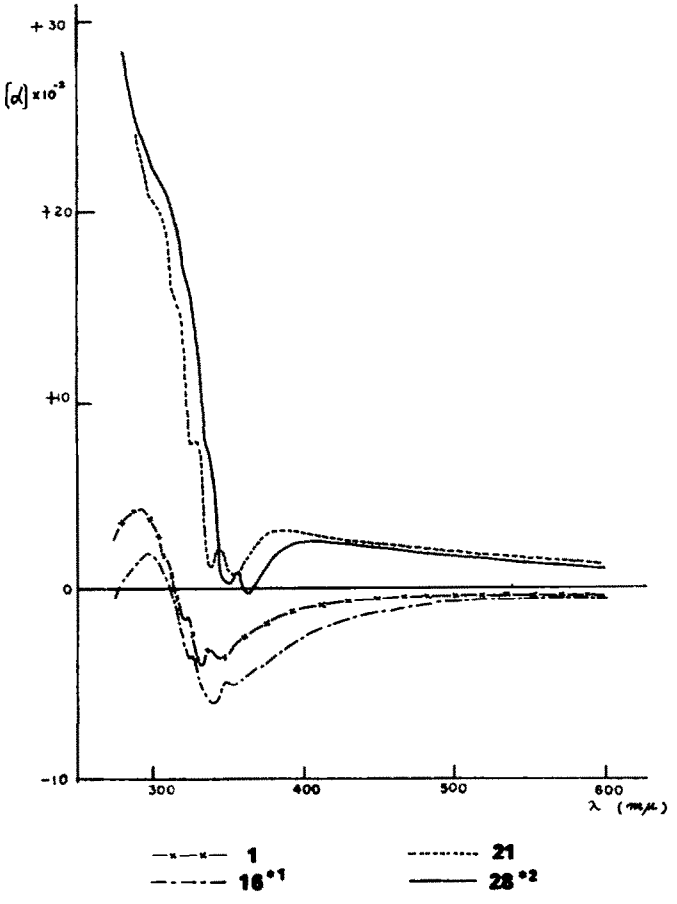


**29**

Finally, torilin (**1**) possesses strong IR peaks at 1745 and 1260 $cm^{-1}$ (acetate), 1700 and 1230 $cm^{-1}$ (angelate or tiglate), 1700 and 1640 $cm^{-1}$ (cyclopentenone) and an UV absorption peak at 236 mμ (log ε 4·26) (cyclopentenone). Although alkaline hydrolysis of **1** under rather severe conditions always gave acetic acid and tiglic acid, GLC analysis of the methyl ester of the acidic fraction obtained under a mild condition revealed a predominant formation of angelic acid (angelic acid 70% and tiglic acid 30%). This indicates that tiglic acid could be an artifact originating from angelic acid under the conditions of alkaline hydrolysis and during isolation. This is supported by the characteristic peak in the NMR spectrum of torilin at 6·1 δ (broad, 1H) attributable to β-proton of the angelate moiety[17] in torilin (**1**).

Concerning the position of the angelate and acetate groups, when torilin (**1**) was distilled at 1 mm, thermal decomposition yielded acetic acid and desacetyltorilin $C_{20}H_{28}O_3$ (**27**), which shows peaks at 4·85 $\delta$ (multiplet, 2H) and at 1·85 $\delta$ (singlet, 3H), both presumbably due to the newly formed $CH_3—C{=}CH_2$ group.

This means that the acetate group is at C-11 and the angelate at C-8. Isolation of 1-epi-anhydroallotorilolone (**10**) upon hydrolysis of desacetyltorilin (**27**) confirmed this conclusion.




[1] Modified from C. Djerassi, J. Osiecki and W. Herz.[15]
[2] Courtesy of Dr. K. Kuriyama, Shionogi Research Laboratory.

FIG. 6 Dioxane.

The (1*R*)-configuration of torilin (**1**) was deduced from the rotatory dispersion curve which is very close to that of geigerin (**16**),[10, 15] but distinctly different from those of isophotosantonic lactone (**28**)[15, 18] and 1-epi-deoxygeigerin (**21**) (Fig. 6). Catalytic hydrogenation of torilin afforded tetrahydrotorilin (**29**) which exhibits a strong positive Cotton effect (Table 1), and gave a saturated keto-glycol together with

α-metylbutyric acid on alkaline hydrolysis. The identity of this keto-glycol with dihydrotorilolone (**24**) supports this configurational assignment, and the complete structure of torilin (**1**) was established.

