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NEW PSEUDOGUAIANOLIDES FROM *AMBROSIA CONFERTIFLORA* DC. (COMPOSITAE)[1]

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Abstract--The structures of confertiflorin and desacetylconfertiflorin, two new sesquiterpene lactones from *Ambrosia confertiflora* DC., are shown to be XIIIa and XIIIb, respectively.

INTRODUCTION

OUR analyses of more than fifty populations of *Ambrosia psilostachya* DC. and selected populations of *A. cumanensis* Kunth for their sesquiterpene lactones demonstrated that intraspecific variation can be an important aspect of the distribution of this class of secondary plant constituents.[3-7] It was of interest to investigate the sesquiterpene lactones in several populations of *A. confertiflora* DC., a species similar in distribution to *A. psilostachya* and considered to be closely related to *A. psilostachya* and *A. cumanensis*. Collections of *A. confertiflora* DC. from two sites in South Texas yielded two new pseudoguaianolides, which we named confertiflorin and desacetylconfertiflorin. This paper describes the structure determinations of these two new sesquiterpene lactones.

Isolation and physical properties of confertiflorin and desacetylconfertiflorin

Plant material collected in October, 1965, near Kenedy and Kingsville, Texas, afforded confertiflorin (I), $C_{17}H_{22}O_5$, m.p. 144–145°, $[\alpha]_D$ +25° in about 1·2% yield and desacetylconfertiflorin (II), $C_{15}H_{20}O_4$, m.p. 202–204°, $[\alpha]_D$ +17·3°, in 0·25% yield. The UV (λ_{max} 208 nm, ε 9,470; 300 nm, ε about 35) and IR (1760, 1730, 1660 and a broad, intense signal at 1250 cm^{-1}) spectral data for the major constituent, confertiflorin indicated the presence of an α,β'-unsaturated γ-lactone, a 5-ring keto group, and an acetate function. The spectral findings for desacetylconfertiflorin (UV: λ_{max} 209 nm, ε 10,890; 295 nm, ε 35; IR: 3450, 1740 and 1645 cm^{-1}) suggested that it differed functionally from confertiflorin by the presence of a OH group and the absence of the acetate moiety.

The NMR spectrum of confertiflorin exhibited signals indicating the presence of one tertiary and one secondary Me group (1·10[8], singlet and 1·20, doublet, J = 7 c/s) and an Ac group (2·08, singlet). In addition, the spectrum displayed three downfield

[1] Supported by a research grant (F-130) from the Robert A. Welch Foundation.
[2] Robert A. Welch postdoctoral fellow, 1965–1966.
[3] T. J. Mabry, H. E. Miller, H. B. Kagan and W. Renold, *Tetrahedron* **22**, 1139 (1966).
[4] H. B. Kagan, H. E. Miller, W. Renold, M. V. Lakshmikantham, L. R. Tether, W. Herz and T. J. Mabry, *J. Org. Chem.* **31**, 1629 (1966).
[5] T. J. Mabry, W. Renold, H. E. Miller and H. B. Kagan, *J. Org. Chem.* **31**, 681 (1966).
[6] T. J. Mabry, H. B. Kagan and H. E. Miller, *Tetrahedron* **22**, 1943 (1966).
[7] H. E. Miller and T. J. Mabry, In preparation.
[8] All chemical shift values are reported in ppm (δ-scale).

doublets typical for protons associated with the α,β'-unsaturated γ-lactone in sesquiterpene lactones from other *Ambrosia* species:[3-7] a doublet for the C-6 lactonic proton at 4·67, J = 8 c/s and a pair of doublets for two C-11 methylene protons at 5·66, J = 3 c/s and 6·32, J = 3 c/s. A one-proton multiplet appeared at 5·40, a chemical shift typical for a proton attached to a carbon atom bearing an Ac group. The NMR spectrum of desacetylconfertiflorin (Table 1) was similar to the spectrum observed

