

Carbon-13 NMR Studies of Labdane Diterpenoids

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Studies of the ¹³C NMR spectra of ten labdane derivatives using shift reagents, deuterium labelled compounds, and spin-lattice relaxation time measurements have permitted assignment of all signals. Axial, and sterically distorted methyl groups are shown to have longer relaxation times than their equatorial counterparts.

Considerable interest has been focused on carbon-13 nuclear magnetic resonance (¹³C NMR) spectrometry of complex natural products¹ and its utility for solving structural,²⁻¹² stereochemical¹³⁻¹⁶ and conformational¹⁷ problems in the terpenoid field has been demonstrated.

The labdane group of diterpenoids is of general occurrence in Nature and comprises members regarded as intermediates in the biosynthesis of tri and tetracyclic diterpenoids.¹⁸ In tobacco, which contains a series of labdanes, some of them probably also constitute precursors of many of the nor-terpenoids encountered.¹⁹ A ¹³C NMR study of the labdanes was therefore deemed of interest and this work * describes the ¹³C NMR spectra of ten labdane derivatives. The utility of spin-lattice relaxation time (*T*₁), which has been shown to reveal unique structural information,²⁰⁻²¹ is also briefly explored as a tool for solving assignment problems in this series.

RESULTS AND DISCUSSION

All compounds studied (I–X) possess a labdane or nor-labdane (IX) skeleton and differ with respect to the oxygenation pattern.

* Part of this work has been presented at Organikerdagarna, Stockholm 1972.

Their pulsed Fourier transform ¹³C NMR spectra were obtained at 25.16 MHz in CDCl₃ using TMS as internal standard; in most cases both proton noise-decoupled and off-resonance decoupled spectra were recorded. The assignments of the observed resonances, which are given in Table 1 and are discussed in some detail below, were in many cases aided by studies of *T*₁ and lanthanide induced chemical shifts (LIS), by intercorrelation and by comparison of literature data for structurally related compounds. The chemical shifts of the quaternary carbons for two of the compounds examined here, manool (VI) and sclareol (VII), have been reported previously, but without assignment.²²

Manoyl oxide (I 8,13-epoxylabd-14-ene).²³ A preliminary assignment of the non-trivial resonances was achieved by comparison with published data¹⁷ and use of additivity rules;^{24,25} for the carbons bound to oxygen, C(8) and C(13), the chemical shift values of C(2) in tetrahydropyran (69.7 ppm) was used as the constant term.²⁶ Some relevant values are included in Table 1 and it follows that there is in most cases an astonishingly good agreement, despite the approximations made, between predicted and observed values in the case of the methylene carbons. However, large deviations are generally encountered for the methyl, methine, and quaternary carbons, some of which therefore are omitted in Table 1.

Although neither the C(5) and C(9) signals, nor the C(8) and C(13) signals could be assigned on a one-to-one basis on the above grounds alone, differentiation could be accomplished with the aid of the shifts encountered on reduction of the C(14)–C(15) double bond (II, IIa) and oxygenation of ring A (III–V) (*vide infra*). Similarly, the C(16) and C(17) resonances could

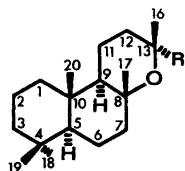
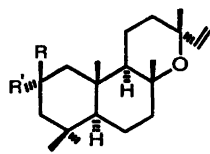
Table 1. Carbon-13 chemical shifts

Compound	Chemical shift in ppm from internal TMS									
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)
I Manoyl oxide	39.0	18.6	42.1	33.2	56.4	19.9	43.2	74.8	55.7	36.9
	37.2	18.3	41.6	28.7	49.6	19.5	42.4	72.1	53.2	33.6
II Dihyromanoyl oxide	39.2	18.7	42.2	33.3	56.5	19.9	43.1	74.5	58.3	36.8
III 2-Oxomanoyl oxide	54.6	211.0	56.4	38.7	55.6	20.1	42.6	74.6	55.1	42.2
IV 2 α -Hydroxymanoyl oxide	48.1	64.8	51.1	34.7	54.8	19.5	43.0	74.5	55.8	38.5
V 3-Oxomanoyl oxide	37.8	33.8	217.3	47.3	54.9	20.8	42.5	74.4	54.9	36.5
VI Manool	39.0	19.3	42.2	33.3	55.6	24.3	38.3	148.6	57.2	39.7
	7	2	0	0	5	2	5	9	15	8
VII Sclareol	39.5	18.8 ^a	41.9	33.1	55.9	20.4	43.9 ^b	74.3	61.4	39.0
VIII Labd-13 <i>E</i> -en-8-ol	39.8	18.5	42.1	33.3	56.2	20.6	43.3	74.1	61.6	39.3
IX 14,15-bisnorlabdan-8-ol-13-one	39.9	18.8	41.9	33.2	56.0	20.4	44.5	73.6	60.6	39.2
X Marrubiin	35.3 ^a	18.2	28.6 ^a	43.9	44.9	76.6	31.6 ^a	32.3	75.7	39.8
	51	79	169	127	137	186	53	81	94	108