## EXPERIMENTAL

M.ps are uncorrected. NMR spectra were run on a JNM-4H-100 and a Varian A-60 spectrometer in $CDCl_3$ with TMS as internal standard with $\delta = 0$. Coupling constants are expressed in Hz, s = singlet, d = doublet, m = multiplet. ORD curves were determined on a Yanagimoto ORD spectrometer and a Rudolph spectropolarimeter. Pet. ether refers to the fraction boiling between 50–60° unless otherwise indicated.

*Extraction and isolation of torilin* (**1**)

Dried seeds of *Torilis japonica* (9·2 kg) were extracted twice with hot MeOH. The extract was concentrated *in vacuo* and the residue (735 g) was chromatographed on alumina (3 kg) in pet. ether soln. The fraction eluted with pet. ether (2 l.) contained hydrocarbon(s). The next fractions eluted with pet. ether (9 l.) and with benzene (19 l.) were combined (carbonyl fractions, IR band at 1700 $cm^{-1}$), concentrated and the residue (195 g) was allowed to stand in a refrigerator. The syrup solidified to give crude torilin (**1**) (40 g). On fractional distillation of the mother liquors in high vacuum, additional crude **1** (11 g) was obtained from the fraction boiling at 120–180°/0·04 mm. These crude samples of **1** were combined, recrystallized from pet. ether to give **1**, m.p. 77–78° (38 g), (0·4% from the seeds). $[\alpha]_D^{14}$ −45·3° ($c$ = 0·848, EtOH); UV $\lambda_{max}$ 236 mμ, log ε 4·29 (EtOH); IR (KBr) 1745, 1260 (acetate), 1700, 1640 (cyclopentenone and angelate), and 1230 $cm^{-1}$ (angelate); NMR (100 Mc) 1·06 (3H, d, $J$ = 6) ($CH_3$—C-10), 1·55 (6H, s) ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·75 (3H, s) ($CH_3$—C-4), 2·01 (6H, m)(two $CH_3$ of angelate), 2·0 (3H, s) (acetate), 5·45 (1H, broad) (H—C-8), and 6·1 (1H, broad) (β-proton of angelate): (Found: C, 70·29; H, 8·72. Calc. for $C_{22}H_{32}O_5$: C, 70·18; H, 8·57%); 2,4-dinitrophenylhydrazone m.p. 165–166° from EtOH (Found: C, 60·59; H, 6·47; N, 10·05. Calc. for $C_{28}H_{36}O_8N_4$: C, 60·42; H, 6·52; N, 10·07%).

*Desacetyltorilin* (**27**)

Dried seeds of *T. japonica* (4·5 kg) were extracted with hot MeOH. The extract was concentrated and the residue dissolved in pet. ether was fractionally distilled at 120–240° (bath temp)/0·9 mm to give a yellow oil (34 g). This fraction was chromatographed on alumina in pet. ether soln and the CO fractions eluted with pet. ether (monitoring on the IR band at 1700 $cm^{-1}$) were combined, and fractionally distilled twice to give a pale yellow oil, desacetyltorilin (**27**) (8·3 g); b.p. 145–156°/0·02 mm; $n_D^{22}$ 1·5209; $[\alpha]_D^{23}$ −65·4° ($c$ = 0·734, EtOH); UV $\lambda_{max}$ 238 mμ, log ε 4·23 (EtOH); IR (liq) 1700, 1640 (cyclopentenone and angelate), 1230 (angelate), and 890 $cm^{-1}$ ($H_2C$=C); NMR (60 Mc) 1·10 (3H, d, $J$ = 5) ($CH_3$—C-10), 1·72 (3H, s) ($CH_3$—C-4), 1·85 (3H, d, $J$ = 1) ($CH_3$—C-11), 1·90 (3H, d, $J$ = 1) and 1·95 (3H, m) (two $CH_3$ of angelate), 4·85 (2H, m) ($H_2C$=C-11), 5·06 (1H, broad) (H—C-8), and 6·08 (1H, m) (β-proton of angelate); 2,4-dinitrophenylhydrazone m.p. 179–180° from EtOH; UV $\lambda_{max}$ 388 mμ, log ε 4·5 ($CHCl_3$). (Found: C, 62·86; H, 6·71; N, 11·52. Calc. for $C_{26}H_{32}O_6N_4$: C, 62·89; H, 6·50: N, 11·28%).