TABLE 1*. NMR SIGNALS OF CONFERTIFLORIN AND DERIVATIVES

	H_6	H_7	H_8	C_5-Me	C_{10}-Me	C_{11}-CH_2	C_{11}-Me	Acetate
I	4·67d(8)	3·54c	5·40c	1·10	1·02d(7·5)	5·66d(3) 6·32d(3) 5·98d(2·5)		2·08
II	4·63d(8·5)	3·32	4·18c	1·03	1·16d(7)	6·34d(3·0) 5·72d(3·0)		
III	4·62d(3·5)	2·95c	4·75c	1·13	1·22d(7)	6·44d(3·5) 5·77d(3·0)		
IV	6·17d(3·5)	3·15c	4·75c	1·01	1·23d(7)	6·34d(3·5)		2·03
V	4·70d(9)	3·21c	5·26c	1·10	1·24d(7)		1·24d(7)	2·04
VI	4·78d(2)		6·03d(7)	0·83	1·05d(7)		1·93d(2)	2·11
VII	4·11d(5·5)		4·68c	1·12	1·22d(7)		1·18d(7)	
VIII	4·63d(8·5)		4·23c	1·07	1·17d(7·5)		1·44d(7)	
IX	5·03d(2)		5·18dd(7;1)	0·75	1·02d(6·5)		1·83d(2)	
XI	4·67br			0·84	1·03d(7)		1·84d(1)	
XIV	4·55d(9)		4·17c	1·07	1·16d(7)		1·36d(7)	
XV	4·57d(9)		5·34c	1·10	1·19d(7)[d]		1·30d(7)[d]	2·07
XVI	4·55d(8·5)		5·20c	1·11	1·20d(7)		1·38d(7)	3·09[e]
XVII	4·49d(8)		5·52c(2H)[b]	1·06	1·16d(8·5)		1·29d(9·5)[d]	

* Spectra were determined in $CHCl_3$ or $CDCl_3$ on a Varian A-60 spectrometer. Values are given in ppm relative to tetramethylsilane as an internal standard. Numbers in parentheses denote coupling constants in c/s. Singlets are unmarked, multiplets are described as follows: d = doublet, t = triplet, c = complex signal whose center is given, br = broad.

[b] C-8 and C-9 proton.

[c] C-4 proton.

[d] The assignments for the C-10 and C-11 methyl groups in this compound may be reversed.

[e] Mesylate methyl.

for confertiflorin except that the 5·40 multiplet was not present and a new multiplet appeared at 4·18. The latter signal was ascribed to a proton on a carbon atom bearing a OH group. A multiplet at 3·32, which was assigned to the vinylogous proton at C-7, was resolved by a 100 mc NMR spectrum.[9] The splitting of the multiplet was consistent with coupling to the C-6 lactonic proton, two C-11 methylene protons, and only one C-8 proton.

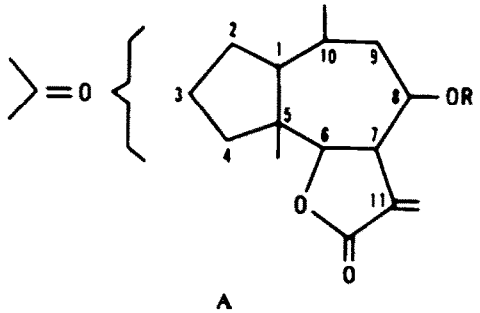
Interconversions of confertiflorin and desacetylconfertiflorin and formation of allo compounds

Desacetylconfertiflorin was converted quantitatively to confertiflorin with acetic anhydride–pyridine. Further support for the close relationship between confertiflorin and desacetylconfertiflorin and the presence of a C-8 oxygen function in both compounds was provided by the hydrolysis of confertiflorin. When confertiflorin was

[9] We thank Dr. H. B. Kagan, Laboratoire de Chimie Organique des Hormones, College de France, Paris, for this data.

treated with aqueous potassium carbonate or sodium hydroxide, desacetylconfertiflorin and a new isomeric substance, $C_{15}H_{20}O_4$, m.p. 172–173°, were obtained. The NMR spectrum of the new substance (Table 1) was consistent with structure III, allodesacetylconfertiflorin.

The spectroscopic findings combined with the interconversion of I and II under mild conditions suggested partial formula A for confertiflorin (R = Ac) and for desacetylconfertiflorin (R = H).[10]



A

Confirmation of the presence of an oxygen function at C-8 in I and II was provided by the following reactions. Hydrogenation of confertiflorin (Scheme 1) with Pd–C as catalyst gave a 1:1 mixture[11] of dihydroconfertiflorin (V), $C_{17}H_{24}O_6$, m.p. 146–147°, and isoconfertiflorin (VI), $C_{17}H_{22}O_6$, m.p. 188–189°. The two compounds were readily separated by fractional crystallization from methanol. Hydrolysis of V with hydrochloric acid in dioxan, aqueous sodium hydroxide or sodium methoxide in methanol yielded quantitatively allodihydrodesacetylconfertiflorin (VII), $C_{15}H_{22}O_4$, m.p. 202°, IR bands at 3400 (hydrogen-bonded OH group), 1750 (γ-lactone), and 1720 cm^{-1} (hydrogen-bonded 5-ring keto group). The NMR spectrum of VII was wholly in accord with the allo structure: the C-6 proton appeared as a doublet at 4·11 (J = 5·5 c/s) and the C-8 lactonic proton occurred as a multiplet at 4·68.

