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SYNTHESES OF OPTICALLY ACTIVE GRASSHOPPER KETONE AND DEHYDROVOMIFOLIOL AS A SYNTHETIC SUPPORT FOR THE REVISED ABSOLUTE CONFIGURATION OF (+)-ABSCISIC ACID[a]

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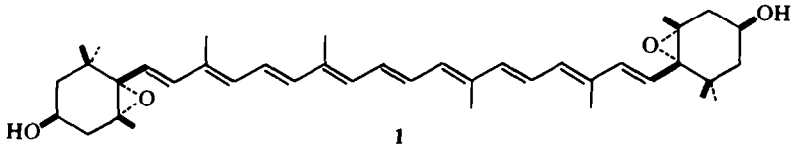
Abstract—Grasshopper ketone (**5**) and dehydrovomifoliol (**6**) were synthesized in their natural and optically active forms. Comments were made on the significance of this work in relation to the (*S*)-stereochemistry of (+)-abscisic acid (**3**). Unusual selective hydrogenation of the more hindered CO group of **7** to give **9** is recorded.

Since Taylor and Burden[1] provided evidence that the absolute configuration of either violaxanthin (**1**)[2] or (+)-abscisic acid (expressed as **2** at that time)[3] had been incorrectly assigned, the absolute configuration of the latter was of considerable recent research interest and finally revised as **3**.[4-8]

Our strategy to attack this problem was to secure a common intermediate (**4**) from which both the grasshopper ketone (**5**)[9] and dehydrovomifoliol (**6**)[10] could be synthesized employing reactions with known steric courses. As the absolute stereochemistry of the former (**5**) had been established by X-ray analysis,[11] this synthesis would enable us to assign the absolute configuration of the latter (**6**) which had been converted by others[7,10] to (+)-abscisic acid (**3**). This paper describes in detail the results obtained along this line which have been preliminarily reported.[12,13]

Synthesis of the optically active ketone (**4**)

The first stage of this work was the synthesis of the key intermediate (**4**). This compound would be of great utility for the preparation of optically active carotenoids or their relatives with C-3 OH group. After several attempts we decided to employ the known diketone (**7**)[14] as the starting material. It was reported to give a ketol (**8**) upon hydrogenation



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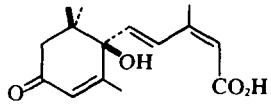

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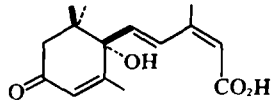

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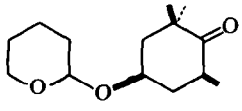

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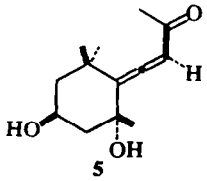

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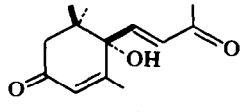

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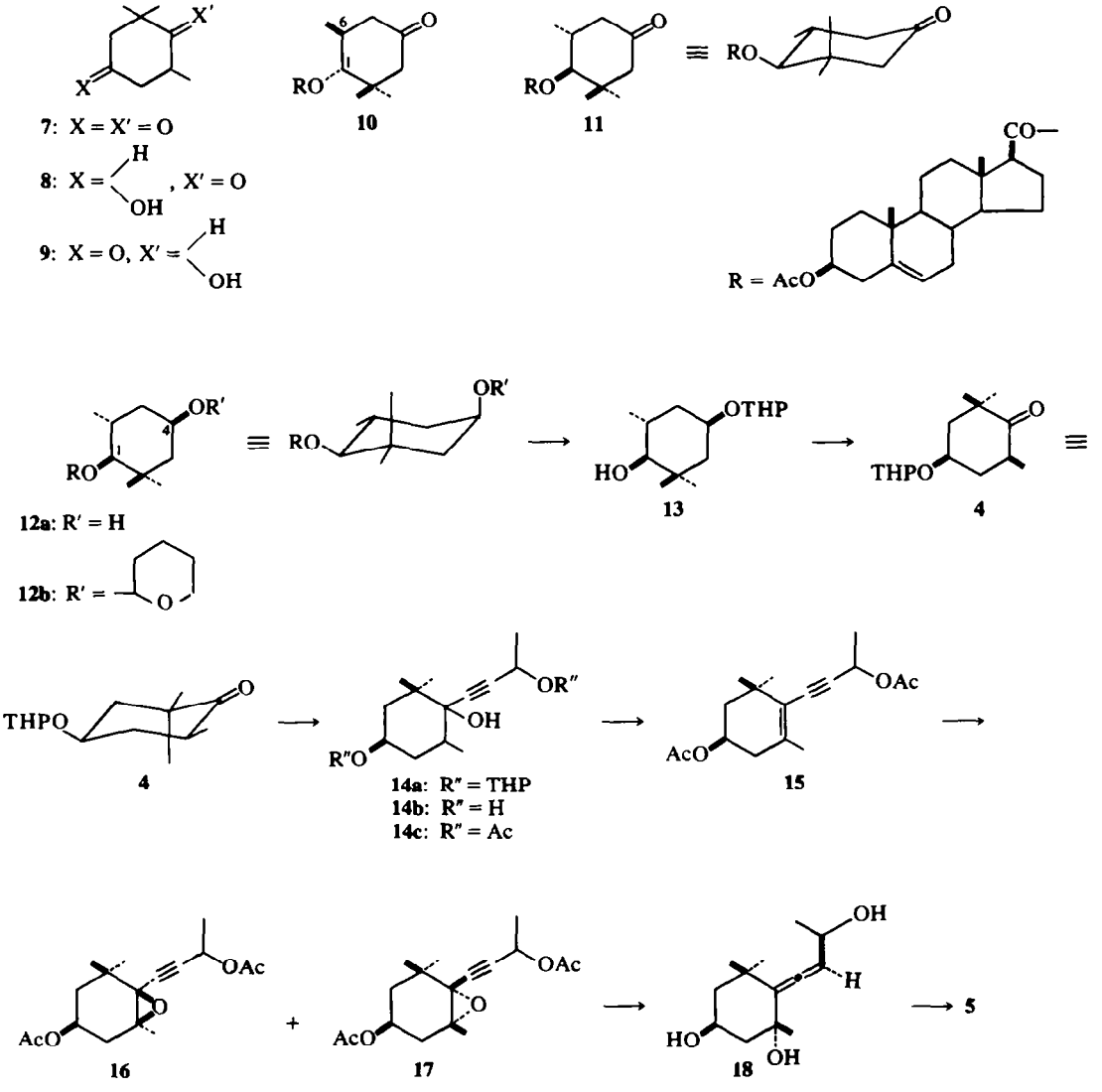
[a] Carotenoids and Degraded Carotenoids—IV. Part III, *Agr. Biol. Chem.* 37, 2927 (1973).

