CHAPTER 5

SOME NOVEL TRANSFORMATIONS OF FUNCTIONAL GROUPS OF ODOLACTONE

SECTION A

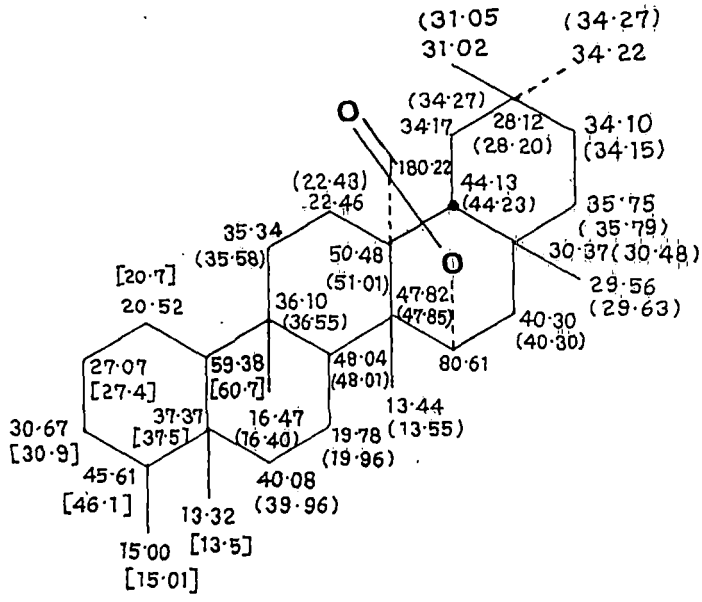
ISOMERIZATION OF γ-LACTONE MOIETY TO δ-LACTONE

In order to prepare some of the derivatives of odolactone (37), it was subjected to modified Wolff-Kishner reduction with hydrazine hydrate and potassium hydroxide in diethylene glycol. The alkaline mixture, after dilution with water was extracted with ether without acidification. While extracting with ether, a portion of the solid material was found to be insoluble in the solvent. It seperated from the alkaline mixture by filtration. The filtrate was acidified and no solid mass separated out.

The ether soluble component was purified by chromatography and crystallized from chloroform-methanol to furnish a crystalline solid A, mp 314-315°, $[\alpha]_D$ - 14.25°. Elemental analysis and MS (Fig 24) established its molecular formula, $C_{30}H_{48}O_2$. The IR spectrum (Fig 25) shows the presence of a γ-lactone moiety (1760 cm^{-1}) and the absence of keto group. The ^1H NMR spectrum (Fig 26) shows the

presence of six tertiary methyl groups at 0.76, 0.82, 0.96, 0.98, 1.02 and 1.16 ppm, a secondary methyl group at 0.71 ppm (d, J = 6.5 Hz) and a proton, geminal to the lactone oxygen at 4.35 ppm (t, J = 3 Hz; cf with the triplet at 4.38 ppm of odolactone). A comparison of methyl absorption region of odolactone and compound A in ^{1}H NMR is shown in Fig 27 and the results are in record with the idea that the only change is the deoxygenation of the 3-keto group. The methyl assigned for C-26, C-28, C-29 and C-30 show very little change in chemical shifts, being far from the perturbing effect of the 3-keto group, while the doublet C-23 methyl moves upfield about 0.20 ppm upon reduction. At the same time, C-25 methyl moves upfield about 0.10 ppm, reflecting its greater distance from the carbonyl group, and C-24 methyl moves downfield slightly, since it projects above the plane of the carbonyl into the region of opposite shielding. Therefore, compound A is friedelan-27→15α-olide (49), named deoxyodolactone. The ^{13}C spectral (Fig 28) data of the compound are also consistent with its structure 49.

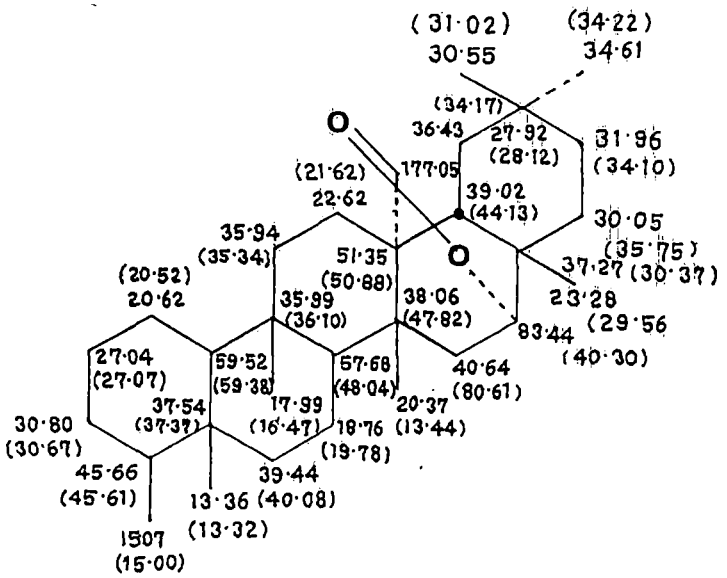
The ether insoluble residue was purified by column chromatography and crystallized from chloroform-methanol to afford a crystalline solid B, mp > 320°, $[\alpha]_D$ + 23°. Elemental analysis and MS (Fig 29) established its molecular formula, $C_{30}H_{48}O_2$. The IR spectrum (Fig 30) shows the presence of a δ-lactone moiety (1725 cm^{-1}) and the absence of the keto group. The ^{1}H NMR spectrum (Fig 31) shows the presence of six tertiary methyls at 0.78, 0.86, 0.95, 1.00, 1.19 and 1.21 ppm and a secondary methyl at 0.72 ppm (d, J = 6.5 Hz); the proton, geminal to the lactone oxygen has appeared at 3.98 ppm (t, J = 3 Hz). The peaks at 1.19 and 1.21 ppm are due to C-26 and C-28 methyls respectively which are remarkably deshielded. These spectral data suggest that the lactone oxygen of deoxyodolactone 49 (γ-lactone) is shifted from C-15 to C-16 to form the



49

Numerical figures are the ^{13}C chemical shifts in ppm of deoxyodolactone (49), figures in parentheses are ^{13}C shifts of odolactone 37 (Fig 10) and those in square brackets are ^{13}C shifts of friedelan-28-ol (compound 22 of Ref 34)

thermodynamically more stable δ-lactone (compound B) under the reaction condition by the action of base as proposed in scheme 2. Therefore, compound B is friedelan-27→16α-olide (50), named iso-deoxyodolactone. The ^{13}C spectral (Fig 32) data of the compound are strongly supporting the structure 50. In going from 49 to 50, the β-effect of the lactone oxygen is removed from C-14 and γ-effect from C-8 and C-26. Thus C-14 is shielded by 9.76 ppm, and C-8 and C-26 are deshielded by 9.64 and 6.93 ppm respectively. On the otherhand, the lactone oxygen has imparted β-effect at C-27 of + 6.90 ppm and γ-effect at C-18, C-22 and C-28 of -5.11, -5.70 and -6.36 ppm respectively. Such type high shielding due to γ-substituent is recorded in the literature[43]. There are also minor changes in chemical shifts for rest of the carbons which are commonly observed for any isomeric changes.