Proof of structures and absolute configurations at all centers except C-7 *and* C-8 *for* I *and* II

The above findings were consistent with structures I and II for confertiflorin and desacetylconfertiflorin, respectively. Final proof of most of the structural features shown in I and II and the stereochemistry at C-1, -5, -6 and -10 were provided by the conversion of the desacetylconfertiflorin to isodamsin (XI), Scheme 2. Hydrogenation of the mesylate material was identical with authentic isodamsin[12] by m.p., mixed m.p., NMR, IR, UV, and mass spectra and ORD curves down to 210 nm.[13] The remarkable direct conversion of the mesylate X to a hydrocarbon by hydrogenation over Pd–C

[10] Desacetylconfertiflorin apparently was not an artifact of the isolation and work-up procedures since both I and II were detected when the plant material was extracted with cold reagent-grade chloroform and the extract was examined directly by silica gel TLC.

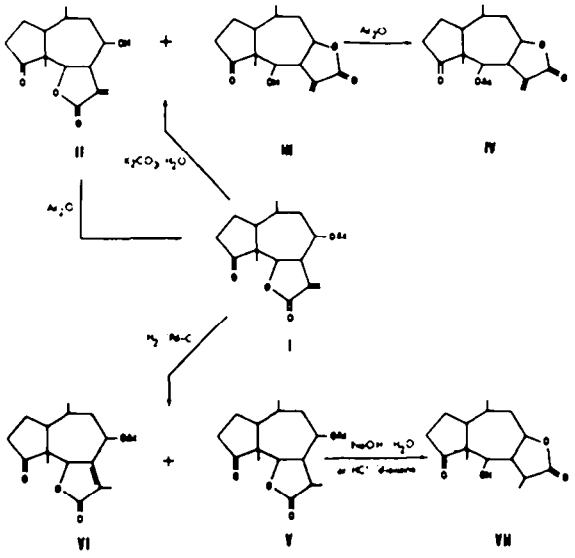
[11] The formation of mixtures of dihydro- and iso-compounds during hydrogenation with Pd–C commonly occurs with sesquiterpenes containing α, β'-unsaturated γ-lactone groups. See Refs. 3,4,5, and 6 for several examples.

[12] For a discussion of the stereochemical features shown in structures XI for isodamsin and XII for damsin, see Ref 4.

[13] We thank Dr. D. J. Cox and Mr. Stanley Cernosek, Dept. of Chemistry, University of Texas, for assistance in obtaining the ORD data.

was probably preceded by the isomerization of the exocyclic double bond, which is known to be a fast migration under these conditions. Thus the compound actually hydrogenated was almost certainly the allylic mesylate.

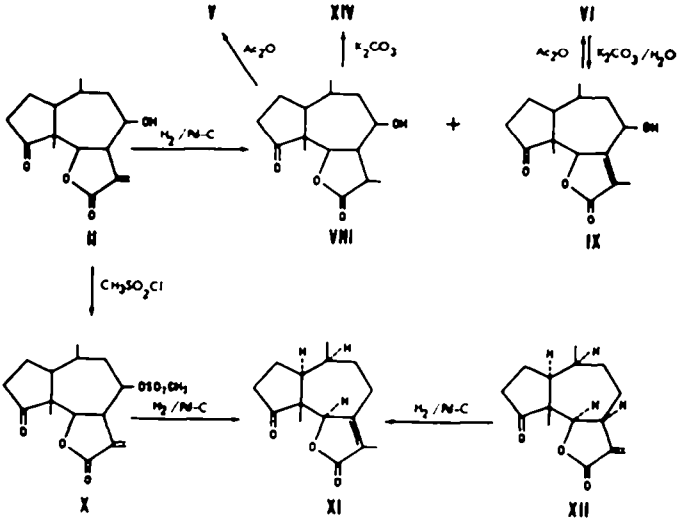
SCHEME 1



Configurations at C-7 *and* C-8 *in* I *and* II

The only remaining questions regarding the structures of confertiflorin and desacetylconfertiflorin concerned the stereochemistry at C-7 and C-8. The beta configuration at C-7 in I and II is favored on biogenetic grounds since all *Ambrosia*

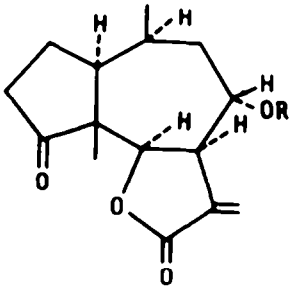
SCHEME 2



species[14] thus far investigated are known to elaborate only sesquiterpene lactones in which the lactones have a C-7 beta attachment. Some support for this stereochemistry at C-7 in I and II was provided by NMR. In the NMR spectra of other sesquiterpene lactones from *Ambrosia* species,[3-7] all of which have a β,β *cis* attachment of the lactone ring, the C-6 and C-7 protons show a spin-spin interaction of about 9 c/s, which is the coupling constant observed for the interaction of the C-6 and C-7 protons in both I and II.

