PART - II

AN UNAMBIGUOUS PARTIAL SYNTHESIS OF METHYL DIHYDROALPHITOLATE FROM BETULINIC ACID.

PART - II

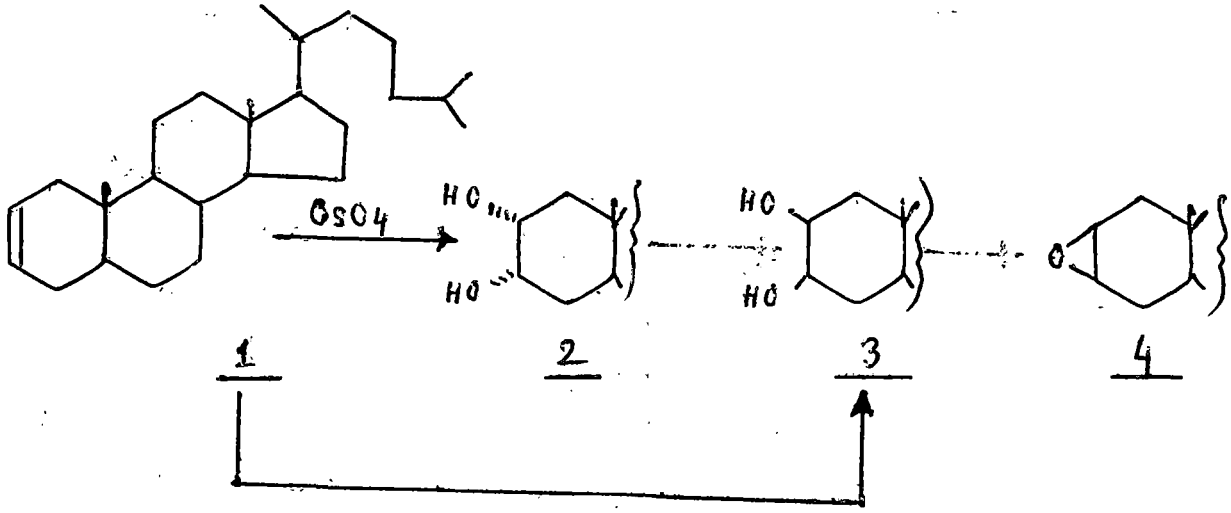
CHAPTER - I

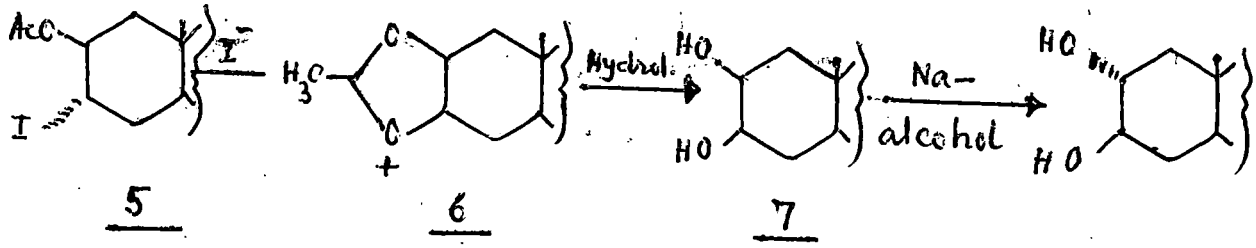
A short review of synthesis of isomeric 2,3-diols of triterpenoids :

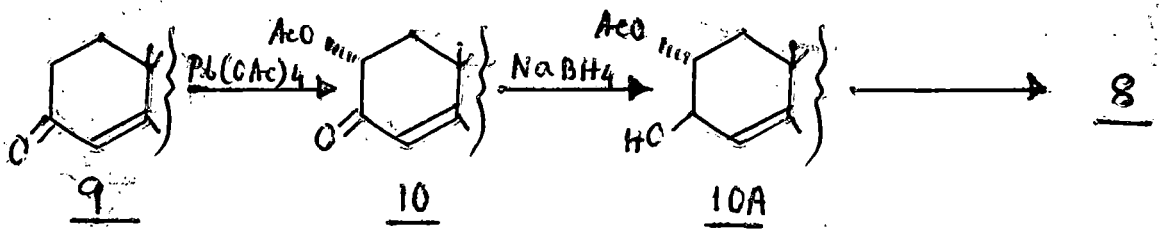
Section A : Introduction:

In the course of elucidation of the configurations of sapogenins containing a 2,3-diol system, methods were developed for production of the four possible isomers in this series. The four cholestane 2,3-diols have also been prepared by the methods developed in this connection[1,2]. Δ^2-Cholestene **1** on reaction with osmium tetroxide gives the 2α,3α-diol **2** whereas peracetic acid oxidation and subsequent hydrolysis affords 2β,3α-diol[1-3] **3**. 2α,3α-or 2β,3β-oxido-cholestanes **4** on diaxial opening also gives the same diol **3** . The 2β,3βdiol **7** has also been prepared[1,2] according to the procedure of Winstein and Buckles[4] by treatment of Δ^2 - cholestene **1** with silver acetate, iodine and moist acetic acid. The reaction probably involves formation of a cyclic 2α,3β-iodonium ion which on acetolysis with inversion at C - 2 gives **5**. Expulsion of iodide ion with inversion at C - 3 forms a resonant oxonium - carbonium ion **6** which leads to a mono-acetate which on hydrolysis gives **7**. As the diol **7** contains one axial substituent at C - 2, it is epimerized by treatment with sodium

in ethanol at 180° to the diequatorial 2α,3β-diol 8. Diol 8 was also obtained from choiestenone 9 which reacts with lead-tetracetate to give in about 10% yield a product 10 having 2α- acetoxy group[5,6]. Reduction of 10 with sodium borohydride followed by hydrogenation gives the 2α, 3β-diol 8.