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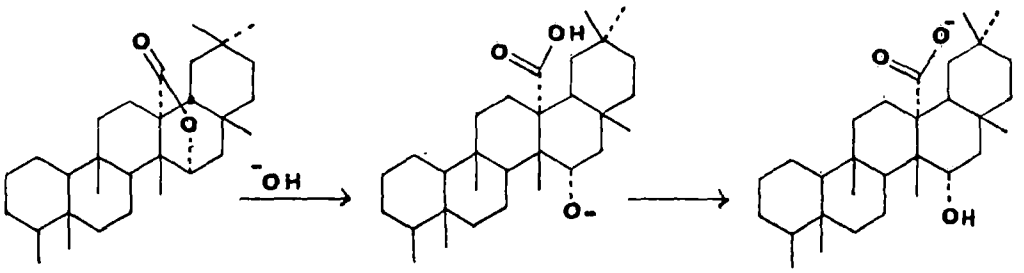
Numerical figures are ^{13}C chemical shifts in ppm of iso-deoxyodolactone (50) and those in parentheses are the ^{13}C shifts of deoxyodolactone (49)

To figure out the exact reaction condition under which this unique rearrangement (γ- to δ- lactone) is taking place, deoxyodolactone (49) was refluxed in diethylene glycolic potassium hydroxide for four hours and it was observed that there was 80% conversion of the γ-lactone to its corresponding δ-lactone (50). This observation could be rationalized in the light of the mechanism outlined in Scheme 2.

In order to make this novel rearrangement of friedelan -27→15α-olide system as a generalized one, experimental endeavour was extended over to two more systems, 3α-hydroxy-friedelan-27→15α-olide (odollactone) and 3-oxofriedelan -27→15α-olide (odolactone) which are chiefly available in G odorata. All the results are recorded in Table 7.

Scheme 2



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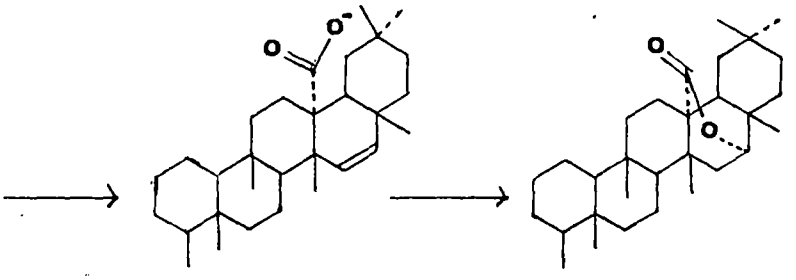

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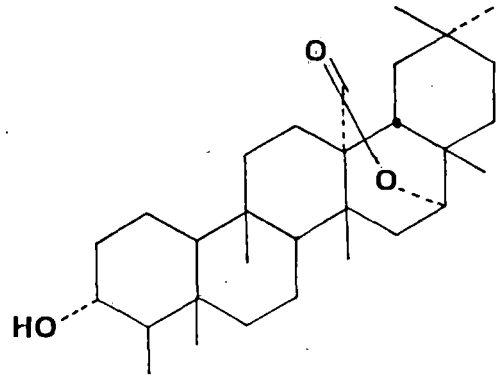
Table 7

Entry	Substrate lactones	Products	Yield
1	Friedelan-27→15α-olide (49) (Deoxyodolactone)	Friedelan-27→16α-olide (50)	80%
2	3α-Hydroxyfriedelan-27→15α-olide (41) (Odollactone)	3α-Hydroxyfriedelan-27→16α-olide (51)	80%
3	3-Oxofriedelan-27→15α-olide (37) (Odolactone)	3α-Hydrofriedelan-27→16α-olide (51)	75%

The product 51 has been characterized from its spectral data. Its IR spectrum (Fig 33) shows characteristic peaks for hydroxy group at 3470 cm^{-1} and for δ-lactone moiety at 1725 cm^{-1}. The proton, geminal to the lactone oxygen appears at 3.96 ppm (t, J = 3 Hz; cf with the triplet at



51

3.98 ppm of iso-deoxyodolactone 50) in the ^{1}H NMR (Fig 34).

The action of KOH-diethylene glycol upon odolactone (37) is somewhat different type in the sense that keto group is reduced to give 3α-hydroxyfriedelan-27→16α-olide (51). There was another fraction (for Entry 3, Table 7) containing a crude mixture and could not be separated due to paucity of material.

The conversion of odolactone (37) to 3α-hydroxyfriedelan-27→16α-olide (51) by the action of KOH-diethylene glycol (reflux) led to a series of reaction on some ketones in order to test the general applicability of the reagent in furnishing alcohols from ketones. These results have been communicated[43]. A reprint of this work is attached towards the end of this dissertation (Appendix 3). Although this reprint had projected the reaction of keto groups to alcohols originated from the observation that methyltrichadonate is converted to its corresponding epimeric alcohols during it hydrolysis with KOH-diethylene glycol. But it would be more appropriate that the reaction of odolactone with KOH-diethylene glycol had been the fountainhead for these and allied series of reactions. Initially, as the CCC2D spectral data had not been available there had been slight confusion over the structure of odolactone.