The stereochemistry at C-8 in II (and therefore in I) was established by the Horeau technique[15] which involves the stereoselective reaction of racemic α-phenylbutyric anhydride with secondary OH groups attached to asymmetric carbon atoms. We previously applied the method to sesquiterpene lactones containing secondary OH groups.[5] When racemic α-phenylbutyric anhydride was reacted with desacetylconfertiflorin, (-)-α-phenylbutyric acid was isolated from the reaction solution; the optical yield[5] was about 15%.[16] The recovery of a *levorotatory* acid from the reaction indicates that the C-8 hydroxyl group in II has the alpha configuration.[5,15]

Based on all the evidence presented above, we propose structure XIIIa for confertiflorin and XIIIb for desacetylconfertiflorin.



XIII a, R = Ac
b, R = H

Conversion of dihydroconfertiflorin to isodamsin

In the course of the structure determinations of I and II, dihydroconfertiflorin (V) was also converted to isodamsin. One reaction in the sequence (Scheme 3) requires comment. The hydrogenation of desacetylconfertiflorin yielded two compounds, dihydrodesacetylconfertiflorin (VIII) and isodesacetylconfertiflorin (IX). It was expected that these same two compounds, VIII and IX, would be obtained on the hydrolysis, respectively, of dihydroconfertifluorin (V) and isoconfertiflorin (VI). In fact, the hydrolysis of isoconfertiflorin did yield the expected product, IX. In contrast, the hydrolysis of dihydroconfertiflorin (V) with a solution of potassium carbonate in water-methanol (1:3) did not yield the expected dihydrodesacetylconfertiflorin (VIII) but instead gave quantitatively a different alcohol, XIV, $C_{15}H_{22}O_4$,

[14] For a recent review of the sesquiterpene lactones in *Ambrosia* species see W. Herz in *Recent Advances in Phytochemistry* (Edited by T. J. Mabry, R. E. Alston and V. C. Runeckles). Appleton-Century-Crofts, New York (1967).

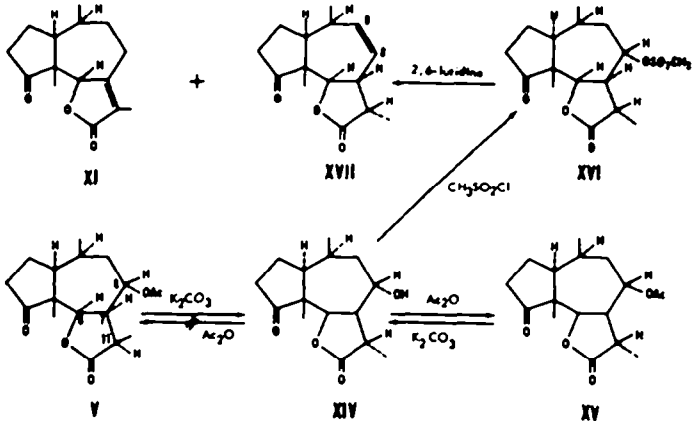
[15] A. Horeau, *Tetrahedron Letters* No. 15, 506 (1961).

[16] The details of this experiment will be discussed in a later communication (in collaboration with Drs. H. B. Kagan and A. Horeau).

m.p. 211–212°, IR bands at 3460 (hydroxyl) and 1745 cm^{-1} (cyclopentanone and γ-lactone), Scheme 3. On acetylation the new alcohol (XIV) was not converted back to V, but gave instead a new acetate, XV, which could be hydrolyzed back to XIV.

In view of the observation by Herz *et al.*[17] that sesquiterpene lactones can give rearranged products when treated with potassium carbonate in aqueous methanol, it was of interest to determine what transformations had occurred in the formation of the new alcohol XIV. It was possible to eliminate the possibility of changes in V at all carbon atoms except at C-7, -8 and -11 by the following reactions. When XVI, the mesylate of the new alcohol XIV, was refluxed with 2,6-lutidine for 20 hr, two