*Hydrolysis of torilin* (**1**)

(a) *Neutral fractions*: *Torilolone* (**2a**) *and allotorilolone* (**3**). A mixture of **1** (1·0048 g) and a soln of KOH (0·422 g) in MeOH (30 ml) was refluxed for 20 min, concentrated, diluted with water and extracted with $CHCl_3$. The extract was evaporated to dryness and the residue was treated with hot pet. ether (150 ml) to separate soluble and insoluble portions. The latter gave **2a** (170 mg, 25%), m.p. 179–180° after recrystallization from EtOH and water. $[\alpha]_D^8$ −25·7° ($c$ = 1·83, $CHCl_3$); UV $\lambda_{max}$ 241 mμ, log ε 4·0 (EtOH); IR ($CHCl_3$) 3450 (OH), 1690 and 1630 $cm^{-1}$ (cyclopentenone); NMR (100 Mc) 1·05 (3H, d, $J$ = 5) ($CH_3$—C-10), 1·34 (3H, s) and 1·42 (3H, s) ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·74 (3H, s) ($CH_3$—C-4), 2·85 (2H, s) (two OH), and 4·45 (1H, broad) (H—C-8). (Found: C, 71·29; H, 9·83. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59%): 2,4-dinitrophenylhydrazone m.p. 237° from EtOH. (Found: C, 58·44; H, 6·47; N, 13·05. Calc. for $C_{21}H_{28}O_6N_4$: C, 58·32; H, 6·53; N, 12·96%); *p*-nitrobenzoate m.p. 183° from EtOH, $[\alpha]_D^8$ −88° ($c$ = 1·295,

$CHCl_3$). (Found: C, 66·42; H, 7·17; N, 3·42. Calc. for $C_{22}H_{27}O_6N$: C, 65·82; H, 6·78; N, 3·49%); 3,5-dinitrobenzoate m.p. 206°, $[\alpha]_D^{8}$ −85·9° (*c* = 0·687, $CHCl_3$). (Found: C, 59·28; H, 6·02; N, 6·33. Calc. for $C_{22}H_{26}O_8N_2$: C, 59·18; H, 5·87; N, 6·28%).

A fraction, soluble in hot pet. ether, was a mixture of **3** and **4** in the ratio of 7:1,* and was sublimed at 130–150°/16 mm to give crude **3** (193 mg, 23·5%). Purification by chromatography on alumina and recrystallization from n-hexane gave pure **3**, 52 mg, m.p. 151–152°. $[\alpha]_D^{28}$ +151·2° (*c* = 0·529, EtOH); UV $\lambda_{max}$ 291 mμ, log ε 1·48 (EtOH); IR (KBr) 33·20 (OH), and 1745 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 0·95 (3H, d, *J* = 5) ($CH_3$—C-10), 1·05 (3H, d, *J* = 8) ($CH_3$—C-4), 1·20 (6H, s) ($CH_3$>C-11), 1·9 (1H, s) (OH), and 4.44 (1H, s) (H—C-8). (Found: C, 71·67; H, 9·77. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59%).

*1-Epi-allotorilolone* (**4**). Hydrolysis of **1** (305 mg) by refluxing with a mixture of KOH (224 mg) and MeOH (10 ml) for 2·5 hr, furnished **2a** (12 mg, 5·9%). The fraction soluble in hot pet. ether, which showed only one peak in GLC, was chromatographed on alumina and recrystallized from pet. ether to yield **4** (30·6 mg, 15%), m.p. 135·5–136·5°; $[\alpha]_D^{14}$ −147·5° (*c* = 0·61, EtOH); UV $\lambda_{max}$ 289·5 mμ, log ε 1·49 (EtOH); IR ($CHCl_3$) 3500 (OH), and 1735 $cm^{-1}$ (cyclopentanone); (KBr) 3500 (OH), 1740 and 1750 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 0·92 (3H, d, *J* = 8) ($CH_3$—C-10), 1·04 (3H, d, *J* = 8) ($CH_3$—C-4), 1·20 (6H, s) ($CH_3$>C-11), 2·5 (1H, s) (OH), and 4·28 (1H, s) (H—C-8). (Found: C, 71·56; H, 9·70. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59%); 2,4-dinitrophenylhydrazone m.p. 240–241° from EtOH. (Found: C, 58·19; H, 6·29; N, 13·07. Calc. for $C_{21}H_{28}O_6N_4$: C, 58·32; H, 6·53; N, 12·96%).

b. *Acidic fractions: tiglic acid and acetic acid.* A mixture of **1** (2·0 g) and KOH (1 g) in MeOH (60 ml) was heated under reflux for 1 hr, concentrated, diluted with water, and was washed with $CHCl_3$ to remove neutral products. The aq soln was acidified with dil $H_2SO_4$, and steam-distilled. The distillate (750 ml) was neutralized with 0·1 N KOH, concentrated *in vacuo* to a small volume, and extracted with ether after acidification. The ether extract was dried and evaporated to yield tiglic acid, 50 mg, m.p. 64° (recrystallized from water and sublimed at 50–60°/10 mm) which was identical with an authentic sample by comparison of IR spectra and the mixed m.p.