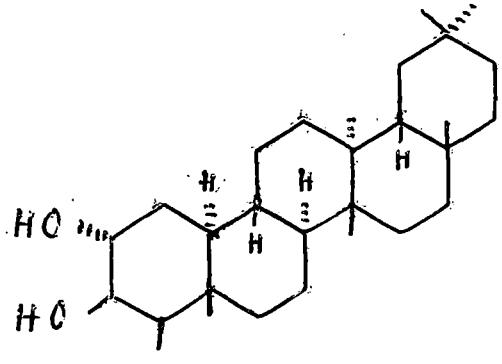




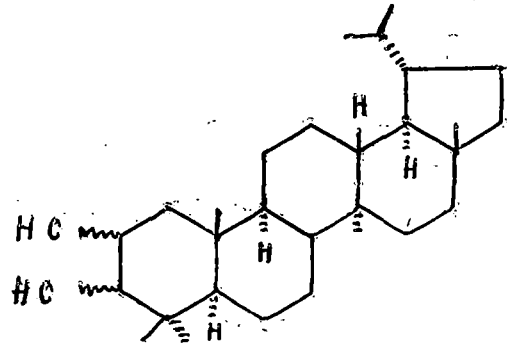


Section B : Synthesis of 2,3-diols of lupane and friedelane series:

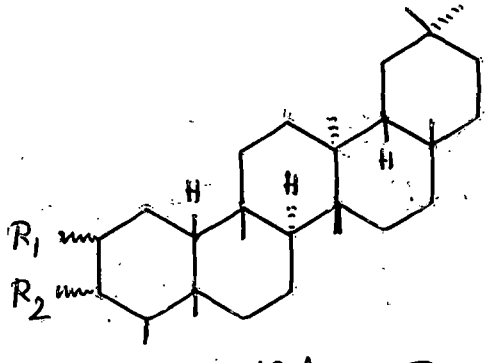
McGinnis[7] et al have reported the preparation of all the four possible stereoisomeric lupane 2,3-diols 12. Samson et al[8] have synthesised 2α, 3α-13 A; 2β, 3β-13 B; 2α, 3-β 13 C friedelane diols and shown that the last named isomer is identical with natural pachysandiol A[9] 11.



11



12 (A, B, C, D)