SCHEME 3



compounds were formed in about a 3:1 ratio. The minor constituent was shown to be identical in all respects with authentic isodamsin (XI). The second product $C_{15}H_{20}O_3$, m.p. 157–158°, was assigned structure XVII. The NMR spectrum of the latter compound exhibited a multiplet centered at 5·52 for the two vinylic protons at C-8 and C-9. The conversion of XIV to isodamsin demonstrated that the stereochemical centers in XIV were identical to those in V with possible exceptions at C-7, -8 and -11. That the stereochemistry at C-7 was not altered during the treatment of V with potassium carbonate in aqueous methanol was confirmed when the hydrolysis of V was carried out with potassium carbonate in D_2O—CH_3OD. The NMR spectrum of the product from this latter experiment still exhibited a doublet ($J = 9$ c/s) at 4·59 for the C-6 lactonic proton, hence a deuterium atom could not be present at C-7 thus excluding the possibility of inversion at C-7. Furthermore, it was evident that the C-11 proton had exchanged with deuterium since the C-11 methyl group appeared as a singlet at 1·36. In contrast, the C-11 methyl group in XIV gave rise to a doublet ($J = 7$ c/s), which was, however, centered at exactly the same chemical shift, 1·36. Since exchange had taken place at C-11, inversion could also have occurred.

We considered the possibility that instead of hydrolysis, an S_N2 displacement of the C-8 acetyl function could have occurred during the treatment of V with potassium carbonate in aqueous methanol. However this reaction was excluded when it was

[17] W. Herz, M. V. Lakshmikantham and R. N. Mirrington, *Tetrahedron* **22**, 1709 (1966).

observed that dihydrodesacetylconfertiflorin (VIII) could be transformed into XIV on treatment with potassium carbonate in aqueous methanol (Scheme 2).

Therefore it was possible to conclude that the alcohol XIV differed from dihydrodesacetylconfertiflorin (VIII) only in stereochemistry at C-11. Thus the only questions remaining regarding the structures of both VIII and XIV concerned their stereochemistry at C-11. The C-11 methyl groups in VIII and XIV are assigned beta and alpha orientations respectively, on the basis of the following arguments. Examination of Dreiding models for confertiflorin (XIIIa) suggested that hydrogenation of XIIIa would yield a product with a beta-oriented C-11 Me group (V, Scheme 3). Furthermore, models of the two possible C-11 isomers of the alcohol derived by hydrolysis of V (Scheme 3) indicated that the isomer with alpha C-11 Me group would be preferred sterically. Therefore, under isomerization conditions, the product should be the sterically favored isomer, i.e., structure XIV.

EXPERIMENTAL[18]

Isolation of confertiflorin and desacetylconfertiflorin

Collections of *Ambrosia confertiflora* DC. were made October 20, 1965 (voucher no. 241880)[19] and May, 1966 (voucher no. 250223) at Kenedy, Texas, and October, 1965 at Kingsville, Texas (voucher no. 241882). Each contained essentially the same distribution of sesquiterpene lactones. A typical isolation is described.

Air-dried, ground plant material was extracted with chf and worked up in the usual manner.[8] From 290 g of plant material were obtained 6·0 g of a thick syrup. NMR analysis indicated the presence of two new sesquiterpene lactones in a 4:1 ratio. When the syrup was triturated with ether, 3·1 g of the major constituent, which we named confertiflorin, crystallized. Recrystallization of the crude material from MeOH afforded pure I, m.p. 145°, $[\alpha]_D^{24}$ +25·0° (MeOH, c = 5·0); λ_{max} 208 nm (ε 9,470), shoulder about 300 nm (ε 35); IR bands at 1760 (α,β'-unsaturated γ-lactone), 1730 (cyclopentanone and acetate), and 1660 cm^{-1} (double bond). [Found: C, 66·49; H, 7·16; O, 26·36. Mol. wt. (mass spec.) 307 ± 2. $C_{17}H_{22}O_6$ requires: C, 66·65; H, 7·24; O, 26·11%. Mol. wt. 306.]

The mother liquor from the syrup which yielded the confertiflorin was concentrated to a dark brown syrup (2·9 g). The syrup was chromatographed over silica gel, using chf as the initial eluting solvent. The first fractions gave a dark brown glass. Later fractions yielded 0·45 g confertiflorin. Elution with MeOH afforded 0·21 g desacetylconfertiflorin. Recrystallization of the crude material from MeOH gave colorless needles of pure II; m.p. 202–204°, $[\alpha]_D^{24}$ +17·2° (MeOH, c = 2·75); λ_{max} 209 nm (ε 10,890), shoulder at 295 nm (ε 35); IR bands at 3450 (OH), 1740, and 1695 cm^{-1} (double bond). [Found: C, 68·14; H, 7·68; O, 24·42. Mol. wt. (mass spec.) 264. $C_{15}H_{20}O_4$ requires: C, 68·15; H, 7·63; O, 24·21%. Mol. wt. 264.]

