Journal of Natural Products
Vol. 49, No. 1, pp. 79-89, Jan-Feb 1986

^{13}C-NMR STUDIES OF CEDRANOLIDES

P. JOSEPH-NATHAN, A. GUTIÉRREZ, J.D. HERNÁNDEZ,[1] L.U. ROMÁN,[1] and R.L. SANTILLAN

Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P.O. Box 14-740, México, D.F., 07000 México

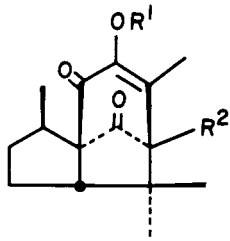
ABSTRACT.—The assignment of the ^{13}C-nmr spectra of several naturally occurring cedranolides, which include the highly oxygenated perezols (**1b, 2b,** and **1c**) and pipitzols (**1a** and **2a**), was completed. For this purpose, it was necessary to prepare a large body of derivatives, many of them regiospecifically labeled with deuterium atoms at several positions. The data are self-consistent and provide a base for the study of other tricyclic sesquiterpenes belonging to the 3,6,8,8-tetramethyl-3a,7-methanoperhydroazulene group.

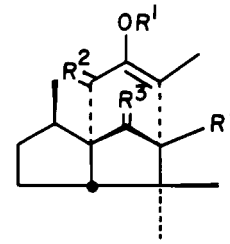
The naturally occurring cedranolides comprise a group of sesquiterpenes possessing the 3,6,8,8-tetramethyl-3a,7-methanoperhydroazulene skeleton. Among these, α-(**1a**) and β-pipitzol (**2a**), isolated from *Perezia cuernavacana* (1-3), as well as cedrol (4,5) and cedrene (**10a**) (4,6,7), constituents of cedar oil, have received considerable attention.

Although cedrol and α-cedrene (**10a**) have been the subjects of several ^{13}C analyses (8-12), there is, to our knowledge, no systematic discussion concerning an array of ^{13}C-chemical shift data on cedrane derivatives. A ^{13}C analysis of a series of these structurally complex molecules may be of great utility in the characterization of natural products possessing similar structures, such as 6,12-epoxycedrane (13), 6,12-cedranolide (13), 6*S*,12-cedranediol (13), cedrolic acid (13), α-biotol (14), β-biotol (14), 5,6-cedranediol (15), 5-cedren-13-ol (13), and juniperol (16).

From a preliminary inspection of the structure of these complex molecules, it seems evident that specific assignments of all signals might be complicated in the molecular framework due to its rigidity, which is associated with some steric factors. Thus, in order to achieve secure spectral assignments, it was necessary to resort to the preparation of a series of cedrane derivatives, some of them labeled with deuterium atoms at specific positions.

The present work describes the ^{13}C-spectral analysis of a series of cedranolides that includes derivatives of the naturally occurring α-(**1a**) and β-pipitzol (**2a**); α-(**1b**), β-(**2b**) and γ-perezol (**1c**); 5-isocedranone (**7a**) and 5-cedranone (**13a**), in which the as-





1a	R^1=H, R^2=H	**2a**	R^1=H, R^2=O, R^3=O, R^4=H
1b	R^1=H, R^2=O Angelate	**2b**	R^1=H, R^2=O, R^3=O, R^4=O Angelate
1c	R^1=H, R^2=OH	**2c**	R^1=Me, R^2=O, R^3=O, R^4=H
1d	R^1=Me, R^2=H	**2d**	R^1=Bz, R^2=O, R^3=O, R^4=H
1e	R^1=Bz, R^2=H	**2e**	R^1=Bz, R^2=H_2, R^3=O, R^4=H
		2f	R^1=Bz, R^2=H_2, R^3=H_2, R^4=H

[1]Present address: Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Mich. 58240 México.

signments of the C-4 and C-12 carbon signals were ascertained by deuteration. It also includes the two pairs of epimeric alcohols: 5-neoisocedranol (**8a**), 5-isocedranol (**9a**), 5-neocedranol (**14a**) and 5-cedranol (**15a**), which were also labeled at positions 4 and 12. Initially, a brief description of the preparation of the molecules is outlined, followed by the discussion of their ^{13}C-nmr spectra.

The natural mixture of α-(**1a**) and β-pipitzol (**2a**) was separated by fractional crystallization of the derived benzoates (**1e** and **2d**) (17), while a sample of 12-deutero-β-pipitzol benzoates, obtained from the thermal transformation of monodeuteroperezone was available from a mechanistic study (2). *O*-Methyl-α-(**1d**) and *O*-methyl-β-pipitzol (**2c**) were prepared by reaction of either **1a** or **2a** with CH_2N_2, and confirmed by the appearance of the methoxyl group at 3.64 and 3.72 ppm in **1a** and **2a**, respectively.

Treatment of either α-(**1e**) or β-pipitzol benzoate (**2d**) with ethanedithiol in the presence of BF_3:OEt_2 followed by desulfuration with neutral Raney-Ni yielded 4-desoxo-α-(**4**) and 4-desoxo-β-pipitzol benzoate (**2e**) (3), respectively, as deduced from the disappearance of the band at 1690 due to the enolized ketone, in the ir spectra.

A second thioketalization-desulfuration sequence of **4** or **2e** afforded the also desired 4,9-*bis*-desoxo-α-(**6a**) and 4,9-*bis*-desoxo-β-pipitzol benzoate (**2f**), respectively (3).

The compounds α-(**1b**), β-(**2b**) and γ-perezol (**1c**) were obtained from the roots of *Perezia hebeclada*, as reported previously (18).

Hydrolysis of 4,9-*bis*-desoxo-α-pipitzol benzoate (**6a**) gave 5-isocedranone (**7a**) (3). The ^{1}H-nmr spectrum of **7a** exhibits two doublets at 0.85 (J=6.5 Hz) and 1.19 (J=7 Hz) for the C-10 and C-11 secondary methyl groups, respectively, and singlets at 0.97 and 1.00 ppm for the *gem*-dimethyl group, while the methine at C-6 appears as a double quartet at 2.55 ppm (J=7 and 2 Hz).

