Configuration of 1,10-Epoxyguaianolides: Stereochemistry of 1,10-Epoxy-8α-hydroxyachillin[1]

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The stereochemistry of 1,10-epoxy-8α-hydroxyachillin (**2a**) has been established on the basis of its chemical transformation into 8α-acetoxy-1,10β-epoxy-3,4-dihydroachillin (**7b**), together with the indirect conversion of 8α-acetoxyachillin (**3a**) into the 8α-acetoxy-1,10β- and -α-epoxy-3,4-dihydroachillins (**7b**) and (**7a**). The structure of the latter compound has been determined by *X*-ray analysis.

Among the various types of sesquiterpene lactones from higher plants, the guaianolides are some of the most characteristic.[2] Oxirane rings are almost exclusively encountered as functional groups in guaianolides belonging to the tribes *Anthemideae*, *Eupatorieae*, *Veronieae*, and *Carduceae* (Compositae family).

^{1}H N.m.r. studies for stereochemical assignment of oxirane rings in this type of sesquiterpene lactone have been widely employed.[3] However, there are limitations in the use of such ^{1}H n.m.r. methods[4] and the conclusions derived from them must be treated with caution.

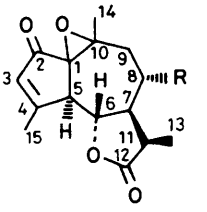
In previous work,[5] the structural elucidation of 1,10-epoxy-8α-hydroxyachillin (**1a**), a guaianolide isolated as its acetate (**1b**) from *Artemisia lanata* Willd, was described. Its structure was determined from chemical and spectral methods, but the stereochemistry of the epoxy group was not established. On the other hand, Mabry and co-workers[6] isolated from *Artemisia frigida* Willd a compound for which they proposed the structure (**1a**), with an α C-1, C-10 epoxy group, on biogenetic grounds. The acetate of this compound has the same physical and spectroscopic data as compound (**1b**).

Attempts to correlate chemically compound (**1a**) with 1,10-epoxyachillin (**2b**), whose stereochemistry at the epoxide is established,[7] were unsuccessful (see Experimental section). In view of the above facts, the object of this work was to settle definitively the total stereochemistry of compound (**1a**) by chemical correlation.

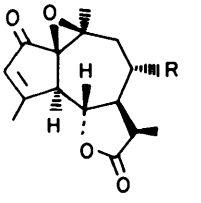
The starting material was the acetate of 8α-hydroxyachillin, (**3a**), a relatively abundant component of *Artemisia lanata*. Selective hydrogenation of compound (**3a**) gave the dihydro derivative (**4**), m.p. 108—110 °C (Scheme). The ^{1}H n.m.r. spectrum showed the characteristic triplet (*J* 10 Hz) of the lactonic proton at δ 3.97, and four methyl signals: acetate, C-4, C-10, and C-11 methyls. The α stereochemistry of the C-4 methyl group was deduced from the coupling $J_{4,5}$ 4 Hz. Epoxidation (alkaline hydrogen peroxide) of the C-1,C-10 double bond in compound (**4**) proceeded in very low yield. Thus, in order to permit attack of the double bond by peracids, compound (**4**) was allowed to react with sodium borohydride in the presence of cerium(III) chloride[7] to give the allylic alcohols (**5a**) (major compound) and (**5b**).

Lactone (**5a**), m.p. 136—137 °C, showed in its ^{1}H n.m.r. spectrum a signal for an allylic proton on a carbon bearing an oxygen atom, at δ 4.75, and a shift of the signal corresponding to the C-10 methyl group (+0.33 p.p.m.). Alcohol (**5b**), m.p. 148—149 °C, was obtained in low yield. In the ^{1}H n.m.r. spectrum, the signal corresponding to 6-H is clearly deshielded (+0.25 p.p.m.) with respect to the same signal in (**5a**), and thus accords with a β-OH group in (**5b**).[8] This suggests that compounds (**5a**) and (**5b**) are epimeric alcohols at C-2.