When the plant material was extracted with cold reagent-grade chf and the extract was examined by silica gel TLC (developing solvent: ether), confertiflorin (R_f 0·49) and desacetylconfertiflorin (R_f 0·23) were both detected.

Hydrolysis of confertiflorin to desacetylconfertiflorin (II) *and allodesacetylconfertiflorin* (III)

To a soln of 3·08 g K_2CO_3 in 65 ml H_2O was added 2·00 g confertiflorin. The mixture was heated on a steam bath for 2·5 hr, cooled and acidified with conc HCl. The solvent was extracted exhaustively with chf. The chf layer was dried with $MgSO_4$ and, after filtering, the solvent was evaporated. A syrupy yellow residue remained, which consisted of a 1:1 mixture of II and III (by NMR analysis). Crystals were obtained from a MeOH soln of the syrup; yield 0·43 g. The crystals were shown to be pure II by m.p., mixed m.p., NMR and IR spectra. The mother liquor afforded 0·185 g of III by chromatography over silica gel (eluting solvent, $CHCl_3$). Recrystallization of the 0·185 g from MeOH gave pure III, m.p. 172–173°, IR bands at 3460 (OH), 1750 (lactone), 1725 (cyclopentanone), and

[18] M.ps are uncorrected. Analyses were determined by Dr. Alfred Bernhardt, Max-Planck Institut für Kohlenforschung, Mülheim, West Germany.

[19] All voucher specimens are deposited in the University of Texas Herbarium, Austin.

1655 cm^{-1} (double bond). [Found: C, 68·44; H, 7·58; O, 24·14. $C_{18}H_{26}O_4$ requires: C, 68·15; H, 7·63; O, 24·21%.]

Acetylation of III with Ac_2O in pyridine afforded IV, m.p. 154–155°; IR bands at 1770 (lactone), 1745 (ketone and acetate), and 1665 cm^{-1} (double bond, weak) [Found: C, 67·02; H, 7·17. $C_{17}H_{22}O_4$ requires: C, 66·65; H, 7·24%.]

When confertiflorin was heated on a steam cone with a 5% NaOH solution for about 30 min the product consisted also of a 1:1 mixture of II and III (by NMR analysis).

Hydrogenation of confertiflorin

A soln of 1·32 g confertiflorin in 10 ml MeOH was hydrogenated with vigorous stirring using 0·10 g 5% Pd–C as catalyst. After 45 min at room temp, the reaction was stopped. The catalyst was filtered off and the solvent evaporated to give a colorless syrup which solidified on trituration with ether. It could be shown by NMR that the material consisted of a mixture of 2 compounds in approximately equal amounts. Careful recrystallization of the material from MeOH yielded bulky large crystals (VI, m.p. 188–189°). On concentrating the mother liquor, needles were obtained (V, m.p. 146–147°).

Isoconfertiflorin (VI) displayed IR bands at 1750 (lactone), 1725 (acetate and cyclopentanone), and 1665 cm^{-1} (double bond). [Found: C, 66·62; H, 7·24; O, 26·13. $C_{17}H_{22}O_4$ requires: C, 66·65; H, 7·24; O, 26·11%.]

Dihydroconfertiflorin (VI) displayed IR bands at 1760 (lactone), and 1725 cm^{-1} (acetate and cyclopentanone). [Found: C, 66·30; H, 7·77; O, 26·05. $C_{17}H_{24}O_4$ requires: C, 66·21; H, 7·85; O, 25·94%.]

Hydrolysis of isoconfertiflorin (VI) *with aqueous* K_2CO_3

Isoconfertiflorin (200 mg) was dissolved in 6·5 ml H_2O containing 210 mg K_2CO_3. The soln was refluxed for 1 hr., then acidified with conc HCl and extracted with CH_2Cl_2. Evaporation of the dried CH_2Cl_2 layer gave 140 mg of colorless crystals. Recrystallization from MeOH yielded pure IX, m.p. 198°, IR bands at 3550 (hydroxyl), 1750 (γ-lactone), 1735 (ketone) and 1670 cm^{-1} (double bond).

Hydrolysis of dihydroconfertiflorin (V)

(a) To a soln of 350 mg of K_2CO_3 in 1·0 ml H_2O and 3·0 ml MeOH was added 250 mg of V. The mixture was refluxed on a steam bath for 45 min. Most of the MeOH was removed *in vacuo*. The concentrate, which was light yellow, gave on acidification with conc HCl a colorless soln. The soln was thoroughly extracted with chf. The colorless syrup, which was obtained upon work-up of the chf layer, crystallized on trituration with ether. Recrystallization of the crude material from MeOH yielded 170 mg of pure XIV, m.p. 211–212°, IR bands at 3460 (OH) and 1745 cm^{-1} (γ-lactone and ketone). [Found: C, 67·52; H, 8·42. $C_{15}H_{22}O_4$ requires: C, 67·74; H, 8·33%.]

