Tetrahedron. Vol. 26, pp. 5699 to 5706. Pergamon Press 1970. Printed in Great Britain

TOTAL SYNTHESIS OF (±)-MARMIN AND RELATED COUMARIN MONOTERPENES*

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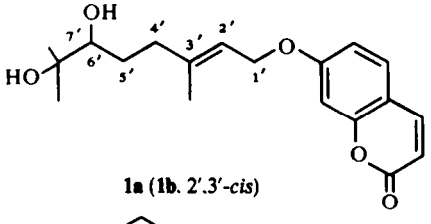
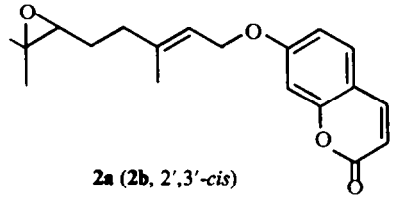
(*Received in the USA* 16 *July* 1970; *Received in the UK for publication* 28 *July* 1970)

Abstract—(±)-Marmin (**1a**) and its *cis* isomer (**1b**) have been synthesized from 7-geranyloxycoumarin (**10a**) and 7-neryloxycoumarin (**10b**), respectively, by way of the corresponding terminal epoxides **2a** and **2a**. The geometrically and positionally specific route confirms the structure and, in particular, the *trans* double bond geometry of natural (+)-marmin and epoxide (+)-**2a**. The latter, upon reaction with stannic chloride in benzene gives rise to the naturally occurring cyclic monoterpene coumarin types **3** and **6** as well as the previously unknown double-bond isomer **13**.

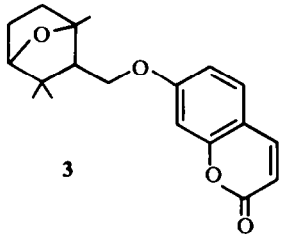
MARMIN is an hydroxylated terpenyl coumarin which has been isolated from the trunk bark of *Aegle marmelos* Correa[1a] and grapefruit (*Citrus paradisi Macf.*) peel oil.[1b, 2] Degradative and spectroscopic evidence have established the structure as **1**, i.e. 7-[(6′,7′-dihydroxy-3′,7′-dimethyl-2′-octenyl)oxy]coumarin.[2, 3] The geometry about the double bond has been suggested to be *trans* (**1a**) rather than *cis* (**1b**) on the basis of fine splitting of the 2-vinyl hydrogen in the NMR spectrum.[2] However, without the *cis* isomer for comparison, this geometrical assignment must be regarded as tentative.



1a (**1b**. 2′,3′-*cis*)



2a (**2b**, 2′,3′-*cis*)



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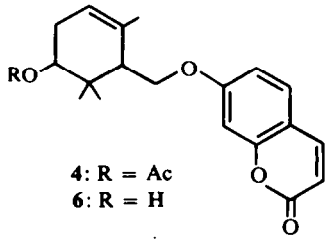
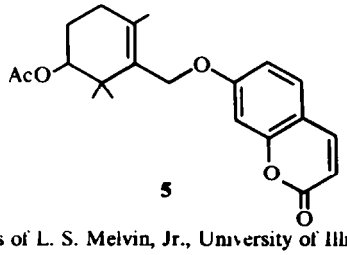


4: R = Ac
6: R = H



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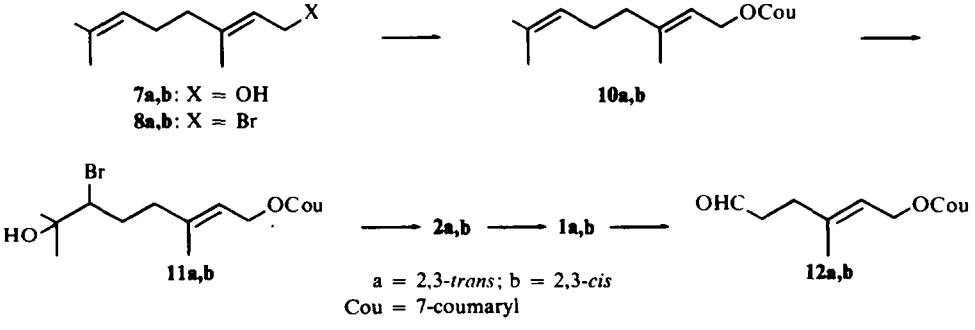
* Taken in part from B.S. thesis of L. S. Melvin, Jr., University of Illinois (1969).
† National Science Foundation undergraduate research participant, summer (1968).