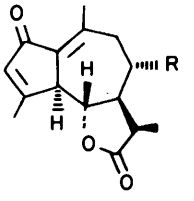
Epoxidation of enol (**5a**) with *m*-chloroperbenzoic acid



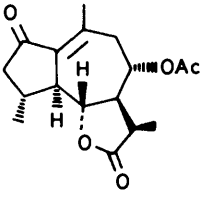
(1) a; R = OH
b; R = OAc
c; R = OMs



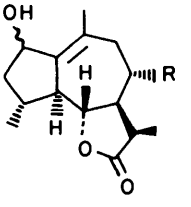
(2) a; R = OH
b; R = H
c; R = OAc



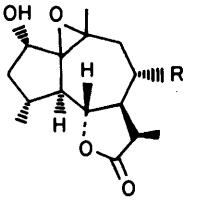
(3) a; R = OAc
b; R = H



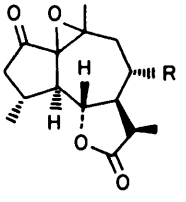
(4)



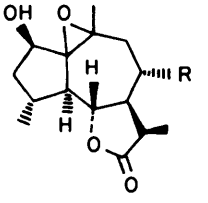
(5) a; C-2 α-OH ; R = OAc
b; C-2 β-OH ; R = OAc
c; C-2 β-OH ; R = H



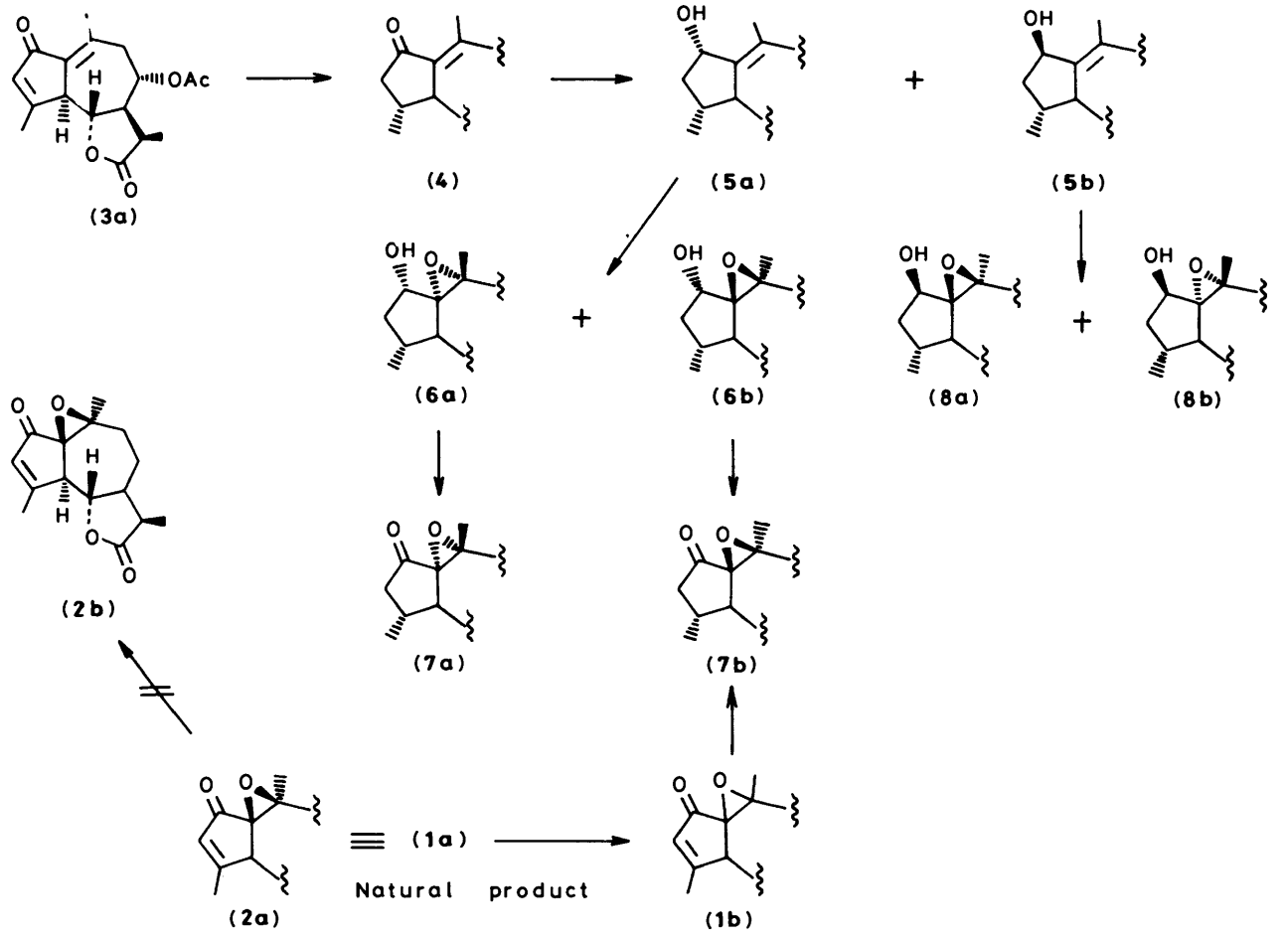
(6) a; α-epoxide; R = OAc
b; β-epoxide; R = OAc
c; α-epoxide; R = H
d; β-epoxide; R = H