be assigned as these were the only methyl signals (28.5 and 25.5 ppm) whose positions changed on hydrogenation.

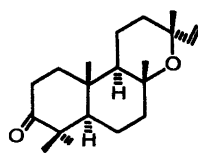
Of the C(18), C(19), and C(20) methyl resonances, that at lowest field was ascribed

to the equatorial C(18), while the highest field signal was associated with C(20), which is subjected to three 1,3-diaxial hydrogen interactions.²⁴ These correlations were confirmed by T_1 measurements (*vide infra*).

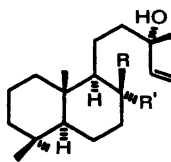
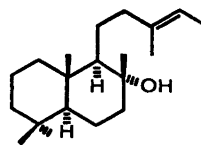
I R = CH=CH₂II R = CH₂CH₃

III R, R' = O

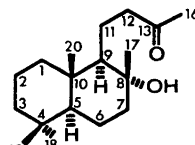
IV R' = OH, R = H



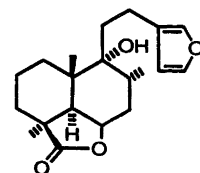
V

VI R, R' = CH₂VII R = CH₃, R' = OH

VIII



IX



X

and lanthanide induced shifts.

C(11)	C(12)	C(13)	C(14)	C(15)	C(16)	C(17)	C(18)	C(19)	C(20)	Comments
15.4 15.7	35.8	73.0	147.8	110.1	28.5	25.5	33.4 30.7	21.3 21.5	15.3 17.4	Predicted
15.4	35.8	72.8	37.9	8.0	27.2	24.8	33.4	21.3	15.7	
15.5	35.5	73.2	147.5	110.4	28.5	25.0	33.4	22.9	16.5	
15.4	35.3	73.0	147.1	109.7	28.6	25.4	33.3	22.1	16.3	
15.6	35.7	73.4	147.9	110.3	28.5	24.8	26.6	20.8	15.0	
17.6 20.0 37	41.4 42.4 51	73.5 164	145.1 41	111.4 44	27.9 25.9 51	106.3 7	33.6 0	21.6 0	14.4 5	Predicted ⁴⁶ Eu(FOD) ₃ LIS(Hz)
18.4 ^a	44.8 ^b	73.0	146.2	110.3	26.2	24.0	33.3	21.4	15.3	<i>a, b</i> : may be interchanged
23.9	44.6 42.0	137.0 135.5	118.3 118.4	13.3 12.8	15.9 15.0	23.9	33.4	21.5	15.5	Predicted ²⁵
18.4	46.2	?	—	—	29.8	24.0	33.4	21.4	15.1	
28.3 81	21.0 40	125.5 22	111.0 18	143.2 31	138.8 31	16.6 33	23.0 158	184.3 666	22.3 113	<i>a</i> : may be interchanged Eu(FOD) ₃ LIS(Hz)

The assignments made for manoyl oxide (I) are in agreement with results obtained for pimaradienes,¹⁷ and podocarpanes.²⁷

Dihydromanoyl oxide (II 8,13-epoxylabdane).^{28,29} The only resonances due to the carbons of rings A and B, including substituents, which do not occur at the same frequencies in the spectra of manoyl oxide (I) and dihydromanoyl oxide (II) are those assigned to the carbons also representing part of ring C, *i.e.* C(8), C(9), and C(17). While these alterations were useful in distinguishing between the methyl signals and between the C(5) and C(9) signals, the minor shifts observed for the other ring C carbon signals did not aid the individual assignment of the C(8) and C(13) resonances. However, examination of a labelled derivative, 14,15-*d*₂₋₄-dihydromanoyl oxide (IIa),²⁹ prepared by catalytic reduction of manoyl oxide using deuterium gas, resolved this ambiguity, since the intensity of the C(13) signal decreased drastically, while that of the C(8) signal remained the same;²⁷ the signals due to C(14) and C(15) were hardly visible.