A sample of 5-isocedranone (**7a**) was reduced by means of $LiAlH_4$, yielding a mixture of 5-isocedranol (**9a**) and 5-neoisocedranol (**8a**) (19) in a 4:96 ratio. The ^{1}H-nmr spectrum of compound **8a** shows doublets at 0.82 (J=7 Hz) and 1.15 (J=7 Hz) for the C-10 and C-11 methyl groups, respectively, and singlets at 0.95 and 1.25 ppm for the *gem*-dimethyl group. It also shows the 5α carbinyl proton at 4.00 (1H, q, J=3 Hz) and the 6α methine at 2.50 (1H, t, J=6 Hz) ppm. The epimeric 5-isocedranol (**9a**) shows the characteristic secondary methyl groups at 0.86 (J=7 Hz) and 1.16 (J=7 Hz) for C-10 and C-11, respectively, two singlets at 0.95 and 1.12 ppm for the *gem*-dimethyl group and the 5β carbinyl proton at 3.82 ppm, in the ^{1}H-nmr spectrum.

Moreover, 5-isocedranol (**9a**) was also obtained by hydroboration-oxidation of α-cedrane (**10a**) (19), as tested by direct comparison with an authentic sample. On the other hand, Jones oxidation of 5-isocedranol (**9a**) regenerates 5-isocedranone (**7a**) (19), while dehydration of the more abundant alcohol **8a** with *p*-toluenesulfonic acid produced α-cedrene (**10a**) as demonstrated again by direct comparison.

The preparation of 5-cedranone (**13a**) was achieved by epoxidation of α-cedrene (**10a**) with *m*-chloroperbenzoic acid to yield *exo*-5,6-epoxycedrane (**11a**), followed by rearrangement with BF_3:OEt_2 (19). The ^{1}H-nmr spectrum of **13a** shows doublets at 0.85 (J=7 Hz) and 1.16 (J=7 Hz) for the C-10 and C-11 methyl groups, respectively. It also shows singlets at 0.98 and 0.99 ppm due to the *gem*-dimethyl group and a broad quartet at 2.72 (J=7 Hz) for the 6β hydrogen.

Reduction of 5-cedranone (**13a**) with $LiAlH_4$ gave a 1:1 mixture of 5-cedranol (**15a**) and 5-neocedranol (**14a**) (19). Proton nmr spectral analyses show that in the case of the *axial* alcohol (**15a**), the carbinyl proton gives rise to a double triplet (J_d=6, J_t=1.5 Hz) at 3.63 ppm, the C-10 and C-11 secondary methyl groups appear as doublets at 0.83 (J=7 Hz) and 0.98 (J=7 Hz), respectively, while the *gem*-dimethyl methyls appear as two singlets at 0.94 and 1.17 ppm. In 5-neocedranol (**14a**), the car-

binyl proton is observed as a complex multiplet at 4.12 ppm, C-10 and C-11 appear as doublets at 0.86 (J=7 Hz) and 0.93 (J=7 Hz), respectively, while the singlets at 0.95 and 1.07 are ascribed to the *gem*-dimethyl group.

Isotopic labeling at the *alpha* to carbonyl position in 5-cedranone (**13a**) and 5-isocedranone (**7a**) was accomplished using 5-isocedranone (**7a**), which was treated with MeONa in MeOD (19). This afforded a mixture of the 4-deuterated analogues **13b** and **7b** in a 93 to 7 ratio, which was separated by column chromatography. The prodominant epimer, 4-deutero-5-cedranone (**13b**), was transformed into 4-deutero-4,9-*bis*-desoxo-α-pipitzol benzoate (**6b**), by treatment with $Bz_2O/HClO_4$ (3). Alkaline hydrolysis of the enol benzoate, yielded additional 4-deutero-5-isocedranone (**7b**) (3).

Treatment of 4-deutero-5-isocedranone (**7b**) and 4-deutero-5-cedranone (**13b**) with $LiAlH_4$ afforded 4-deutero-5-neoisocedranol (**8b**), 4-deutero-5-isocedranol (**9b**), 4-deutero-5-neocedranol (**14b**), and 4-deutero-5-cedranol (**15b**) (19).

A sample of 4-deutero-6-isocedrol (**12b**) was obtained from 4-deutero-5-neoisocedranol (**8b**). For this purpose, dehydration of **8b** with *p*-toluenesulfonic acid initially gave the also desired 4-deutero-α-cedrene (**10b**), which subsequently was treated with *m*-chloroperbenzoic acid to yield 4-deutero-5,6-epoxycedrane (**11b**). Compound **11b** was then reduced by means of $LiAlH_4$ to yield **12b**, as tested by direct comparison (19).

Moreover, in order to unambiguously ascribe the methyl signals in the ^{13}C-nmr spectra of 5-cedranone (**13a**), 5-isocedranone (**7a**), 5-cedranol (**15a**), 5-neocedranol (**14a**), 5-isocedranol (**9a**), and 5-neoisocedranol (**8a**), it was necessary to resort to deuterium labeled α-cedrene (21). Thus, 12-deutero-α-cedrene (**10d**) was obtained from cedrol using the eight step sequence described previously (21) and then transformed into compounds **13c, 7c, 15c, 14c, 9c,** and **8c,** labeled at C-12 as indicated in the reactions summarized in Figure 1.

The simplest way to follow the ^{13}C-nmr assignment of all the cedranolides studied in the present work is to inspect the case of γ-perezol (**1c**). For this molecule, the cyclopentanone carbonyl signal at 205.5 ppm can be readily distinguished from the six-membered α,β-unsaturated ketone at 192.7 ppm. Moreover, differentiation of the two sp^2 carbons can also be attained easily since one is an oxycarbon at 143.9 ppm. The assignment of the sole sp^3 carbon bearing an oxygen atom, which appears at 87.4 ppm, is trivial. The remaining two quaternary sites, at C-3a and C-8, were assigned to the signals at 69.8 and 40.6 ppm, respectively, in agreement with an earlier analysis of these centers in α-cedrene (**10a**), 6-isocedrol (**12a**), and cedrol (21). The two methylenes at C-1 and C-2 can be distinguished considering substituent effects caused by the secondary methyl group. Thus, the signal at 26.8 ppm was ascribed to C-1 while C-2 appears at 36.7 ppm. These assignments are in agreement with the double-quantum coherence measurements reported for cedrol (21). Similar considerations allow tentative ascription of the two methine carbons at C-3 (35.3 ppm) and C-8a (58.1 ppm) when the effects of the *gem*-dimethyl and secondary methyl groups are taken into account. The secondary methyl group maintains an essentially constant chemical shift throughout the series and was ascribed to the signal at 14.5 ppm, while the vinyl methyl corresponds to the highest field signal (11.9 ppm), as evidenced by the absence of long range coupling constants in the coupled spectrum of **1c**. Finally, the specific assignment of the remaining methyl signals to the *gem*-dimethyl group is not directly possible. However, it follows after evaluation of those signals corresponding to other molecules of the series where one of these methyl groups was isotopically labeled.