(PtO_2/MeOH).[15] This seemed quite natural on the commonly accepted assumption that the less hindered CO group should be reduced more rapidly. Actually the diketone (**7**) very rapidly absorbed 1 mole of H_2 upon hydrogenation to give a crystalline ketol. In order to rigorously determine the position of the OH group, the ketol was submitted to the Huang Minlon reduction. The Jones oxidation of the resulting alcohol unexpectedly gave 2,2,6-trimethylcyclohexanone, instead of dihydroisophorone derivable from **8**, as revealed by IR, NMR and GLC comparisons with an authentic sample. This unambiguously established the structure of the ketol as 1-hydroxy-2,2,6-trimethylcyclohexan-4-one (**9**). The relative stereochemistry of the OH and Me groups as *trans*-diequatorial was concluded from the large coupling constant (J = 10 Hz) exhibited by CHOH proton. This surprising selective hydrogenation of the more hindered CO group of the diketone (**7**) is an interesting phenomenon and deserves further study.

The optical resolution of this ketol (**9**) was achieved by the use of 3β-acetoxy-etienic acid as a resolving agent.[16,17] Acylation of the ketol (**9**) with 3β-acetoxy-etienoyl chloride gave a mixture of two diastereomeric esters (**10** and **11**). This was separated by fractional crystallization to give a more soluble etienate (**10**) and the less soluble one (**11**) with a higher m.p. The latter was sparingly soluble in EtOAc and hence could be purified relatively easily. The absolute configurations as shown in **10** and **11** were deduced from the ORD data. The more soluble ester showed a negative



Cotton effect and hence should be **10** as deduced from the octant rule. The sparingly soluble ester (**11**) exhibited a positive Cotton effect curve. As the purification of the more soluble ester (**10**) was rather difficult, we used the sparingly soluble one (**11**) for subsequent works.

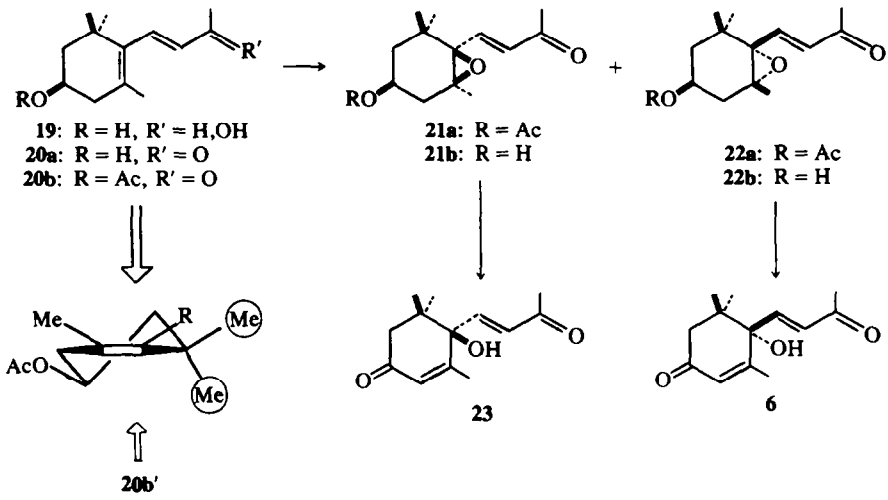
In order to obtain the key intermediate (**4**), it was necessary to reverse the oxidation states at C-1 and C-4 of **11** involving asymmetric reduction of the CO group at C-4. A model experiment of this process with racemic compounds was described previously.[18] Thus **11** was reduced with $LiAlH(OBu^t)_3$ to give, after chromatography over alumina, an axial alcohol (**12a**) whose CHOH proton resonated at δ 3·99 with $W_{1/2} = 6$ Hz, indicating the β-axial configuration of the newly generated OH group. After protection of the OH group as a THP ether (**12b**), the steroidal portion was removed by reductive cleavage with LAH to give an alcohol (**13**). Its oxidation with the Jones chromic acid followed by equilibration over basic alumina gave the desired key intermediate (**4**) as a dextrorotatory oil. This ketone exhibited a positive Cotton effect in accord with the assigned absolute stereochemistry. The equatorial nature of the THPO group was proved by conversion of racemic **4** into the corresponding ketol (**8**) whose NMR spectrum definitely revealed the presence of an axial CHOH proton.[18] It was very fortunate that the less soluble and hence more readily available steroidal ester (**11**) afforded this ketol THP ether (**4**) of the desired absolute configuration. It should also be added that the racemic ketol (**8**)[18] could not be resolved by the etienate method.

Synthesis of the optically active grasshopper ketone (**5**)