The corresponding epoxide **2a** and the biogenetically related cyclic monterpene coumarins **3**, **4**, and **5** have recently been isolated from various Aster species.[4] This family of sesquiterpenes bears a close resemblance to the farnesiferols, a group of sesquiterpene coumarins.[5] In this paper we report a synthesis of marmin (**1a**), epoxide **2a**, and the cyclic terpenyl coumarins **3** and **6**, following the biogenetic-type synthesis of the farnesiferols.[6]

In order to provide unequivocal evidence concerning the 2',3- double bond configuration in marmin and epoxide **2a**, we have synthesized both isomer pairs **1a,b** and **2a,b** by means of parallel routes from 7-geranyloxycoumarin **10a** (auraptene), a well known naturally occurring coumarin,[7] and the previously unknown 7-neryloxycoumarin **10b**. Although the synthesis of **10a** has been reported in the lit,[8, 9] the yield was low (5–11%); consequently the *trans* assignment for the 2',3' double bond,[8] having been based in large measure upon this synthesis, becomes open to question.

We have prepared 7-geranyloxycoumarin in 63% yield by the reaction of geranyl bromide (**8a**), obtained from geraniol (**7a**)* and phosphorous tribromide,[10] with the sodium salt of umbelliferone (**9**, 7-hydroxycoumarin) in DMF at room temperature, conditions known to result in improved yields and an overall geometrically specific sequence.[6, 10] 7-Neryloxycoumarin (**10b**) is similarly produced from neryl bromide in 52% yield. The distinct m.ps (65–67° and 54–56°), depressed mixed m.p. (40–49°), slight differences in the NMR spectra (Table 2), and the relatively high yields affirm that the two products are indeed the *trans* and *cis* isomers, **10a** and **10b** respectively, and that the natural coumarin (lit.[8] m.p. 68°) is represented by **10a**.

The selective hydroxylation of **10a** and **10b** was achieved by a route successfully performed on the higher isoprenylogue umbelliprenin.[6] The key step is the terminal hypobromination method of van Tamelen and Curphey.[11] Upon treatment with N-bromosuccinimide in aqueous 1,2-dimethoxyethane, **10a** and **10b** afforded the *mono*-bromohydrins **11a** (69%) and **11b** (93%) respectively. That predominant reaction had occurred at the terminal double bond is evident from the appearance of two saturated Me groups and one vinyl Me group in the NMR spectrum of each. From **11a** a small amount (15%) of *bis*-bromohydrin was also obtained.



The two bromohydrins are converted to the corresponding epoxides, **2a** and **2b**, by the action of potassium carbonate in methanol. The crystalline *trans* isomer (m.p. 55–57°) was shown to be identical to the natural epoxide (isolated as an oil)[4] by a

* The commercial grade geraniol used consisted of 72% geraniol and 23% of an impurity which is probably citronellol. The 63% yield is based upon the geraniol present and excludes the possibility that the purified product isolated was derived from the impurity.

direct spectral (NMR and IR) comparison.* The terminal glycols are obtained by perchloric acid-catalyzed hydrolysis of the isomeric epoxides in aqueous dioxan. Although it is clear from the method of synthesis, the m.ps (114–117° and 76·5–78°), and mixed m.p. (73–98°) that the two diols **1a** and **1b** are different compounds, their IR and NMR spectra are very similar. The lack of significant differences in the IR spectra is due to the dominant contribution of the coumarin moiety and is observed in the entire series of coumarin derivatives.