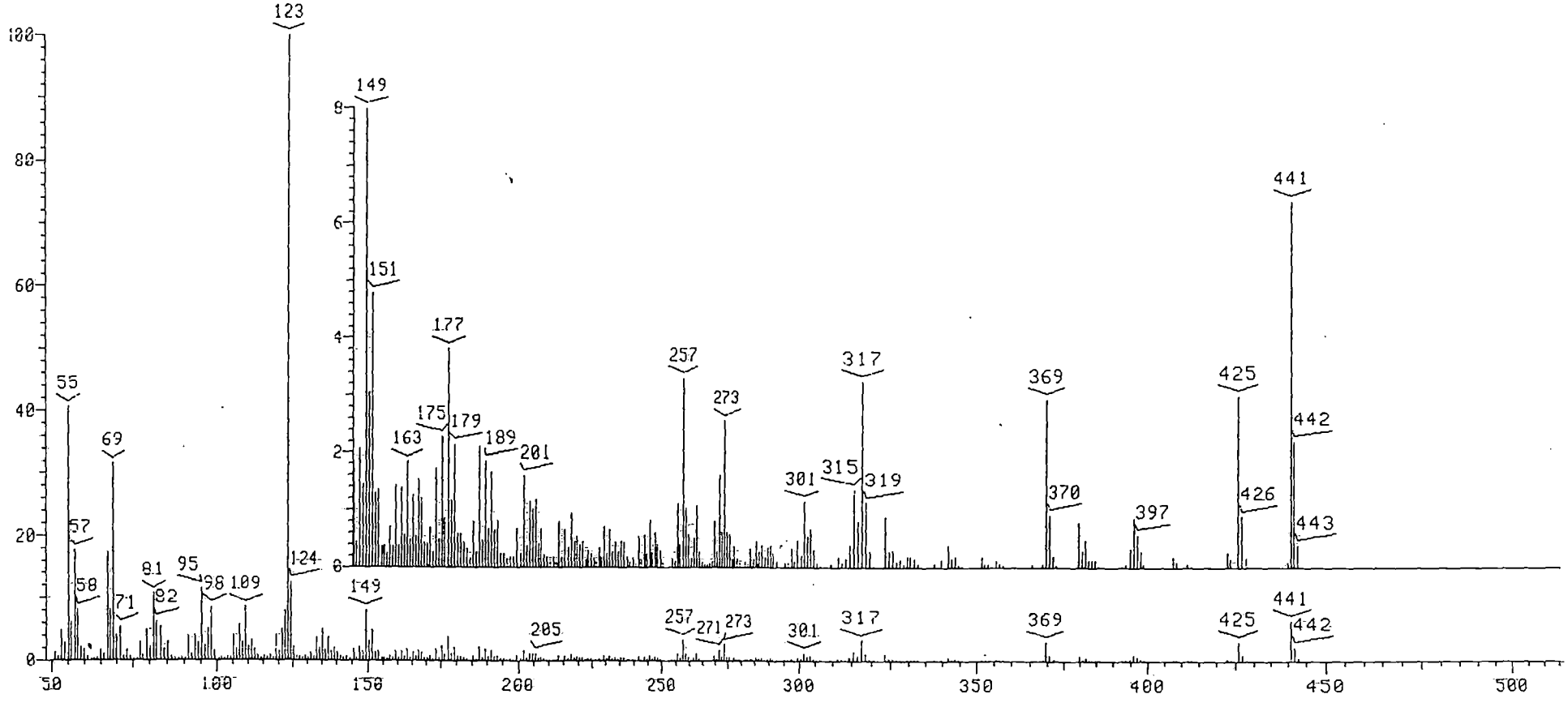


Fig 24. MS spectrum of deoxyodolactone (49)

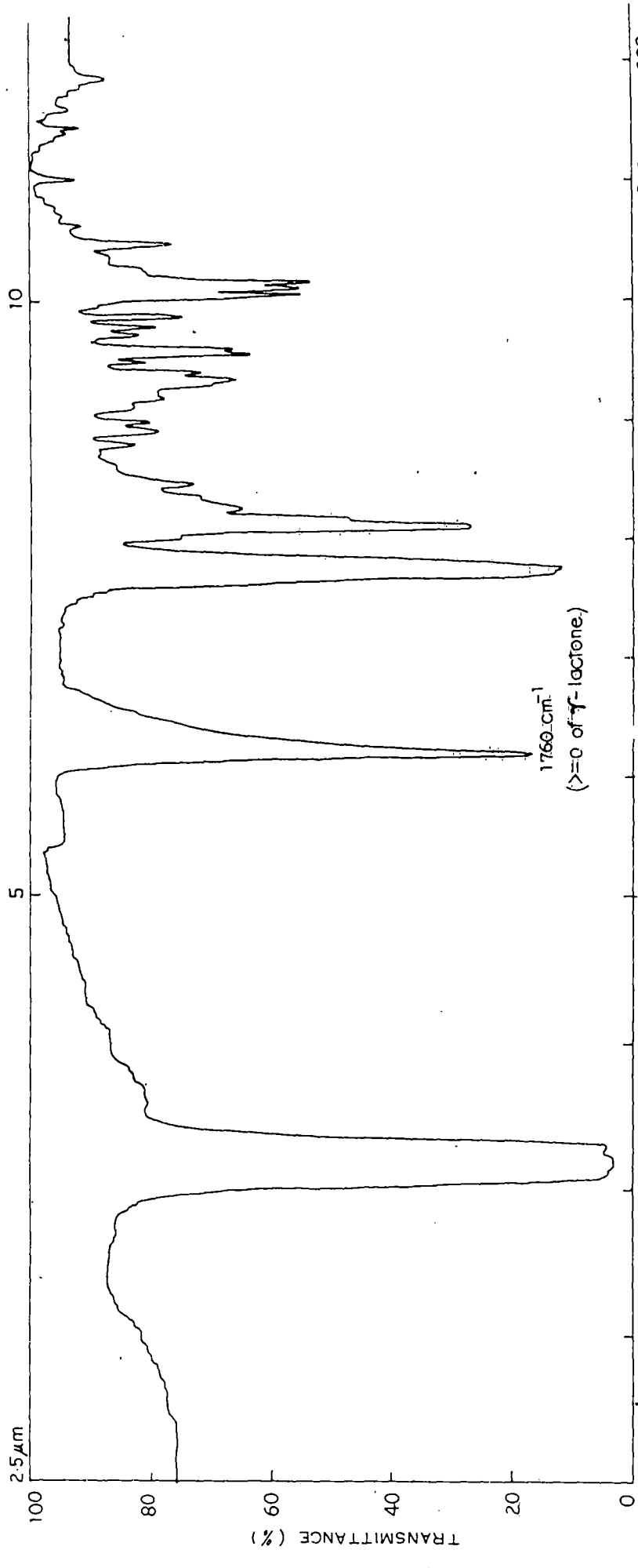


Fig 25. IR spectrum of deoxyodolactone (49)

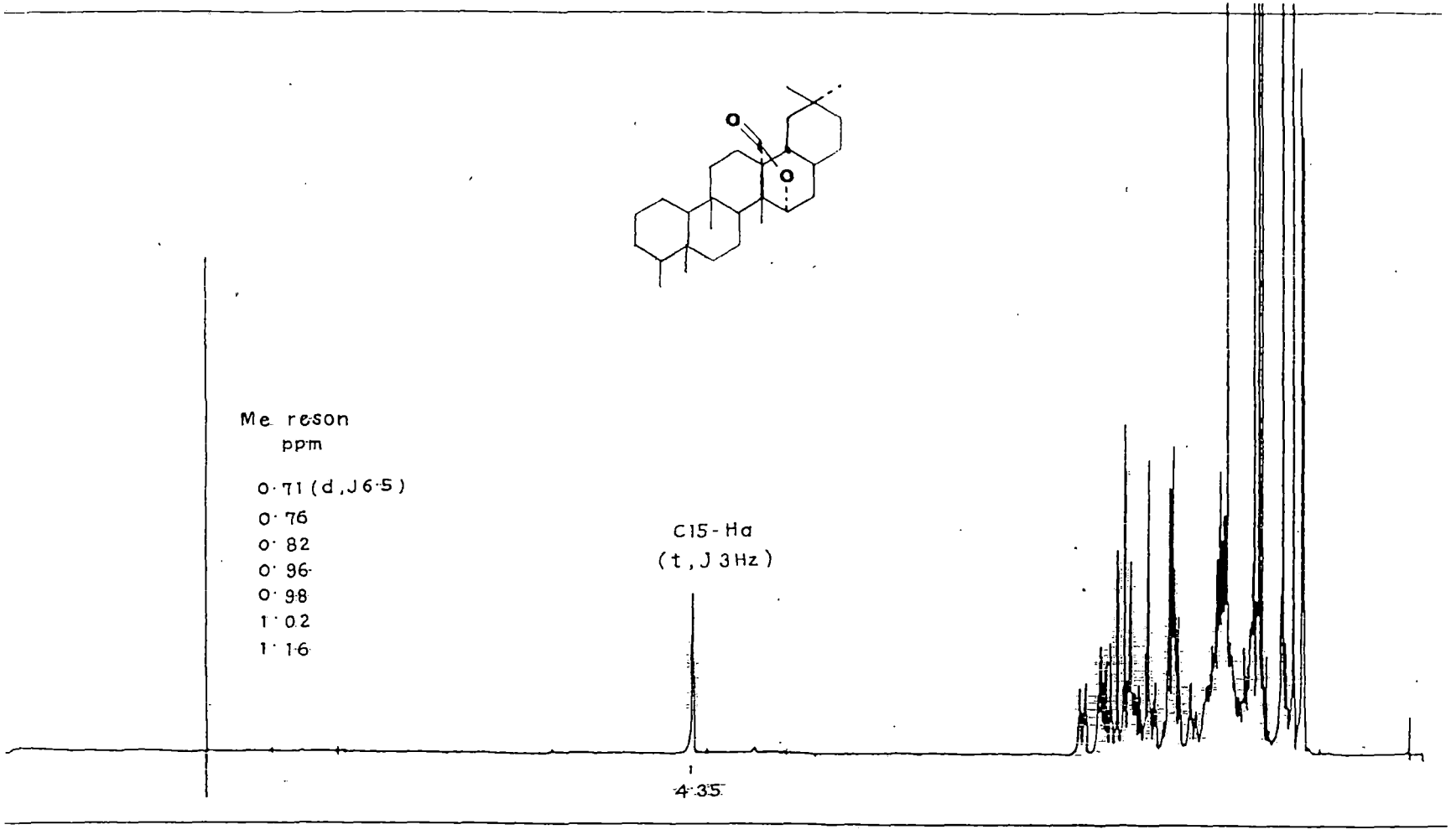


Fig 26. ^{1}H NMR spectrum of deoxyodolactone (49) at 400 MHz.