Substitution of the hydroxyl group at C-7 by an angeloyl ester (**1b**) leads to no significant variations in the chemical shift of all signals, as shown in Table 1. As for the signals owing to the ester residue, they can be easily ascribed with reference to a recent

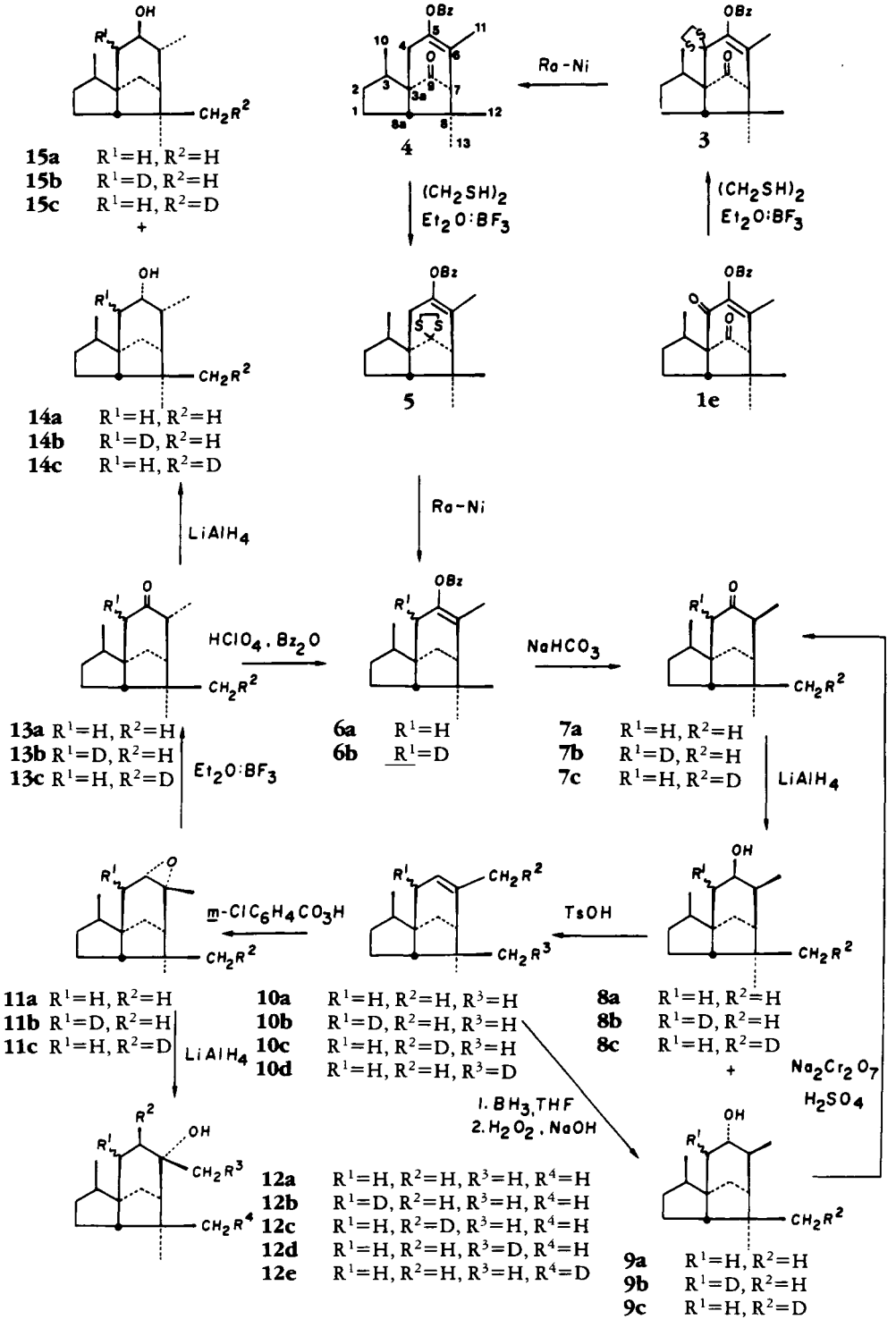


FIGURE 1. Synthetic route for the preparation of deuterated samples derived from α-cedrene (**10a**).

two-dimensional ^{1}H- ^{13}C-nmr study of angelic acid (22).

Comparison of the data of γ-perezol (**1c**) with α-pipitzol (**1a**) shows a significant variation in the chemical shift of C-7 which is shifted upfield to 69.0 ppm by removal of

TABLE 1. ^{13}C-Chemical Shifts of Cedranolides[a,b]

