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CMR SPECTROSCOPY OF LABDANIC DITERPENES AND RELATED SUBSTANCES[1,2]

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ABSTRACT.—A carbon-shift analysis of labdanic diterpenes of the manool, agathic acid, and sciadin types is presented. The C-12 and C-20 configurations of sciadin have been determined and the structure of potamogetonin has been revised.

Structure analyses (1-3) and chemical transformations (4) of dicarbocyclic diterpenes of the labdane type have led to the accumulation of a number of structurally related compounds whose similarity made them fine substrates for cmr analysis and thus for the acquisition of physical data of significance for further research in diterpene chemistry. Structures **1-11** represent substances whose carbon shifts are listed in Table 1. The assignment of the δ values derived from proton-decoupled and single-frequency off-resonance decoupled spectra was based on chemical shift theory and on analogy with carbon shifts of decalin models (5), some labdane models (5-13), and tricarbocyclic diterpene systems (14,15).

As the shift comparison of manool (**1a**) and its dihydro derivative (**1b**) indicates, the side-chain double bond has only a small effect on its neighbors, *e.g.*, C-12 (0.08 ppm), leaving other shifts, even that of C-13, unaffected. Similarly, C-13 epimeric alcohols (**1a-4h, 1f**) do not reveal the C-13 stereochemistry by differences of the chemical shifts of C-13 on neighboring carbons. The 7α substituents are axial, as seen by the γ effects on C-5 and C-9 (*cf.* Δδ values for the **1a-3a** and **1c-2c** pairs of compounds), and exert an unusual shielding effect on C-20 (16). The increased C-19/C-20 steric interaction on introduction of a hydroxy group at C-19 (*cf.* compounds **4h, k, n** and **p**) causes deshielding of C-20 (*cf.* Δδ values for the **1a-4h** and **1n-4n** pairs of substances), while the γ-effects exerted by the hydroxy function, strongly shielding C-3 and C-18, reveal the oxygen to be oriented gauche to these carbons in the preferred conformation of their hydroxymethyl groups. A 4β-carboxy or -carbomethoxy group (as in **6m-n, 7c, j** and **n**) is known to eclipse the C-3/C-4 bond (17). As a comparison of the shifts of **1c** and **7c** reveals, this preferred rotamer population causes deshielding of C-2 and C-6 and noticeable shielding of C-20. The C-20 shift change is similar to that encountered on removal of the 4β substituent (*cf.* Δδ values of the **1n-8n** pair of substances).

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[1]Dedicated to Professor Edgar Lederer on the occasion of his seventy-fifth birthday.

[2]Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances, LXXXI. For the previous paper see S.C. Sharma, J.S. Tandon, B. Porter, M.S. Raju, and E. Wenkert, *Phytochemistry*, **23**, 1194 (1984).

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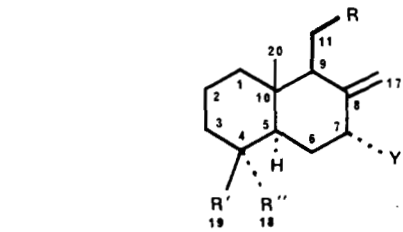
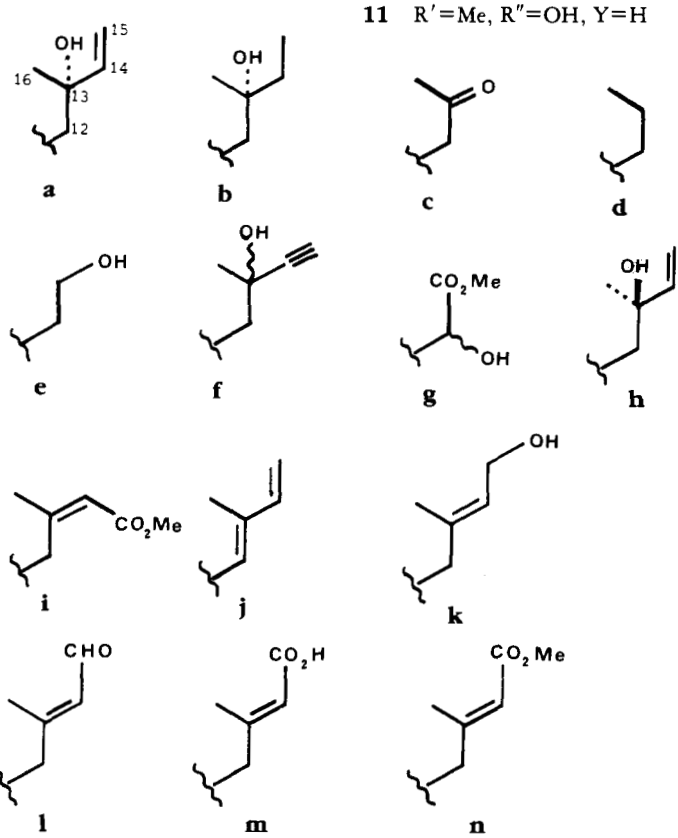