The next stage was the synthesis of grasshopper ketone (**5**). Treatment of the ketone (**4**) with a Grignard reagent prepared from EtMgBr and but-3-yn-2-ol THP ether gave **14a** which was treated with *p*-TsOH/MeOH to give a triol (**14b**). Further transformation to grasshopper ketone (**5**) was carried out in the same manner as described by Weedon[19] for the synthesis of the racemic ketone (**5**). The triol (**14b**) was converted to a diacetate (**14c**) which in turn was dehydrated with $POCl_3$ in pyridine to give an enyne diacetate (**15**). Epoxidation of **15** with *m*-chloroperbenzoic acid in $CHCl_3$ gave a mixture of two epoxides (**16** and **17**) which was partly separable by chromatography over alumina. The fractions rich in the more strongly adsorbed *trans*-epoxide (**17**) were combined and reduced with LAH to give a crude allenic triol (**18**). This was oxidized with MnO_2 in acetone and purified by preparative TLC to give the optically active grasshopper ketone (**5**). The IR and NMR spectral properties of the synthetic ketone (**5**) were in good agreement with those of the natural product.[9,19] Moreover, the CD curve of the snythetic material was qualitatively identical with that of the semi-synthetic grasshopper ketone (**5**) prepared from fucoxanthin.[11] The unpublished CD spectrum of the fucoxanthin degradation product (**5**) was kindly made available to us by Professor Weedon which enabled us to estimate the optical purity of our synthetic material to be at least 63%. This unsatisfactory optical purity was the cause of our inability to get crystalline **5**. Due to the limited availability of the pure steroidal ester (**11**) at the time of the present synthesis we had to use somewhat impure starting material (**11**, 83% purity as judged by its $[\alpha]_D$ value). Anyway, the key intermediate (**4**) correctly led to grasshopper ketone (**5**) in its natural configuration as expected, definitely establishing the absolute stereochemistry of **4**.

Synthesis of the optically active dehydrovomifoliol

The final stage of this work was the synthesis of the optically active dehydrovomifoliol (**6**). In order to secure the entirely pure final product, the starting steroidal ester (**11**) was prepared in a large quantity and purified carefully. Then it was converted to the enyne diacetate (**15**) as described above. This was treated with LAH to give 3β-hydroxy-β-ionol (**19**), which in turn was oxidized with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in dioxane. The product was chromatographed over alumina to give (−)-3β-hydroxy-β-ionone (**20a**). Subsequent epoxidation of the corresponding acetate (**20b**) with *m*-chloroperbenzoic acid in $CHCl_3$ yielded two crystalline epoxides after chromatographic purification over silicic acid. The steric course of this type of epoxidation was studied by Weedon *et al.* in the cases of 4-acetoxy-2,2,6-trimethylcyclohexene,[2] the enyne diacetate (**15**)[19] and zeaxanthin diacetate,[2] and known to give a *cis*-epoxide as a major and less strongly adsorbed product. For example, the minor product of the epoxidation of **15** was a *trans*-epoxide (**17**), since it could be converted to grasshopper ketone (**5**) with a secondary β-OH and a tertiary α-OH groups. This preferred generation of a *cis*-epoxide could be rationalized on the basis of a stereoformula **20b'** where the steric hindrance caused by the quasi-axial Me group was clearly seen, while the AcO group was not in the position to alter the effect of the Me group. The very broad seven-line pattern ($W_{1/2} = 15$ Hz) at δ 4·98 in the NMR spectrum of 3β-acetoxy-β-ionone (**20b**) is due to the axial AcOCH proton and supports the conformation **20b'**. Barton recently reported a similar situation in the epoxidation of 2β-hydroxycholest-4-en-7-one.[20] In the present case the major product obtained in 20% yield after several recrystallizations was therefore the (+)-*cis*-epoxide (**21a**) with a positive Cotton effect in its CD spectrum. The minor and less easily eluted product (**22a**) was obtained in 6·4% yield. This (−)-*trans*-epoxide with an α-epoxy ring was entirely identical



with the degradation product of violaxanthin (**1**)[21] kindly supplied by Dr. R. S. Burden on the basis of m.m.p. (124–125°), IR, NMR and CD (a negative Cotton effect) spectra.

Conversion of the *trans*-epoxide **22a**, (−)-3(*S*)-acetoxy-5(*R*), 6(*S*)-epoxy-β-ionone), to (*S*)-dehydrovomifoliol (**6**) was effected by alkaline hydrolysis to a ketol (**22b**) followed by its oxidation with chromic anhydride-pyridine. During the Sarett oxidation, base-catalyzed cleavage of the epoxy ring took place to give **6**. This reaction is known to result in the retention of the configuration of the C—O bond at C-6.[20] The IR and NMR spectra of the resulting oily hydroxy diketone (**6**) was superimposable on those of an authentic racemate ($\frac{1}{2}$**6** + $\frac{1}{2}$**23**)[22] and the chiroptical data were in good accord with those reported for the natural (+)-dehydrovomifoliol.[10] Hence the absolute configuration of the dextrorotatory natural product was (*S*). In the same manner the *cis*-epoxide (**21a**) gave the antipodal hydroxy diketone, (*R*)-(−)-**23**, as an oil. The conversion of (+)-dehydrovomifoliol (**6**) into (+)-abscisic acid is well-documented.[7,10] The (+)-acid, therefore, must be represented by **3** with (*S*)-configuration at C-6.

In conclusion the present synthesis starting from the common intermediate (**4**) provided a link between grasshopper ketone (**5**) and (+)-abscisic acid (**3**). In view of the established stereochemistry of the former by X-ray analysis,[11] this work confirmed the revised (*S*)-stereochemistry (**3**) of the latter as well as the accepted stereochemistry of violaxanthin (**1**).

EXPERIMENTAL

All m.ps were uncorrected. IR spectra refer to Nujol mulls for crystalline samples and films for oils and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 or 100 MHz with TMS as an internal standard. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ORD and CD spectra were recorded on a Jasco J-20 ORD/CD spectro-polarimeter. GLC analyses were performed on a Yanaco G80 gas chromatograph.

1-Hydroxy-2,2,6-trimethylcyclohexan-4-one (**9**). A soln of **7** (13·0 g) in MeOH (100 ml) was shaken with Adams' PtO_2 (0·5 g) under H_2 at room temp. After 30 min the rate of H_2 uptake remarkably decreased when *ca* 2 litre (1 eq) of H_2 had been absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with a small amount of ether-light petroleum and left to stand in a refrigerator to give 10 g (76%) of crystals. Recrystallization from ether-light petroleum gave needles, m.p. 75–76° (lit[15] 56°); ν_{max} ~3400, 1710 (br), 1280, 1245, 1160, 1075, 1050, 1030, 990, 850 cm^{-1}; δ (60 MHz, $CDCl_3$) 0·86 (3H, s), 1·08 (3H, s), 1·09 (3H, d, *J* = 6 Hz), 3·37 (1H, d, *J* = 10 Hz); GLC: *Rt* 12·1 min, Column: LAC 2R-446 1·5 m × 3 mm i.d. at 160°, carrier gas, N_2, 1·0 kg/cm^2. (Found: C, 69·18; H, 10·21. $C_9H_{16}O_2$ requires: C, 69·19; H, 10·32%).