Compound	Structure	Carbon Number														
		1	2	3	3a	4	5	6	7	8	8a	9	10	11	12	13
α-Pipitzol	**1a**	26.0	38.2	34.9	75.0	193.7	144.6	127.2	69.0	37.3	57.4	203.6	14.9	17.8	24.4	25.5
β-Pipitzol	**2a**	24.7	35.2	35.0	76.2	193.4	144.6	129.0	68.9	37.4	55.5	203.3	13.4	17.9	26.5	24.0
α-Perezol	**1b**	26.4	36.6	35.2	70.3	192.1	143.4	127.8	91.5	39.9	57.5	198.1	14.4	12.8	25.1	20.6
β-Perezol	**2b**	25.1	34.7	34.9	72.0	191.6	143.7	129.8	90.6	39.8	55.1	197.6	13.4	13.0	25.4	18.3
γ-Perezol	**1c**	26.8	36.7	35.3	69.8	192.7	143.9	130.3	87.4	40.6	58.1	205.5	14.5	11.9	24.7	19.8
*O*Me-α-pipitzol	**1d**	26.1	38.2	35.3	76.7	193.5	149.9	141.8	69.0	37.9	57.4	204.2	14.8	18.7	26.3	25.6
*O*Me-β-pipitzol	**2c**	24.6	35.2	34.9	77.9	192.9	149.6	143.4	68.8	37.9	55.2	203.8	13.5	18.7	26.5	24.0
α-Pipitzol benzoate	**1e**	26.0	38.1	35.2	76.5	190.0	144.7	128.2	69.0	38.5	56.6	203.6	14.8	18.8	26.4	25.5
β-Pipitzol benzoate	**2d**	24.6	35.2	34.9	77.7	189.9	146.0	128.3	68.8	38.6	54.5	203.4	13.5	19.0	26.6[d]	24.0
4-Desoxo-α-pipitzol benzoate	**4**	24.4	35.9	33.6	60.2	41.8	129.2	124.6	63.2	42.5	56.6	215.4	14.9	17.7	25.9	24.3
4-Desoxo-β-pipitzol benzoate	**2e**	24.1	35.6	41.5	58.8	44.8	129.2	124.7	63.9	42.3	56.5	215.7	13.1	17.7	26.0	23.3
4,9-*Bis*-desoxo-α-pipitzol benzoate	**6a**	24.7	36.0	41.2	54.9	40.1[d]	130.0	126.5	54.2	48.6	58.7	40.5	15.4	17.5	27.6	25.7
4,9-*Bis*-desoxo-β-pipitzol benzoate	**2f**	24.0	34.4	34.4	56.0	41.5	129.9	126.6	52.9	49.5	58.1	42.3	13.6	17.6	27.8	25.0
5-Isocedranone	**7a**	25.8	37.0	41.6	56.5	51.6[d]	212.4	51.9	56.4	44.4	59.5	46.4	15.6	14.6	28.3[d]	28.4
5-Neoisocedranol	**8a**	25.2	35.7	42.0	53.3	43.0[d]	69.9	43.5	53.7[c]	44.0	54.8[c]	47.4	15.6	17.2	28.4[d]	28.9
5-Isocedranol	**9a**	25.7	36.7	41.8	54.9	43.9[d]	73.0	46.3	55.1	44.0	58.3	46.9	15.5	17.9	27.9[d]	28.8
5-Cedranone	**13a**	25.7	36.8	41.6	55.1	49.6[d]	215.3	46.8	55.7	42.7	58.5	37.6	15.3	18.0	26.9[d]	26.9
5-Neocedranol	**14a**	25.7	36.6	41.5	54.3	39.5[d]	69.0	34.8	56.2	42.0	56.3	37.7	15.4	13.0	25.0[d]	27.7
5-Cedranol	**15a**	25.0	35.5	41.7	53.7	42.0[d]	72.3	38.0	55.1[c]	42.7	55.7[c]	37.0	15.4	21.4	26.9[d]	27.1
α-Cedrene[e]	**10a**	24.8	36.1	41.5	53.8	38.8[d]	119.1	140.1	54.9	48.0	58.9	40.6	15.4	24.7[d]	27.6[d]	25.5
6-Isocedrol[e]	**12a**	25.3	36.9	41.7	53.3	30.5[d]	34.3	73.1	61.4	41.8	56.2	39.9	15.4	30.6[d]	28.1[d]	29.0
Cedrol[e]		25.4	37.0	41.5	54.1	31.6	35.3	75.0	61.0	43.4	56.6	42.0	15.6	30.2	27.7	28.9

[a]In ppm relative to internal TMS in $CDCl_3$.

[b]Chemical shifts of *O*-substituents are given in the Experimental Section.

[c]Tentative assignment.

[d]Labeled with deuterium.

[e]Joseph-Nathan *et al.* (21).

the hydroxyl group. Moreover, this also results in a downfield shift for the C-11 (17.8 ppm), C-12 (24.4 ppm), and C-13 (25.5 ppm) methyl groups, thus allowing confirmation of the assignment for C-10 to the signal at 14.9, which remains essentially constant throughout the series.

The ^{13}C-nmr data of α-pipitzol benzoate (**1e**), when compared to those of α-pipitzol (**1a**), again show no significant variation in the chemical shift of all signals. In contrast, in the *O*-methyl ether **1d**, the main chemical shift difference is the downfield shift induced at C-6 (141.8 ppm). This effect is reminiscent of the shift induced at the *beta* carbon of hydroxybenzoquinones upon methylation (23).

Removal of the C-4 carbonyl in α-pipitzol benzoate (**1e**) affords the desoxo derivative (**4**). This corroborates the carbonyl groups assignment in the already discussed cases (**1a, 1b, 1c, 1d,** and **4**). The predictable shielding of the C-3a signal in **4**, now *alpha* to only one carbonyl group, further confirms its assignment to the signal at 60.2 ppm. The assignment of the new methylene at 41.8 ppm to C-4 follows straightforward.

Similarly, comparison of 4-desoxo-α-pipitzol benzoate (**4**) with 4,9-*bis*-desoxo-α-pipitzol benzoate (**6a**) allowed us to draw similar conclusions concerning the C-3a signal which is further upfield shifted to 54.9 ppm. The C-7 signal at 54.2 ppm, being also close to the variation site was ascribed on the same basis. Further confirmation of the C-7 assignment was obtained by comparison of the chemical shift for this signal with the corresponding carbon in α-cedrene (**10a**), since both remain essentially invariant (21). However, differentiation between the C-4 and C-9 methylene signals in 4,9-*bis*-desoxo-α-pipitzol benzoate (**6a**) cannot be accomplished solely on elimination of the second carbonyl group since both methylene signals appear now within 0.4 ppm. This distinction was easily performed using 4-deutero-4,9-*bis*-desoxo-α-pipitzol benzoate (**6b**).

Similar reasoning in the β-pipitzol series lead to the assignment of the carbon chemical shifts of compounds **2a** to **2f** to the values summarized in Table 1.

Concerning the ^{13}C-assignment of 5-cedranone (**13a**) and 5-isocedranone (**7a**), deuterium labelings at positions 4 and 12 and comparisons within the same series allow ascription of all carbon signals. In the case of **13a**, the fact that only 14 of the 15 expected carbon signals were observed, required the use of the paramagnetic relaxation agent tris (acetylacetonate) Cr(III) to demonstrate superposition of two quartets at 26.9 ppm due to the *gem*-dimethyl group.

The ^{13}C-nmr data of 5-cedranol (**15a**), 5-neocedranol (**14a**), 5-isocedranol (**9a**), and 5-neoisocedranol (**8a**) provide an opportunity to evaluate some spectral characteristics in isomeric molecules differing in the chirality of two centers.

Analyses of the ^{13}C resonances of alcohols **15a, 14a, 9a,** and **8a** show a substantial degree of variation attributable to electronic effects operating on these highly substituted molecules. It has been pointed out (19) that the ^{1}H-nmr chemical shifts in these alcohols deviate considerably from expectations.

The ^{13}C-nmr data given in Table 1 show that there exists an upfield shift induced at C-9 in 5-neocedranol (**14a**) and 5-cedranol (**15a**) when compared to **8a** and **9a**. This may be attributed to a γ-gauche effect due to the C-6 α-*axial* methyl group.

In 5-isocedranol (**9a**), where there is an α-*equatorial* hydroxyl group, C-5 (73.0 ppm) is shifted downfield compared to the corresponding carbon in 5-neoisocedranol (**8a**) (69.9 ppm), which has a β-*axial* hydroxyl group. Although this observation does not seem to agree for the *alpha* carbon in 5-neocedranol (**14a**) (α-*equatorial* OH, C-5, 69.0 ppm) and 5-cedranol (**15a**) (β-*axial* OH, C-5, 72.3 ppm), it has to be pointed out that the molecular conformation of the compounds (**15a, 14a, 9a,** and **8a**) is secured from the ^{1}H-nmr data (19).