1 R′=R″=Me, Y=H
2 R′=R″=Me, Y=OH
3 R′=R″=Me, Y=OAc
4 R′=CH_2OH, R″=Me, Y=H
5 R′=CH_2OAc, R″=Me, Y=H
6 R′=CO_2H, R″=Me, Y=H
7 R′=CO_2Me, R″=Me, Y=H
8 R′=Y=H, R″=Me
9 R′=OH, R″=Me, Y=H
10 R′=Me, R″=Y=H
11 R′=Me, R″=OH, Y=H

R:



a **b** **c** **d** **e** **f** **g** **h** **i** **j** **k** **l** **m** **n**

The movement of a double bond from the exocyclic, C-8/C-17 position to the endocyclic, C-8/C-9 location introduces several interesting shift changes. Thus, as a comparison of the δ values of manool (**1a**) with those of its isomer **12** portrays, the reciprocal γ effects between C-11 and C-20 in manool are lost on flattening of ring B, leading to strong deshielding of these carbons in the isomer (**12**). The ring deformation causes shielding of C-1 in compound **12**. The endocyclic double bond system converts C-5 and C-6 into homoallyl sites, hence leading to their shielding (14, 15). Finally, the double bond isomerization strongly affects the chemical shift of allylic carbon 7. The change of C-8 stereochemistry of the epoxides **13** and **14** manifests itself in shift alterations at carbons 6-9 and 17.

Structures **15-19** represent 8-ketones, C-8 methylcarbinols, and 8α,17-epoxides whose carbon shifts are depicted in Table 2.

Replacement of a methylene by oxygen on the double bond emanating from C-8 (*e.g.*, **1c→15a, 1d→15b**) affects predictably all ring B carbon shifts and those of the C-9 side-chain neighbors, except for the C-6 resonance (18). Conversion of the exo-

TABLE 1. Carbon Shifts of Substances **1-11**[a]