The only discernible difference in the 100 MHz NMR of the isomeric glycols is the complexity of the absorption at τ 7·6 from the vinyl methylene group. Whereas the spectrum of the *trans* diol exhibits a complex multiplet ranging from τ 7·5 to 7·9, the spectrum of the *cis* has a clean triplet at τ 7·61 (J = 7 Hz), observable even at 60 MHz. The spectrum of natural marmin, kindly supplied by Dr. H. Nordby, corresponded closely to the general features of the two synthetic diols, and in addition displayed a complexity in the region of τ 7·6 similar to the *trans* isomer.

Unfortunately it was not possible to take advantage of the characteristic m.p. behavior of the synthetic glycols to confirm the *trans* configuration in natural marmin, the synthetic substances being racemic mixtures. Instead, we elected to remove the asymmetric center by oxidative cleavage to the aldehydes **12a** and **12b**. Reaction of the *trans* diol with lead tetraacetate in acetic acid gave rise to the crystalline aldehyde **12a** in 90% yield, m.p. 101–102° (lit.[2] 104·6°). The *cis* isomer produced a liquid aldehyde **12b**. Both aldehydes along with the aldehyde similarly derived from (+)-marmin were transformed into their respective 2,4-dinotrophenylhydrazones. From the m.p. data in Table 1 and the preceding NMR comparison, it is evident that natural marmin has the structure and double bond configuration portrayed in **1a**.

TABLE 1. M.P. DATA FOR DNP DERIVATIVES

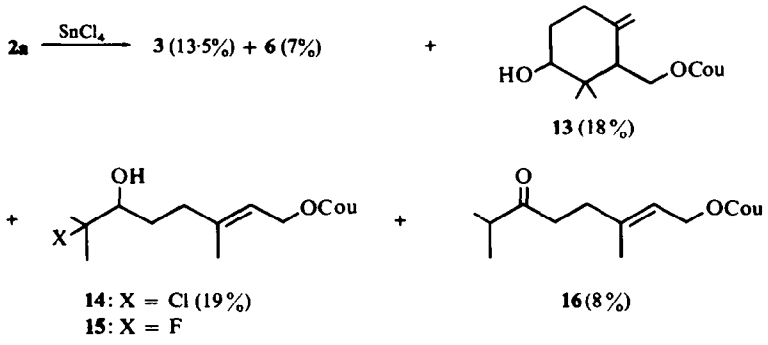
Compound (or Mixture)	M.p. Range
12a-DNP (*trans*)	166°
12b-DNP (*cis*)	202°
Natural-DNP	165–166°
12a-DNP + **12b**-DNP	168–188°
12a-DNP + Natural-DNP	165–166°
12b-DNP + Natural-DNP	161–180°

Treatment of the *trans* epoxide (**2a**) with stannic chloride in benzene affords the mixture of products shown in the scheme below. The structures are based principally upon the NMR data (Table 2) and analogy with similar reactions with umbelliprenin epoxide.[6] An NMR and IR spectral comparison between synthetic and natural cyclic isomers **3** and **6** established their identities. Although synthetic **6** could only be obtained about 80% pure, the coincidence† of the eight line pattern for the $-CH_2O-$ group (as well as all the other major absorptions) in the NMR spectra adds strength to this comparison. The stereochemical relationship between the ether methylene and the other oxygen function in **3**, **6**, and **13** is assigned as *cis* in view of the stereochemistry of

* This comparison was performed on the same instruments by Prof. Bohlmann to whom we are very grateful.

† The chemical shift data originally reported are in error (1 ppm too high field);[4] Prof. Bohlmann private communication.

other similar epoxide cyclizations.[12] The reaction of **2a** with boron trifluoride etherate in benzene produced mainly the acyclic ketone **16** (41%) along with lesser amounts of the fluorohydrin **15** (6·5%) and **13** (3·5%).