Conversion of **9** *to* 2,2,6-*trimethylcyclohexanone*. A soln of KOH (0·5 g) in H_2O (0·5 ml) and 80% $N_2H_4.H_2O$ (0·5 ml) were added to a soln of **9** (150 mg) in diethylene glycol (5 ml). The mixture was heated under reflux for 30 min and then heated at 200–210° for 2·5 h with removal of N_2H_4 and H_2O. After cooling, the mixture was diluted with water and extracted with ether. The ether extract was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was dissolved in acetone (5 ml) and oxidized with Jones CrO_3 (0·2 ml). After 3 min at room temp, the excess CrO_3 was destroyed by the addition of MeOH and the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether extract was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (100 mg). The following IR, NMR and GLC data were identical with those of an authentic sample; ν_{max} 1710, 1130, 1020, 995, 960, 850 cm^{-1}; δ (60 MHz, CCl_4) 0·95 (3H, d, *J* = 6 Hz), 1·01 (3H, s), 1·16 (3H, s), ~2·5 (1H, m); GLC: *Rt* 3·8 min, Column: LAC 2R-446 (5%) at 150°, carrier gas, He, 1·0 kg/cm^2. The identity was also proved by the coinjection with an authentic sample.

The optical resolution of **9** *via* 3β-*acetoxyetienates* (**10** and **11**). Oxalyl chloride (35 g) was added to an ice-cooled

and stirred suspension of 3β-acetoxyetienic acid (20 g) in dry C_6H_6 (200 ml). After 30 min the acid dissolved completely. After another 30 min at room temp, the soln was concentrated *in vacuo*. The crystalline acyl chloride was dissolved again in dry C_6H_6 (100 ml) and concentrated *in vacuo* to remove the final trace of the excess oxalyl chloride. To an ice-cooled soln of the acyl chloride in dry pyridine (200 ml), a soln of **9** (6·0 g) in dry pyridine (30 ml) was added and the mixture was left to stand at room temp for 15 h. This was poured into ice and 3N-HCl (700 ml) and the mixture was extracted with a large amount (5l) of EtOAc. The extract was washed with dil HCl, H_2O, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was fractionally crystallized from EtOAc-light petroleum. The sparingly soluble **11** (3·7 g) and more soluble **10** (3·9 g) were obtained. Conventional chromatography over Woelm neutral alumina did not effect good separation of the diastereomers. *The less soluble diastereomer* (**11**) crystallized from EtOAc–light petroleum as needles, m.p. 243–244°, ν_{max} 1730 (s), 1280 (w), 1250 (s), 1195 (m), 1170 (m), 1150 (w), 1140 (w), 1080 (w), 1060 (w), 1035 (m), 1020 (w), 1000 (w), 980 (w), 960 (w), 940 (w), 920 (w), 900 (w), 850 (w), 820 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0·78 (3H, s), 0·95 (3H, s), 0·97 (3H, d, $J = 6$ Hz), 1·02 (3H, s), 2·00 (6H, s), 4·62 (1H, m), 5·00 (1H, d, $J = 11$ Hz), 5·42 (1H, m). $[\alpha]_D^{24} - 31·0$ ($c = 3·7\%$ in dioxane); ORD: Positive Cotton effect curve ($c = 0·2\%$ in MeOH), $[\phi]_{308} - 100°$ (peak); $[\phi]_{270} - 500°$ (trough); $[\phi]_{233} + 2000°$ (second peak due to the steroidal ester portion). (Found: C, 74·50; H, 9·21. $C_{31}H_{46}O_5$ requires: C, 74·66; H, 9·30%). *The more soluble diastereomer* (**10**) crystallized from EtOAc–light petroleum as prisms, m.p. 184·5–186°, ν_{max} 1730 (s), 1290 (w), 1250 (s), 1195 (w), 1170 (m), 1160 (m), 1060 (w, sh), 1040 (m), 1020 (w, sh), 1000 (w), 960 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0·81 (3H, s), 0·95 (6H, s, 1·00 (3H, d, $J = 6$ Hz), 1·04 (3H, s), 2·02 (3H, s), 4·60 (1H, m), 4·98 (1H, d, $J = 11$ Hz), 5·41 (1H, m); $[\alpha]_D^{24} - 13°$ ($c = 3·7\%$ in dioxane); ORD: Negative Cotton effect curve ($c = 0·2\%$ in MeOH), $[\phi]_{308} - 500°$ (trough); $[\phi]_{233} + 2500°$ (peak). (Found: C, 74·47; H, 9·27. $C_{31}H_{46}O_5$ requires: C, 74·60; H, 9·30%).