Similar trends are observed for C-6 in 5-isocedranol (**9a**) (46.3 ppm) and 5-neoisocedranol (**8a**) (43.5) which have a β-*equatorial* methyl group when compared to 5-cedranol (**15a**) (38.0 ppm) and 5-neocedranol (**14a**) (34.8 ppm), where the methyl group is α-*axial*.

Significant variations in chemical shifts are also observed for C-4, C-7, C-11, and C-12. Comparison of the chemical shifts of C-12 shows that this carbon is shifted downfield in 5-neoisocedranol (**8a**) (28.4 ppm) and 5-cedranol (**15a**) (26.9 ppm) which have the 5β-*axial* OH, compared to 5-isocedranol (**9a**) (27.9 ppm) and 5-neocedranol (**14a**) (25.0 ppm) with a 5α-*equatorial* OH.

It seems evident that although considerable deviations are expected in hydrocarbons upon substitution with hydroxyl groups, ^{13}C chemical shifts are very sensitive to molecular geometry. A more detailed evaluation of the effects involved is not possible at the present stage of the art since the molecular rigidity deviates from a more general trend. This is clearly evident from the longitudinal relaxation times determined for cedrene (**10a**). The pertinent values are depicted in Figure 2 in which it can be seen that

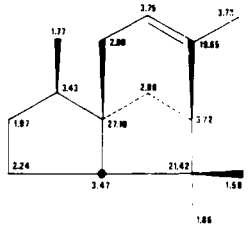


FIGURE 2. ^{13}C spin lattice relaxation times (T_1, sec) of α-cedrene (**10a**).

(a) methylene residues show T_1 values in the order of 2 sec, (b) methynes provide values around 3.6 sec, and (c) the two sp^3 quaternaries show 21.4 and 27.1 sec. The sp^2 CH and C provide 3.75 and 19.65 sec, respectively. These data are in severe contrast (24) to those of less rigid molecules such as the steroid skeleton, where average values of 4.5, 0.7, and 0.4 sec are observed for sp^3 C, CH, and CH_2 sites, respectively, and where a CH=C gives values around 0.7 and 5.6 sec, respectively.

The complete ^{13}C assignment of the present series of cedrane derivatives not only provides a useful basis for future elucidation of structurally related molecules but also settles the controversy concerning the ^{13}C spectral assignment of cedrene (**10a**). Thus, deuteration at C-4 further confirmed that the assignments of C-4 and C-9 were reversed in one report (11). Also, the pairs C-12/C-13 and C-7/C-8a were incorrectly assigned in another report (12). In addition, a literature search for the closely related natural product cedrol revealed erroneous assignments (25) for the pairs C-7/C-8a and C-2/C-4, when these are compared with our recently published (21) double quantum coherence measurements. Furthermore, the ^{13}C-nmr chemical shifts of cedrol and 6-isocedrol (**12a**) are very closely related. Thus, further confirmation for the already described assignment of the ^{13}C-nmr spectrum of 6-isocedrol (21) was obtained for the C-4 and C-5 atoms from deuterated samples (**12b** and **12c**). This allowed unambiguous ascription of C-9 to the signal at 39.9 ppm.

EXPERIMENTAL

The nmr spectra were measured from $CDCl_3$ solutions containing TMS as the internal reference. ^1H measurements were determined on a Varian Associates EM-390 spectrometer and ^{13}C spectra on a Varian Associates XL-100A-FT-16K. T_1 measurements were performed on a Nicolet NT-360 spectrometer. Ir spectra were obtained on a Perkin=Elmer 421 spectrometer in CCl_4 solution. Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

NATURAL PRODUCTS.—Samples of α-(**1a**) and β-pipitzol (**2a**) and of α-(**1b**), β-(**2b**), and γ-perezol (**1c**) were available from our previous studies on the constituents of *Perezia cuernavacana* (17). and *Perezia hebeclada* (18), while α-cedrene (**10a**) was commercially available. The ^{13}C-nmr chemical shifts for the angelate of **1b** are: δ 165.0 (CO), 127.2 (C), 139.3 (CH), 20.5 (C-*Me*) and 15.7 (CH-*Me*). Those of **2b** are: δ 165.1 (CO), 127.2 (C), 139.4 (CH), 20.6 (C-*ME*) and 15.7 (CH-*Me*) ppm.

PREVIOUSLY REPORTED α-(**1a**) AND β-PIPITZOL (**2a**) DERIVATIVES.—Samples of α-(**1e**) and β-pipitzol benzoate (**2d**) of the corresponding 4-desoxo- (**4** and **2e**) and 4,9-*bis*-desoxo-derivatives (**6a** and **2f**) were prepared as we previously described (3), their identity being established by direct comparison with retention samples. The ^{13}C-nmr chemical shifts see Table 2.

TABLE 2. The ^{13}C-nmr Chemical Shifts for Benzoate Derivatives

Compound	CO	i	o	m	p
1e	164.1	142.6	130.1	128.4	133.6
2d	164.0	142.5	130.1	128.4	133.7
4	164.2	141.0	129.7	128.4	133.3
2e	164.2	140.9	129.7	128.4	133.2
6a	164.6	141.4	129.6	128.2	132.8
2f	164.7	141.5	129.6	128.2	132.8

O-METHYL-α-PIPITZOL (**1d**).—A sample of α-pipitzol (**1a**) (100 mg) was dissolved in 2 ml of MeOH and treated with 4 ml of an ethereal CH_2N_2 solution (prepared from 300 mg of *N*-nitroso-*N*-methylurea) at 4° for 8 days. The solution was partitioned with Et_2O/H_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina eluting with hexane and hexane-C_6H_6 (1:1) to give 75 mg (71%) of **1d** (oil). The title compound shows ir ν max ($CHCl_3$) 1760, 1675, 1620 cm^{-1}; nmr (CCl_4, 90 MHz) δ 1.00 (3H, s, CH_3-12), 1.06 (3H, s, CH_3-13), 1.30 (3H, s, CH_3-11), 3.64 (3H, s, OCH_3) ppm. The ^{13}C-chemical shift for the methoxyl group is 59.6 ppm.