13A $R_1 = R_2 = \alpha$-OH

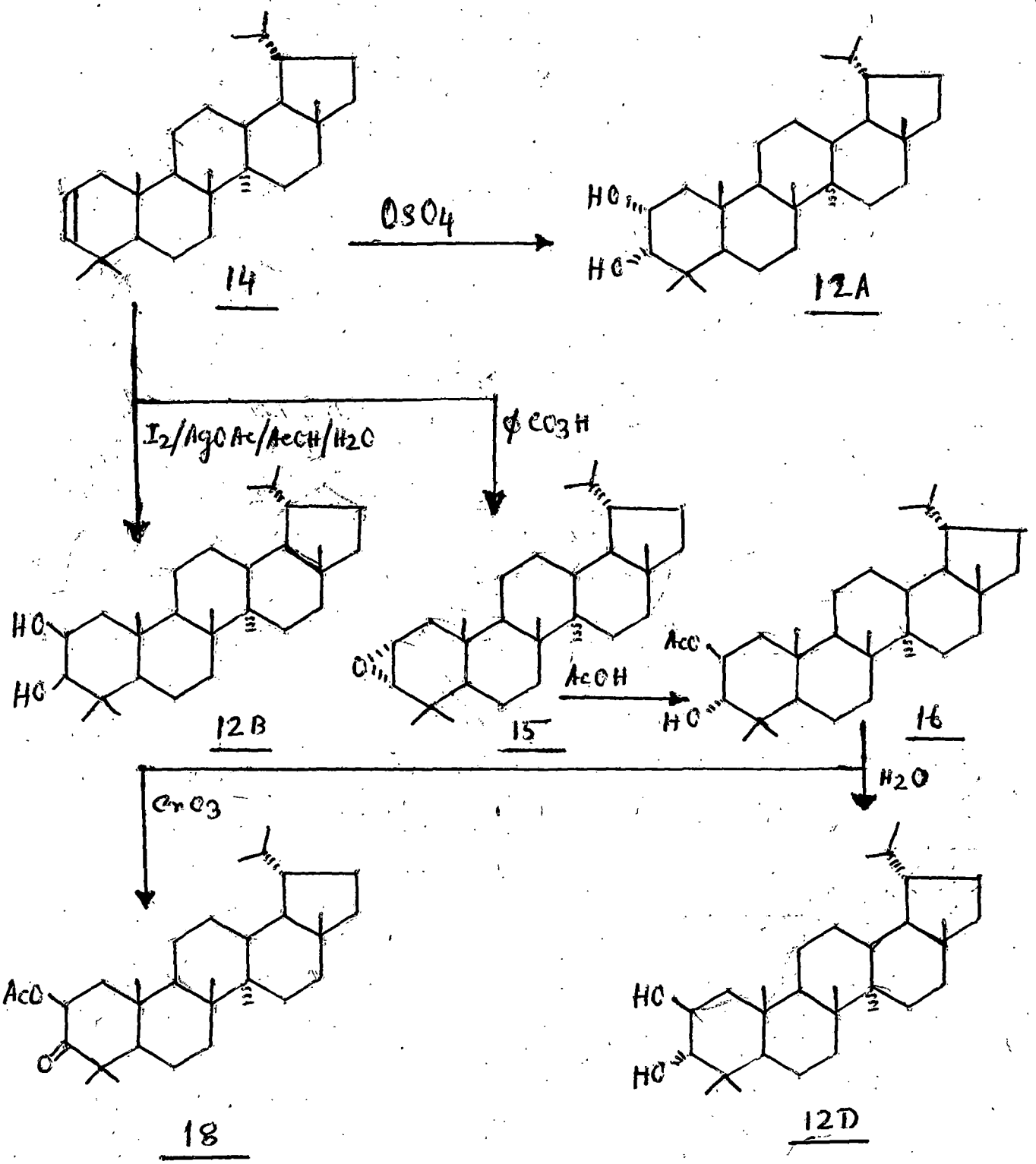
13B $R_1 = R_2 = \beta$-OH

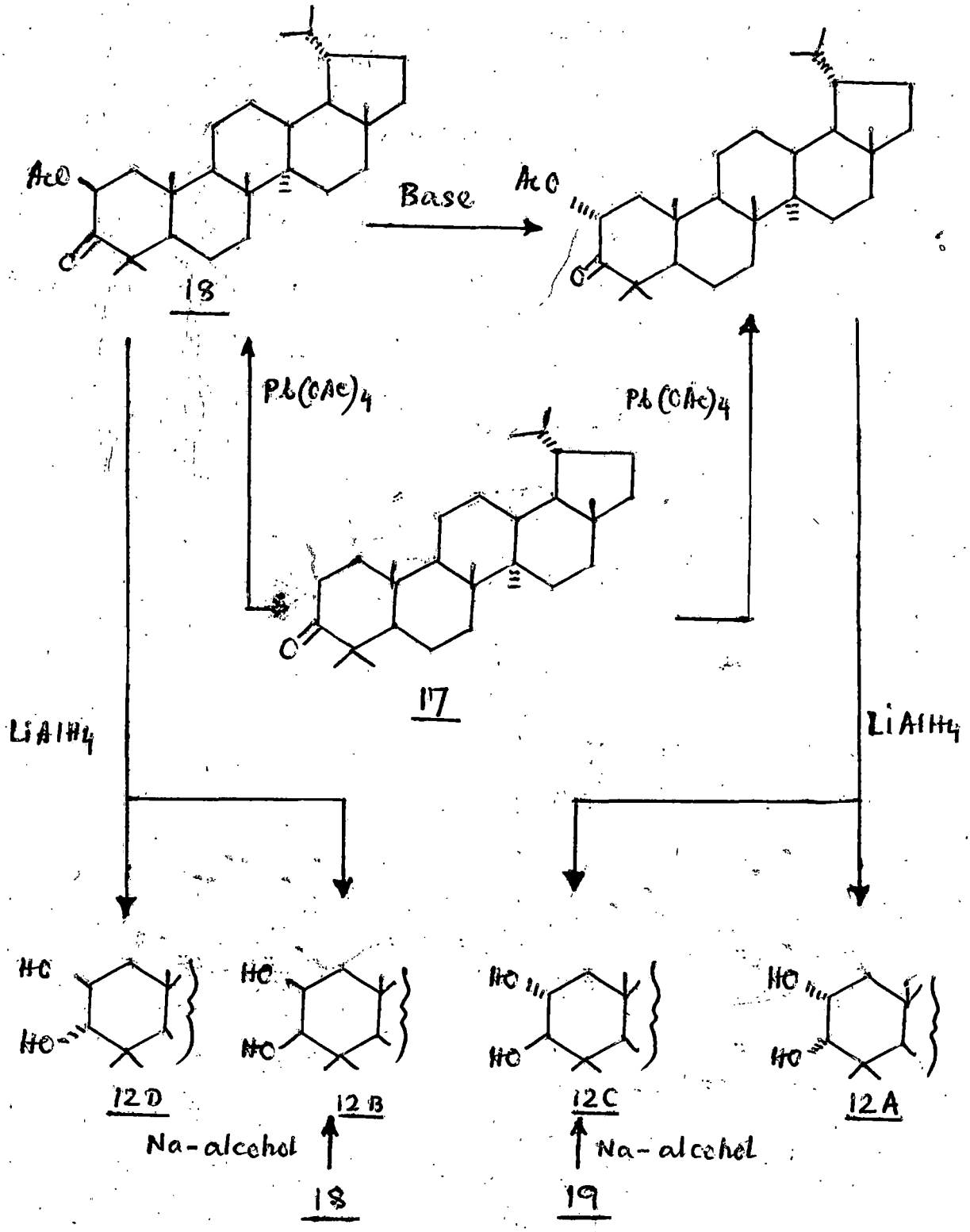
13C $R = \alpha$-OH ; $R_2 = \beta$-OH

Synthesis of Lupane-2,3-diols[7] 12 (Chart I)

Lup-2-ene 14 was converted to lupane-2α,3α-diol 12 A, lupane-2β,3β-diol 12 B and lupane-2α,3α-epoxides 15 by the action of osmium tetroxide, iodine-silveracetate-acetic acid and perbenzoic acid respectively. The epoxide 15 was opened with acetic acid to give 2β-acetoxy-lupane-3α-ol 16 which on mild alkaline hydrolysis yielded the diaxial trans diol, lupane 2β,3α-diol 12 D. In order to increase the poor yield of the 2β,3β-diol 12 B obtained by the above procedure and also to prepare the remaining isomer; lupane 2α,3β-diol 12 C, lupane-3-one 17 was treated with lead tetracetate to give 2β-acetoxy-lupane-3-one 18 and 2α-acetoxy-lupane-3-one 19 as the major and minor products respectively. The 2β-acetoxy isomer 18 could also be prepared by the chromic acid oxidation of 2β-acetoxy-lupane-3α-ol 16. This acetoxy ketone 18 upon equilibration with base furnished the 2α-acetoxy-3-ketone 19 which was then reduced with lithium aluminium hydride mainly to lupane-2α, 3α-diol 12 A and with sodium and isopropanol to lupane-2α, 3β-diol 12 C. The 2β-acetoxy-3-ketone 18 was similarly reduced with lithium aluminium hydride to give the 2β, 3α-diol 12 D as the main product and with sodium and isopropanol to the 2β, 3β-diol 12 B.