The mother liquor after recrystallization was steam-distilled. Discarding the first distillate (15 ml), the next (350 ml) was neutralized with 0·1 N KOH, and concentrated to 15 ml. After being made slightly acidic with one drop of dil HCl, the soln was treated with *p*-bromophenacylbromide (800 mg) in EtOH (15 ml) and heating under reflux for 1 hr. After cooling the ppt was recrystallized from EtOH and water to yield *p*-bromophenacylacetate, 17 mg, m.p. 84·5–85·5°, which was identical with an authentic sample by comparison of IR spectra and the mixed m.p.

*Angelic acid.* A mixture of torilin (1 g) and KOH (0·5 g) in MeOH (30 ml) was heated under reflux for 1 hr, concentrated, diluted with water and washed with $CHCl_3$ to remove neutral products. After acidification followed by the extraction with ether, the ether extract was dried and evaporated to yield a mixture of acetic, angelic and tiglic acid (the ratio was estimated on 1:7:3 by GLC on the methyl ester)† which was allowed to stand in a refrigerator. The syrup solidified to give angelic acid, 11 mg, m.p. 42–43° (purified by sublimation) which was identical with an authentic sample by comparison of IR spectra and the mixed m.p.

*Isomerization of torilolone* (**2a**) *to 1-epi-allotorilolone* (**4**)

A mixture of **2a** (95 mg) and KOH (212 mg) in MeOH (4 ml) was heated under reflux for 2·5 hr, diluted with water and was extracted with $CHCl_3$. The extract was dried and evaporated to dryness and the residue was treated with hot pet. ether. The fraction soluble in hot pet. ether, which showed only one peak in GLC, was purified by sublimation and recrystallization to give **4**, (47 mg, 50%), m.p. 134–135°. Compound **2a** (17 mg, 15%) was recovered from the insoluble fraction.

* The mixture was analyzed by GLC. (Column 1 m, 10% silicone grease on firebrick. Retention times at 211°, He flow 40 ml/min; **3**, 12·4 min; **4**, 14·8 min.)

† Column: 2 m; 25% DOP on firebrick. Retention times at 104°, He flow 40 ml/min; methyl acetate, 3·9 min; methyl angelate, 26 min; methyl tiglate, 37·4 min.

*Isomerization of* 1-*epi-allotorilolone* (**4**) *to torilolone* (**2a**)

Compound **4** (1·5 g) was treated in the manner described above to give **2a** (0·16 g, 10%), m.p. 179–180° after recrystallization from EtOH and water.

*Isomerization of allotorilolone* (**3**) *to* 1-*epi-allotorilolone* (**4**)

Compound **3** (61·1 mg) was treated in the manner described above to give **2a** (4·8 mg, 8%), m.p. 179–180°, and **4** (42 mg, 69%), m.p. 136–136·5° after purification. The fraction soluble in hot pet. ether showed only one peak (corresponding to that of **4**) in GLC.

1-*Epi-allotorilolol* (**7**)

A soln of **4** (1 g) in ether (80 ml) was added dropwise to a stirred soln of LAH (0·2 g) in dry ether (40 ml). The reaction mixture was refluxed for 1·5 hr and yielded **7**, 0·8 g, m.p. 128° from pet. ether, $[\alpha]_D^{24}$ ±0° ($c$ = 1·004, EtOH). (Found: C, 71·21; H, 10·44. Calc. for $C_{15}H_{26}O_3$: C, 70·83; H, 10·30%).