2-Oxomanoyl oxide (III 8,13-epoxylabd-14-

en-2-one).^{30,31} The spectrum of this compound confirmed most of the assignments made for the ring A carbons of manoyl oxide (I). Thus the resonances for C(1) and C(3) are displaced 15.6 and 14.3 ppm downfield in agreement with what has been found on introducing a keto group into cyclohexanes³² and steroids.^{33,34} A deshielding of C(4) and C(10) by 5.5 and 5.3 ppm was also observed and since this is a noticeably larger effect than that encountered for the cyclohexanes and steroids, it might partially be associated with a conformational change on introduction of the keto group. The resonances due to the proximate methyls, C(18), C(19), and C(20) all move less than 2 ppm downfield.

2 α -Hydroxymannoyl oxide (IV; 8,13-epoxylabd-14-en-2 α -ol).³¹ As for 2-oxomanoyl oxide (III), the changes in chemical shifts caused by introduction of an oxygen function confirmed the initial assignments made for manoyl oxide (I). Thus, the 46.2, 9.0, and 9.1 ppm shifts towards lower field of the C(2), C(3), and C(1) signals and the 1.6 ppm upfield shift of the C(5) signal agree well with values re-

ported for cyclohexanols.³⁶ In contrast, the C(10) and C(4) resonances move 1.6 and 1.5 ppm to lower field, a result which differs from that reported for cyclohexanols but is in accord with results obtained for steroids.³⁴

*3-Oxomanoyl oxide (V; 8,13-epoxylabd-14-en-3-one).*³⁷ The chemical shifts of the B- and C-ring carbons remained, as expected, approximately the same as in manoyl oxide (I). The downfield shifts of 15.2 and 14.1 ppm observed for the C(2) and C(4) signals, and the upfield shifts of 1.2 and 1.5 ppm for the C(1) and C(5) signals conform with steroid results.³⁴ The

carbonyl group exerts a marked effect on the vicinal geminal dimethyl groups, C(18), C(19), as already noted for corresponding triterpenes (upfield shifts of 6.8 and 0.5 ppm).^{16,38}

*Manool (VI; labd-8(17),14-dien-13-ol).*³⁹ Although manoyl oxides functionalized in rings B and C are known,⁴⁰⁻⁴² none of these were available to us in sufficient quantities. Some bicyclic labdane diterpenoids (VI-X) capable of providing similar information were examined instead. The resonances due to the ring A carbons were readily assigned on the basis of the results obtained for manoyl oxide (I).