CHART I

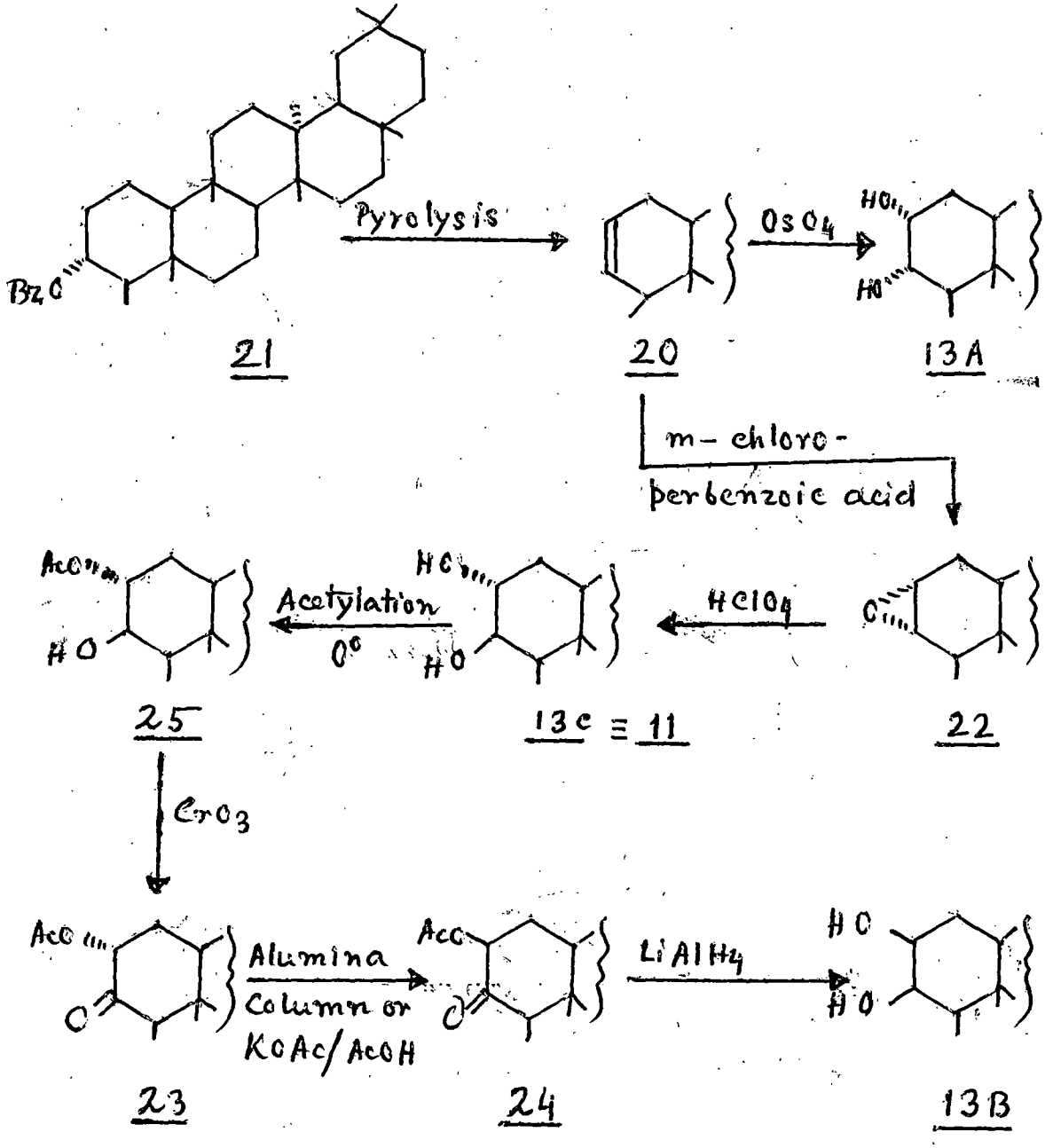

OsO4
14
12A
I2/AgOAc/AcOH/H2O
ϕCO3H
12B
15
AcOH
16
H2O
CrO3
18
12D


AcO
Base
AcO
18
Pb(OAc)4
Pb(OAc)4
17
LiAlH4
LiAlH4
HO
HO
12D
12B
Na-alcohol
18
12C
Na-alcohol
19
12A

Synthesis of Friedelane-2α, 3α 13 A; 2β, 3β-13 B; 2α, 3β-13 C - diols[8] : (Chart II)

Friedel-2-ene 20, obtained by the pyrolysis of friedelanol benzoate 21 was converted to friedelane- 2α, 3α-diol 13 A by the action of osmium tetroxide and a 2, 3-epoxide 22 by the action of m-chloroperbenzoic acid. The 2,3-epoxide 22 was opened with perchloric acid to yield friedelane 2α, 3β-diol 13 C identical with naturally occuring pachysandiol A[9] 11. Kikuchi and Toyoda[9] has suggested that cerin acetate was 2α-acetoxy friedelan-3-one 23, contrary to its previous formulation as 2β-acetoxy-friedelanϕ-3-one 24 on the following grounds: Paschysandiol A-2-monoacetate 25 obtained by the acetylation of Pachysandiol A 11 at 0°, could be oxidised to cerin acetate 23 with chromic acid. The cerin acetate so obtained, on prolonged absorption on alumina, was isomerized to another 2-acetoxy-3-ketone 24 which must hence be the more stable 2β-(e, equatorial)-acetoxy isomer. Consequently the original cerin acetate must be less stable 2α-(axial) acetoxy isomer 23. Samson et al[8] isomerized cerin acetate 23 with potassium acetate in acetic acid and reduced the resulting 2β-acetoxy-friedelan-3-one 24 with lithium aluminium hydride and thus synthesised friedelane-2β, 3β-diol 13 B. (Chart II)

CHART - II


BzO
Pyrolysis
OsO4
HO
HO
21
20
13A
m-chloro-
perbenzoic acid
AcO
HO
Acetylation
0°
HO
HO
HClO4
Cl
25
13c ≡ 11
22
CrO3
AcO
O
Alumina
Column or
KOAc/AcOH
AcO
O
LiAlH4
HO
HO
23
24
13B

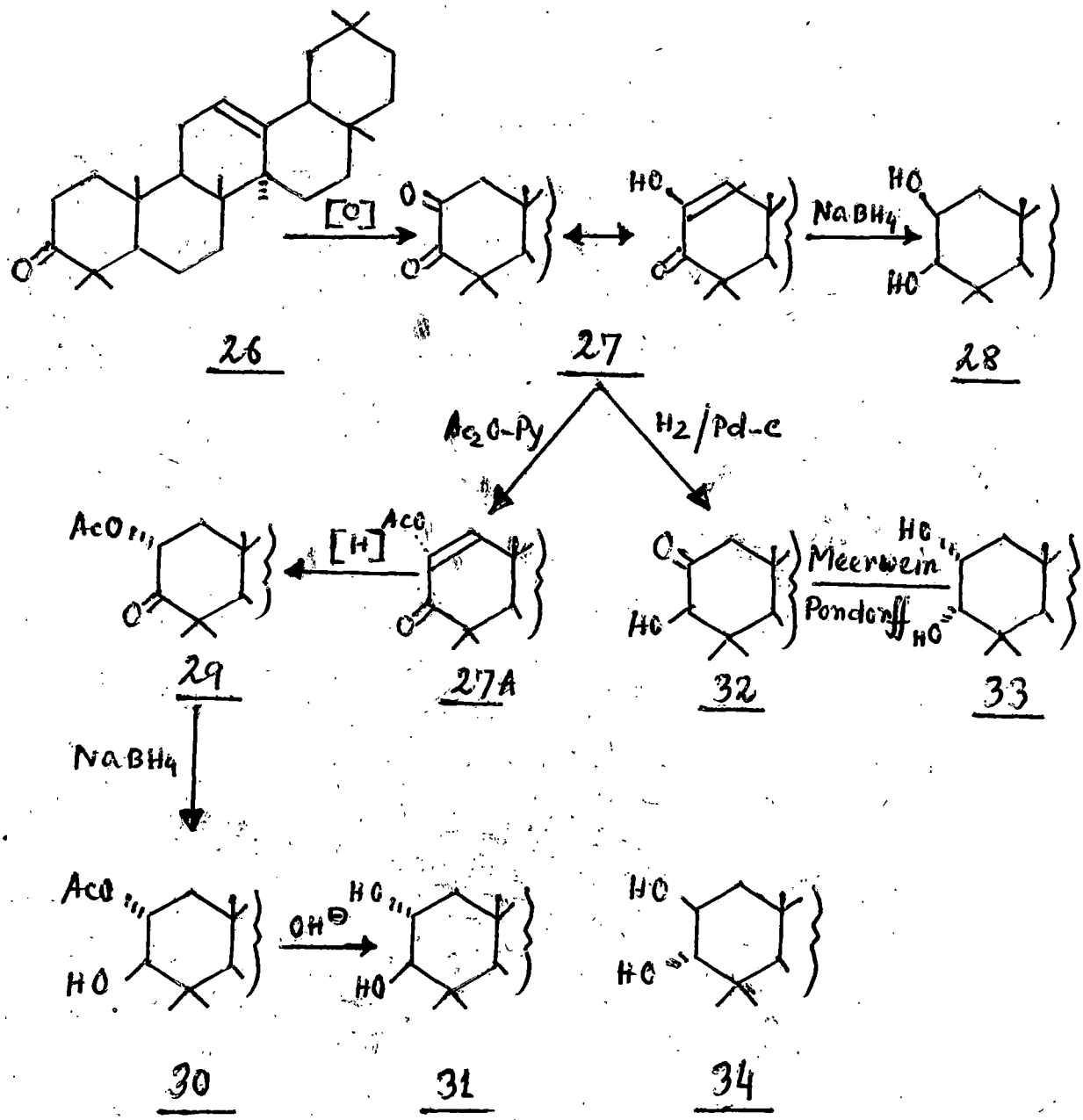
Section C: A short review of synthesis of isomeric Δ^{12}-Oleanene 2,3-diols[10a]:

A number of 2,3-diols of triterpenoids have been isolated from natural sources. Recently Khastgir et al[10a] have synthesised three out of the four isomeric 2,3-diols (Chart IV) by using diosphenol 27 as the intermediate, prepared from β-amyrone 26. Δ^{12}-oleanene 2β, 3β-diol[28] m.p. 240-42°, $(\alpha)_D$ +101.88° [28] was obtained by sodium borohydride reduction of 27. Acetylation of 27 followed by hydrogenation gave 2α acetoxy-β-amyrone 29 which on sodium borohydride reduction at PH-8 gave 2α-acetoxy-β-amyrin 30 which on hydrolysis gave the most stable Δ^{12}-oleanene 2α, 3β-diol 31. Hydrogenation of 27 gave 32 which on Meerwein Pondorff reduction afforded Δ^{12}-Oleanene-2α, 3α-diol, 33 having m.p. 278-81°, $(\alpha)_D$ 71.28°. The sterically most unstable 2β, 3α-diol 34 was also synthesised. The configurations assigned have been confirmed from NMR spectral evidence. The melting points and rotations of the isomeric diols, their diacetates and their acetonide derivatives have been shown in Chart III.

Chart III

	DIOL		DIACETATE		ACETONIDE DERIVATIVE	
	m.p.	$(\alpha)_D$	m.p.°	$(\alpha)_D$	m.p.	$(\alpha)_D$
2β, 3β	240-42°	101.88°	221-22°	83.63°	180-2°	102.50°
2α, 3α	278-82°	71.28°	180-82°	40.77°	199-201°	97°
2α, 3β	202-4°	60.00°	216-18°	73.42°	173-4°	-
2β, 3α	250-52°	12°	161-63°	-	-	-

Chart IV

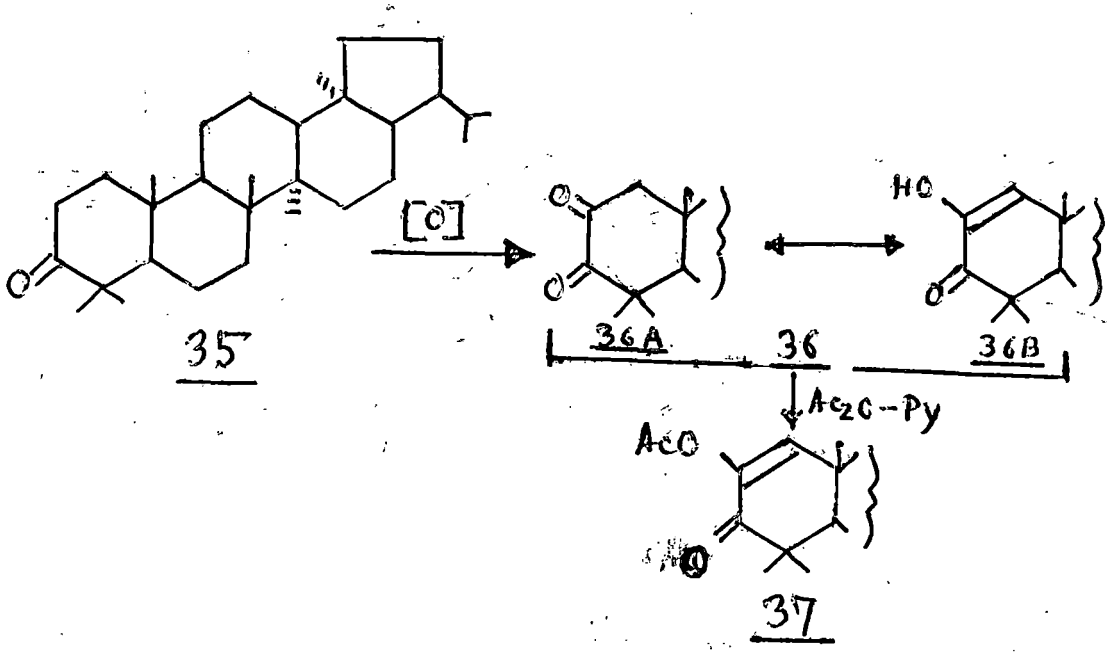

[O]
NaBH4
Ac2O-Py
H2/Pd-C
[H]
Meerwein
Ponndorff
NaBH4
OH⊖
26
27
28
29
27A
32
33
30
31
34

Section D : A short review on the synthesis of isomeric 2,3-diols of isohopane (moretane)[10b] :

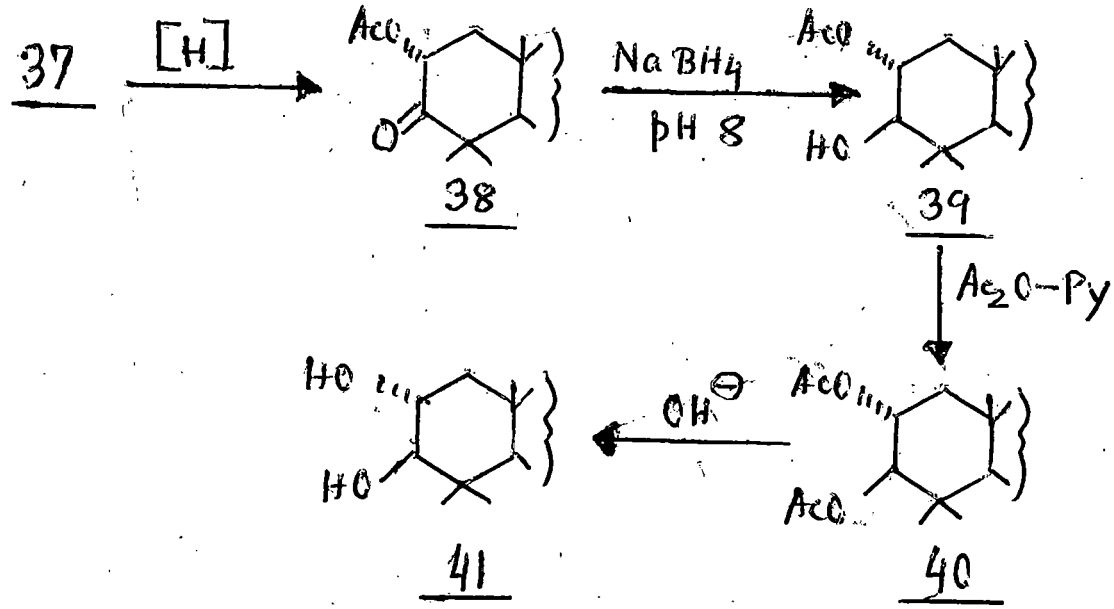
Khastgir et al[10b] have been able to prepare all the four isomeric diols using diosphenol obtained by the autoxidation of moretanone.