14: X = Cl (19%)
15: X = F

16 (8%)

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer Infracord Spectrophotometer (Model 137). Since all the coumarin derivatives exhibited the same characteristic absorption bands (1720, 1610, 1550, 1505, 1400, 1355, 1275, 1230–1215, 1160, 1125, 1000, 895, and 838 cm^{-1}) and very similar spectra overall, only the presence or absence (by omission) of the OH band is indicated. NMR spectra were obtained on Varian A-60, A-60A, and HA-100 instruments. The data are compiled in Table 2. M.ps were determined with a Thomas-Hoover apparatus and are uncorrected.

1-*Bromo*-3,7-*dimethyl*-trans-2,6-*octadiene* (*geranyl bromide*, **8a**)[10]

Procedure A. A soln of 5·01 g (32·5 mmoles) geraniol (Columbia Organic Chemical Co.: 72% geraniol, and 23% of an impurity which is probably citranellol by GLC analysis) and 75 ml pentane was cooled to 0°. A soln of 4·39 g (16·2 mmoles) PBr_3 and 75 ml pentane cooled to 0° was added dropwise over a period of 10 min to the stirred soln of geraniol. After stirring for 30 min the reaction was diluted with 75 ml water and extracted with pentane. The extracts were washed with 5% $NaHCO_3$ aq and sat NaCl aq. Evaporation of the solvent (<25°) gave 5·91 g (84%) of a slightly yellow oil which was stored at −15° for 12 hr before use.

7-[(3′,7′-*Dimethyl*-trans-2′,6′-*octadienyl*)*oxy*]*coumarin* (**10a**)

Procedure B. To a mixture of 738 mg (30·8 mmoles) NaH and 60 ml DMF was added a soln of 4·64 g (28·6 mmoles) of **9** in 50 ml DMF. A soln of 5·91 g (27·2 mmoles) of **8a** and 20 ml DMF was added to the soln of the Na salt of **9**. The reaction was stirred at room temp under N_2 for 6 hr, then it was diluted with water and extracted with 1:1 benzene-hexane. The extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvents yielded 7·32 g crude material. This material was purified by several recrystallizations from hexane and MeOH and column chromatography of the mother liquors (4·08 g) on 120 g silica gel, H/D = 6·2, and elution with 0–40% ether-hexane. The product (3·90 g, 63% based on geraniol present) is a white solid, m.p. 65–67°, lit.[8] 68°. (Found: C, 76·49; H, 7·56. Calc. for $C_{19}H_{22}O_3$: C, 76·48: H, 7·43%).

7-[(6′-*Bromo*-3′,7′-*dimethyl*-7′-*hydroxy*-trans-2′-*octenyl*)*oxy*]*coumarin* (**11a**)

Procedure C. A soln of 2·98 g (9·99 mmoles) of **10a**, 44·6 ml 1,2-dimethoxyethane, and 13·1 ml water was cooled to 5 ± 2°. Over a period of 5 min 2·30 g (12·9 mmoles) N-bromosuccinimide was added to the stirred soln. The reaction was stirred in the dark at 5–12° for 1 hr, diluted with water and extracted with ether. The extracts were washed with water and NaCl aq, and dried over $NaSO_4$. Evaporation of the solvent yielded a viscous oil. Chromatography of the oil (4·47 g) on 179 g of 10% water-silica gel, H/D = 8·7, and elution with 25–100% ether-benzene yielded 2·72 g (69%) of **11a**, m.p. 64–67°, ν_{max}^{film} 3470 cm^{-1}. (Found: C, 57·78; H, 5·91; Br, 19·95. Calc for $C_{19}H_{23}O_4Br$: 57·75; H, 5·86; Br, 20·21%) and 728 mg (15%) of the *bis*-bromohydrin m.p. 124–126° dec. (Found: C, 46·54; H, 4·92; Br, 31·97. Calc for $C_{19}H_{24}O_5Br_2$: C, 46·36; H, 4·91; Br, 32·26%).