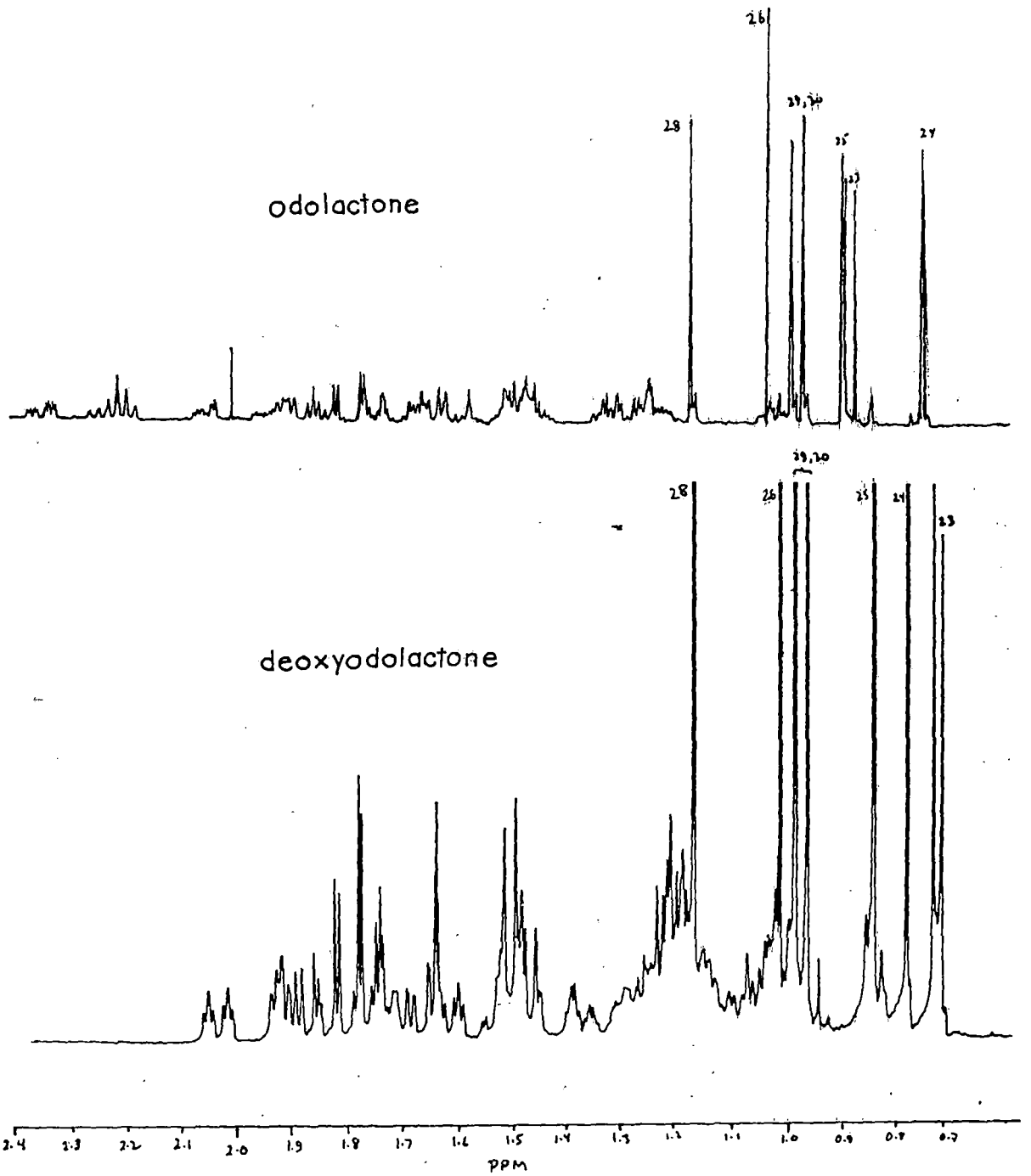


Fig 27. Composite ^1H spectra of odolactone (37) and deoxyodolactone (49) at 400 MHz.

CH	CH_3
80.61	34.22
59.38	31.02
48.04	29.56
45.07	16.47
44.13	15.00
	13.44
	13.32

$-\overset{|}{\underset{|}{C}}-$	CH_2
180.22	40.30
50.88	40.08
47.82	35.75
37.37	35.34
36.10	34.17
30.37	34.10
28.12	30.67
	27.05
	22.46
	20.52
	19.78