1. Synthesis of 2α, 3β- dihydroxy isohopane (moretane) 41 :

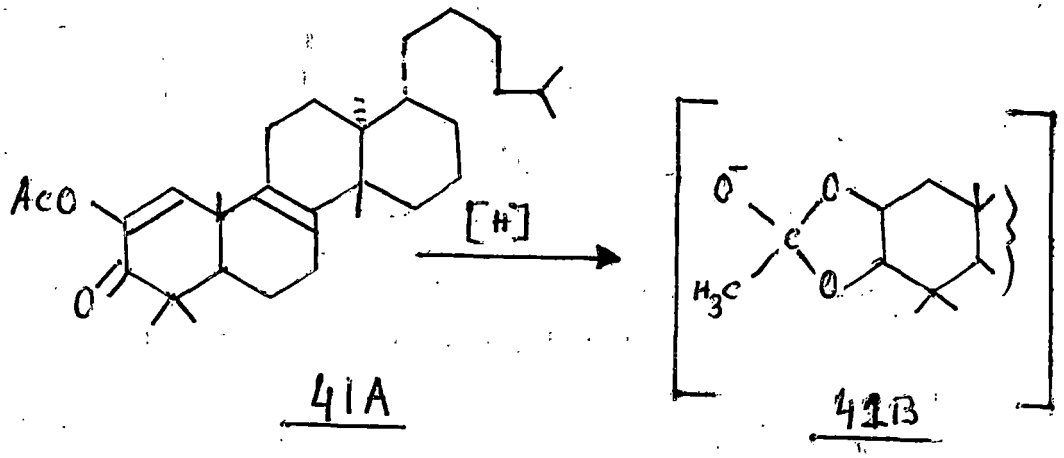
Moretanone 35 obtained by hydrogenation of moretenone[10c] was oxidised by passing oxygen through a suspension of 35 in dry t-butanol containing potassium tertiary butoxide[11,12,13,14]. The product, α-diketone derivative 36, m.p. 190-2°, $(\alpha)_D$ 40.00° showed two spots on chromatoplate indicating the presence of a mixture of two compounds. The compound 36 showed positive ferric chloride test. The assignment of structures 36 A and 36 B are consistent with the UV and IR spectral data.



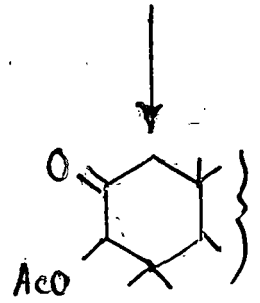
Acetylation of 36 with acetic anhydride and pyridine gave the corresponding acetate 37 (single spot in TLC). The diosphenol acetate 37 on hydrogenation in presence of 10% palladium-on-charcoal catalyst in ethanol solution gave 38, m.p. 179-81°, $(\alpha)_D$ 86.31°, λ_{max} 276 mμ (ε 82) NMR spectrum was consistent with the structure 38. Sodium borohydride reduction of 38 in dioxan solution buffered at pH-8 to reduce isomerisation gave the crystalline 2α-acetoxy-3β-hydroxy compound 39, m.p. 199-200°, $(\alpha)_D$ 95.35°. The latter on acetylation with pyridine and acetic anhydride gave the 2α, 3β-diacetate 40, m.p. 228-30°, $(\alpha)_D$ 50.60° which on alkaline hydrolysis afforded the corresponding 2α, 3β-diol 41, m.p. 242-3°, $(\alpha)_D$ 82.86°. From examination of the NMR spectrum of the diol 41 and its diacetate 40, they confirmed unequivocally the diequatorial 2α, 3β configuration of the hydroxyl groups in the diol 41.



In this connection it is necessary to mention that Lavie and co-workers during their studies on autoxidation in euphol series claimed that hydrogenation of diosphenol acetate of dihydroeuphone 41 A gave a product which was identical with C - 3 acetate 41 C i.e., a 2-keto-3-acetoxy derivative. Migration of the acetoxy group from C - 2 to C - 3 position was proposed through cyclic intermediate 41 B[15]. These results are contrary to the observations reported in the β-amyrone series[10a] and also in the moretanone series[10b] where they obtained the corresponding 2α-acetoxy-3-keto compounds with 1,2-addition of hydrogen.