*Dehydrogenation of* 1-*epi-allotorilolol* (**7**), S-*guaiazulene* (**8a**)

Compound **7** (1·7 g) was heated at 150–160° with powdered $KHSO_4$ (1 g) for 45 min. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water and $Na_2CO_3$ aq, dried and evaporated. The residue was heated with 10% Pd-C (1 g) at 250° under $N_2$ for 1 hr, cooled, diluted with pet. ether and filtered. The violet soln was extracted with 80% $H_3PO_4$ and the extract was poured onto ice to regenerate azulene which was extracted with pet. ether and chromatographed on alumina (neutral, activity 4). The violet elutate (pet. ether soln), containing 69 mg of azulene (calculated from the UV absorption), was concentrated and treated with TNB (90 mg) in EtOH to give TNB adduct as dark violet needles, 110 mg, m.p. 147–148° from EtOH, which was identical with an authentic sample of TNB adduct of S-guaiazulene (**8a**), m.p. 150–151° (prepared by dehydrogenation of guaiol), by comparison of IR spectra and the mixed m.p. (Found: C, 61·48; H, 5·14; N, 10·48. Calc. for $C_{15}H_{18}\cdot C_6H_3O_6N_3$: C, 61·31; H, 5·15; N, 10·21%). The soln of adduct (8·69 mg) in pet. ether (b.p. 30–45°) was passed through alumina to regenerate **8a**, which was diluted to 5 ml with pet. ether (b.p. 30–45°). The following UV spectrum was observed: $\lambda_{max}$ 604 mμ, ε 437; $\lambda_{inf}$ 630 mμ, ε 378; $\lambda_{max}$ 658 mμ, ε 352; $\lambda_{max}$ 740 mμ, ε 120.

7-*Isopropyl*-1,2,4-*trimethyl-azulene* (**8b**)

A soln of **4** (1·2 g) in dry ether (80 ml) was added to the Grignard reagent prepared from Mg (0·4 g) and MeI (2·3 g) in dry ether (40 ml). The reaction mixture was refluxed for 3·5 hr, decomposed with sat $NH_4Cl$ aq, and extracted with ether. The ether extract was dried and evaporated and the residue was recrystallized from pet. ether to give needles, **9**, 1·2 g, m.p. 115–116°, $[\alpha]_D^{24}$ −26·3° ($c$ = 0·38, EtOH). (Found: C, 71·74; H, 10·53. Calc. for $C_{16}H_{28}O_3$: C, 71·60; H, 10·52%).

Compound **9** (1·2 g) was heated at 140° with $KHSO_4$ (1·2 g) for 40 min. The dehydration product was dehydrogenated with 10% Pd-C (0·6 g) at 350–260° for 75 min and treated as described to yield **8b** (81 mg, calculated from the UV absorbance), TNB adduct, 102 mg, m.p. 167–169° from EtOH. (Found: C, 61·89; H, 5·44; N, 9·52. Calc for $C_{16}H_{20}\cdot C_6H_3O_6N_3$: C, 62·16; H, 5·45; N, 9·88%).

Azulene **8b** which was regenerated from TNB adduct, showed the following UV spectrum in pet. ether (b.p. 30–45°) $\lambda_{max}$ 355 mμ, ε 4400; $\lambda_{max}$ 373 mμ, ε 1400; $\lambda_{max}$ 590 mμ, ε 370; $\lambda_{inf}$ 630 mμ, ε 320.

*Anhydroallotorilolone* (**22**)

To a soln of **3** (102 mg) in pyridine (1·5 ml), $POCl_3$ (0·5 ml) was added with cooling. After standing 2 days at room temp, the mixture was poured onto ice–water and extracted with ether. The ether extract was washed with dil $Na_2CO_3$ aq followed by water, dried and evaporated to yield **22**, needles, 20 mg, m.p. 102–102·5° from EtOH and water; $[\alpha]_D^{30}$ +170·5° ($c$ = 0·129, EtOH); IR (KBr) 1740 (cyclopentanone), 3060, 1642 and 886 $cm^{-1}$ (C=$CH_2$); NMR (100 Mc) 1·0 (3H, d, $J$ = 5) ($CH_3$—C-10), 1·10 (3H, d, $J$ = 8) ($CH_3$—C-4), 1·77 (3H, s) ($CH_3$—C-11), 4·30 (1H, s) (H—C-8), 4·67 (1H, s) and 4·77 (1H, s) ($H_2C$=C-11). (Found: C, 76·10; H, 10·30. Calc. for $C_{15}H_{22}O_2$: C, 76·22; H, 10·24%).

1-*Epi-anhydroallotorilolone* (**10**)

(a) A soln of **4** (5 g) in pyridine (62 ml) was treated with $POCl_3$ (16 ml) as described to yield **10**, 2·7 g,

m.p. 92–93° from pet. ether. $[\alpha]_D^{24}$ −152° (*c* = 0·63, EtOH); IR (KBr) 3070, 1820, 1645 and 910 $cm^{-1}$ (C=$CH_2$) and 1740 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 0·92 (3H, d, *J* = 8) ($CH_3$—C-10), 1·06 (3H, d, *J* = 8) ($CH_3$—C-4), 1·74 (3H, s) ($CH_3$—C-11), 4·13 (1H, s) (H—C-8), 4·67 and 4·77 (1H, s, each) ($H_2C$=C-11). (Found: C, 76·86; H, 9·38. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%).