O-METHYL-β-PIPITZOL (**2c**).—This compound was prepared from β-pipitzol (**2a**) following the procedure described for the preparation of **1d**. Compound **2c** shows mp 72-74°; ir ν max ($CHCl_3$) 1760, 1675, 1620 cm^{-1}; nmr (CCl_4, 60 MHz) δ 1.04 (6H, s, CH_3-12, 13), 1.26 (3H, d, J=6.5 Hz, CH_3-10), 2.03 (3H, s, CH_3-11), 2.61 (1H, s, H-7), 3.72 (3H, s, OCH_3) ppm.

EXO-5,6-EPOXYCEDRANE (**11a**).—α-Cedrene **10a** (20.4 g) was dissolved in 150 ml of $CHCl_3$ and cooled to 0° (19). To the vigorously stirred solution, *m*-chloroperbenzoic acid (21 g) in $CHCl_3$ was added, and the mixture was allowed to react for 30 min at 10°. After filtration, the $CHCl_3$ solution was washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with petroleum ether to yield 18 g of **11a** (oil); bp lit. 120/2 mm (19); nmr ($CDCl_3$, 90 MHz) δ 0.83 (3H, d, J=6.5 Hz, CH_3-10), 1.00 (3H, s, CH_3-13), 1.19 (3H, s, CH_3-12), 1.45 (3H, s, CH_3-11), 3.03 (1H, d, J=4 Hz, H-5β) ppm.

5-CEDRANONE (**13a**).—*exo*-5,6-Epoxycedrane (1.1 g) (**11a**) was dissolved in 50 ml of dry C_6H_6 (19). The solution was stirred vigorously at 0° under N_2 atmosphere, and 1.0 ml of BF_3:OEt_2 was added. The reaction was allowed to proceed for 5 min, treated with 10 ml of a saturated solution of $NaHCO_3$, washed with brine, and extracted with Et_2O. The combined extracts were dried (Na_2SO_4), concentrated, and the residue was dissolved in light petroleum ether and chromatographed. The combined light petroleum ether fractions afforded 950 mg of **13a** (oil), bp lit. 115/1.2 mm (19); ir ν max (CCl_4) 1703 cm^{-1}; nmr ($CDCl_3$, 90 MHz) δ 0.85 (3H, d, J=7 Hz, CH_3-10), 0.98 (3H, s, CH_3-13), 0.99 (3H, s, CH_3-12), 1.16 (3H, d, J=7 Hz, CH_3-11), 2.72 (1H, broad q, J=7 Hz, H-6β) ppm.

5-CEDRANOL (**15a**) AND 5-NEOCEDRANOL (**14a**).—To a solution of 1.65 g of 5-cedranone (**13a**) in 20 ml of anhydrous Et_2O was added 500 mg of $LiAlH_4$ (19). The suspension was allowed to reflux for 20 h with stirring under N_2. After cooling to room temperature, a H_2O-EtOAc mixture was added carefully to destroy the excess of the reducing agent, and the mixture was filtered. The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in light petroleum ether and chromatographed on a silica gel column. Elution with light petroleum ether-Et_2O (94:6) yielded 750 mg of cedranol (**15a**), bp lit. 120/1.5 mm (19); ir ν max 3584 (OH); nmr (CCl_4, 90 MHz) δ 0.83 (3H, d, J=7 Hz, CH_3-10), 0.94 (3H, s, CH_3-13), 0.98 (3H, d, J=7 Hz, CH_3-11), 1.17 (3H, s, CH_3-12), 3.63 (1H, J_d=6, J_t=1.5 Hz, H-5α) ppm.

Subsequent elution with a mixture of light petroleum ether-Et_2O (90:10) afforded 700 mg of 5-neocedranol (**14a**), mp 78-80° [lit. 84° (19)]; nmr ($CDCl_3$, 90 MHz) δ 0.86 (3H, d, J=7 Hz, CH_3-10), 0.93 (3H, d, J=7 Hz, CH_3-11), 0.95 (3H, s, CH_3-13), 1.07 (3H, s, CH_3-12), 4.12 (1H, complex multiplet, H-5β) ppm.

5-ISOCEDRANOL (**9a**).—α-Cedrene (**10a**) (20.4 g) was dissolved in 35 ml of THF and the solution maintained at 5° under N_2 atmosphere (19). Addition of 70 ml of a diborane solution in THF was performed in 30 min with stirring. The solution was stirred 3 additional h at 10°, followed by 3 h at room temperature. The excess diborane was destroyed by careful addition of H_2O. 5-Isocedranol (**8a**) was obtained by oxidation of the reacting mixture with NaOH (35 ml, 3N) and H_2O_2 (35 ml, 30%). The product was crystallized from $CHCl_3$/hexane giving 20 g of solid **8a**, mp 146-147° [lit. 146-147° (19)]; ir ν max (CCl_4) 3575, 3415 cm^{-1} (OH); nmr ($CDCl_3$, 90 MHz) δ 0.86 (3H, d, J=7 Hz, CH_3-10), 0.95 (3H, s, CH_3-13), 1.12 (3H, s, CH_3-12), 1.16 (3H, d, J=7 Hz, CH_3-11), 3.82 (1H, complex, H-5β) ppm.

5-ISOCEDRANONE (**7a**).—*Method A*.—5-Isocedranol (**9a**) (5 g) was dissolved in 200 ml of Et_2O, and the solution was stirred vigorously at 0°. A chromic acid solution, prepared from 5 g of $Na_2Cr_2O_7 \cdot 2H_2O$, 7 g of H_2SO_4, and sufficient H_2O to make a 25 ml solution, was slowly added (19), and the reaction was allowed to proceed for 5 min. Cold H_2O was added, and the ethereal extract was washed several times with H_2O, $NaHCO_3$ solution, and H_2O. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column. The light petroleum ether fractions afforded 3.9 g (80%) of **7a**, mp 31-32° [lit. 31-32° (19)]; ir ν max (CCl_4) 1710 cm^{-1} (C=O) (19); nmr ($CDCl_3$, 90 MHz) δ 0.85 (3H, d, 6.5 Hz, CH_3-10), 0.97 (3H, s, CH_3-13), 1.00 (3H, s, CH_3-12), 1.19 (3H, d, J=7 Hz, CH_3-11), 2.55 (1H, dq, J=7, J=2 Hz, H-6α) ppm.

Method B.—A solution of 4,9-*bis*-desoxo-α-pipitzol benzoate (**6a**) (700 mg) in 250 ml of MeOH was hydrolyzed using $NaHCO_3$ (1 g) in 1 ml of H_2O at reflux temperature for 3 h (3). The solution was concentrated, H_2O was added, and the organic phase extracted with Et_2O, dried (Na_2SO_4), and concentrated. The residue was chromatographed on alumina. The light petroleum ether fractions afforded unreacted **6a** while elution with a hexane-C_6H_6 (1:1) mixture gave 400 mg of 5-isocedranone (**7a**). This compound showed identical spectral properties to the sample obtained by oxidation of 5-isocedranol (**9a**).