3β-Acetoxyetienate at C-1 of 2,2,6α-trimethylcyclohexane-1β,4β-diol (**12a**). A soln of $LiAlH(OBu^t)_3$, was prepared from LAH (2 g) and Bu^tOH (11·7 g) in dry THF (75 ml) by stirring for 2 h at 0°. A soln of **11** (11·5 g) in dry THF (100 ml) was added dropwise to the stirred and ice-cooled soln of $LiAlH(OBu^t)_3$ at 0–5°. The mixture was left to stand overnight at 0–5°. Then it was poured into ice-dil HCl–NH_4Cl and extracted with EtOAc. The extract was washed with sat NH_4Cl soln, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade III, 400 g, 31 × 4·5 cm in C_6H_6). Elution with C_6H_6–MeOH (200: 1, 2·4 litre; 100: 1, 1·2 litre; 50: 1, 1·2 litre) gave 8·95 g (78%) of needles, m.p. 209–210°. TLC (silical gel G, ether) revealed that this material contained a trace of 4α-equatorial alcohol (R_f 0·52) in addition to the desired **12a** (R_f 0·63). So this was re-chromatographed over Woelm neutral alumina (grade II, 1·1 kg, 46 × 6 cm in C_6H_6). The crude **12a** (8·9 g) was dissolved in EtOAc (100 ml) and mixed with Woelm grade II neutral alumina (100 g). The mixture was dried up *in vacuo* and placed on the top of the column. Elution with C_6H_6–MeOH (100: 1, 2 litre after 3·6 litre of forerun) gave 6·6 g (57%) of pure **12a**. Recrystallization from EtOAc-light petroleum gave needles, m.p. 211–212°, ν_{max} 3550 (m), 1730 (s), 1700 (s), 1380 (m), 1370 (m), 1295 (w), 1250 (s), 1230 (m), 1200 (s), 1170 (m), 1150 (w), 1120 (m), 1080 (w), 1050 (m), 1030 (m), 940 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0·76 (3H, s), 0·81 (3H, d, $J = 6$ Hz), 0·87 (3H, s), 1·01 (3H, s), 1·15 (3H, s), 2·00 (3H, s), 3·99 (1H, t, $W_{1/2} = 6$ Hz), 4·60 (1H, d, $J = 11$ Hz), 5·82 (1H, m); $[\alpha]_D^{23} - 40·2°$ ($c = 1·025\%$ in dioxane). (Found: C, 74·57; H, 9·70. $C_{31}H_{46}O_5$ requires: C, 74·36; H, 9·66%). For the synthesis of grasshopper ketone, **11** with $[\alpha]_D^{24} - 28·0°$ ($c = 1\%$ in dioxan) was used as the starting material to give **12a** with $[\alpha]_D^{24} - 39·4°$ ($c = 1·0\%$ in dioxan).

3β-Acetoxyetienate of 4β-tetrahydropyranyloxy-2,2,6α-trimethylcyclohexan-1β-ol (**12b**). Dihydropyran (4·5 ml) and *p*-TsOH (0·2 g) were added to a soln of **12a** (8·0 g) in $CHCl_3$ (60 ml) and the soln was left to stand overnight at room temp. Then it was washed with K_2CO_3 soln, dried (K_2CO_3) and evaporated *in vacuo*. Crystallization of the residue from EtOAc-light petroleum gave 6·0 g of **12b**. The mother liquor was chromatographed over Woelm neutral alumina (grade I, 55 g, 17 × 2 cm in n-hexane). Elution with C_6H_6-n-hexane gave 1·0 g of **12b**. The total yield was 7·0 g (75%). Recrystallization from EtOAc-light petroleum gave prisms, m.p. 195–200°, ν_{max} 1725 (s), 1250 (s), 1200 (m), 1165 (w), 1150 (w), 1130 (m), 1105 (m), 1080 (w), 1020 (s), 1000 (m), 980 (m), 960 (w), 860 (w), 810 (w), 760 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0·80 (3H, s), 0·85 (3H, d, $J = 6$ Hz), 0·90 (3H, s), 1·05 (3H, s), 1·12 (~2H, s), 1·18 (~1H, s), 2·04 (3H, s), 3·6, 3·94, 4·5, 4·7, 5·45 (1H, m); $[\alpha]_D^{23} - 26·9°$ ($c = 1·10\%$ in dioxane); TLC (silica gel G, C_6H_6–EtOAc 15:1): R_f 0·40. (Found: C, 73·92; H, 9·66. $C_{36}H_{56}O_6$ requires: C, 73·93; H, 9·65;).

4β - Tetrahydropyranyloxy - 2,2,6α - trimethyl - cyclohexan - 1β - ol (**13**). A soln of **12b** (6·95 g) in dry THF (50 ml) was added to a stirred and ice-cooled suspension of LAH (2·5 g) in dry ether (300 ml) at 0–10°. After stirring overnight at room temp, the mixture was poured into ice-cooled soln of Rochelle salt (25 g) and NaOH (5 g) in water (100 ml). The mixture was thoroughly extracted with ether. The extract was washed with sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo*. The residue was mixed with light petroleum and the insoluble steroid alcohol was removed by filtration. Concentration of the filtrate afforded 2·9 g (98%) of **13**. This was employed for the next step without further purification. ν_{max} ~3420, 1200, 1130, 1110, 1080, 1050, 1030, 1020, 1000, 980, 950, 865, 805, 760 cm^{-1}; TLC (silica gel G, C_6H_6–EtOAc 15:1): R_f 0·23.

4β - Tetrahydropyranyloxy - 2,2,6β - trimethylcyclohexanone (**4**). The Jones 8N-CrO_3 (4·0 ml) was added to an ice-cooled soln of **13** (2·9 g) in acetone (20 ml) at 0–5°. After 10 min at 0–5°, the excess CrO_3 was destroyed by the addition of MeOH. The soln was made basic with K_2CO_3 and concentreated *in vacuo*. The residue was diluted with water and extracted with ether. The ether extract was washed with water and sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over Wako basic alumina (55 g, 18 × 2 cm) in n-hexane. Elution with n-hexane (600 ml) and ether–n-hexane (1:4, 600 ml) gave 1·97 g (67%) of **4**, ν_{max} 1705 (s), 1200 (w), 1130 (m), 1110 (m), 1070 (m), 1055 (w), 1020 (s), 980 (m), 860 (w) cm^{-1}; δ (60 MHz, CCl_4). The NMR spectrum was rather complicated due to the stereoisomerism at the anomeric carbon of the tetrahydropyranyl group. 0·94, 0·98, 1·20, 1·18, 1·25, 1·30, 1·60, ~3·5, ~4·0, 4·70; $[\alpha]_D^{19} + 36·6°$ ($c = 1·6\%$ in $CHCl_3$); CD: Positive Cotton effect ($c = 0·22\%$ in MeOH), $[\theta]_{300}$

+ 1530. (Found: C, 70·07; H, 9·95. $C_{14}H_{24}O_3$ requires: 69·96; H, 10·07%).