	1a[b]	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**[c]	**1i**[d]	**1n**[d,e]	**2c**	**3a**[f]	**4h**	**4k**	**4l**	**4n**[d]	**5n**[d,g]	**6nn**[h]	**6n**[d,h]	**7c**[d]	**7j**[d]	**7n**[b,d]	**8n**[d]	**9n**[d]	**10n**[d]	**11n**[d]
C-1	39.0	39.1	39.0	39.2	39.2	39.2	38.9	39.1	39.3	38.6	38.7	38.7	38.0	38.0	38.0	39.6	39.9	39.9	39.1	39.4	39.2	37.6	37.8	38.3	37.6
C-2	19.0	19.4	19.4	19.5	19.4	19.4	19.4	19.5	19.5	19.2	19.2	19.0	19.0	19.0	19.0	18.9	20.8	20.8	20.0	20.1	20.0	21.5	18.6	17.9	20.3
C-3	42.1	42.2	42.2	42.4	42.3	42.3	42.1	42.3	42.3	41.9	41.9	35.5	35.5	35.5	35.4	36.2	39.5	39.4	38.7	38.6	38.8	36.0	41.0	30.1	42.7
C-4	33.5	33.5	33.6	33.7	33.6	33.6	33.7	33.7	33.7	33.0	32.9	39.8	39.6	39.6	39.6	37.3	44.6	44.5	44.3	44.4	44.4	31.4	72.2	33.8	72.2
C-5	55.5	55.5	55.5	55.8	55.7	55.7	55.4	55.7	55.8	47.5	48.6	56.4	56.4	56.4	56.3	56.2	56.8	56.8	55.5	56.4	56.4	53.1	53.8	49.4	56.7
C-6	24.4	24.5	24.5	24.6	24.5	24.5	24.4	24.6	24.6	31.0	28.8	24.5	24.5	24.5	24.5	24.5	27.1	27.1	26.3	26.1	26.3	27.0	23.3	29.6	23.2
C-7	38.3	38.3	38.3	38.5	38.4	38.4	38.4	38.5	38.5	73.7	76.2	38.0	38.0	39.0	38.0	38.5	39.0	39.0	38.2	38.3	38.3	38.3	38.6	38.9	38.1
C-8	148.4	148.5	148.3	148.9	148.7	148.5[i]	148.4	148.5	148.3	149.0	144.9	148.3	148.1	147.8	147.8	147.5	149.0	148.9	147.8	146.6	147.8	148.0	147.8	148.0	147.4
C-9	57.2	57.5	56.3	57.0	56.8	57.0[i]	55.7	57.3	56.4	50.2	52.2	57.4	56.5	56.4	56.3	56.2	56.3	56.3	56.3	56.4	55.5	54.2	55.2	56.0	55.7
C-10	39.8	39.8	39.7	39.7	39.7	39.9	39.3	39.9	39.9	39.8	39.5	38.9	38.9	38.9	38.9	38.8	41.1	41.1	40.4	40.3	40.3	39.3	39.5	33.4	40.1
C-11	17.6	17.6	17.6	23.3	19.8	18.7	38.2	22.5	21.8	17.1	17.2	17.9	22.2	21.5	21.7	21.6	22.5	22.5	17.7	23.1	21.8	22.0	21.4	21.4	21.6
C-12	41.3	40.5	42.8	31.1	32.0	42.5[i]	69.2[i]	32.8	40.0	42.4	41.9	41.4	38.0	39.0	38.0	39.6	40.4	40.4	42.8	140.3	39.8	39.6	39.8	39.8	39.5
C-13	73.4	73.1	209.0	23.3	63.4	71.3	176.6	160.9	161.0	209.1	73.3	73.6	140.2	164.7	160.9	160.8	161.1	161.1	208.7	132.2	160.7	160.7	160.9	160.7	160.8
C-14	144.9	34.1				88.0		115.8	115.2		144.8	145.2	123.2	127.2	115.0	115.0	116.2	115.8		132.6	115.1	114.7	115.0	115.0	114.8
C-15	111.4	8.2				68.4		166.7	167.3		111.5	111.6	59.3	191.4	167.3	167.3	176.7	177.2		108.8	177.2	167.0	167.0	167.3	167.0
C-16	27.9	26.3	29.9	14.1		29.7[i]		25.3	18.9	29.8	28.0	28.0	16.3	17.7	18.9	18.9	18.7	18.7	29.8	11.7	18.8	18.6	18.9	18.9	18.7
C-17	106.2	106.2	106.3	106.2	106.4	106.5[i]	106.7	106.5	106.5	109.3	112.0	106.7	106.6	106.7	106.7	106.7	106.7	106.7	106.4	106.6	106.5	106.4	107.0	106.6	106.8
C-18	33.5	33.5	33.6	33.7	33.6	33.6	33.7	33.7	33.7	33.2	33.1	27.2	27.1	27.1	27.1	27.5	29.3	29.3	28.8	28.8	28.8	20.3	31.0		
C-19	21.7	21.7	21.8	21.8	21.7	21.8	21.7	21.8	21.8	21.4	21.4	65.1	64.9	65.1	65.1	66.7	176.8	176.8	177.4	177.6	177.6			15.2	22.9
C-20	14.4	14.5	14.3	14.5	14.4	14.5	14.6	14.6	14.6	13.2	13.5	15.3	15.3	15.3	15.3	15.2	13.3	13.2	12.4	12.7	12.6	12.6	14.1	14.6	13.7

[a]In ppm downfield from TMS; δ (TMS)=δ ($CDCl_3$)+76.9 ppm.