41A 41B



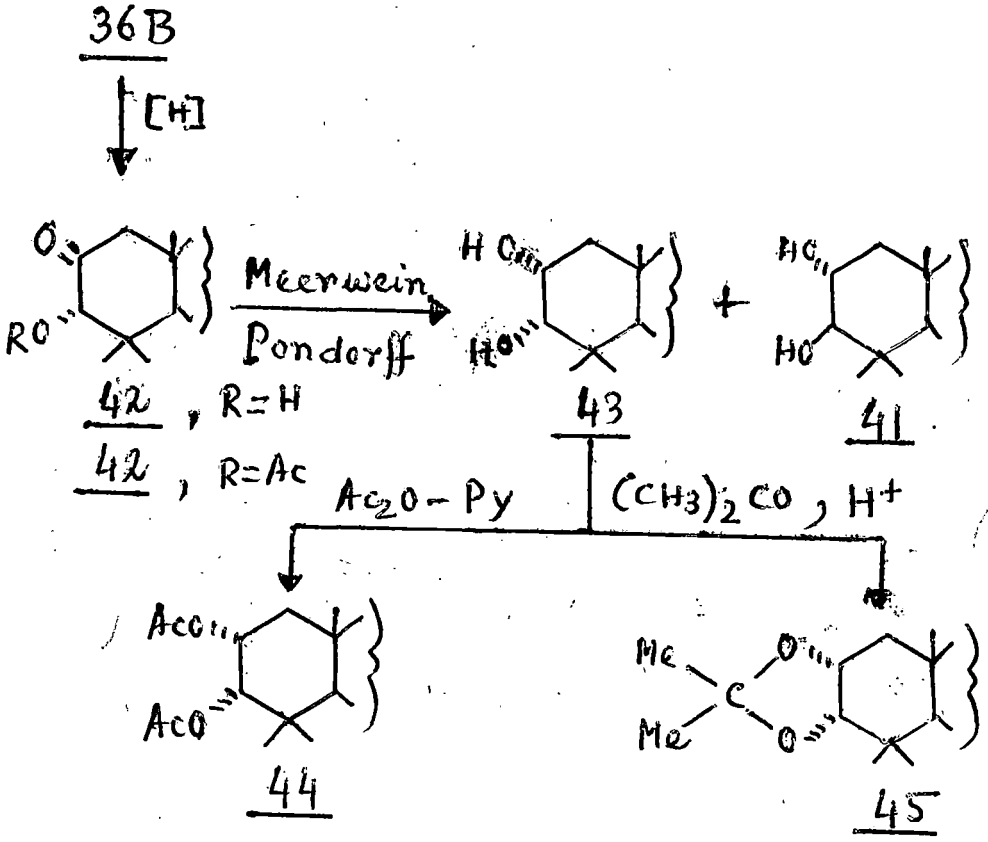
41C

In order to provide a reasonable explanation for the different behaviour shown by these compounds (dihydroeuphone, β-amyrone and moretanone) they examined the Drieding models of euphol, β-amyrin and moretane derivatives. In the euphol series the presence of a double bond in 8,9 position causes deformation[16] and has a modified chair conformation which confers additional strain in the molecule whereas in the β-amyrin series as well as in moretane (isohopane) series (having A/B chair - chair conformation) this strain is not present. They assumed that the 2α-acetoxy-3-keto compound which presumably is formed at first on hydrogenation of 41 A isomerises to 41 C via 41 B to release additional strain in the molecule. Therefore, they proposed 38 for the structure of 2α-acetoxy moretanone the acetoxy group being at C - 2 with α-configuration.

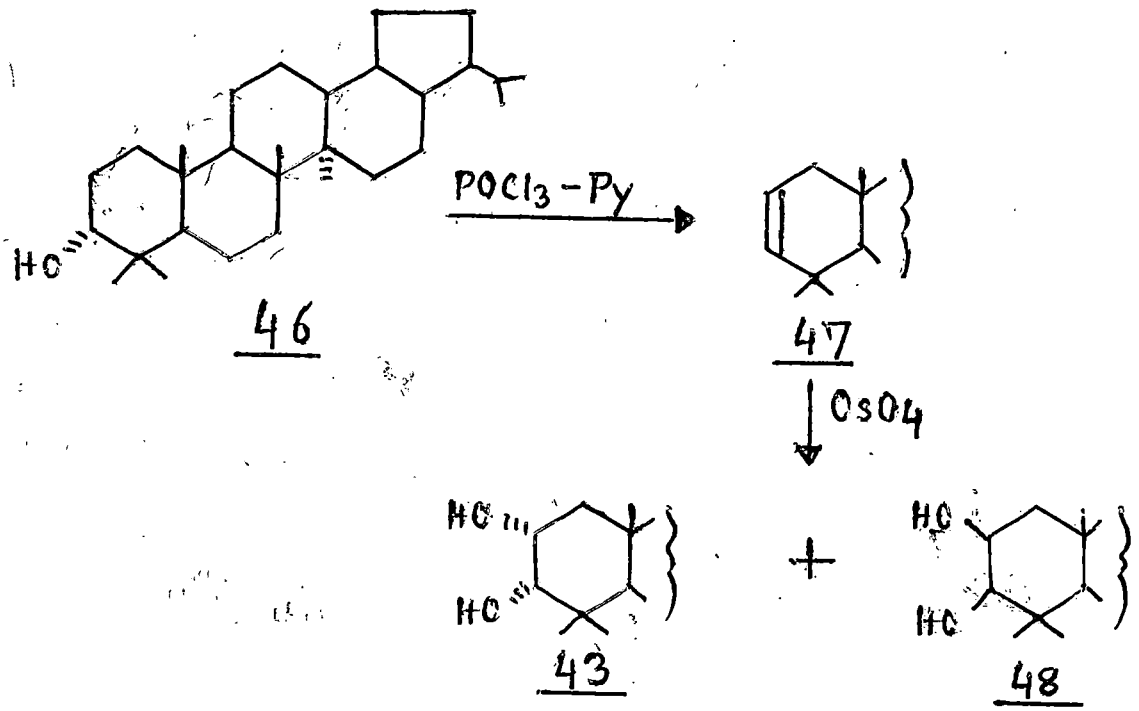
2. Synthesis of 2α, 3α-dihydroxy isohopane (Moretane) 43 :

Diosphenol 36 B on hydrogenation in presence of 10% palladium-on-charcoal catalyst in ethanol solution afforded 2-keto-moretanol 42, m.p. 181-3°, $(\alpha)_D$ 29.41°, which on acetylation with pyridine and acetic anhydride afforded the corresponding acetate 42 A, m.p. 264-7°, $(\alpha)_D$ 82.61°. They reported that the NMR spectra was consistent with the structures 42 and 42 A assigned to them. Meerwein-Pondorff reduction of 2-keto

moretanol 42 furnished a crystalline solid which exhibited two distinct spots on chromatoplate. Chromatography of the solid, first eluted a solid compound which after crystallisation from methanol and chloroform mixture afforded a crystalline solid 43, m.p. 250-51°, $(\alpha)_D$ 9.37°, γ_{max} 3420, 2960, 1450, 1370, 1350, 1042 cm^{-1} in 92% yield. The latter on acetylation with pyridine and acetic anhydride afforded an acetate 44, m.p. 185-7°. The more polar solid obtained from the chromatogram in about 5% yield had the m.p. 242-3° and was found to be identical with 2α, 3β-diol 41, by m.m.p. and IR comparison. The assignment of stereochemistry of the hydroxyl groups in the diol 43 as 2α, 3α was based on the following chemical and physical evidence.