4 - (1',4'β - *Dihydroxy* - 2',2',6' - *trimethylcyclohexyl*) *but* - 3 - *yn* - 2 - *ol* (**14b**). A Grignard reagent was prepared from EtBr (4·0 g) and Mg (0·9 g) in dry ether (20 ml). To this was added a soln of 3-butyn-2-ol THP ether (6·1 g) in dry THF. The mixture was stirred at 40–50° for 1 h under N_2. A soln of **4** (1·8 g) in dry THF (10 ml) was added to the Grignard soln and the mixture was stirred and heated under reflux for 1·5 h at 50–60° under N_2. After 15 h at room temp, the mixture was poured into ice-dil HCl-NH_4Cl and extracted with ether. The ether extract was washed with sat NH_4Cl and sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo* to give 6 g of crude oil including the starting acetylene. No CO absorption was observable in its IR spectrum. This was dissolved in MeOH (100 ml) containing *p*-TsOH (0·1 g) and left to stand for 7 h at room temp. The soln was made basic with K_2CO_3 and concentrated *in vacuo*. The residue was diluted with sat NaCl soln and extracted with ether. The ether extract was washed with sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo* to give 1·7 g (quantitative) of oily **14b**, ν_{max} ~ 3300 (s), 1460 (m), 1380 (s), 1340 (m), 1300 (m), 1120 (s), 1080 (s), 1060 (s), 1030 (s), 980 (m), 970 (m), 920 (w), 900 (w) cm^{-1}. The IR spectrum was identical with that of a crude racemic **14b** prepared by the method of Weedon *et al.*[19] This crude triol was employed for the next step without further purification.

2 - *Acetoxy* - 4 - (4'β - *acetoxy* - 1' - *hydroxy* - 2',2',6' - *trimethylcyclohexyl*) *but* - 3 - *yne* (**14c**). Ac_2O (10 ml) was added to a soln of **14b** (1·7 g) in dry pyridine (10 ml) and the mixture was left to stand overnight at room temp. Then it was poured into water and extracted with ether. The ether extract was washed with dil HCl and sat $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade II, 51 g, 16 × 2 cm) in n-hexane. Elution with n-hexane–ether (4:1 ~ 3:1, 1 litre) gave 2·273 g (97%) of **14c**, ν_{max} 3500 (m), 1730 (s), 1240 (s), 1175 (m), 1140 (m), 1020 (s), 970 (m), 940 (m), 880 (w), 860 (w), 840 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 1·01 (3H, d, *J* = 6 Hz), 1·08 (6H, s), 1·50 (3H, d, *J* = 6 Hz), 1·94 (3H, s), 2·02 (3H, s), 4·90 (1H, m), 5·37 (1H, q, *J* = 6 Hz); TLC (silica gel G C_6H_6–EtOAc 9:1): R_f 0·46; MS: *m/e* 310 ($M^+ = C_{17}H_{26}O_5$).

2 - *Acetoxy* - 4 - (4'β - *Acetoxy* - 2',6',6' - *trimethylcyclohex* - 1' - *enyl*) *but* - 3 - *yne* (**15**). $POCl_3$ (2·5 ml) was added to a soln of **14c** (2·2 g) in dry pyridine (15 ml) and the mixture was heated under N_2 at 90–100° for 12 h. After cooling it was poured into ice water and extracted with ether. The ether extract was washed with water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade II, 13·5 × 2 cm) in n-hexane. Elution with n-hexane–ether (4:1, 500 ml) gave 793 mg (37%) of **15**, ν_{max} 2950 (m), 2200 (w), 1735 (s), 1440 (m), 1360 (s), 1330 (m), 1300 (w), 1230 (s), 1190 (s), 1180 (sh, m), 1140 (w), 1080 (m), 1020 (s), 980 (w), 940 (m), 835 (w) cm^{-1}; δ (60 MHz, CCl_4) 1·14 (6H, s), 1·48 (3H, d, *J* = 6 Hz), 1·85 (3H, s), 1·95 (3H, s), 2·00 (3H, s), 4·95 (1H, m), 5·50 (1H, q, *J* = 6 Hz); TLC (silica gel G, C_6H_6–EtOAc 9:1): R_f 0·68. (Found: C, 69·32; H, 8·28. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%).

3β-*Acetoxy*-5β,6β-*epoxy*-7,8-*dehydro*-β-*ionol acetate* (**16**) *and its* 5α,6α-*epoxy isomer* (**17**). A soln of *m*-chloroperbenzoic acid (91 mg) in $CHCl_3$ (1·5 ml) was added to a soln of **15** (120 mg) in $CHCl_3$ (1 ml) at 0–5°. The mixture was left to stand overnight in a refrigerator. Then it was washed with sat $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade II, 9 g, 10·5 × 1 cm) in light petroleum. Elution with light petroleum–ether (95:5) gave 55 mg of epoxides (**16** and **17**). The later fractions (25 mg) were combined and used for the next step as crude **17**, ν_{max} 2950 (s), 1740 (s), 1440 (m), 1360 (m), 1330 (w), 1300 (w), 1230 (s), 1170 (m), 1150 (w), 1080 (m), 1030 (m), 970 (w), 950 (w), 900 (w), 850 (w) cm^{-1}; TLC (silica gel G C_6H_6–EtOAc 15:1): R_f 0·40. In a model experiment with racemic **15**, the product could be cleanly separated by chromatography over Mallinckrodt silicic acid (AR 100 mesh). Thus 1·83 g of (±)-**15** was epoxidized and chromatographed over silicic acid (130 g, 20·5 × 4 cm). Elution with n-hexane–EtOAc (7:1) gave 468 mg of **16** and 229 mg of **17** plus 213 mg of **16** + **17**. NMR data of racemic **16** and **17** were as follows: Compound **16**: δ (100 MHz, $CDCl_3$) 1·15 (3H, s), 1·19 (3H, s), 1·43 (3H, s), 1·46 (3H, d, *J* = 6 Hz), 1·97 (3H, s), 2·03 (3H, s), 4·80 (1H, m), 5·42 (1H, q, *J* = 6 Hz). Compound **17**: δ (100 MHz, $CDCl_3$) 1·12 (3H, s), 1·21 (3H, s), 1·46 (3H, s), 1·48 (3H, d, *J* = 6 Hz), 1·97 (3H, s), 2·03 (3H, s), 4·80 (1H, m), 5·42 (1H, q, *J* = 6 Hz).