[b]Data from Buckwalter *et al.* (5).

[c]δ (OMe)=52.5 ppm.

[d]δ (OMe)=50.7±0.4 ppm.

[e]Methyl copalate δ values nearly identical with those of methyl copaiferate (5).

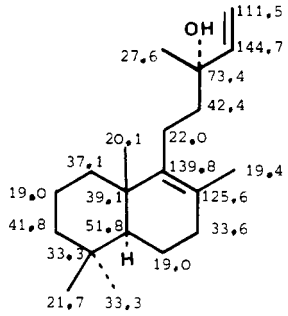
[f]Acetyl group: δ (Me)=21.4 ppm, δ (CO)=170.0 ppm.

[g]Acetyl group: 20.8 and 171.3 ppm.

[h]d_6-Acetone solution containing TMS.

[i]C-13 epimer: 148.7, 57.1, 42.3, 29.9, 106.7 ppm, respectively.

[j]C-12 epimer: 70.8 ppm.



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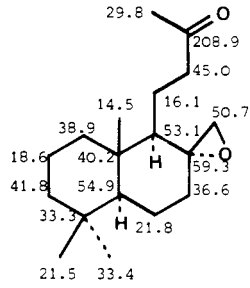

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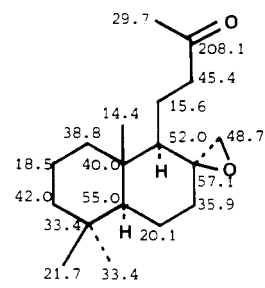

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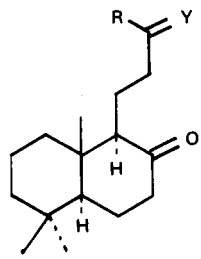
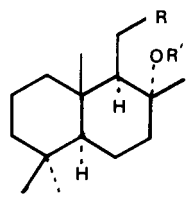
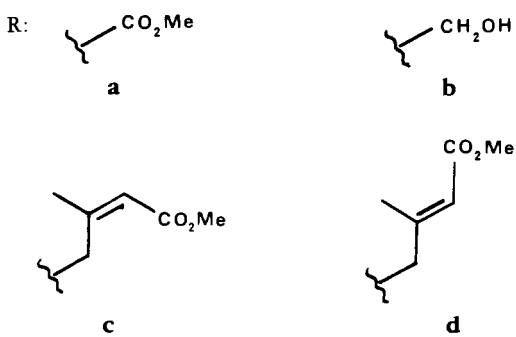


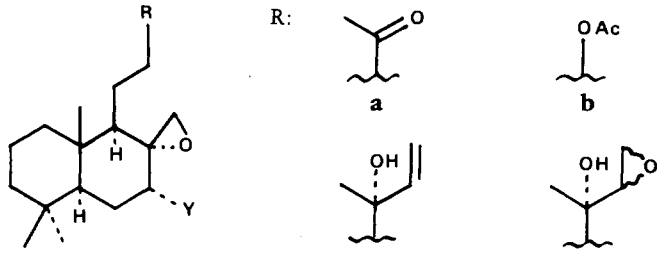
15a R=Me, Y=O
15b R=Me, Y=H_2
15c R=OMe, Y=O