(b) Compound IV (100 mg) was hydrolyzed in a soln of 75 mg K_2CO_3 in 0·3 ml D_2O and 1·2 ml CH_3OD using the same conditions and work-up procedures described in (a) except that the soln was acidified by adding $SOCl_2$ to the chilled reaction mixture. The NMR spectrum of the alcohol (75 mg), m.p. 208–209°, obtained from the reaction, showed a doublet (4·59, $J \simeq 9$) for the C-6 lactonic proton, a singlet (1·07) for the C_8-Me and a doublet (1·16, $J = 7$) for the C_{10}-Me. A singlet for the C_{11}-Me (1·36) indicated that the proton at C-11 had been exchanged by deuterium.

Acetylation of XIV

Treatment of XIV (59 mg) with Ac_2O in pyridine afforded 48 mg pure XV, m.p. 115–116°; IR bands at 1765 (γ-lactone), 1725 (ketone and acetate) and 1245 cm^{-1} (acetate).

Hydrolysis of XV

Treatment of XV (45 mg) with K_2CO_3 in MeOH–water, using the ratio and conditions described above, gave 27 mg of crystals, which were identical with XIV by mixed m.p. and NMR analysis.

Allodihydro-desacetylconfertiflorin (VII)

(a) *Hydrolysis of dihydroconfertiflorin* (V) *with aqueous* NaOH. A mixture of 135 mg of V and 3 ml 5% NaOH was heated on a steam bath until soln was complete. The cold reaction mixture was

acidified with conc HCl whereupon 98 mg crystalline material precipitated. Recrystallization from MeOH gave pure VII, m.p. 202°, IR bands at 3400 (OH), 1750 (γ-lactone), and 1720 cm^{-1} (ketone). [Found: C, 67·69; H, 8·25; O, 24·22. $C_{15}H_{20}O_4$ requires: C, 67·64; H, 8·33; O, 24·03%.]

(b) *Hydrolysis of* V *with* MeONa *in* MeOH. To a methanolic soln of MeONa (prepared from 100 mg Na and 5 ml MeOH) were added 80 mg of V. The reaction mixture was refluxed for 3 hr, diluted with H_2O and acidified with conc HCl. A thorough extraction was made with CH_2Cl_2. Work up of the extract in the usual manner afforded 51 mg of crystals, m.p. 202°, which were shown to be VII by m.p., mixed m.p. and NMR analysis.

(c) *Acid hydrolysis of* V. A soln of 0·2 g of V in 0·7 ml conc HCl and 5 ml dioxane was refluxed for 22 hr. The mixture on evaporation to dryness yielded 0·15 g of crystals, m.p. 202°, which were identical with VII by m.p., mixed m.p., NMR and IR analyses.

Hydrogenation of desacetylconfertiflorin (II)

Desacetylconfertiflorin (350 mg) was hydrogenated in 10 ml MeOH for 19 hr with 50 mg 5% Pd–C as catalyst. After filtering off the catalyst the soln was concentrated to a colorless syrup. NMR analysis of the syrup indicated the presence of two compounds in a 1:4 ratio, which were separated by chromatography over silica gel, using ether as the eluting solvent. The less polar compound, m.p. 198°, was shown to be IX by mixed m.p., and IR and NMR analysis. The more polar substance, VIII, m.p. 201–202°, was obtained in a low yield (27 mg). It displayed IR bands at 3460 (OH) and 1745 cm^{-1} (ketone and γ-lactone).

When IX and VIII were acetylated with Ac_2O in pyridine in the usual manner, VI and V were obtained quantitatively, respectively. The latter two compounds were also obtained by the hydrogenation of I, as already described.

Treatment of dihydrodesacetylconfertiflorin (VIII) *with* K_2CO_3 *in* H_2O—MeOH

Compound VIII (15 mg) was refluxed for 30 min in a soln of 13 mg of K_2CO_3 in 0·5 ml of a mixture of 1 part H_2O and 4 parts MeOH. The reaction mixture was acidified with conc HCl and extracted exhaustively with CH_2Cl_2. The CH_2Cl_2 layer was dried with $MgSO_4$ and evaporated to yield 10·5 mg of a colorless syrup which crystallized on trituration with ether. TLC and NMR analyses of the crude crystals indicated the presence of 2 compounds. The two substances were separated by preparative TCL on silica gel, using ether as the developing solvent. The less polar material (about 5 mg) was shown to be VII by NMR analysis. The more polar compound was recrystallized from MeOH to yield 4·0 mg of crystals, m.p. 206–208°. The material was identical with XIV by mixed m.p., IR and NMR analyses.