(7) a; α-epoxide; R = OAc
b; β-epoxide; R = OAc
c; α-epoxide; R = H
d; β-epoxide; R = H



(8) a; β-epoxide; R = OAc
b; α-epoxide; R = OAc
c; β-epoxide; R = H
d; α-epoxide; R = H



Scheme.

(MCPBA) gave the epoxides (**6a**), m.p. 151—152 °C (major compound), and (**6b**), m.p. 243—245 °C (Scheme).

The ^{1}H n.m.r. spectrum of compound (**6b**) was very similar to that of compound (**6a**), except for the lactonic proton 6-H which appeared downfield from the corresponding signal of (**6a**) (+0.20 p.p.m.). Inspection of stereomodels of compounds (**6a**) and (**6b**) showed that the hydroxy group at C-2 in both compounds is situated far from the lactonic proton 6-H. Therefore, the influence of the OH group over the chemical shift of 6-H must be insignificant. The difference of 0.20 p.p.m. found between the 6-H signals in epoxides (**6a**) and (**6b**) can be attributed to the downfield shift caused by the epoxide ring, thus suggesting that the oxirane group in compound (**6b**) must be β.

Chromium trioxide–pyridine oxidation of epoxides (**6a**) and (**6b**) afforded the epoxy ketones (**7a**) and (**7b**) respectively (Scheme).

Compound (**7b**), m.p. 200—202 °C, showed a ^{1}H n.m.r. spectrum very similar to that of (**7a**), m.p. 196—198 °C, and the difference in chemical shift of 6-H in both lactones was very small (0.06 p.p.m.). We have found a wide range of values for this difference (Table 1) on comparison of diastereoisomers of various compounds obtained in the course of our synthesis.

From the above results it can be concluded that, although the criterion based on chemical-shift differences for the lactonic proton can be helpful in predicting the stereochemistry of the oxirane ring in 1,10-epoxyguaianolides,[9–14] the result cannot be used with certainty.

At this stage we succeeded in correlating chemically our natural product with epoxy ketone (**7b**) by hydrogenation of the

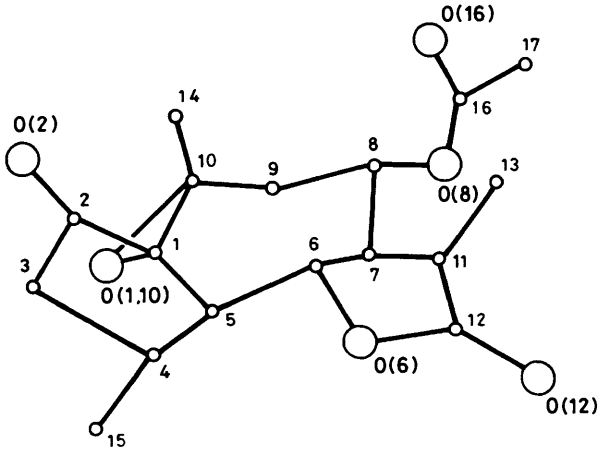


Figure.

natural acetate (**1b**) with chlorotris(triphenylphosphine)rhodium as catalyst, obtaining a compound identical with epoxy ketone (**7b**) (Scheme). Only in the case of epimer (**7a**) we were able to obtain suitable crystals for *X*-ray diffraction analysis.[15] A perspective view is shown in the Figure and the bond lengths (Å) and angles (°) are in Table 2.