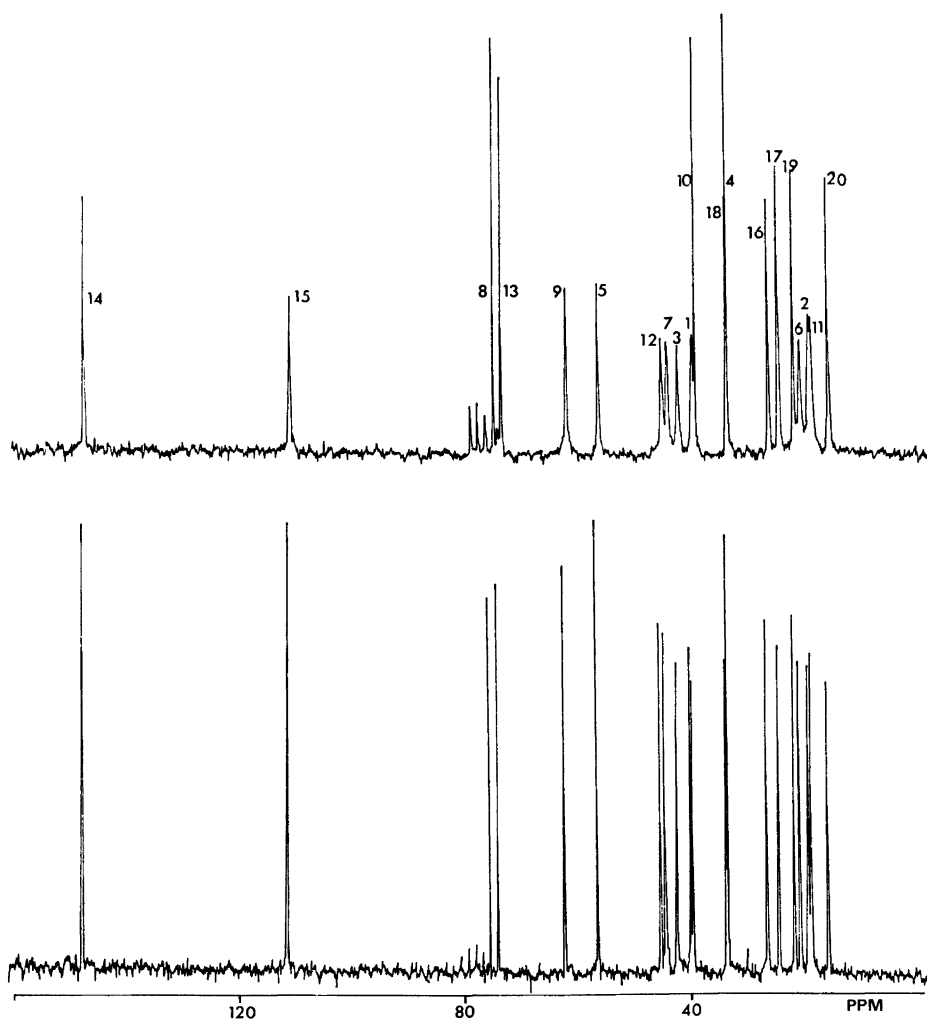


Fig. 1. ^{13}C NMR spectra of sclareol (VII) recorded at 25.18 MHz as 3.2 M (upper) and 1.3 M (lower) solutions in CDCl_3 .

Addition of $\text{Eu}(\text{FOD})_3$,^{43,44} allowed the two exo-methylene carbon signals, C(15) and C(17) to be distinguished as the former, due to the carbon closest to the coordination site, suffered the largest shift.

Although the europium shift reagents are known to cause considerable contact shifts in addition to the pseudocontact interaction,⁴⁵ they were found useful for the present spectral assignment. The observed LIS, listed in Table 1, along with corresponding estimated chemical shifts,^{24,25} allowed unambiguous assignment of all signals. The shifts of the side-chain aliphatic carbons were estimated from values for the appropriate alkane (2,5-dimethyl-heptane)⁴⁶ allowing for the influence of the double bond⁴⁷ and the hydroxyl group³⁶ and in the case of C(11) accounting for two γ -interactions from C(17) and C(20). The main reason for the 4.4 ppm deshielding of C(6) in manool relative the corresponding carbon in manoyl oxide, is considered to be due to the removal of one of the three methyl 1,3-diaxial interactions with the β -hydrogen on this carbon.

Sclareol (VII; *labd-14-ene-8,13-diol*).³⁹ The proton noise-decoupled spectrum of a concentrated solution of sclareol, Fig. 1, showed large differences in the peak heights, the quaternary carbon signals being highest, followed in turn by the methyl, methine, and methylene carbon resonances. Dilution of the sample produced a spectrum with peaks of roughly the same heights. This broadening of the peaks in the spectra of the concentrated solution is ascribed to a more effective spin-spin relaxation because of increased viscosity,²⁰ the effect being most noticeable for carbons with short T_1 's, *i.e.* the methylenes. This can effectively be used for an estimate of T_1 's, yielding information otherwise also available from off-resonance decoupling experiments.

Assignment of the resonances was based in the case of the A and B ring carbons and methyls on a comparison with the values for manoyl oxide (I) and in the case of the side chain carbons with those for manool (VI). Unequivocal distinction between C(2) and C(11), between C(7) and C(12), and between C(16) and C(17) could not be made at this stage due to the small shift differences, but confirmatory evidence for the assignments made in Table 1 was obtained from the spectrum of labd-

13*E*-en-8-ol (VIII) and from T_1 measurements (*vide infra*).

Labd-13E-en-8-ol (VIII).⁴⁸ The ring A and B carbons were again readily identified utilizing the results for sclareol (VII) and manoyl oxide (I) and comparison with values for 3-methyl-2*E*-hexene²⁵ (relevant values are included in Table 1) allowed unambiguous assignment of the side-chain resonances. The chemical shifts for C(2), C(7), and C(17) were virtually the same as those for the corresponding carbons in sclareol and hence strongly support the assignments made for the latter compound. The only remaining signal not accounted for is due to C(11) and appears at an expected position, *i.e.* 5.5 ppm downfield of the C(11) resonance in the sclareol spectrum.