5-ISOCEDRANOL (**9a**) AND 5-NEOISOCEDRANOL (**8a**).—$LiAlH_4$ (500 mg) was added to 1.65 g of 5-isocedranone (**7a**) in 50 ml to THF, and the reaction was stirred at room temperature overnight (19). Excess of hydride was destroyed by adding a H_2O-EtOAc mixture cautiously. The suspension was filtered and worked up in the usual manner. The residue was dissolved in light petroleum ether and chromatographed on a silica gel column. The combined petroleum ether-Et_2O fractions (94:6) afforded 1.5 g of 5-neoisocedranol (**8a**) (oil) bp lit. 120°/2 mm (19); nmr ($CDCl_3$, 90 MHz) δ 0.82 (3H, d, J=7 Hz, CH_3-10), 0.95 (3H, s, CH_3-13), 1.15 (3H, d, J=7 Hz, CH_3-11), 1.25 (3H, s, CH_3-12), 2.50 (1H, t, J=6 Hz, H-6α), 4.00 (1H, q, J=3 Hz, H-5α) ppm.

Subsequent elution with light petroleum ether-Et_2O (90:10) yielded 60 mg of 5-isocedranol (**9a**) mp 146-147 [lit. 146-147° (19)].

6-ISOCEDROL (**12a**).—$LiAlH_4$ (1.5 g) was slowly added at room temperature to a solution of 2.2 g of *exo*-5,6-epoxycedrane (**11a**) in 5 ml of THF (19). The mixture was kept at room temperature overnight with stirring. The excess hydride was destroyed by careful addition of H_2O-EtOAc, and the suspension was filtered. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on a silica gel column using light petroleum ether as the eluent, giving 1.2 g of **12a** (oil), bp lit. 118-120°/1.4 mm (19); ir ν max (neat) 3390, 3384, 2952, 2937, 1459, 1376, and 1150 cm^{-1}; nmr ($CDCl_3$, 90 MHz) δ 0.85 (3H, d, J=6.5 Hz, CH_3-10), 1.02 (3H, s, CH_3-13), 1.14 (3H, s, CH_3-12), 1.32 (3H, s, CH_3-11) ppm.

4-DEUTERO-5-ISOCEDRANONE (**7b**) AND 4-DEUTERO-5-CEDRANONE (**13b**).—A sealed ampul containing 5-isocedranone (**7b**) (1 g) and 6 ml of 1M solution of $NaOCH_3$ in MeOD was stored at room temperature during 48 h. The solution was evaporated to dryness and the residue subjected to successive chromatography on a silica gel column with light petroleum ether giving a 93:7 ratio of 4-deutero-5-cedranone (**13b**) to 4-deutero-5-isocedranone (**7b**). The title compounds exhibited identical properties to the unlabeled compound except for the decrease in the C-4 signals at 51.6 and 49.6 ppm in the ^{13}C-nmr spectrum of **7a** and **13a**, respectively.

4-DEUTERO-4,9-BIS-DESOXO-α-PIPITZOL (**6b**).—A mixture of 4-deutero-5-cedranone (**13b**) (2 ml), Bz_2O (8 g), and 65% $HClO_4$ (3 drops) in 25 ml of CH_2Cl_2 was stirred at room temperature under N_2 for 24 h (3). After workup, the residue was chromatographed on 50 g of alumina eluting with light petroleum ether. Successive column chromatography afforded 1.0 g of **6b** which was recrystallized from MeOH, mp 49-50° [lit. 50-51° (3)]. This compound (**6b**) showed identical spectral properties to the unlabeled sample except for the decrease in the ^{13}C signal due to the incorporation of deuterium at C-4.

4-DEUTERO-5-ISOCEDRANOL (**9b**) AND 4-DEUTERO-5-NEOISOCEDRANOL (**8b**).—These compounds were prepared from 4-deutero-5-isocedranone (**7b**) using the procedure described for the preparation of **8a** and **9a**. Alcohols **8b** and **9b** showed identical properties to the unlabeled compounds except for the C-4 signal at 43.9 ppm in **9b** and 43.0 ppm in **8b** which decreased in intensity in the ^{13}C-nmr spectra.

4-DEUTERO-5-CEDRANOL (**15b**) AND 4-DEUTERO-5-NEOCEDRANOL (**14b**).—Reduction of 4-deutero-5-cedranone (**13b**) was performed using the procedure described previously for the preparation of **14a** and **15a**. The products exhibited identical spectral properties to the unlabeled sample except for the decrease in the ^{13}C signal for C-4.

4-DEUTERO-α-CEDRENE (**10b**).—4-Deutero-5-neoisocedranol (300 mg) (**8a**) was dissolved in 10 ml of toluene followed by addition of 8 mg of *p*-toluenesulfonic acid. The mixture was refluxed for 1.5 h using a Dean-Stark apparatus. After the reaction had subsided, EtOAc was added, and the organic layer was washed with a $NaHCO_3$ solution and H_2O. The EtOAc extract was dried (Na_2SO_4), concentrated, and purified by chromatography on a silica gel column. Elution with light petroleum ether afforded 260 mg of 4-deutero-α-cedrene (**10b**); nmr ($CDCl_3$, 90 MHz) δ 0.85 (3H, d, J=6.5 Hz, CH_3-10), 0.95 (3H, s, CH_3-13), 1.02 (3H, s, CH_3-12), 1.68 (3H, q, J=1.3 Hz, CH_3-11), 5.20 (1H, m, H-5) ppm. The presence of the label was evidenced by the decrease in the C-4 signal at 38.8 ppm in the ^{13}C-nmr spectrum.

4-DEUTERO-5,6-EPOXYCEDRANE (**11b**).—This compound was prepared from 4-deutero-α-cedrene (250 mg) (**10b**) using the procedure described for the preparation of **11a**. The compound exhibited identical properties to the unlabeled compound except for the decrease in the intensity of the C-4 signal in the ^{13}C-nmr spectrum.

4-DEUTERO-6-ISOCEDROL (**12b**).—This compound was prepared from 4-deutero-*exo*-5,6-epoxycedrane (**11b**) using the procedure described for the preparation of 5-deutero-6-isocedrol (**12c**). Compound **12b** exhibited identical properties to the unlabeled compound except for the decrease in the C-4 signal at 30.5 ppm in the ^{13}C-nmr spectrum.