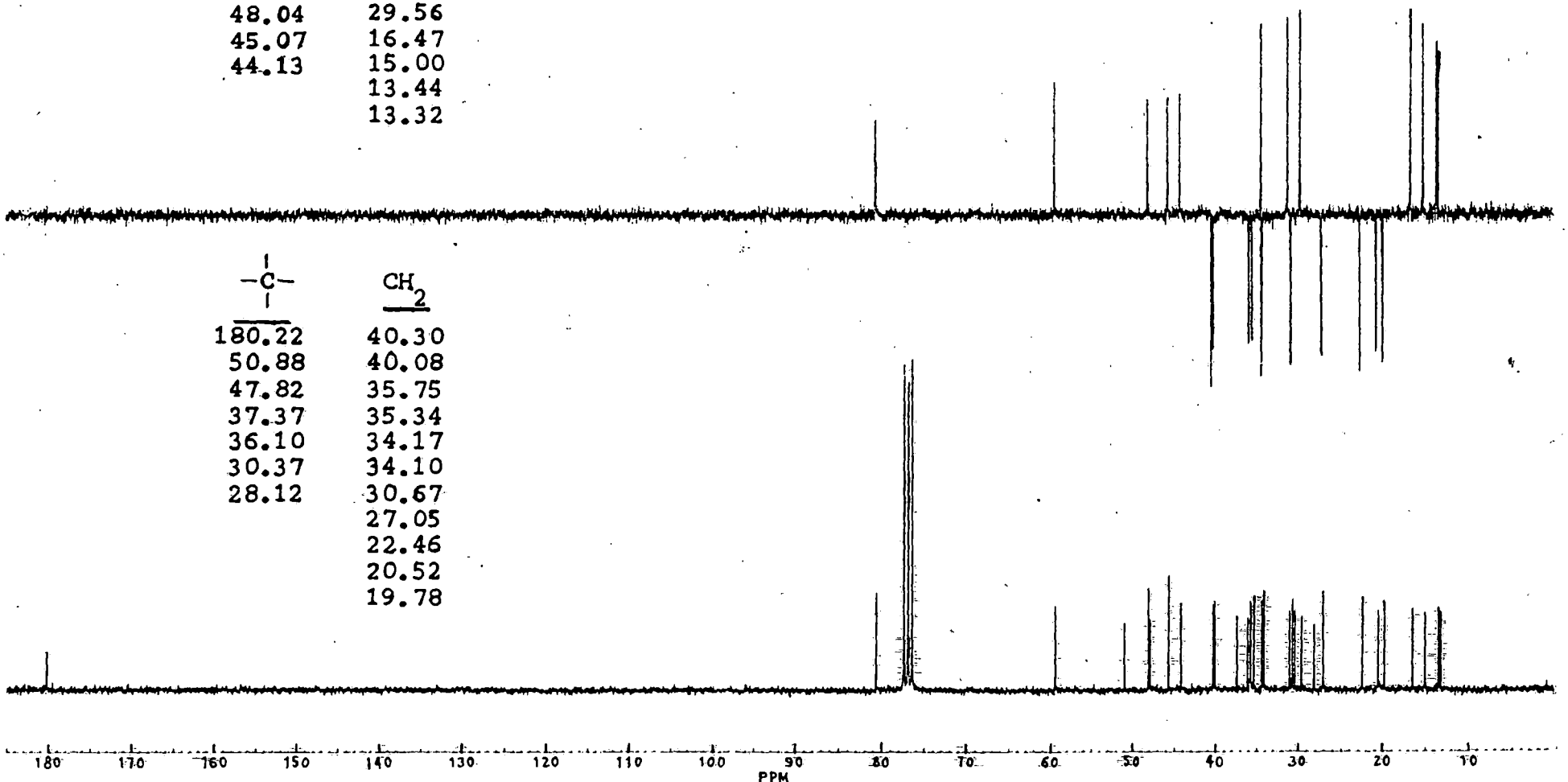
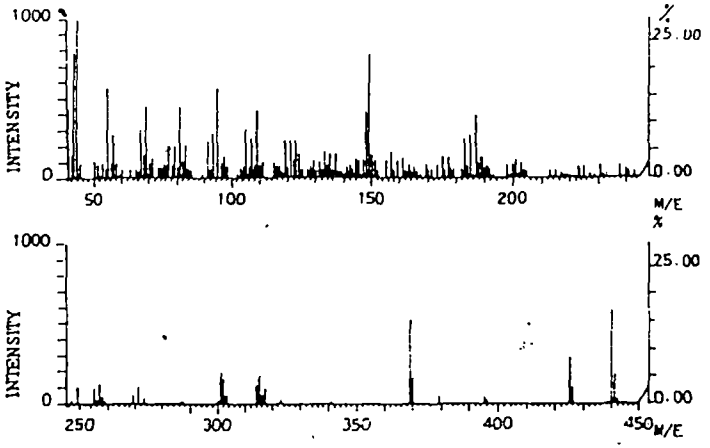


Fig 28. ^{13}C NMR spectrum of deoxyodolactone (49) at 75 MHz.



BASE PEAK : M/E 40.0 INT 116.6

M/E	RAW INT	R.INT	SIGMA(%)	
301.0	2.2	19.1	7.37	
302.0	1.8	15.9	6.16	
314.0	1.4	12.5	4.84	
315.0	2.0	17.7	6.86	
317.0	1.1	9.9	3.83	
369.0	6.1	52.3	20.20	
370.0	1.9	16.4	6.36	
425.0	3.3	28.7	11.11	
426.0	1.2	10.7	4.14	
440.0	6.6	57.0	22.02	
441.0	2.1	18.3	7.07	END

Fig 29. MS spectrum of iso-deoxyodolactone (50)

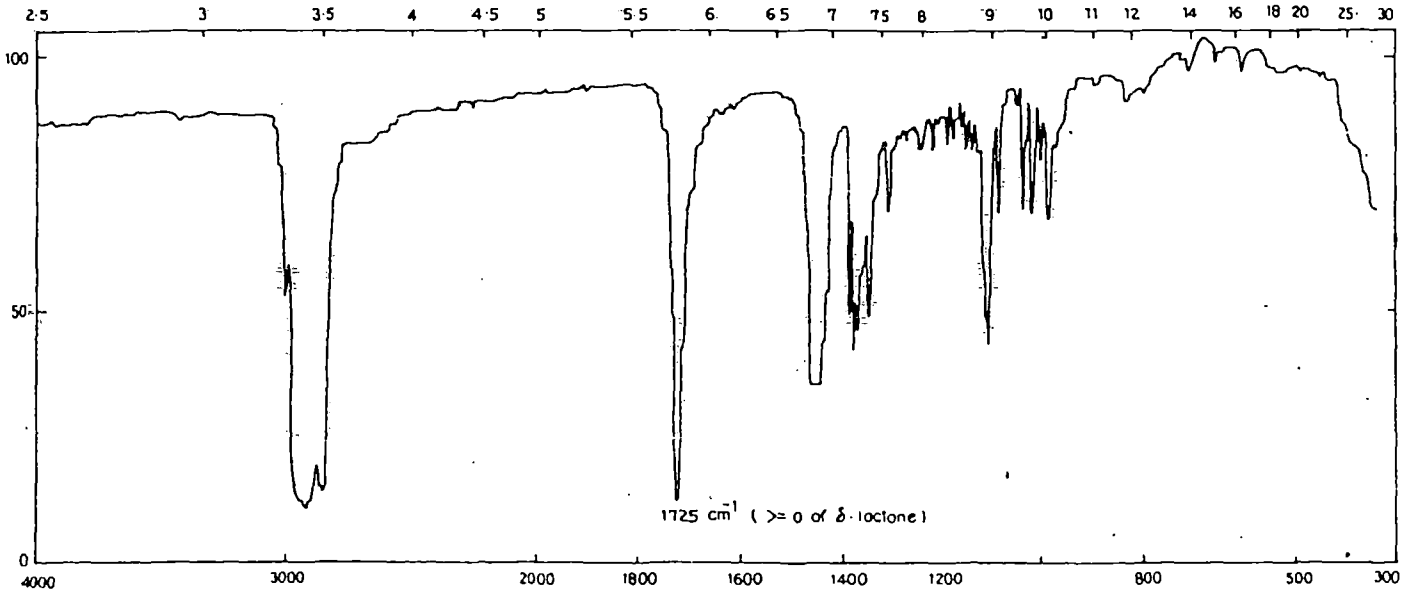


Fig 30. IR spectrum of iso-deoxyodolactone (50)