Bis-14,15-norlabdan-8-ol-13-one (IX).⁴⁹ Comparison with the data for sclareol (VII) and labd-13*E*-en-8-ol (VIII) leaves only the C(11), C(12) and C(16) resonances to be accounted for. Of these, the signal at 29.8 ppm is clearly due to C(16), a value consistent with previously published results for long-chain methyl ketones,⁵⁰ and hence that at 46.2 ppm due to C(12), since C(12) is expected to resonate at lower field than C(11).*

Marrubiin (X; *15,16-epoxy-9-hydroxy-8a-labda-13(16),14-dien-19,6 β -olide*).⁵³ Assignment of the signals due to the carbonyl,⁵⁴ furyl,⁵⁵ and hydroxylated carbons left 13 resonances to be considered more closely and required the use of $\text{Eu}(\text{FOD})_3$ and selective decoupling.⁵⁶

Coordination of the shift reagent is expected to take place mainly at the lactone carbonyl and the tertiary hydroxyl group, and to a much lower extent at the furan oxygen. This was largely confirmed by the strong shifts observed for the unambiguously identified resonances of the carbons in the vicinity of the lactone ring. Thus C(19), C(6), C(5), and C(4) are shifted 26.5, 7.1, 5.5, and 5.1 ppm, respectively, while the hydroxylated C(9) and the vicinal C(8) and C(10) are shifted 3.7, 3.2, and 4.3 ppm respectively. Selective proton irradiation at

* The C(12) and C(16) resonances are weaker than those of the other carbons, either due to longer relaxation times, or because of the presence of small amounts of the ring-closed vinyl ether (IXa), easily formed in acidic media.^{51,52} The spectrum of the latter compound is expected to differ from that of the parent ketone (IX) only with respect to the C(12), C(13), and C(16) signals.

2.34 ppm, the expected position for the 5β -H resonance in the proton spectrum, sharpened the two peaks at 44.9 [C(5)] and 32.3 [C(8)] ppm.

The methylene resonances were assigned as follows. The signal at 21.0 ppm, undergoing the smallest LIS, is assigned to C(12) and is sharpened on irradiation of the proton triplet at 2.57 ppm. As introduction of the axial hydroxyl group at C(9) is expected to shift the C(1) signal about 5 ppm towards higher field relative to that for sclareol (VII), the 35.3 ppm resonance can be ascribed to C(1). Of the resonances at 28.6 and 31.6 ppm, the former, being the more strongly shifted on Eu(FOD)₃ addition, is assigned to C(3) and the latter to C(7). Only one methylene signal (28.3 ppm) then remains to accommodate C(11).

Of the three methyl signals the least shifted (16.6 ppm) is ascribed to C(17), while the most shifted one, also appearing at the lowest field, is assigned to C(18), thereby leaving only C(20) to account for the 22.3 ppm signal. Selective decoupling of the C(18) methyl proton singlet at 1.34 ppm sharpened the corresponding carbon signal at 23.0 ppm, while irradiation at the C(20) methyl proton singlet at 1.11 ppm and the C(17) methyl proton doublet at 0.99 ppm removed the splittings of the corresponding carbon peaks at 22.3 and 16.6 ppm.

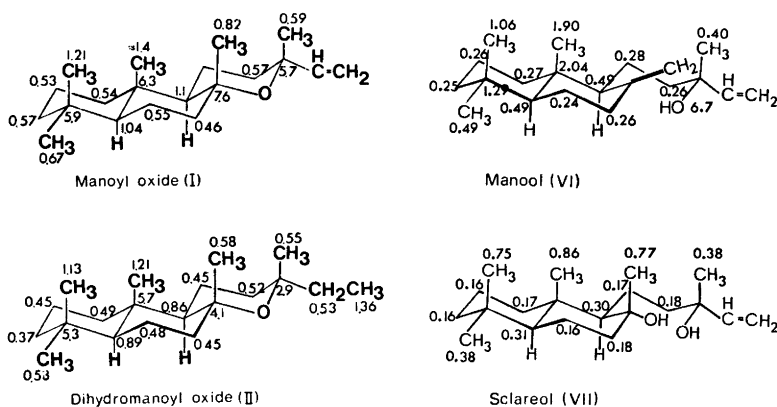
The above assignments are consistent with results obtained for other similar lactones.¹²

SPIN-LATTICE RELAXATION DATA

Spin-lattice relaxation times were determined according to the inversion-recovery method.⁶⁷ The relaxation times of individual carbons were measured for manool oxide (I), dihydromanool oxide (II), manool (VI), and sclareol (VII) and the data are given in Scheme 1.