TABLE 2. NMR DATA[a]

Compound	$(CH_3)_2C$	$(CH_3)C=$	$-CH_2O-$	$=CHCH_2O-$	$(CH_3)_2CXCHY-$	Other
10a	8·33, 8·40	8·23	5·41 (d, 6·5)	4·53 (t, 6·5)	$(CH_3)_2C=CH-$ 4·91 (b)	$-(CH_2)_2-$ 7·86, 7·91 (1·5:2·5)[b]
10b	8·33, 8·39	8·20	5·48 (d, 6·5)	4·56 (t, 7)	$(CH_3)_2C=CH-$ 4·92 (b)	$-(CH_2)_2-$ 7·86, 7·90 (2·5:1·5)[b]
11a	8·67	8·22	5·39 (d, 6·5)	4·44 (t, 7)	6·07 (2d, 3, 9)	
11b	8·63	8·19	5·38 (d, 6·5)	4·43 (t, 6·5)	6·06 (2d, 3, 9)	
2a	8·70, 8·72	8·21	5·39 (d, 6·5)	4·48 (t, 6·5)		 CH 7·29 (t, 6·0)
2b	8·69, 8·72	8·15	5·38 (d, 6·5)	4·41 (t, 6·5)		 CH 7·25 (t, 6·0)
1a	8·76, 8·78	8·17	5·32 (d, 6·5)	4·40 (t, 6)	6·58 (2d, 3, 9)	$-CH_2(CH_3)C=$ 7·66 (m)
1b	8·75, 8·78	8·14	5·29 (d, 6·5)	4·40 (t, 6)	6·57 (2d, 3, 10)	$-CH_2(CH_3)C=$ 7·61 (t, 7)
(+)-marmin	8·73, 8·78	8·16	5·33 (d, 6·5)	4·40 (t, 6)	6·58 (2d, 3, 9)	$-CH_2(CH_3)C=$ 7·65 (m)
12a		8·21	5·40 (d, 6·5)	4·50 (t, 7)		H—C(=O)— 0·12 (t, 2)
(±)-**3**	8·84, 8·92		6·01 (d, 7·5)		6·20 (d, 4)	$CH_3-C(=O)-O$, 8·60
(±)-**6**	8·90	8·20	5·56, 5·82 (2d, 10, 4)		6·45 (t, 5)	=CH—, 4·46 (m)
13	8·93, 8·99		5·78 (d, 6·5)	7·09 (t, 6·5)	6·45 (b)	$=CH_2$, 5·39, 5·02 (b)
14	8·42, 8·45	8·22	5·39 (d, 6·5)	4·48 (t, 6·5)	6·52 (2d, 3, 9)	
15	8·68 (d, 22)	8·24	5·42 (d, 6·5)	4·49 (t, 6·5)		
16	8·90 (d, 7)	8·22	5·43 (d, 6·5)	4·53 (t, 7)		

[a] The coumarin ring in all cases show characteristic absorptions at 3·77 (d, 9·5, 1 H); 3·13 (m, 2 H); 2·62 (d, 9·0, 1 H); 2·36 (d, 9·5, 1 H). The NMR spectra were run in $CDCl_3$ or CCl_4 with TMS, as internal standard. Chemical shifts are τ values. Within parenthesis d = doublet, t = triplet, m = multiplet, b = broad and the numbers are coupling constants in Hz. All spectra were recorded at 60 MHz, except for **1a**, **1b**, and (+)-marmin which were obtained at 100 MHz.

[b] Approximate ratio.

7-[(3,7-*dimethyl*-6-*epoxy*-trans-2-*octenyl*)*oxy*]*coumarin* (**2a**)

Procedure D. To a soln of 1·31 g (3·31 mmoles) of **11a** in 35 ml MeOH was added 515 mg (3·72 mmoles) K_2CO_3. This mixture was stirred for 30 min under N_2. The reaction was then diluted with water and extracted with ether. The water phase was neutralized with ammonium chloride and again extracted with ether. The extracts were dried over Na_2SO_4 and the solvent evaporated leaving an oil which crystallized at $-15°$ to a white solid. Recrystallization from ether and chromatography of the material recovered from the mother liquors (322 mg) on 16 g of silica gel (H/D = 7·1) and elution with 70% benzene-ether gave 821 mg (79%) of (±)-**2a**, m.p. 55·3–57·5°. (Found: C, 72·68; H, 7·31. Calc. for $C_{19}H_{22}O_4$: C, 72·59; H, 7·05%). The NMR and IR spectra of this material are identical with those of the natural epoxide (comparison by Prof. Bohlmann).[4]