The direct transformation of acetate (**1b**) into its reduced derivative (**7b**), together with the indirect conversion of dienone (**3a**) into epoxides (**7a**) and (**7b**), establishes the configuration of

Table 1.

Compd.	δ(6-H)	Δδ	Compd.	δ(6-H)	Δδ
(**6a**)	4.02	0.20	(**7c**)	4.16	0.04
(**6b**)	4.22		(**7d**)	4.20	
(**6c**)	4.08	0.18	(**8a**)	4.23	0.08
(**6d**)	3.90		(**8b**)	4.15	
(**7a**)	4.21	0.06	(**8c**)	4.24	0.16
(**7b**)	4.27		(**8d**)	4.08	

Table 2. Bond lengths (Å) and angles (°) for compound (**7a**); standard deviations are in the ranges 0.004—0.007 Å for distances and 0.3—0.4 for angles

C(1)–C(2)	1.516	C(7)–C(11)	1.531
C(1)–C(10)	1.485	C(11)–C(13)	1.540
C(1)–O(1,10)	1.443	C(11)–C(12)	1.540
C(1)–C(5)	1.536	C(12)–O(12)	1.191
C(2)–C(3)	1.503	C(12)–O(6)	1.361
C(2)–O(2)	1.209	C(8)–C(9)	1.531
C(3)–C(4)	1.529	C(8)–O(8)	1.451
C(4)–C(5)	1.558	O(8)–C(16)	1.359
C(4)–C(15)	1.528	C(16)–O(16)	1.194
C(5)–C(6)	1.522	C(16)–C(17)	1.482
C(6)–C(7)	1.532	C(9)–C(10)	1.517
C(6)–O(6)	1.456	C(10)–C(14)	1.515
C(7)–C(8)	1.511	C(10)–O(1,10)	1.448
C(2)–C(1)–C(5)	106.6	O(12)–C(12)–C(11)	129.9
C(2)–C(1)–O(1,10)	114.2	C(12)–C(11)–C(13)	110.6
C(5)–C(1)–C(10)	125.3	C(12)–C(11)–C(7)	101.2
C(10)–C(1)–C(2)	123.8	C(13)–C(11)–C(7)	116.1
C(10)–C(1)–O(1,10)	59.2	C(11)–C(7)–C(8)	117.8
C(1)–C(2)–C(3)	107.8	C(6)–C(7)–C(8)	112.8
C(1)–C(2)–O(2)	125.3	C(11)–C(7)–C(6)	101.3
C(3)–C(2)–O(2)	126.7	C(7)–C(8)–C(9)	111.3
C(2)–C(3)–C(4)	103.3	C(7)–C(8)–O(8)	104.7
C(3)–C(4)–C(5)	103.5	O(8)–C(8)–C(9)	108.3
C(3)–C(4)–C(15)	111.4	C(8)–O(8)–C(16)	116.8
C(5)–C(4)–C(15)	110.4	O(8)–C(16)–C(17)	111.4
C(4)–C(5)–C(1)	103.7	O(8)–C(16)–O(16)	122.5
C(4)–C(5)–C(6)	111.2	O(16)–C(16)–C(17)	126.0
C(6)–C(5)–C(1)	109.4	C(8)–C(9)–C(10)	113.0
C(5)–C(6)–O(6)	108.9	C(1)–C(10)–C(14)	122.1
C(5)–C(6)–C(7)	115.5	C(9)–C(10)–C(1)	119.7
O(6)–C(6)–C(7)	102.7	C(9)–C(10)–C(14)	114.5
C(6)–O(6)–C(12)	110.0	C(14)–C(10)–O(1,10)	115.1
O(6)–C(12)–C(11)	109.4	O(1,10)–C(10)–C(1)	58.9
O(6)–C(12)–O(12)	120.7	C(10)–O(1,10)–C(1)	61.8

our natural product (**2a**). Since 8α-acetoxy-1,10-epoxyachillin (**2c**) was identical with the acetate of the natural product isolated by Mabry and co-workers,[6] the configuration of the epoxide group in the latter compound must be β.