5-DEUTERO-6-ISOCEDROL (**12c**).—Lithium aluminum deuteride (1.5 g) was slowly added at room temperature to a solution of *exo*-5,6-epoxycedrane (**11a**) (2.2 g) following the procedure described for the preparation of **12a**. The introduction of the label was confirmed by the decrease in the C-5 signal at 73.0 ppm in the ^{13}C-nmr spectrum.

12-DEUTERO-EXO-5,6-EPOXYCEDRANE (**11c**).—Compound **11c** was prepared (21) from 12-deutero-α-cedrene (**10d**) using the procedure described for the preparation of *exo*-5,6-epoxycedrane (**11a**). The product exhibited an identical proton nmr spectrum except for the integrated peak area corresponding to the CH_2D-12 signal.

12-DEUTERO-5-CEDRANONE (**13c**).—A compound **13c** was prepared from 12-deutero-*exo*-5,6-epoxycedrane (**11c**) using the procedure described for the preparation of 5-cedranone (**13a**). Compound **13c** showed an identical ^{1}H-nmr spectrum to the unlabeled compound except for the integrated peak area corresponding to the CH_2D-12 signal.

12-DEUTERO-5-CEDRANOL (**15c**) AND-12-DEUTERO-5-NEOCEDRANOL (**14c**).—These compounds were prepared from 12-deutero-5-cedranone (**13c**) using the procedure described for the preparation of 5-cedranol (**15a**) and 5-neocedranol (**14a**). Both compounds exhibited identical ^{1}H-nmr spectra to the unlabeled compound except for the integrated peak area corresponding to the CH_2D-12 signal.

12-DEUTERO-5-ISOCEDRANOL (**9c**).—Compound **9c** was prepared from 12-deutero-α-cedrene (**10d**) using the procedure described for the preparation of 5-isocedranol (**9a**). The product exhibited an ^{1}H-nmr spectrum identical to the unlabeled compound, except for the integrated peak area corresponding to the CH_2D-12 signal.

12-DEUTERO-5-ISOCEDRANONE (**7c**).—This compound was prepared by Jones oxidation of 12-deutero-5-isocedranone (**8c**) using the procedure described for the preparation of 5-isocedranone (**7a**). Compound **7c** exhibited an ^{1}H-nmr spectrum identical to the unlabeled compound, except for the integrated peak area corresponding to the CH_2D-12 signal and the decrease in the ^{13}C-nmr spectrum for C-12.

12-DEUTERO-5-NEOISOCEDRANOL (**8c**).—The title compound was prepared from 12-deutero-5-isocedranone (**7c**) using the procedure described previously for the preparation of 5-neoisocedranol (**7a**). The compound exhibited an ^{1}H-nmr spectrum identical to the unlabeled compound except for the integrated peak area corresponding to the CH_2D-12 signal.

ACKNOWLEDGMENTS

We are indebted to Dr. L.F. Johnson (General Electric, former Nicolet, Fremont, CA) and Dr. O.

Castañeda (Nicolet-México) for the T_1 measurements and to CoNaCyT (México) for partial financial support.

LITERATURE CITED

1. F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, and J. Romo, *Tetrahedron Lett.*, 1577 (1965).
2. P. Joseph-Nathan, V. Mendoza, and E. García G., *Tetrahedron*, **33**, 1573 (1977).
3. P. Joseph-Nathan, L.U. Román, J.D. Hernández, Z. Taira, and W.H. Watson, *Tetrahedron*, **36**, 731 (1980).
4. G. Stork and F.H. Clarke Jr., *J. Am. Chem.*, **77**, 1072 (1955).
5. G. Stork and F.H. Clarke, Jr., *J. Am. Chem. Soc.*, **83**, 3114 (1961).
6. G. Stork and Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953).
7. P.A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Kläui, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953).
8. E. Wenkert, A.O. Clouse, D.W. Cochnan, and D. Doddrell, *J. Am. Chem. Soc.*, **91**, 6879 (1969).
9. L.F. Johnson and W.C. Jankowski, *Carbon-13 NMR Spectra*, John Wiley and Sons, New York, 1972, p. 466.
10. J.M. Briggs, F.A. Hart, G.P. Moss, E.W. Randall, K.D. Sales, and M.L. Staniforth, in: *Nuclear Magnetic Shift Reagents*. Ed. by R.E. Sievers. Academic Press, New York, 1973, p 197.
11. E. Wenkert, B.L. Buckwalter, I.R. Burfitt, M.J. Gasic, H.E. Gottlieb, E.W. Hagaman, F.M. Schell, and P.M. Wovkulich, in: *Topics in Carbon-13 NMR Spectroscopy*. Ed. by G.C. Levy, vol. 2, chap. 2, Wiley-Interscience, New York, 1976, pp. 95-97.
12. F. Bohlmann and C. Zdero, *Chem. Ber.*, **112**, 427 (1979).
13. K.H. Baggaley, H. Erdtman, and T. Norin, *Tetrahedron*, **24**, 3399 (1968).
14. B. Tomita, Y. Hirose, and T. Nakatsuka, *Tetrahedron Lett.*, 843 (1968).
15. V.M. Patwarhan, J.B. Lal, and G.N. Gupta, *Indian Perfum.*, **10**, 39 (1968).
16. S. Akiyoshi, H. Erdtman, and T. Kubota, *Tetrahedron*, **9**, 237 (1960).
17. F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar, and J. Romo, *Tetrahedron*, **22**, 2387 (1966).
18. P. Joseph-Nathan, Ma. P. González, and V.M. Rodríguez, *Phytochemistry*, **11**, 1803 (1972).
19. S.P. Acharya and H.C. Brown, *J. Org. Chem.*, **35**, 196 (1970).
20. P. Teisseire, M. Plattier, W. Wojnarowski, and G. Ourisson, *Bull. Soc. Chem. Fr.*, 2749 (1966).
21. P. Joseph-Nathan, R.L. Santillan, and A. Gutiérrez, *J. Nat. Prod.*, **47**, 924 (1984).
22. P. Joseph-Nathan, J.R. Wesener, and H. Günther, *Org. Magn. Resonance*, **22**, 190 (1984).
23. P. Joseph-Nathan, D. Abramo-Bruno, and D.A. Ortega, *Org. Magn. Resonance*, **15**, 311 (1981).
24. G.C. Levy and U. Edlund, *J. Am. Chem. Soc.*, **97**, 5031 (1975).
25. A.F. Thomas and M. Ozainne, *Helv. Chim. Acta*, **62**, 361 (1979).

Received 29 April 1985