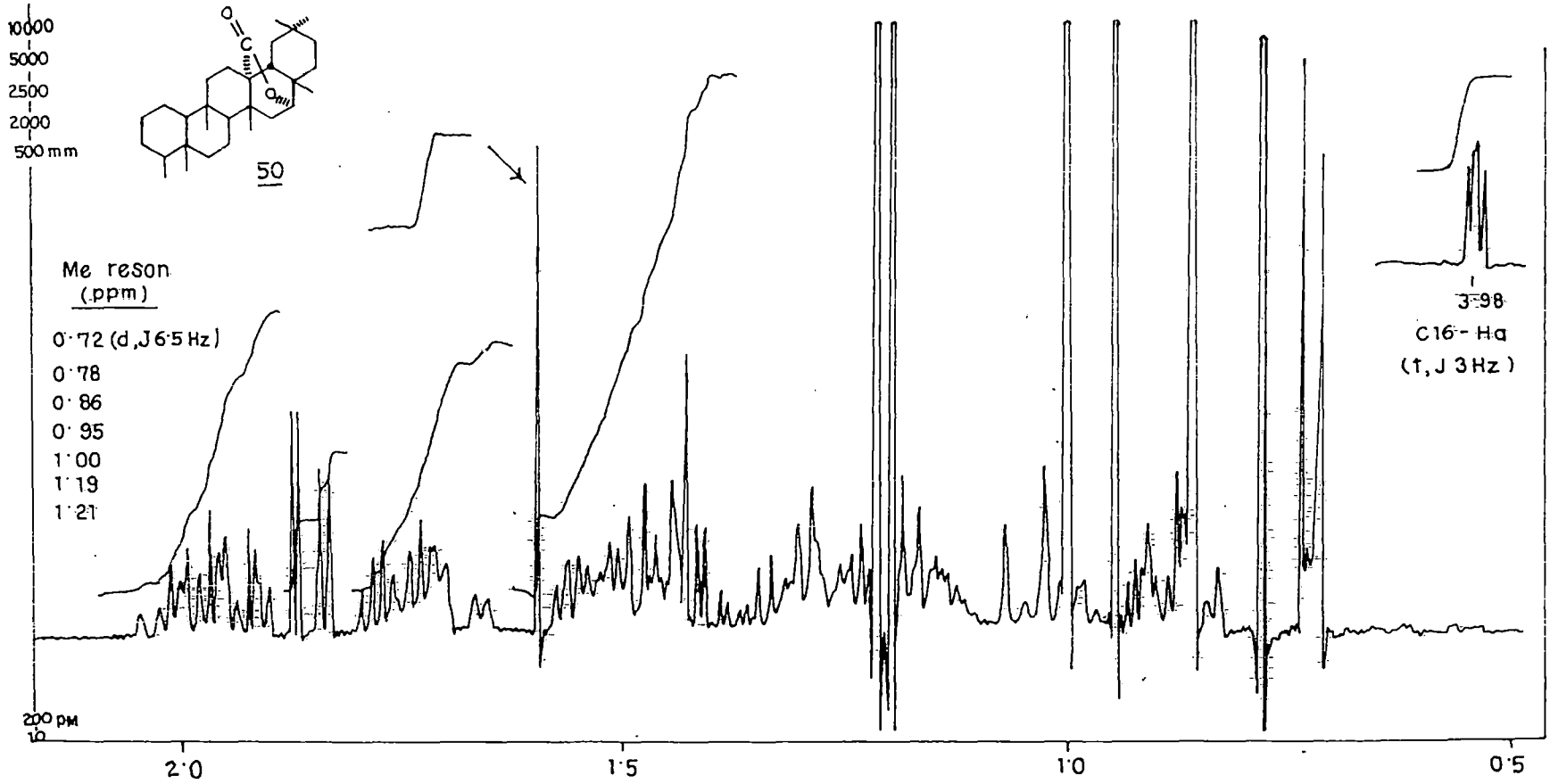


Fig 31. ^{1}H NMR spectrum of iso-deoxyodolactone (50) at 300 MHz

PPM	PPM
177.05 (s)	31.46 (t)
83.44 (d)	30.80 (t)
59.52 (d)	30.52 (q)
57.68 (d)	30.05 (t)
51.35 (s)	27.92 (s)
45.66 (d)	27.04 (t)
40.64 (t)	23.28 (q)
39.44 (t)	21.59 (t)
39.02 (d)	20.62 (t)
38.06 (s)	20.37 (q)
37.27 (s) → 37.54 (t)	18.76 (t)
36.43 (t)	17.99 (q)
35.99 (s)	15.07 (q)
35.94 (t)	13.36 (q)
34.61 (q)	