Experimental

M.p.s are determined with a Kofler hot-plate apparatus and are uncorrected. I.r. spectra were recorded on a Digilab FTS-IMX spectrometer in solution using $CHCl_3$, n.m.r. spectra on a Hitachi-Perkin-Elmer H-24B (60 MHz) or a Varian FT-80A spectrometer using Me_4Si as internal standard, and mass spectra on a VG-Micromass ZAB-2F spectrometer. For column chromatography the silica gel was Merck (0.06—0.2 mm). Preparative (thickness 2 mm) t.l.c. were carried out on silica gel Merck (60G). Spots were revealed by spraying with 'oleum' (H_2SO_4–H_2O–AcOH, 4:16:80) and heating at 100 °C.

Attempted Correlation of 1,10-*Epoxy*-8α-*hydroxyachillin* (**1a**) *with* 1,10-β-*Epoxyachillin* (**2b**).—(a) The lactone (**1a**) (30 mg) was dissolved in the minimum quantity of dry pyridine (0.5 ml), and mesyl chloride (30 mg) was added to the solution at 0 °C. The mixture was kept at room temperature for 24 h. The usual work-up and column chromatography [benzene–ethyl acetate (8:2) as eluant] gave the mesyl derivative (**1c**) (20 mg) as an oil, δ_H ($CDCl_3$; 60 MHz) 6.24 (1 H, br 3-H), 4.85 (1 H, dt, *J* 3 and 10 Hz, 8-H), 4.25 (1 H, t, *J* 10 Hz, 6-H), 3.40 (1 H, d, *J* 10 Hz, 5-H), 3.10 (3 H, s, SMe), 2.45 (3 H, s, 4-Me), 1.70 (3 H, s, 10-Me), and 1.25 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 340 (M^+, 3%).

(b) The mesyl ester (**1c**) (50 mg) and activated zinc[16] (50 mg) were heated under reflux in 1,2-dimethoxyethane (3 ml) for 1.5 h. Usual work-up and column chromatography of the residue (25 mg) afforded lactone (**3b**) instead of the expected epoxy ketone (**2a**).

Selective Hydrogenation of 8α-*Acetoxyachillin* (**3a**).—A solution of the lactone (**3a**) (1 g) in a 1:1 mixture of benzene–ethyl acetate containing $[(C_6H_5)_3P]RhCl$ was stirred for 1.5 h under hydrogen. The reaction mixture was chromatographed [silica gel; benzene–ethyl acetate (8:2) as eluant] to give the dihydro derivative (**4**) (420 mg), which was crystallized from n-hexane–ethyl acetate, m.p. 108—110 °C; $\nu_{max.}$ 1 775, 1 740, 1 710, and 1 630 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.80 (1 H, dt, *J* 3 and 10 Hz, 8-H), 3.97 (1 H, t, *J* 10 Hz, 6-H), 2.36 (3 H, s, 10-Me), 2.09 (3 H, s, OAc), 1.23 (3 H, d, *J* 6 Hz, 4-Me), and 1.13 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 306 (M^+, 2%).

Reduction of Compound (**4**) *with Sodium Borohydride–Cerium*(III) *Chloride*.—The lactone (**4**) (400 mg) was dissolved in 0.4M-methanolic $CeCl_3 \cdot 7H_2O$. Sodium borohydride (0.063 g) was added in portions under continuous agitation during 5 min and the reaction mixture was then diluted with water. Usual work-up and column chromatography [benzene–ethyl acetate (7:3)], afforded allylic alcohols (**5a**) (100 mg) and (**5b**) (30 mg). Compound (**5a**) had m.p. 136—137 °C; $\nu_{max.}$ 3 450, 1 770, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.70 (2 H, br m, 2- and 8-H), 3.79 (1 H, t, *J* 9.5 Hz, 6-H), 2.03 (3 H, s, OAc), 1.90 (3 H, br s, 10-Me), 1.20 (3 H, d, *J* 6 Hz, 4-Me), and 1.10 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 308 (M^+, 2.5%). Lactone (**5b**) had m.p. 148—149 °C, $\nu_{max.}$ 3 450, 1 770, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 60 MHz), 4.80 (2 H, br m, 2- and 8-H), 4.05 (1 H, t, *J* 10 Hz, 6-H), 2.10 (3 H, s, OAc), 2.02 (3 H, br s, 10-Me), 1.20 (3 H, d, *J* 6 Hz, 4-Me), and 1.15 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 308 (M^+, 2.7%).