Extremely rapid relaxation was found for the carbons of the rigid backbone of the bicyclic molecules (VI, VII). This is due to molecular association which tends to slow down over-all molecular motion. Longer T_1 's, however, are observed in the case of the tricyclic compounds (I, II), which is a consequence of more rapid tumbling due to the absence of polar groups. The almost equal T_1 values obtained for the backbone methylene carbons within each compound suggest essentially isotropic over-all motion. Under these circumstances the dipolar relaxation rate is proportional to the number of directly bonded protons⁶⁸ in agreement with the experimental results.

It is known that internal motion is equivalent to a shortening of the effective correlation time τ_{eff} thus resulting in lengthened T_1 's.⁶⁹ However, no significant increase in the T_1 's of the sidechain carbons 11 and 12 was observed for the bicyclic compounds (VI, VII) suggesting low conformational mobility for these carbons, at the concentration used.



Scheme 1. Spin lattice relaxation times (T_1) for the various carbons of manool oxide (I), dihydromanool oxide (II), manool (VI), and sclareol (VII) measured as ca. 2.0 and 1.3 M solutions in CDCl_3 at 50°C.

Particularly well investigated is the internal rotation of a group having only one degree of internal motion.^{60,61} For a methyl group undergoing internal rotation at a rate which is fast compared to over-all motion, one expects a relaxation time, $T_1(\text{CH}_3)$, which is nine times longer than in the absence of internal motion.⁵⁹ This behaviour was for example shown to apply for the angular methyl carbon in cholesterol chloride. In manool (VI), the T_1 's of the methyl carbons were found to range from 0.40 to 1.90 s, clearly showing that some methyl groups do not spin freely. It has been demonstrated by several workers⁶¹⁻⁶⁴ that steric crowding lowers the barrier to internal rotation. The concomitant increased rotation rates lead to lengthened spin-lattice relaxation times. In the case of manool, the methyl carbon 20, experiencing 1,3 diaxial interactions with the 2 β and 6 β protons and the 19 methyl group, exhibits the longest T_1 (1.90 s) of the methyl carbons, while C(19) displays a T_1 of 1.06 s. The equatorial C(18) as well as the sidechain C(16) give rise to significantly lower values (0.49 and 0.40 s). Analogous findings were made for the other three compounds (I, II, and VII). Although in sclareol (VII) much shorter T_1 's were generally observed, again a significantly increased relaxation time was found for C(20) when compared with that of the remaining methyl relaxation times in this molecule. It should be pointed out in this context, that absolute values of the methyl relaxation times are of no relevance when a comparison of data is made for different molecules. This is only valid on condition that the T_1 's are normalized, which can be done by dividing $T_1(\text{CH}_3)$ by $T_1(\text{CH})$, where the latter implies the relaxation time of a methine carbon which does not undergo internal re-orientation.⁶⁵ These results suggest that examination of methyl carbon T_1 's provides a useful assignment technique in the diterpenoid field.

EXPERIMENTAL

The Fourier transform ¹³C NMR spectra were obtained on a Varian XL-100-12 WG spectrometer operating at 25.16 MHz and equipped with an S-124 XL FT accessory. The instrument was controlled *via* a Varian 620 L 16 K computer.

The samples were usually examined as 1–2 M solutions in CDCl₃ using TMS as internal

standard. The influence of concentration on chemical shifts, as judged from data obtained for sclareol (VII) at two concentrations (3.2 and 1.3 M), was negligible, except for C(7), C(8) and C(12)–C(16), which ranged from 0.15 to 0.35 ppm.

An RF flip-angle of about 45° was usually used to achieve optimum sensitivity enhancements in survey spectra. 8 K datapoints were used in all experiments and the precision of the peak positions in the proton noise-decoupled (PND) spectra was about ±0.05 ppm. Single frequency off-resonance (SFOR) spectra were obtained by irradiating 400 Hz upfield from TMS in the proton spectrum. Partially relaxed Fourier transform (PRFT) spectra were obtained by a modified inversion-recovery method^{67,68} in which a pulse sequence of (90°–T–180°–t–90°–T) was employed.

Acknowledgements. Thanks are due to Dr. P. K. Grant, Otago University, Dunedin, New Zealand, and Dr. J. Morgan, Forest Prod. Res. Lab., Aylesbury, England, for generous gifts of some of the compounds.

Note added in proof: We are grateful to Professor E. Wenkert for informing us prior to publication about his ¹³C NMR results on labdanes, which are consistent with ours except for some assignments of a few closely spaced peaks.

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Received January 11, 1975.