7-[(6',7'-*Dihydroxy*-3',7'-*dimethyl*-trans-2'-*octenyl*)*oxy*]*coumarin* ((+)-*marmin*, **1a**)

Procedure E. To a soln of 516 mg (1·64 mmoles) of **2a** in 9 ml dioxan was added 4·5 ml 3% perchloric acid; the soln was then stirred for 30 min. The reaction was diluted with water and extracted with chloroform. The extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a white solid which upon recrystallization from EtOAc at $-15°$ gave 459 mg (84%) of (±)-**1a**, m.p. 114–117° (lit.[2] m.p. 125° for (+)-marmin), $\nu_{max}^{CHCl_3}$ 3540 cm^{-1}. (Found: C, 68·41; H, 7·04. Calc. for $C_{19}H_{24}O_5$: C, 68·66; H, 7·28%).

1-*Bromo*-3,7-*dimethyl*-cis-2,6-*octadiene* (*neryl bromide*, **8b**)

Commercial nerol (Givaudan Corp.) was first purified by column chromatography on silica gel to remove contaminating geraniol. Nerol (5·02 g, 32·5 mmoles, 98·5% purity by GLC analysis) was treated with 4·45 g (16·4 mmoles) PBr_3 in light petroleum (30–60°) as described in procedure A. The resulting slightly yellow liquid (6·62 g, 94%) was used immediately.

7-[(3',7'-*Dimethyl*-cis-2',6'-*octadienyl*)*oxy*]*coumarin* (**10b**)

With procedure B, 6·62 g (30·5 mmoles) neryl bromide, 5·19 g (32·0 mmoles) 7-hydroxycoumarin and 800 mg (33·5 mmoles) NaH were allowed to react for 18 hr. The crude product was recrystallized from ether-hexane and the material recovered from the mother liquors (3·49 g) chromatographed on 140 g silica gel (H/D = 3·6) eluting with 10–20% ether-hexane: yield 4·66 g (52%) of **10b** m.p. 54–56°. (Found: C, 76·26; H, 7·19. Calc. for $C_{19}H_{22}O_3$: C, 76·48; H, 7·43%).

7-[(6'-*Bromo*-3',7'-*dimethyl*-7'-*hydroxy*-cis-2'-*octenyl*)*oxy*]*coumarin* (**11b**)

With procedure C, 3·03 g (10·1 mmoles) of **10b** and 2·26 g (12·7 mmoles) N-bromosuccinimide were allowed to react for 1·5 hr at 5 ±2° in the dark. The resulting viscous oil (4·26 g) was chromatographed on 160 g of 10% water-silica gel, H/D = 3·8; elution with 10–20% ether-benzene afforded 3·62 g (93%) of **11b** as a viscous oil (ν_{max}^{film} 3560 cm^{-1}) which could not be crystallized. (Found: C, 57·99; H, 5·74; Br, 20·18. Calc. for $C_{19}H_{23}O_4Br$: C, 57·75; H, 5·86; Br, 20·21%). No *bis*-bromohydrin was found.

7-[(3',7'-*Dimethyl*-6'-*epoxy*-cis-2'-*octenyl*)*oxy*]*coumarin* (**2b**)

With procedure D, 1·72 g (4·34 mmoles) of **11b** and 667 mg (4·84 mmoles) anhyd K_2CO_3 were allowed to react for 45 min. Recrystallization of the product from ether-hexane gave 1·23 g (91%) of **2b**, m.p. 66·5–67·5°. (Found: C, 72·47; H, 7·00. Calc. for $C_{19}H_{22}O_4$: C, 72·59; H, 7·05%).