Epoxy Alcohols (**6a**) *and* (**6b**).—MCPBA (90 mg) was added to a stirred solution of compound (**5a**) (90 mg) in chloroform (3 ml) at 0 °C. The mixture was stirred for 1 h at 0 °C, and washed successively with aq. sodium hydrogen carbonate and water, dried over sodium sulphate, and concentrated to give a crystalline material (70 mg). This was subsequently chromatographed over silica gel [benzene–ethyl acetate (1:1)] to give the epoxides (**6a**) (40 mg) and (**6b**) (9 mg). Epoxy alcohol (**6a**) had m.p. 151—152 °C; $\nu_{max.}$ 3 500, 1 775, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.85 (1 H, dt, *J* 2 and 10.5 Hz, 8-H), 4.10 (1 H, m, 2-H), 4.02 (1 H, t, *J* 10 Hz, 6-H), 2.08 (3 H, s, OAc), 1.53 (3 H, s, 10-Me), 1.22 (3 H, d, *J* 6 Hz, 4-Me), and 1.15 (3 H, s, *J* 7 Hz, 11-Me); *m/z* 324 (M^+, 1.9%). Epoxy alcohol (**6b**) had m.p. 245—247 °C; $\nu_{max.}$ 3 500, 1 775, and 1 740 cm^{-1}; δ_H ($CDCl_3$; 80 MHz), 4.88 (1 H, dt, *J* 3.7 and 11 Hz, 8-H), 4.22 (1 H, t, *J* 10.5 Hz, 6-H), 4.05 (1 H, br t, *J* 4 and 2.3 Hz, 2-H), 2.05 (3 H, s, OAc), 1.37 (3 H, s, 10-Me), 1.16 (3 H, d, *J* 6.5 Hz, 4-Me), and 1.13 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 324 (M^+, 3%).

Epoxy Alcohols (**8a**) *and* (**8b**).—A solution of compound (**5b**) (30 mg) in chloroform (2 ml) was treated with MCPBA as previously described for the preparation of compounds (**6a**) and (**6b**). Work-up afforded a residue, which was chromatographed [benzene–ether acetate (1:1)] to give epoxy alcohols (**8a**) (5 mg)

and (**8b**) (7 mg.) Epoxy alcohol (**8a**) had m.p. 195—197 °C; $\nu_{max.}$ 3 500—3 400, 1 780, and 1 740 cm^{-1}; δ_H ($CDCl_3$; 80 MHz), 4.83 (1 H, dt, *J* 4.25 and 11 Hz, 8-H), 4.24 (1 H, t, *J* 10 Hz, 6-H), 4.16 (1 H, br t, *J* 2.5 and 4.5 Hz, 2-H), 2.02 (3 H, s, OAc), 1.47 (3 H, s, 10-Me), 1.21 (3 H, d, *J* 7 Hz, 4-Me), and 1.06 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 324 (M^+, 3.5%). Epoxy alcohol (**8b**), m.p. 120—123 °C; $\nu_{max.}$ 3 500, 1 775, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 80 MHz) 4.89 (1 H, dt, *J* 3 and 8.5 Hz, 8-H), 4.15 (1 H, t, *J* 10 Hz, 6-H), 4.03 (1 H, br t, *J* 5.6 and 4.8 Hz, 2-H), 2.07 (3 H, s, OAc), 1.40 (3 H, s, 10-Me), 1.17 (3 H, d, *J* 7 Hz, 4-Me), and 1.13 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 324 (M^+, 2.6%).

8α-*Acetoxy*-1,10α-*epoxy*-3,4-*dihydroachillin* (**7a**).—Epoxy alcohol (**6a**) (30 mg) was dissolved in pyridine (2 ml) and chromium trioxide (150 mg) was added. The usual work-up yielded a syrup, which was chromatographed [benzene–ethyl acetate (8:2) as eluant] to give epoxy ketone (**7a**) (25 mg), m.p. 196—198 °C; $\nu_{max.}$ 1 780, 1 740, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.89 (1 H, dt, *J* 2 and 11 Hz, 8-H), 4.21 (1 H, t, *J* 10 Hz, 6-H), 2.09 (3 H, s, OAc), 1.61 (3 H, s, 10-Me), 1.17 (3 H, d, *J* 7 Hz, 4-Me), and 1.14 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 322 (M^+, 3%).