16 R'=H
17 R'=Ac



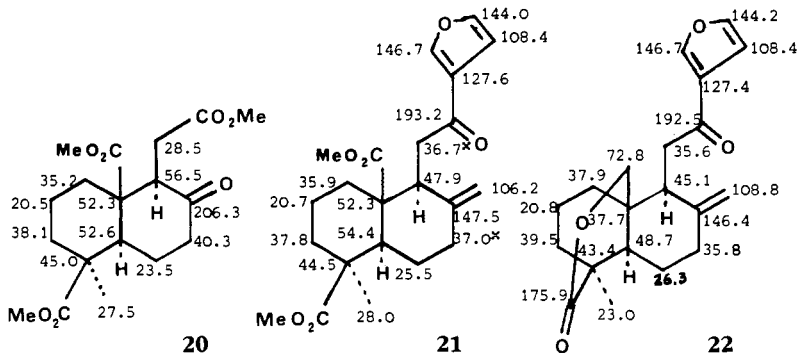
cyclic double bond into a methylcarbinol (*e.g.*, **1i**→**16c**, **1n**→**16d**) causes shielding of C-6, due to a γ-effect, and mild deshielding of C-20, owing to a δ effect. The stereoisomerism of the crotonic ester moiety in the side-chains of esters **1i** and **16c** vs. **1n** and **16d**, respectively, is reflected by the *ca.* 7 ppm shielding of C-12 or C-16 *cis*oid to the carbomethoxy group. Transformation of the C-8/C-17 double bonds into an α-



18 Y=H
19 Y=OH

epoxide (*e.g.*, **1a→18c, 1c→13, 2c→19a**) induces shielding of the protonated allylic carbons (19). Because the attachment of the two C-8 substituents of the 8α-epoxides to each other in the form of a three-membered ring reduces the axiality of C-17 and equatoriality of the oxygen toward ring B and thus their γ, δ- and γ-antiperiplanar hetero-atom effects (20), C-6 is more shielded and C-20 more deshielded in the methylcarbinols, *e.g.*, **16d**, than in the 8α-epoxides, *e.g.*, **13**.

Some time ago, the Japanese plant *Sciadopitys verticillata* Sieb. et Zucc. was shown to yield *inter alia* three labdanes of high level of oxidation—dimethyl sciadinonate, sciadinone, and sciadin—whose chemical degradations have led to yet other oxidized carbobicycles (1). The accumulation of these substances now permits their cmr spectral analysis. The shift assignment of the simplest compound, ketotriester (**20**), is based on the carbon shifts of decalone models (5) and dimethyl agathate (**7n**) (see Table 1). The line shape and multiplicity of certain signals in the single-frequency off-resonance spectra of this compound and its relatives were of importance in the δ value designation. The carbon shifts of the triester **20**, dimethyl sciadinonate (**21**), sciadinone (**22**), 20-hydroxysciadinone (**23**), and 20-acetoxysciadinone (**24**) are exhibited on the formulas.



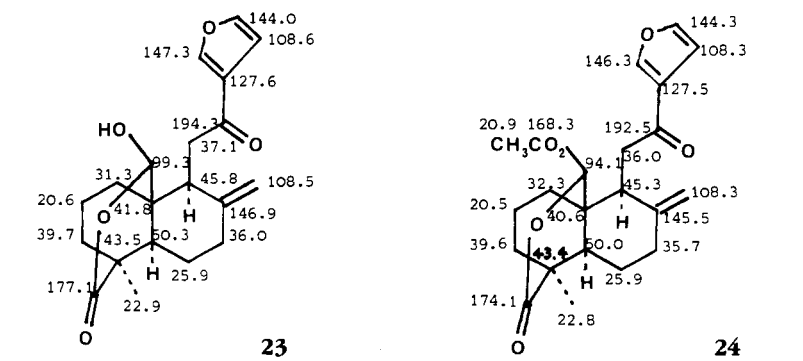


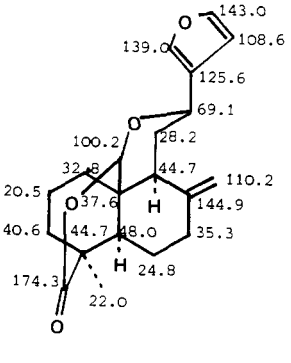
TABLE 2. Carbon Shifts of Substances **15-19**[a]