(b) Compound **27** (1·4 g) was hydrolysed with 1·3% MeOH–KOH (30 ml) under reflux for 5 hr to give **10** as a neutral fraction (1·3 g) which was recrystallized from pet. ether, m.p. 92–93°.

*Deoxyallotorilolone* (**23**)

A soln of **22** (80 mg) in EtOH (10 ml) was hydrogenated over 10% Pd-C (32 mg) to give **23**, 54 mg, m.p. 86–87° from EtOH and water; $[\alpha]_D^{30}$ +194·7° (*c* = 0·19, EtOH); IR (KBr) 1740 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 0·89 (3H, d, *J* = 8) ($CH_3$—C-10), 0·90 (6H, d, *J* = 8) ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·06 (3H, d, *J* = 8) ($CH_3$—C-4), and 4·30 (1H,s) (H—C-8). (Found: C, 76·10: H, 10·30. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

1-*Epi-deoxyallotorilolone* (**12**)

A soln of **10** (1·308 g) in EtOH (50 ml) was hydrogenated over 5% Pd-C (0·5 g). After uptake of the theoretical amount of $H_2$ during 10 min, absorption ceased and the mixture was filtered. The filtrate was evaporated to yield **12**, 1 g, m.p. 62–63° from EtOH and water; $[\alpha]_D^{21}$ −144·8° (*c* = 0·511, EtOH); IR (Nujol) 1745 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 0·9 (9H, d, *J* = 8) ($CH_3$—C-10) and ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·05 (3H, d, *J* = 8) ($CH_3$—C-4), and 4·1 (1H, s) (H—C-8). (Found: C, 76·00; H, 10·14. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%); 2,4-dinitrophenylhydrazone, yellow needles, m.p. 223–224° from EtOH. (Found: C, 60·65; H, 6·87; N, 13·21. Calc. for $C_{21}H_{28}O_5N_4$: C, 60·56; H, 6·78; N, 13·45%).

*Isomerization of deoxyallotorilolone* (**23**) *to* 1-*epi-deoxyallotorilolone* (**12**)

Compound **23** (29·9 mg) was heated with a soln of KOH (80 mg) in MeOH (10 ml) under reflux for 2·5 hr. The reaction mixture was diluted with water and extracted with ether. The ether extract was dried and evaporated to give an oil which was a mixture of **23** and **12** (the ratio was 1:36).*

*Ozonolysis of* 1-*epi-anhydroallotorilolone* (**10**)

Ozonized $O_2$ was passed through a soln of **10** (475 mg) in $CCl_4$ (20 ml) at 0° for 1 hr. After evaporation of the solvent *in vacuo*, the ozonide was decomposed with water. The reaction mixture was steam-distilled into a sat soln of dimedone in 50% EtOH–water to afford a formaldehyde dimedone derivative (118 mg, 20%), m.p. 185–186° from MeOH and water, which was undepressed on admixture with an authentic methylene-bisdimedone. (Found: C, 70·15; H, 8·37. Calc. for $C_{17}H_{24}O_4$: C, 69·83; H, 8·27%).

The non-steam-volatile fraction was extracted with ether. The ether extract was dried and evaporated to give **11** as needles, m.p. 136–137° from ether; $[\alpha]_D^{21}$ −134·9° (*c* = 0·456, EtOH); IR (Nujol) 1750 (cyclopentanone), and 1700 $cm^{-1}$ (methyl ketone); NMR (60 Mc) 0·92 (3H, d, *J* = 7) ($CH_3$—C-10), 1·04 (3H, d, *J* = 7) ($CH_3$—C-4), 2·18 (3H, s) ($CH_3$—CO), and 4·42 (1H, s) (H—C-8). (Found: C, 71·07; H, 8·48. Calc. for $C_{14}H_{20}O_3$: C, 71·16; H, 8·53%).