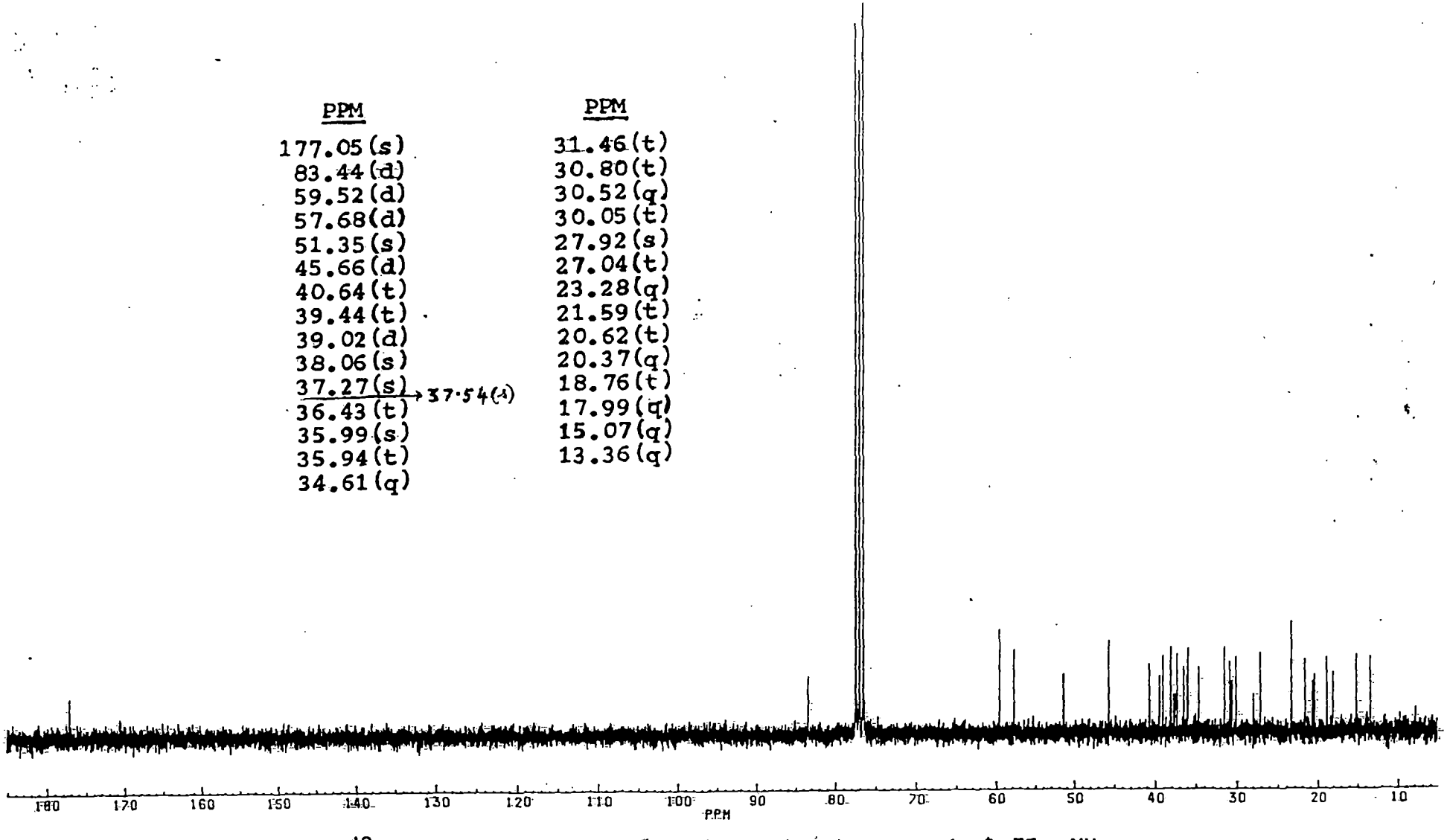


Fig 32. ^{13}C NMR spectrum of iso-deoxyodolactone (50) at 75 MHz

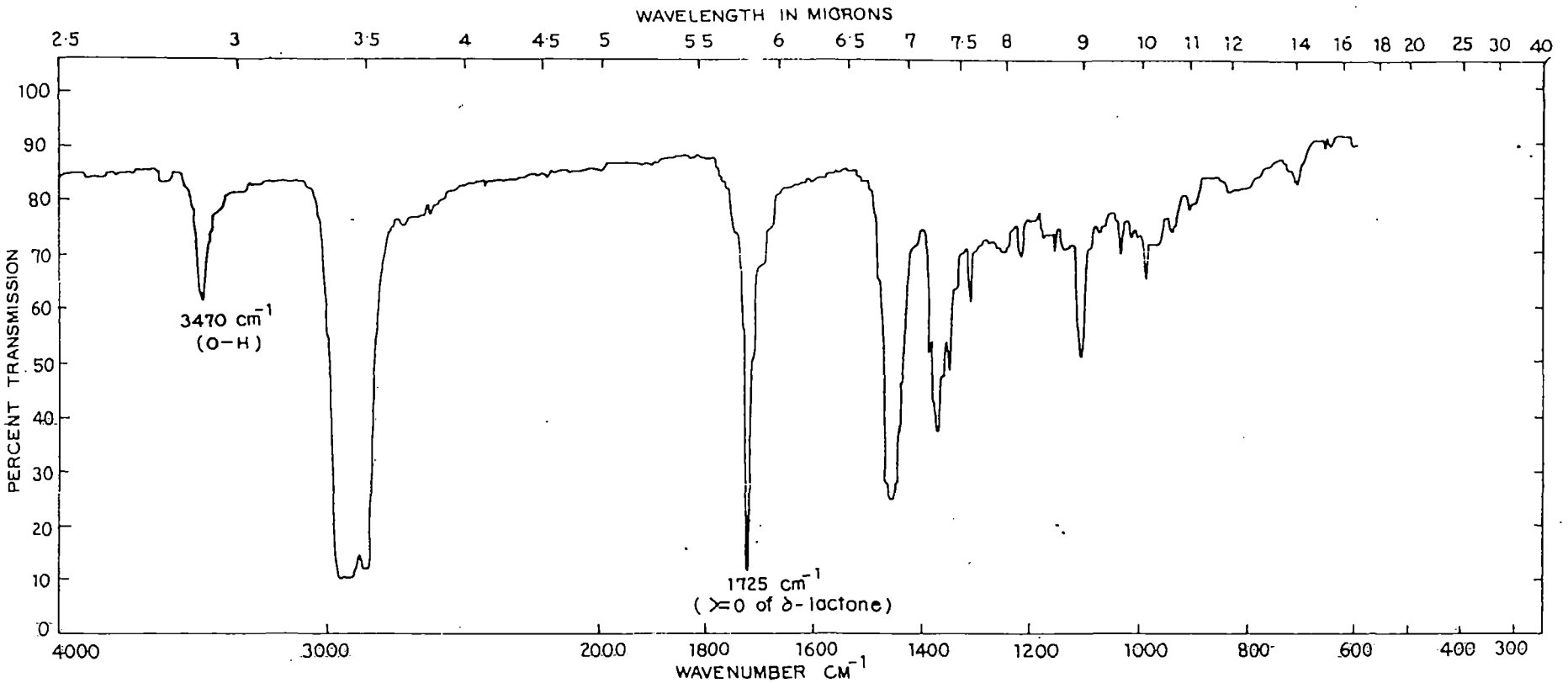


Fig. 33. IR Spectrum of 3α- hydroxyfriedelan-27→16α-olide (51)

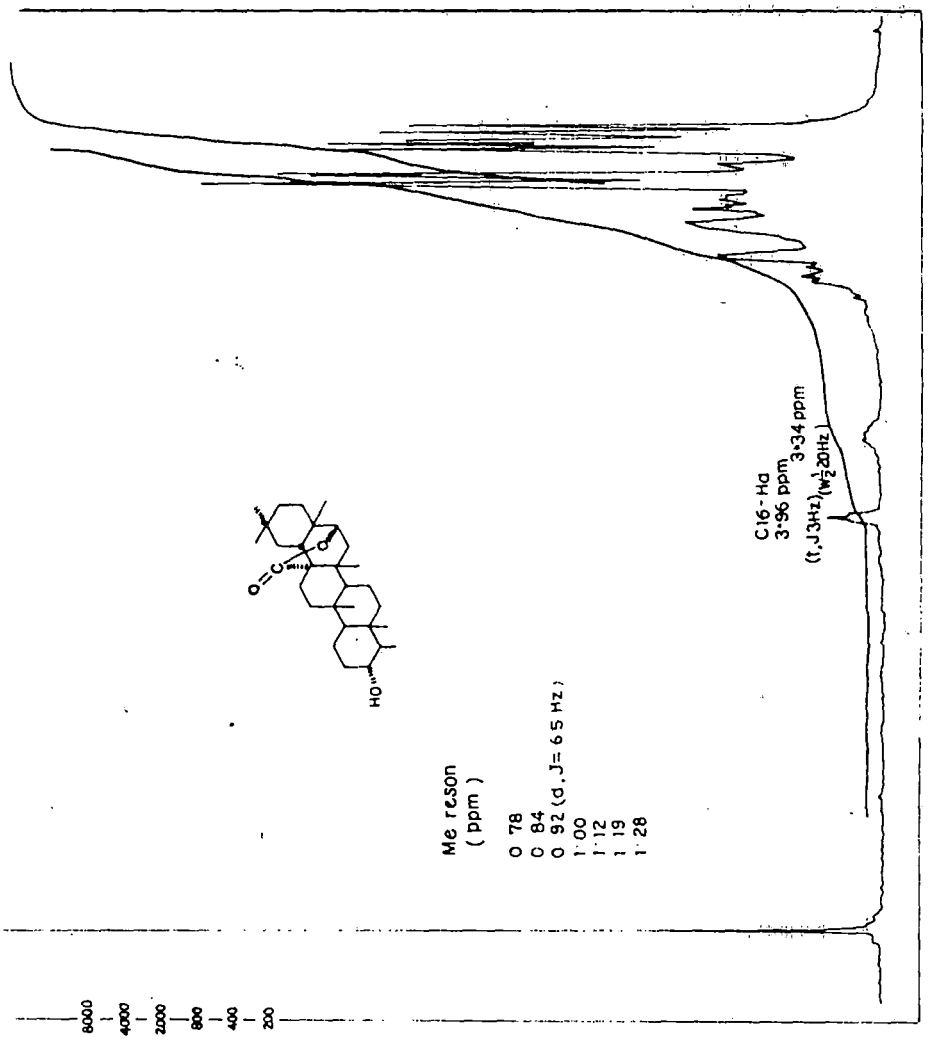


Fig 34 ^{1}H NMR spectrum of 3α- acetoxyfriedelan-27→16α- olide (51) at 100 MHz

SECTION B

REDUCTIVE CLEAVAGE OF LACTONE RINGS WITH LITHIUM-ETHYLENEDIAMINE

Triterpenoids of friedelane group possessing angular carboxylic function at C-24[45], C-25[46], C-26[33], C-27[41,42], C-28[47], C-29[48] and C-30[32] are known in the literature. The position of the lactone carbonyl carbon of odolactone could be determined if it be converted to a reported acid or its derivative of authentic structure. With this objective, attempts were made to open the lactone ring of odolactone by conventional methods (eg by the action of acids, alkali and lithium aluminium hydride) and had been unsuccessful.