7-[(6',7'-*Dihydroxy*-3',7'-*dimethyl*-cis-2'-*octenyl*)*oxy*]*coumarin* ((±)-cis-*marmin*, **1b**)

The epoxide **2b**, (730 mg, 2·32 mmoles), 6 ml dioxan, and 5 ml of 3% perchloric acid were allowed to react according to procedure E. The oily product was crystallized at $-20°$ from ether to give 717 mg (93%) of **1b**, m.p. 76·5–78°, $\nu_{max}^{CHCl_3}$ 3350 cm^{-1}. (Found: C, 68·63; H, 7·20. Calc. for $C_{19}H_{24}O_5$: C, 68·66; H, 7·28%).

7-[(3'-*Methyl*-6'-*oxo*-trans-2'-*hexenyl*)*oxy*]*coumarin* (**12a**)

To a soln of 164 mg (0·495 mmoles) of **1a** in 6·5 ml AcOH was added 241 mg (0·545 mmoles) lead tetraacetate.[2] The reaction was stirred for 18 hr and then diluted with water, neutralized with $NaHCO_3$, and extracted with chloroform. The extracts were washed with $NaHCO_3$ aq and water and the solvent evaporated leaving an oil. The oil was crystallized at $-15°$ from yielding 121 mg (90%) of **12a**, m.p. 101–102°, lit.[2] m.p. 104·6°. (Found: C, 70·63; H, 5·96. Calc. for $C_{16}H_{16}O_4$: C, 70·58; H, 5·92%).

7-[(3'-Methyl-6'-oxo-cis-2'-hexenyl)oxy]coumarin (**12b**)

To a soln of 115 mg (0·346 mmoles) of **1b** in 3 ml AcOH was added 245 mg (0·554 mmoles) lead tetraacetate. The reaction was stirred in the dark for 1 hr, and then neutralized with $NaHCO_3$. The resulting mixture was extracted with EtOAc. The extracts were washed with water, dried over Na_2SO_4 and the solvent removed leaving a colorless oil. This oil could not be crystallized and due to its instability was stored at −15°. The oil was homogeneous on TLC and had identical R_f values and spectra with **12a**

Aldehyde of (+)-marmin

To a soln of 41·1 mg (0·124 mmoles) (+)-marmin in 1·1 ml AcOH was added 68·7 mg (0·155 mmoles) lead tetraacetate. The reaction was stirred for 1 hr, and then neutralized with $NaHCO_3$. The resulting mixture was extracted with EtOAc. The extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvents gave 33·7 mg (100%) white solid.

The 2,4-dinitrophenylhydrazone[13] of the aldehyde is a yellow-orange powder, m.p. 165–166°, lit.[2] 153·5°. (Found: C, 58·53; H, 4·52; N, 12·41. Calc. for $C_{22}H_{20}O_7N_4$: C, 58·41; H, 4·46; N, 12·38%).

2,4-Dinitrophenylhydrazones of **12a** *and* **12b**. The derivative of **12a** is a yellow-orange powder, m.p. 166°. (Found: C, 58·55; H, 4·54; N, 12·37. Calc. for $C_{22}H_{20}O_7N_4$: C, 58·41; H, 4·46; N, 12·38%). The derivative of **12b** is a yellow-orange powder, m.p. 202°. (Found: C, 58·56; H, 4·52; N, 12·50. Calc. for $C_{22}H_{20}O_7N_4$: C, 58·41; H, 4·46; N, 12·38%).

Reaction of stannic chloride with 7-[(3',7'-dimethyl-6'-epoxy-trans-2'-octenyl)oxy]coumarin (**2a**)

Stannic chloride (1·99 g, 7·63 mmole) was rapidly injected into a soln of 1·98 g (6·31 mmoles) of **2a** and 100 ml dry benzene at room temp and under N_2. The reaction was stirred for 70 sec and poured into 300 ml of 1:1 water:ether. The resulting mixture was shaken until the yellow color disappeared. The ether fraction was washed with water and sat NaCl, and dried over Na_2SO_4.