	15a	**15b**	**15c**[b]	**16b**	**16c**[b]	**16d**[b]	**17a**[b,c]	**18c**	**18d**	**19a**	**19b**[d]
C-1	39.2	39.4	39.2	39.5	39.5	39.9	39.0	39.0	39.1	38.7	38.6
C-2	19.1	19.1	19.0	18.4	18.6	18.5	18.4	18.7	18.7	18.6	18.6
C-3	41.9	42.1	41.9	42.0	42.2	42.0	41.7	42.1	42.1	41.8	41.7
C-4	33.7	33.8	33.7	33.3	33.5	33.4	33.2	33.5	33.5	32.9	32.9
C-5	54.2	54.5	54.2	56.1	56.3	56.2	55.4	55.2	55.2	46.9	46.8
C-6	24.0	24.2	24.0	20.5	20.4	20.6	19.9	21.9	21.9	28.5	28.4
C-7	42.5	42.7	42.5	44.3	43.4	44.4	38.8	36.6	36.7	73.3	73.1
C-8	212.0	211.4	211.7	73.0	74.0	74.1	86.3	59.5	59.4	62.0	61.4
C-9	63.2	64.6	63.1	59.2	61.8	61.5	55.2	54.2	54.5[e]	46.0	43.2
C-10	42.5	42.7	42.5	39.0	39.0	39.3	38.7	40.5	40.5	40.1	39.8
C-11	16.2	21.3	17.4	28.0	24.4	23.7	30.4	16.0	15.4	15.3	20.9
C-12	42.8	33.6	33.1	64.1	37.6	44.8	174.7	43.8	40.6[e]	44.9	65.2
C-13	208.9	23.3	173.4		161.9	161.3		73.3	69.4[e]	208.8	
C-14					115.3	114.8		145.6	57.7[e]		
C-15					167.1	167.3		111.2	42.3[e]		
C-16	29.8	14.0			25.7	19.1		27.8	23.1[e]	29.9	
C-17				24.6	24.4	24.0	22.6	50.8	50.9	50.1	50.0
C-18	33.6	33.6	33.5	33.4	33.5	33.3	33.3	33.5	23.5	33.1	33.1
C-19	21.8	21.7	21.7	21.5	21.5	21.5	21.4	21.7	21.7	21.4	21.4
C-20	14.6	14.7	14.6	15.3	15.6	15.5	15.7	14.6	14.7	13.8	13.8

[a]In ppm downfield from TMS; δ (TMS)=δ ($CDCl_3$)+76.9 ppm.
[b]δ (OMe)=51.1±0.4 ppm.
[c]Acetyl group: δ (Me)=20.1 ppm, δ (CO)=169.8 ppm.
[d]Acetyl group: δ (Me)=20.9 ppm, δ (CO)=170.8 ppm.
[e]C-14 epimer: 54.6, 43.0, 69.6, 56.9, 43.1, 25.8 ppm, respectively.

The strong shielding of C-1 by the introduction of 20-oxy substituents (**22**↦**23** or **24**) shows the latter to be oriented toward ring A in lactol **23** and its acetate (**24**). The large Δδ (C-20) value of these two substances suggests that the acetyl group of ester **24** occupies a preferred rotamer population in which its carbonyl oxygen is oriented toward H-20.

The carbon shifts of sciadin (**25**) and its carbinolamide ether transformation products (**26** and **27**) are delineated on the formulas. In view of the proximity of the carbonyl oxygen of lactones **22-25** and lactams **26-27** to the 4α-methyl group, the latter is shielded strongly, when compared with its field position in 4β-carbomethoxy compounds (**7**, **20**, and **21**). The lack of serious change of the C-1 resonance in lactol **23** vs. lactol ether **25** shows the C-20 configuration of the two compounds to be identical. Furthermore, because the 20-hydroxy group of lactol **23** is oriented equatorially to the