*Cleavage of ether linkage in* 1-*epi-deoxyallotorilolone* (**12**)

(a) *With formic acid.* Compound **12** (1 g) was treated with formic acid (20 ml) under reflux for 3·5 hr. Formic acid was removed *in vacuo*, the residue was diluted with water and extracted with ether. The ether extract was washed with water and dil $NaHCO_3$ aq, dried and fractionally distilled to yield **13** as a pale yellow oil, 0·78 g, b.p. 115–130°/0·2 mm; $n_D^{20.5}$ 1·5200; $[\alpha]_D^{15}$ +69·6° (*c* = 1·06, EtOH); UV $\lambda_{max}$ 242 mμ, log ε 4·08 (EtOH); IR (liq) 1720, 1178 (formate), 1695 and 1633 $cm^{-1}$ (cyclopentenone); NMR (60 Mc) 0·80 (3H, d, *J* = 7),

* The mixture was analyzed by GLC. (Column 2 m, 10% silicon grease on firebrick; Retention times at 213°, He flow 50 ml/min; **23**, 10·9 min; **12**, 13·0 min.)

0·96 (3H, d, $J = 6$) and 1·0 (3H, d, $J = 6$) ($CH_3$—C-10 and $\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·75 (3H, s) ($CH_3$—C-4), 5·6 (1H, broad) (H—C-8), and 8·1 (1H, s) (H—C(=O)—O—); 2,4-dinitrophenylhydrazone, red needles, m.p. 218° from EtOH and EtOAc; UV $\lambda_{max}$ 393 mμ, log ε 4·49 (EtOH). (Found: C, 59·48; H, 6·54; N, 12·50. Calc. for $C_{22}H_{28}O_6N_4$: C, 59·44; H, 6·35; N, 12·61%).

Formate **13** (243 mg) was refluxed with 2% MeOH–KOH (10 ml) for 1 hr, diluted with water and extracted with ether. The ether extract was dried and evaporated to yield **12**, m.p. 61°, after sublimation at 120°/0·2 mm and recrystallization from EtOH and water.

(b) *With hydrobromic acid.* A mixture of **12** (0·8 g) and 47% HBr (6 ml) was heated on steam bath for 10 hr, diluted with water and extracted with ether. The ether extract was washed with dil $Na_2CO_3$ aq, dried and evaporated. A dark residue was chromatographed on alumina in pet. ether soln. The elutate was fractionally distilled at 100–120°/0·08 mm to yield **14** as a pale yellow oil, 0·5 g. $n_D^{22}$ 1·5379; $[\alpha]_D^{15}$ +104·9° ($c$ = 0·972, EtOH); UV $\lambda_{max}$ 296 mμ, log ε 4·17 (EtOH); IR (liq) 1690, 1630 and 1595 $cm^{-1}$ (dienone); NMR (60 Mc) 1·04 (3H, d, $J = 8$) ($CH_3$—C-10), 1·1 (6H, d, $J = 7$) ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 1·75 (3H, s) ($CH_3$—C-4), and 6·3 (1H, s) (H—C-6); 2,4-dinitrophenylhydrazone (dark violet) m.p. 196–197° from EtOH and EtOAc; UV $\lambda_{max}$ 411 mμ, log ε 4·53 (EtOH). (Found: C, 63·23; H, 6·68; N, 13·98. Calc. for $C_{21}H_{26}O_4N_4$: C, 63·30; H, 6·58; N, 14·06%).

1-*Epi-deoxygeigerin* (**21**).

(a) 1-*Epi-anhydroallotorilolol* (**18**). A soln of **10** (0·9 g) in ether (50 ml) was added dropwise to a stirred soln of LAH (0·5 g) in dry ether (30 ml). The reaction mixture was refluxed for 2 hr and yielded crude crystalline **18**, 0·8 g.

(b) *Hydroboration and oxidation of* **18**. To a well stirred suspension of $NaBH_4$ (1·8 g) in THF (100 ml) containing **18** (5·5 g), $BF_3$-etherate (3·8 g) in THF (24 ml) was added over a period of 20 min under $N_2$. After standing for 3 hr at room temp, 10% NaOH (22 ml) was added and the product was oxidized with 30% $H_2O_2$ (22 ml) which was added slowly over a period of 1 hr. The reaction mixture was diluted with water (150 ml) and extracted with ether. The ether extract was dried and evaporated to give **19** as a viscus oil.