Grasshopper ketone (**6**) *via* **18**. The above described optically active epoxide (**17**, 22 mg) was dissolved in dry THF (10 ml). LAH (150 mg) was added to the soln and the mixture was stirred and heated under reflux for 13 h. After cooling, the excess LAH was destroyed with a few drops of water and the mixture was diluted with ether. Inorganic matters were removed by filtration and the filtrate was concentrated *in vacuo* to give 15 mg of crude **18**, ν_{max} ~ 3300, 1950 (w), 1050 cm^{-1}. Its TLC (silica gel G, EtOAc) revealed presence of two impurities at R_f 0·80, and 0·53 besides the clear spot of **18** at R_f 0·25. This crude allenic alcohol (**18**, 15 mg) was dissolved in acetone (8 ml). To this soln MnO_2 (1·0 g) was added and the mixture was stirred for 8 h at 40–50° and then 12 h at room temp. MnO_2 was filtered off and washed with acetone. The combined filtrate and washings were concentrated *in vacuo* and the residue was purified by preparative TLC (silica gel GF_{254}, EtOAc–C_6H_6, 7:3, R_f 0·24) to give 4 mg of **5**, ν_{max} ~ 3300 (s), 2920 (s), 1935 (m), 1660 (s), 1450 (m), 1360 (m), 1240 (m), 1180 (w), 1150 (m), 1070 (w), 1040 (m), 990 (w), 950 (w), 860 (w), 810 (w), cm^{-1}; δ (100 MHz, $CDCl_3$), 1·17 (3H, s), 1·40 (3H, s), 1·45 (3H, s), 2·19 (3H, s), 4·30 (1H, m), 5·87 (1H, s); CD (*c* = 0·04% in dioxane): $[\theta]_{\sim 300}$ 0; $[\theta]_{253}$ − 7600; $[\theta]_{239}$ 0; $[\theta]_{228}$ + 8400; $[\theta]_{214}$ 0; $[\theta]_{211}$ − 3800; MS: *m/e* 224 ($M^+ = C_{13}H_{20}O_3$). *cf* CD data of fucoxanthin degradation product (**5**): $[\theta]_{255}$ − 11300; $[\theta]_{240}$ 0; $[\theta]_{229}$ + 9830; $[\theta]_{216}$ 0; $[\theta]_{211}$ − 6040. The IR and NMR data are in good accord with the published values of **5**. The CD spectrum was qualitatively in good accord with that of fucoxanthin degradation product.

3β-*Hydroxy*-β-*ionol* (**19**). LAH (0·7 g) was added to a soln of **15** (754 mg) in dry THF (40 ml) and the mixture was stirred and heated under reflux for 15 h under N_2. Then it was poured into ice-cooled 20% Rochelle salt soln and extracted with ether. The ether extract was washed with sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo* to give 520 mg (97%) of **19**, ν_{max} 3300 (s), 1140 (m), 1040 (s), 970 (m), 940 (m), 870 (w) cm^{-1}. This was employed for the next step without further purification.

3β-*Hydroxy*-β-*ionone* (**20a**). DDQ (800 mg) was added to a soln of **19** (518 mg) in dry dioxane (25 ml) under shaking. The resulting dark soln was left to stand overnight at room temp under N_2. The precipitated hydroquinone was removed by filtration. The filtrate was

diluted with an equal volume of CH_2Cl_2 and submitted to filtration chromatography over Woelm neutral alumina (grade I, 30 g, 10 × 2 cm) in CH_2Cl_2. Elution with CH_2Cl_2 (300 ml) gave 487 mg of crude **20a**. This was further purified by chromatography over Woelm neutral alumina (grade II, 15 g, 8 × 1·6 cm) in n-hexane. Elution with n-hexane–ether (4:1) gave 227 mg (44%) of pure **20a**, ν_{max} 3400 (s), 2960 (s), 2920 (s), 2850 (m), 1690 (m, sh), 1670 (s), 1605 (s), 1450 (m), 1370 (s), 1300 (w), 1260 (s), 1200 (w), 1170 (m), 1120 (w), 1050 (s), 980 (m), 950 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) δ 1·09 (3H, s), 1·17 (3H, s), 1·74 (3H, s), 2·24 (3H, s), 3·95 (1H, m), 6·05 (1H, d, J = 16 Hz) 6·97 (1H, d, J = 16 Hz); MS: m/e 208 ($M^+ = C_{13}H_{20}O_2$); $[\alpha]_D^{22}$ − 76·8° (c = 1·08% in $CHCl_3$); TLC (silica gel G, n-hexane–acetone 4:1): R_f 0·22.

2β-Acetoxy-β-ionone (**20b**). Ac_2O (1 ml) was added to a soln of **20a** (217 mg) in dry pyridine (2 ml) and the mixture was left to stand overnight at room temp. Then it was poured into ice-water and extracted with ether. The ether extract was washed with sat $NaHCO_3$ soln and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 205 mg (79%) of **20b**, ν_{max} 1740 (s), 1700 (m), 1680 (s), 1615 (m), 1340 (s), 1250 (vs), 1180 (w), 1150 (w), 1120 (w), 1035 (m), 990 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 1·10 (3H, s), 1·15 (3H, s), 1·74 (3H, s), 2·02 (3H, s), 2·27 (3H, s), 4·98 (1H, $W_{1/2}$ = 15 Hz, Jaa′ = 5 Hz), 6·07 (1H, d, J = 16 Hz), 7·14 (1H, d, J = 16 Hz). These IR and NMR data were identical with those of racemic **20b**.[22]