8α-*Acetoxy*-1,10β-*epoxy*-3,4-*dihydroachillin* (**7b**).—Epoxy alcohol (**6b**) was oxidized with chromium trioxide–pyridine complex as described for compound (**6a**). Epoxy ketone (**7b**) was obtained as a crystalline compound, m.p. 200—202 °C; $\nu_{max.}$ 1 780, 1 740, and 1 735 cm^{-1}; δ_H ($CDCl_3$; 80 MHz) 4.89 (1 H, dt, *J* 3.8 and 10 Hz, 8-H), 4.27 (1 H, t, *J* 10 Hz, 6-H), 2.07 (3 H, s, OAc), 1.59 (3 H, s, 10-Me), 1.24 (3 H, d, *J* 6 Hz, 4-Me), and 1.17 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 322 (M^+, 2.8%).

1,10α-*Epoxy*-3,4-*dihydroachillin* (**7c**) *and* 1,10β-*Epoxy*-3,4-*dihydroachillin* (**7d**).—Epoxy alcohols (**6c**) and (**6d**), obtained from achillin,[7] were treated as described for their acetates (**6a**) and (**6b**). The usual work-up yielded a syrup, which was chromatographed [benzene–ethyl acetate (8:2) as eluant] to give epoxy ketones (**7c**) (20 mg) and (**7d**) (15 mg) respectively. Epoxy ketone (**7c**) had m.p. 185—186 °C; $\nu_{max.}$ 1 770 and 1 740 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.16 (1 H, t, *J* 10 Hz, 6-H), 1.55 (3 H, s, 10-Me), 1.23 (3 H, d, *J* 6 Hz, 4-Me), and 1.15 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 264 (M^+, 2.4%). Epoxy ketone (**7d**) had m.p. 189—190 °C; $\nu_{max.}$ 1 770 and 1 745 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 4.20 (1 H, t, *J* 10 Hz, 6-H), 1.55 (3 H, s, 10-Me), 1.38 (3 H, d, *J* 6 Hz, 4-Me), and 1.15 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 264 (M^+, 3.1%).

Epoxy Alcohols (**8c**) *and* (**8d**).—Allylic alcohol (**5c**) (80 mg) obtained from achillin[7] was treated with MCPBA as described for compound (**5a**). Work-up afforded a crude mixture, which was chromatographed [benzene–ethyl acetate (1:1) as eluant] to give epoxides (**8c**) (30 mg) and (**8d**) (20 mg). Epoxy alcohol (**8c**) had m.p. 207—209 °C; $\nu_{max.}$ 3 600 and 1 765 cm^{-1}; δ_H ($CDCl_3$; 80 MHz) 4.24 (1 H, t, *J* 10 Hz, 6-H), 4.12 (1 H, d, 2-H), 1.30 (3 H, s, 10-Me), 1.21 (3 H, d, *J* 6.5 Hz, 4-Me), and 1.13 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 266 (M^+, 3.2%). Epoxy alcohol (**8d**) had m.p. 140—142 °C; $\nu_{max.}$ 3 600 and 1 770 cm^{-1}; δ_H ($CDCl_3$; 80 MHz) 4.08 (1 H, t, *J* 10 Hz, 6-H), 3.95 (1 H, d, *J* 5 Hz, 2-H), 1.40 (3 H, s, 10-Me), 1.25 (3 H, d, *J* 6.5 Hz, 4-Me), and 1.15 (3 H, d, *J* 7 Hz, 11-Me); *m/z* 266 (M^+, 2.7%).

Correlation of the Acetate of the Natural Compound (**1a**) *with Epoxy Ketone* (**7b**).—Lactone (**1b**) (60 mg) was hydrogenated as described for compound (**3a**). Work-up and column chromatography yielded a compound identical with 8α-acetoxy-1,10β-epoxy-3,4-dihydroachillin (**7b**).

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