To a stirred soln of crude **19** in AcOH (25 ml), $Na_2Cr_2O_7 \cdot 2H_2O$ (11·5 g) in acetic acid (35 ml) was added dropwise with cooling in ice-water. After standing for 12 hr at room temp, the reaction mixture was diluted with water and extracted with ether. The ether extract was treated with 5% $Na_2CO_3$ aq and the alkaline layer was extracted with ether after acidification. The ether extract was dried and evaporated to yield an acid, **20**, as a viscus oil, 2·8 g, which was freed from AcOH by heating at 100° for 3 hr *in vacuo*; IR ($CHCl_3$) 1740 (cyclopentanone), 2600 and 1700 $cm^{-1}$ (COOH); *p*-bromophenacyl ester, m.p. 168–169° from EtOH

(c) 1-*Epi-deoxygeigerin* (**21**). A soln of crude **20** (2·7 g) in 5% $Na_2CO_3$ aq (20 ml) was allowed to stand for 3 hr at room temp and was extracted with ether after acidification with dil HCl. The ether layer was washed with 5% $Na_2CO_3$ aq, dried and evaporated to yield a neutral fraction, 0·5 g. The acid **20**, 2·0 g, recovered from the alkaline layer, was dissolved in 5% $Na_2CO_3$ aq (20 ml) and again allowed to stand for 2 days at room temp. A neutral fraction, 0·6 g, and an acidic fraction, 1·14 g, (recovered) were obtained after treating in the manner described. Treatment of this acidic fraction with $Na_2CO_3$ twice as described above yielded a neutral fraction (344 mg and 196 mg respectively). An acidic fraction, 256 mg, was recovered. The neutral fractions were combined (total 1·64 g) and chromatographed on alumina using a mixture of pet. ether and benzene (1 : 1) as the elutent. The fractions containing crystalline material were combined and rechromatographed to give **21**, 270 mg, m.p. 128–129° from EtOAc, which was identical with an authentic sample of 1-epi-deoxygeigerin by comparison of IR spectra and the mixed m.p. $[\alpha]_D^{31}$ +130·8° ($c$ = 0·474, EtOH); UV $\lambda_{max}$ 238 mμ, log ε 4·17; and $\lambda_{max}$ 288 mμ, log ε 1·14 (EtOH); IR (KBr) 1760 (γ-lactone), 1700 and 1650 $cm^{-1}$ (cyclopentenone); NMR (60 Mc) 1·0 (3H, d, $J = 7$) ($CH_3$—C-10), 1·3 (3H, d, $J = 7$) ($CH_3$—C-11), 1·7 (3H, d, $J = 2$) ($CH_2$—C-4), and 4·58 (1H, m) (H—C-8). (Found: C, 72·57; H, 8·11. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12%).

*Dihydrotorilolone* (**24**)

(a) *From torilolone* (**2a**). **2a** (210 mg) was hydrogenated in EtOH (10 ml) over 10% Pd-C (110 mg). After up-take of 2 moles of $H_2$ during 2 hr, absorption ceased and the mixture was filtered and the filtrate was evaporated to give **24**, 50 mg, m.p. 107–108° from n-hexane; $[\alpha]_D^{20}$ +127·4° ($c$ = 0·415, MeOH); IR (KBr) 3250 (OH), and 1740 $cm^{-1}$ (cyclopentanone); NMR (100 Mc) 1·0 (3H, d, $J$ = 5) ($CH_3$—C-10), 1·1 (3H, d, $J$ = 8) ($CH_3$—C-4), 1·36 (6H, s) ($\begin{matrix}CH_3\\CH_3\end{matrix}$>C-11), 3·18 (2H, s) (OH), and 4·53 (1H, broad) (H—C-8). (Found: C, 70·83; H, 10·30. Calc. for $C_{15}H_{26}O_2$: C, 70·76; H, 10·34%).

(b) *From tetrahydrotorilin* (**29**). Compound **1** (1·085 g) was hydrogenated in EtOH (50 ml) over 10% Pd-C (428 mg). After up-take of 1·5 mole of $H_2$, the mixture was filtered and the filtrate was evaporated. The residue was fractionally distilled to yield **29** as a viscous oil, 830 mg, b.p 118–120°/$10^{-3}$ mm; $[\alpha]_D^{20}$ +43° ($c$ = 2·06, $CHCl_3$); $n_D^{28}$ 1·4739; IR (liq) 1740 (shoulder) (cyclopentanone) and 1730 $cm^{-1}$ (saturated ester).

Compound **29** was hydrolysed with 5% MeOH–KOH under reflux for 1 hr to yield **24**, m.p. 106–107° from EtOH and pet. ether. The acidic fraction of the hydrolysis products was identical with α-methylbutyric acid by GLV analysis.*

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* Column; 1 m, 18% silicon grease and 5% stearic acid on firebrick. The retention times at 153°, $H_2$ flow 50 ml/min; the acidic fraction, 7·0 min; α-methylbutyric acid, 7·0 min.