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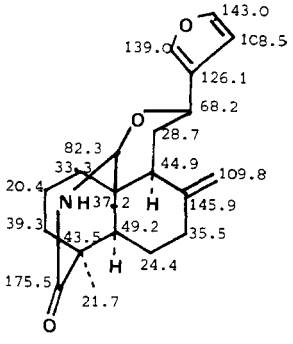

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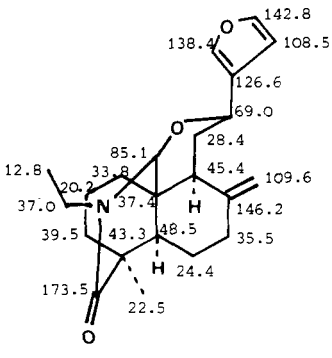

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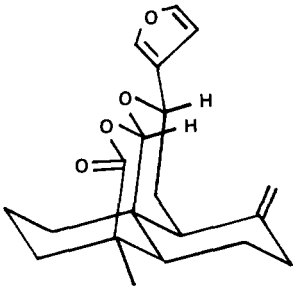
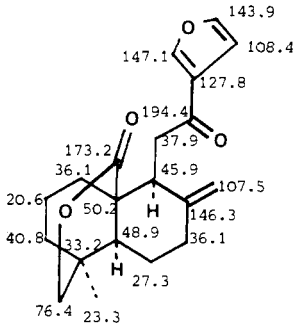
lactone, the tetrahydropyran-δ-lactone heterobicycle of sciadin (**25**) must be in a *trans*-configuration. Finally, the β-furyl group can be only an equatorial substituent in the tetrahydropyran ring of sciadin (**25**) and its lactam equivalents (**26** and **27**), because in the conversion of the natural terpene into the nitrogenous derivatives by NH_3 or ethylamine treatment (1), the tetrahydropyran ring would not have reformed with the furyl unit in an axial disposition. This discussion pinpoints for the first time the C-12 and C-20 stereochemistry of sciadin (**25**) and limits its structure to that portrayed in formula **28**.

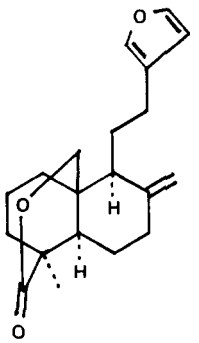


28

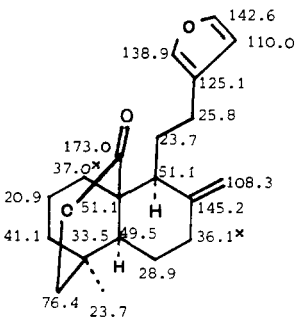


29

The carbon shifts of lactone **29**, an isomer of sciadinone (**22**), appear changed only minimally from those of the latter substance. The deshielding of C-11 can be attributed to a δ effect from the oxygen of the 20-oxo unit. In the presence of the cmr data for lactones **22** and **29**, it now is possible to reinspect the cmr spectral analysis of a labdanic diterpene, potamogetonin, to which structure **30** has been attributed (21). Reassignment of its carbon shifts reveals its lactone carbonyl group having been misplaced and the structure best fitting formula **31**.[4]



30



31

EXPERIMENTAL

The spectra were recorded on Varian CFT-20 and XL-100-15 NMR spectrometers, the latter operating at 25.2 MHz in the Fourier transform mode. The δ values on formulas **12-14, 20-27, 29** and **31** are derived from $CDCl_3$ solutions; δ (TMS)=δ ($CDCl_3$)+76.9 ppm. The starred numbers indicate possible

[4]A long time after the completion of the present work, there appeared a similar revision of the potamogetonin structure by S. Hasegawa and Y. Hirose, *Chem. Lett.*, 1 (1983). However, their C-1 and C-3 cmr signal assignments for the diterpene and its 20-oxo derivative (**29**) require interchange.

signal reversal. The ester shifts of **20** are δ (Me)=51.1, 51.1, 51.6 ppm; δ (CO)=172.8, 173.0, 175.2 ppm and those of **21** δ (Me)=50.4, 50.8 ppm; δ (CO)=172.8, 175.9 ppm.

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