Mesylate of desacetylconfertiflorin (X)

Desacetylconfertiflorin (100 mg) was dissolved in 1 ml of pyridine and the soln was cooled in an ice bath. Mesyl chloride (0·2 ml) was added to the cold soln and the reaction mixture was left in a refrigerator for 2 hr. The ppt that formed was filtered and washed with cold MeOH; 101 mg colorless mesylate X, m.p. 218–219°, IR bands at 1760 (γ-lactone), 1730 (ketone) and 1340 and 1170 cm^{-1} (mesylate).

Conversion of mesylate X *to isodamsin* (XI)

Because of the low solubility of the mesylate X in all common solvents a slurry of X (40 mg) in 300 ml MeOH was prepared. The slurry was treated for 24 hr under hydrogenation conditions with 5% Pd–C as catalyst. After filtering off the catalyst, the solvent was evaporated to give a solid residue. An ether extract of the residue afforded 9·5 mg colorless needles, m.p. 160°, IR bands at 1745 (γ-lactone), 1730 (ketone) and 1670 cm^{-1} (double bond). [Found: C, 72·63; H, 8·13; O, 19·56. Mol. wt. (mass spec.) 248. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12; O, 19·33%. Mol. wt. 248.] The material showed no m.p. depression when mixed with authentic isodamsin prepared by the hydrogenation of damsin.[20] The material from confertiflorin was also identical with the material from damsin by IR and NMR analyses. Furthermore the two samples of isodamsin displayed identical ORD curves down to 210 nm: (0·007 g in 100 ml) $[\alpha]_{360}$ +340, $[\alpha]_{325}$ +790, $[\alpha]_{300}$ −860, $[\alpha]_{284}$ +750, $[\alpha]_{257}$ −14300, $[\alpha]_{210}$ +10000 (last reading).

[20] M. Suchy, V. Herout and F. Sorm, *Czech. Chem. Commun.* **28**, 2259 (1963) and F. Sorm, M. Suchy and V. Herout, *Ibid.* **24**, 1548 (1959).

Mesylate XVI

A soln of XIV (0·355 g) in 2 ml pyridine was chilled with an ice bath, mixed with 1·2 ml mesyl chloride, and kept in the refrigerator for 15 hr. The dark brown reaction mixture was mixed with crushed ice and finally extracted with CH_2Cl_2. A crystalline product (0·145 g) was obtained on concentration of the CH_2Cl_2 soln. Recrystallization from chf afforded light brown rods, XVI, m.p. 202–203°, IR bands at 1755 (γ-lactone), 1725 (ketone), 1340 and 1170 cm^{-1} (mesylate).

Synthesis of isodamsin from mesylate XVI

A soln of 0·167 g of XVI in 2 ml of 2,6-lutidine was refluxed for 19 hr under N_2 (about $\frac{1}{2}$ of the starting material was recovered when a reaction soln which had been refluxed for only 8 hr was worked up). The soln was poured over crushed ice, acidified with conc HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated *in vacuo* to yield 150 mg of a light brown crystalline material. NMR analysis indicated that the crude material was a mixture of 2 sesquiterpene lactones The compounds were separated by preparative TLC on silica gel, using ether as eluent. The more polar material, 11·8 mg of colorless needles, m.p. 160°, was shown to be identical with XI by m.p., mixed m.p., IR and NMR analyses.

The less polar material was recrystallized from MeOH to yield 20 mg of pure XVII, m.p. 157–158°, IR bands at 1760 (γ-lactone) and 1730 cm^{-1} (ketone). [Found: C, 72·61; H, 8·43; O, 19·58. Mol. wt. (mass spec.) 248. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12; O, 19·33%. Mol. wt. 248.]

Determination of the configuration at C-8 *in desacetylconfertiflorin* (II) *by Horeau's method*[14]

Racemic α-phenylbutyric anhydride (197·21 mg, 0·63 mmoles) and 115·2 mg (0·437 mmoles) of desacetylconfertiflorin were dissolved in 2·5 ml pyridine and the mixture was allowed to stand overnight at room temp. The reaction mixture was worked up as previously described.[4] The NMR of the EtOAc fraction (183·0 mg) indicated that the product was totally esterified. The $NaHCO_3$ extract yielded 104·0 mg of α-phenylbutyric acid, $[\alpha]_D^{24}$ + 7·62°. For a 100% optical yield the recovered acid would have shown $[\alpha]_D^{24}$ −50·5°. Therefore, the optical yield is 15%, (7·62/50·5 × 100), in levorotatory acid.

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