The residue after evaporation of the ether was applied to a 500 g column silica gel (H/G, 6·2). After initial elution with 2 l pentane, elution was continued with 40% ether-pentane collecting 20 ml fractions at 3 min intervals. Every fifth fraction was analyzed by TLC and then appropriate fractions were combined. Fractions 121–210 afforded a mixture (451 mg) composed mainly of the oxide (**3**, 62%) and the acyclic ketone (**16**, 33%) according to NMR analysis. Crystallization from ether-pentane yielded pure (±)-**3** (180 mg); m.p. 155–156°. (Found: C, 72·70; H, 7·06. Calcd. for $C_{19}H_{22}O_4$: C, 72·59; H, 7·05%). The NMR and IR spectra correspond to those of natural (−)-**3**, m.p. 187° (see discussion section).[4]

Fractions 220–240 yielded a mixture mixture (135 mg) of **14** (57%) and the exocyclic alcohol **13** (43%) and fractions 241–300 gave 764 mg of a mixture of **14** (42%) and **13** (48%), according to NMR analysis. Crystallization of the latter mixture from ether-pentane at 0° afforded 261 mg of **13**: m.p. 137–138°, ν_{max} 3540 cm^{-1}. (Found: C, 72·77; H, 6·95. Calcd. for $C_{19}H_{22}O_4$: C, 72·59; H, 7·05%). The chlorohydrin (**14**) was obtained in a state of 75% purity (the remainder being **13**) by evaporation of the mother liquor.

Fractions 331–360 (93 mg) and 361–420 (82 mg) contained mainly (±)-**6** in purity estimated at 78% and 76% respectively by means of NMR analysis. This material was further purified by preparative TLC (silica gel GF, 1:1 EtOAc-pentane and 3:7 EtOAc-chloroform). However, small amounts of impurities were not removed, thus (±)-**6** could be obtained in at best about 80–85% purity. However, a 100 MHz NMR spectral comparison with natural **6** established its identity (see discussion section).[4]

The total product distribution as estimated from NMR analysis of the preceeding combined fractions are as follows: (±)-**3** (13·5%), **16** (8%), **14** (19%), **13** (18%), and (±)-**6** (7%).

Reaction of boron trifluoride etherate with 7-[(3',7'-dimethyl-6'-epoxy-trans-2'-octenyl)oxy]coumarin (**2a**)

The reaction was performed exactly as with stannic chloride using 1·93 g (6·13 mmole) of **2a** in 100 ml dry benzene and 1·04 g (7·36 mmole) BF_3-etherate. The crude product (isolated as above) was chromatographed on 100 g silica gel (H/D = 5·1) eluting 20 ml fractions with 60% ether-pentane. Fractions 15–19 yielded 349 mg of **16** which after recrystallization had m.p. 79·5–80·5°. (Found: C, 72·51; H, 7·02. Calcd. for $C_{19}H_{22}O_4$: C, 72·59; H, 7·05%).

Fractions 11–14 and 20–29 were combined (1·1 g) and rechromatographed as before with 120 g of silica gel (H/D = 6·2) eluting with 40% ether-pentane. Fractions 29–38 contained 293 mg of **16** while fractions 39–46 (196 mg) contained mixtures of **15** and **16**. Fractions 48–58 afforded either mixtures of **15** and **13** or pure **13**. By means of crystallization 40 mg of **13** was isolated. The fluorohydrin **15** was obtained in about 80% purity (the remainder being **13**) from certain fractions and its structure assigned on the basis of the NMR data in Table 2.

The final product distribution, as estimated from fraction weights and NMR analysis, was **16** (41%), **15** (6·5%), and **13** (3·5%).

Acknowledgement—The authors wish to thank the National Science Foundation and the National Institutes of Health for partial support of this research, Dr. H. Nordby of the Fruit and Vegetable Products Laboratory (Winter Haven, Florida) for a generous sample of (+)-marmin, and Professor F. Bohlmann for the spectral comparisons.

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