3β-Acetoxy-5β,6β-epoxy-β-ionone (**21a**) *and 3β-acetoxy-5α,6α-epoxy-β-ionone* (**22a**). A soln of *m*-chloroperbenzoic acid (210 mg) in $CHCl_3$ (2 ml) was added to an ice-cooled soln of **20b** (205 mg) in $CHCl_3$ (1 ml) at 0–5° and the mixture was left to stand overnight in a refrigerator. Then it was diluted with $CHCl_3$, washed with K_2CO_3 soln, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over Mallinckrodt AR 100 mesh silicic acid (14 g, 14 × 1·6 cm) in n-hexane–EtOAc (9:1). Elution with the same solvent system gave the following fractions (80 ml each): No. 3–5: Crude crystalline **21a** (108 mg). This was recrystallized four times from ether–light petroleum to give 40 mg (20%) of pure **21a**. No. 6: A Crystalline mixture of **21a** and **22a** (26 mg). No. 7–9: Crude crystalline **22a** (49 mg). This was recrystallized twice from ether–light petroleum to give 13 mg (6·4%) of pure **22a**. The cis-*epoxide* (**21a**) crystallized from ether–light petroleum as prisms, m.p. 110–111°, ν_{max} 1735 (s), 1675 (s), 1380 (m), 1270 (m), 1250 (s), 1240 (s, sh), 1200 (w), 1180 (w), 1160 (w), 1140 (w), 1120 (w), 1070 (w), 1035 (m), 1000 (w), 990 (w), 980 (w), 970 (w), 950 (w), 935 (w), 920 (w), 900 (w), 805 (w), 730 (w), 700 (w) cm^{-1}; δ (100 MHz, CCl_4) 0·97 (3H, s), 1·15 (3H, s), 1·27 (3H, s), 1·92 (3H, s), 2·17 (3H, s), 4·75 (1H, m), 6·15 (1H, d, J = 16 Hz), 6·79 (1H, d, J = 16 Hz); λ_{max} (EtOH) 230 nm (ϵ 12900); CD (c = 0·026% in MeOH): $[\theta]_{231}$ + 22500; $[\alpha]_D^{22}$ + 3·7° (c = 0·6% in $CHCl_3$). (Found: C, 67·87; H, 8·33. $C_{15}H_{22}O_4$ requires: C, 67·64; H, 8·33%). The *trans*-epoxide (**22a**) crystallized from ether–light petroleum as rhombs, m.p. 125–126°. The mixture m.p. with Dr. Burden's authentic sample was 124–125°. The synthetic material showed the following spectral properties which were entirely identical with those of Dr. Burden's violaxanthin degradation product: ν_{max} 1730 (s), 1670 (s), 1660 (m), 1630 (w), 1380 (m), 1370 (m), 1300 (w), 1270 (s), 1250 (s), 1240 (m), 1220 (w), 1180 (w), 1160 (w), 1130 (w), 1060 (w), 1040 (m), 1030 (m), 985 (m), 960 (w), 950 (w), 920 (w), 900 (w), 870 (w), 805 (w), 750 (w), 720 (w), 690 (w) cm^{-1}; δ (100 MHz, CCl_4) 0·96 (3H, s), 1·15 (3H, s), 1·18 (3H, s), 1·92 (3H, s), 2·17 (3H, s), 4·75 (1H, m), 6·18 (1H, d, J = 16 Hz), 6·85 (1H, d, J = 16 Hz); λ_{max} (EtOH) 230 nm (ϵ 11800); CD (c = 0·039% in MeOH): $[\theta]_{232}$ − 34300; $[\alpha]_D^{22}$ − 90·2° (c = 0·41% in $CHCl_3$). (Found: C, 67·69; H, 8·37. $C_{15}H_{22}O_4$ requires: C, 67·64; H, 8·33%). CD of Dr. Burden's sample (c = 0·031% in MeOH): $[\theta]_{232}$ − 34700.

(S)-(+)-Dehydrovomifoliol (**6**) *and* (R)-(−)-*dehydrovomifoliol* (**23**)

(*a*) *Compound* **6** *from* **22a**. The (−)-*trans*-epoxide (**22a**, 12 mg) was dissolved in 5% KOH in MeOH (1 ml) and the resulting soln was left to stand overnight at room temp. Then it was concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with sat NaCl aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue spontaneously crystallized to give crude **22b** (10 mg), m.p. 55–56°, ν_{max} 3500, ~ 3300, 1660, 1380, 1180, 1150, 1050, 1030, 975, 910 cm^{-1}. This, without further characterization, was dissolved in dry pyridine (0·5 ml) and added to the Sarett reagent prepared from CrO_3 (50 mg) in dry pyridine (0·5 ml). The mixture was left to stand overnight at room temp. Then it was poured into water and extracted with ether. The ether extract was washed with water and sat NaCl aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over Mallinckrodt AR 100 mesh silicic acid (0·4 g, 3 × 0·6 cm) in C_6H_6. Elution with C_6H_6–ether (1:1) gave 6 mg (60%) of pure **6**, as an oil, ν_{max} ~ 3400 (s), 2950 (m), 1660 (vs), 1430 (m), 1360 (s), 1320 (m), 1260 (s), 1220 (w), 1180 (w), 1135 (m), 1080 (w), 1030 (w), 995 (m), 920 (w), 880 (w), 840 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 1·02 (3H, s), 1·10 (3H, s), 1·87 (3H, d, J = 1·5 Hz), 2·26 (1H, d, J = 17 Hz), 2·50 (1H, d, J = 17 Hz), 2·60 (1H, br. s), 5·92 (1H, s), 6·42 (1H, d, J = 16 Hz), 6·82 (1H, d, J = 16 Hz); λ_{max} (MeOH) 237 nm (ϵ 18500); MS: m/e 222 ($M^+ = C_{13}H_{18}O_3$); $[\alpha]_D^{21}$ + 266·3° (c = 0·3% in $CHCl_3$) (lit[10] $[\alpha]_D$ + 159° or + 172°); CD (c = 0·0006% in MeOH): $[\theta]_{320}$ − 7400; $[\theta]_{243}$ + 150000; $[\theta]_{209}$ − 110000. (lit[7] $[\theta]_{320}$ − 7500; $[\theta]_{242}$ + 127000; $[\theta]_{208}$ − 99600. lit[10] $[\theta]_{318}$ − 6400; $[\theta]_{240}$ + 91000); TLC (silica gel G, ether): R_f 0·43.

(*b*) *Compound* **23** *from* **21a**. The (+)-*cis*-epoxide (**21a**, 23 mg) was treated in the same manner as described above to give 15 mg (80%) of **23** as an oil whhich showed the same IR, NMR, UV and mass spectra as those of **6**, $[\alpha]_D^{21}$ − 229·3° (c = 0·3% in $CHCl_3$); CD (c = 0·007% in MeOH): $[\theta]_{320}$ + 7900; $[\theta]_{243}$ − 120000; $[\theta]_{209}$ + 79000.

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