Literature survey showed that Barton et al[49-52] reported deoxygenation of hydroxy groups of alcohols by alkali metal-amine reduction of their derived esters with carboxylic acids. The only side reaction was the regeneration of the starting alcohol. This type of deoxygenation, by the action of lithium-ethylenediamine, had also been reported by two other groups of workers[42,53].

Lactones may be considered as intramolecular esters which are formed by condensation of hydroxy groups with carboxylic acid functions of the same molecule. Therefore, it was envisaged that lactone oxygen might be deoxygenated

from its point of attachment by the action of lithium -ethylenediamine. This application of lithium-ethylenediamine on lactones from G odorata for reductive cleavage of their lactone rings had been successful[35]. The reaction was carried out successfully on several other lactones and the results are shown in Table 8.

Table 8

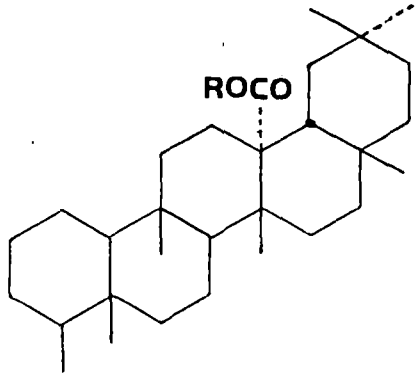
Entry	Substrate lactones	Products*	Yield
1	3α-Hydroxyfriedelan-27→15α-olide (41) (Odollactone)	3α-Hydroxyfriedelan-27-oic acid (43)	80%
2	3α-Acetoxyfriedelan-27→15α-olide (40) (O-Acetylodollactone)	a) Friedelan-27-oic acid (52)	40%
		b) 3α-Hydroxyfriedelan-27-oic acid (43)	40%
3	3-Oxofriedelan-27→15α-olide (37) (Odolactone)	3α-Hydroxyfriedelan-27-oic acid (43)	80%
4	Friedelan-27→15α-olide (49) (Deoxyodolactone)	Friedelan-27-oic acid (52)	80%
5	Friedelan-27→16α-olide (50) (Iso-deoxyodolactone)	a) Friedelan-27-oic acid (52)	20%
		b) Friedelan-16α, 27-diol (54)	60%
6	3β-Acetoxyoleanan-18α-H-28→13β-olide (56)[54]	a) Oleanan-18α-H-28-oic acid (59)	40%
		b) 3β-Hydroxyoleanan-18α-H-28-oic acid (57)	40%

Table 8 (contd)

7	3-Oxooleanan-18α-H-28→13β-olide (55)[54]	3β-Hydroxyoleanan-18α-H-28-oic acid (57)	85%
8	3β-acetoxyoleanan-18α-H-28→19β-olide (60)[54]	a) oleanan-18α-H-28-oic acid (59)	30%
		b) 3β-Hydroxyoleanan-18α-H-28-oic acid (57)	30%
		c) Oleanan-18α-H-3β, 19β, 28-triol (61)[54]	15%

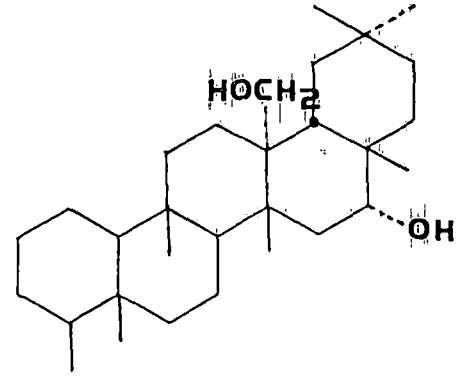
*The products are characterized from their spectral data.

From the above study, it may be concluded that lactone rings could be cleaved by the action of lithium-ethylene-diamine where tertiary lactones (eg 55 & 56) and sterically constrained lactones (eg 37, 40, 41 and 49) are exclusively converted to acids whereas the stable lactones (eg 50) yield the diols in substantial amount. This novel method of lactone ring opening may be applied to those cases where lactones are considerably resistant to the conventional reagents. Moreover, the conventional methods lead to the introduction of a hydroxy group at the position where the lactone oxygen is attached whereas the above method obviates this when not desired.



52 R=H

53 R=CH_3



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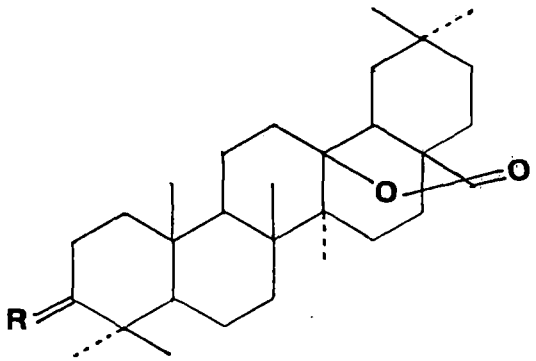
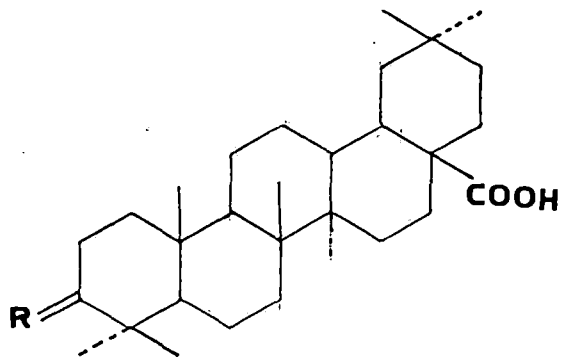


55 R = O

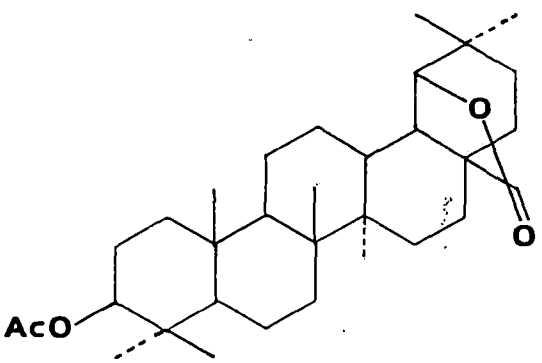
56 R = β-OAc, α-H



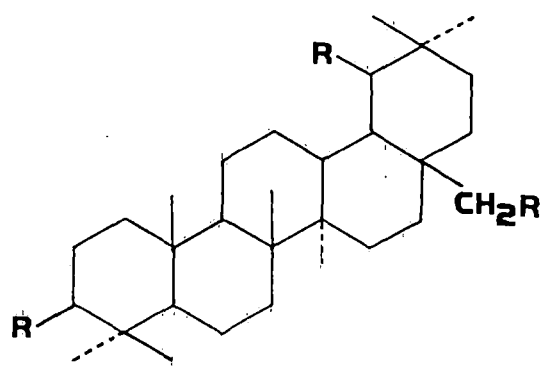
57 R = β-OH, α-H

58 R = β-OAc, α-H

59 R = H_2



60



61 R = OH

62 R = OAc