Δ^{2}-moretane 47 prepared by dehydration of epi-moretanol 46 with phosphorous oxychloride and pyridine, was treated with osmium tetroxide in pyridine solvent and the product obtained after chromatography melted at 235-40° and showed two spots on chromatoplate. The separation of the two compounds could not be sucessfully accomplished by column chromatography. However, on careful fractional crystallisation (chloroform - methanol mixture) they first obtained a diol, m.p. 250-51°, $(\alpha)_D$ 9.83° as the major component (87%). From the mother-liquor a second diol, m.p. 261-3°, $(\alpha)_D$ 23.68° was isolated as a minor product (8%). They identified the latter as the 2β, 3β-diol 48 from its m.m.p. and IR comparison with an authentic sample of 2β, 3β-diol (described on page 98). The major diol 250-51°, $(\alpha)_D$ 9.83° afforded a diacetate 44, m.p. 185-87°. The diol and the diacetate were found

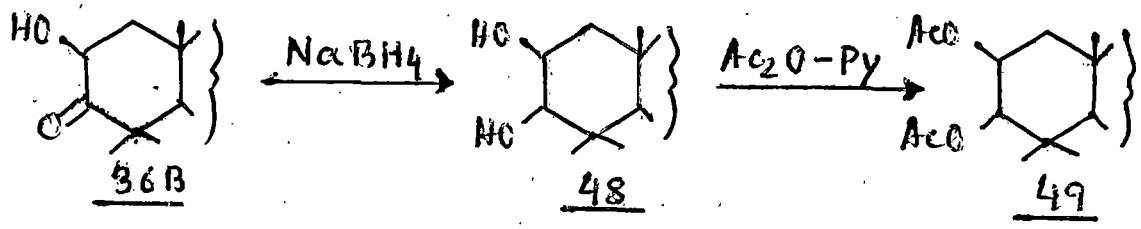


to be identical with the diol and diacetate respectively obtained by the Meerwein - Pondorff reduction of 2-keto-moretanol 42 described above. They argued that since osmylation could afford only two cis isomers, the stereochemical assignments of the diol 43 having m.p. 250-51° and its diacetate 44, m.p. 185-87° must have 2 α, 3 α- configuration as depicted in 43 and 44 respectively. NMR spectra of the diol 43 and its diacetate 44 are in good agreement with their stereochemical assignments 43 and 44.

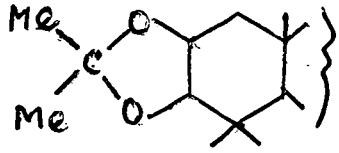
The diol 43 on treatment with acetone in presence of catalytic amount of p-toluene sulfonic acid gave an acetonide derivative 45, m.p. 186-88°, $(\alpha)_D$ 19.04°.

3. Synthesis of 2β, 3β-dihydroxy isohopane (moretane) 48 :

Diosphenol 36 B on sodium borohydride reduction gave a compound 48, m.p. 262-64°, $(\alpha)_D$ 23.68°, ν_{max}^{nujol} 3420, 2950,



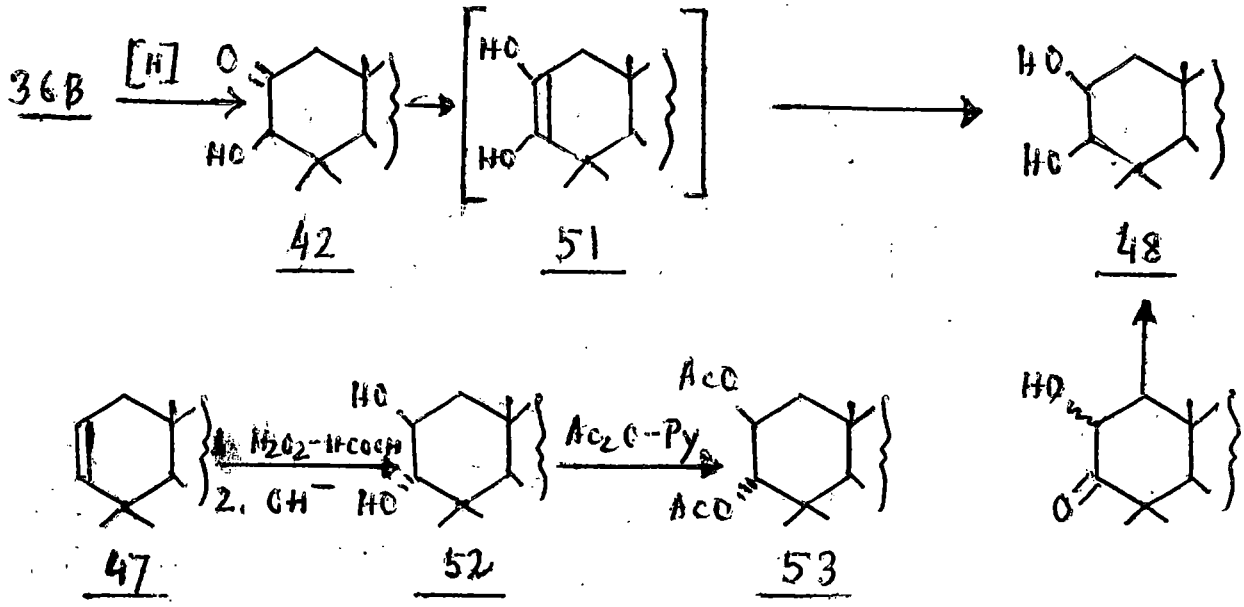
36 B 48 49



50

1460, 1275, 1250 cm^{-1}. The latter on acetylation with acetic anhydride and pyridine gave the diacetate 49, m.p. 214-15°, $(\alpha)_D$ 31.25°. NMR of 48 showed a multiplet at 3.23 ppm and a broad unresolved multiplet at about 4.60 ppm which collapsed to a doublet (J = 3.6 Hz) and a multiplet (J = 6 Hz) respectively upon exchange of hydroxyl proton with D_2O. This data was in good agreement with the equatorial orientation (Ha) of the hydroxyl group at C - 3 and the axial orientation (He) at C - 2 . In the NMR spectra of the diacetate 49 these signals were shifted downfield to 4.97 ppm (doublet, J = 3Hz) and at about 5.25 ppm (broad multiplet).

Compound 48 on treatment with acetone in presence of catalytic amount of p-toluene sulfonic acid gave an acetonide derivative 50, m.p. 239-41°, $(\alpha)_D$ 29.85°. They explained the formation of the 2β, 3β-diol 48 by the following mechanism via intermediate 51.



4. Synthesis of 2β, 3α-dihydroxy isohopane (moretane) 52 :

The sterically most unstable 2β, 3α-diol (axial-axial) was prepared by them by the known method[1,2,3] described in the literature. The method involved the oxidation of Δ^2-moretane 47 with performic acid and subsequent hydrolysis of the ester with alkali solution. By following the above procedure they obtained a crystalline diol 52, m.p. 221-24°, $(\alpha)_D$ 21.18°. IR spectrum of the diol showed peaks at 3560, 2980, 1455 cm^{-1}. Acetylation of the diol with acetic anhydride and pyridine afforded the crystalline 2β, 3α-diacetate 53, m.p. 145-47°, $(\alpha)_D$ 31.40°. NMR spectrum of the diacetate was consistent with the structure and stereochemical assignment as in 52 and also by analogy with the previous work reported in the literature[10a,17].

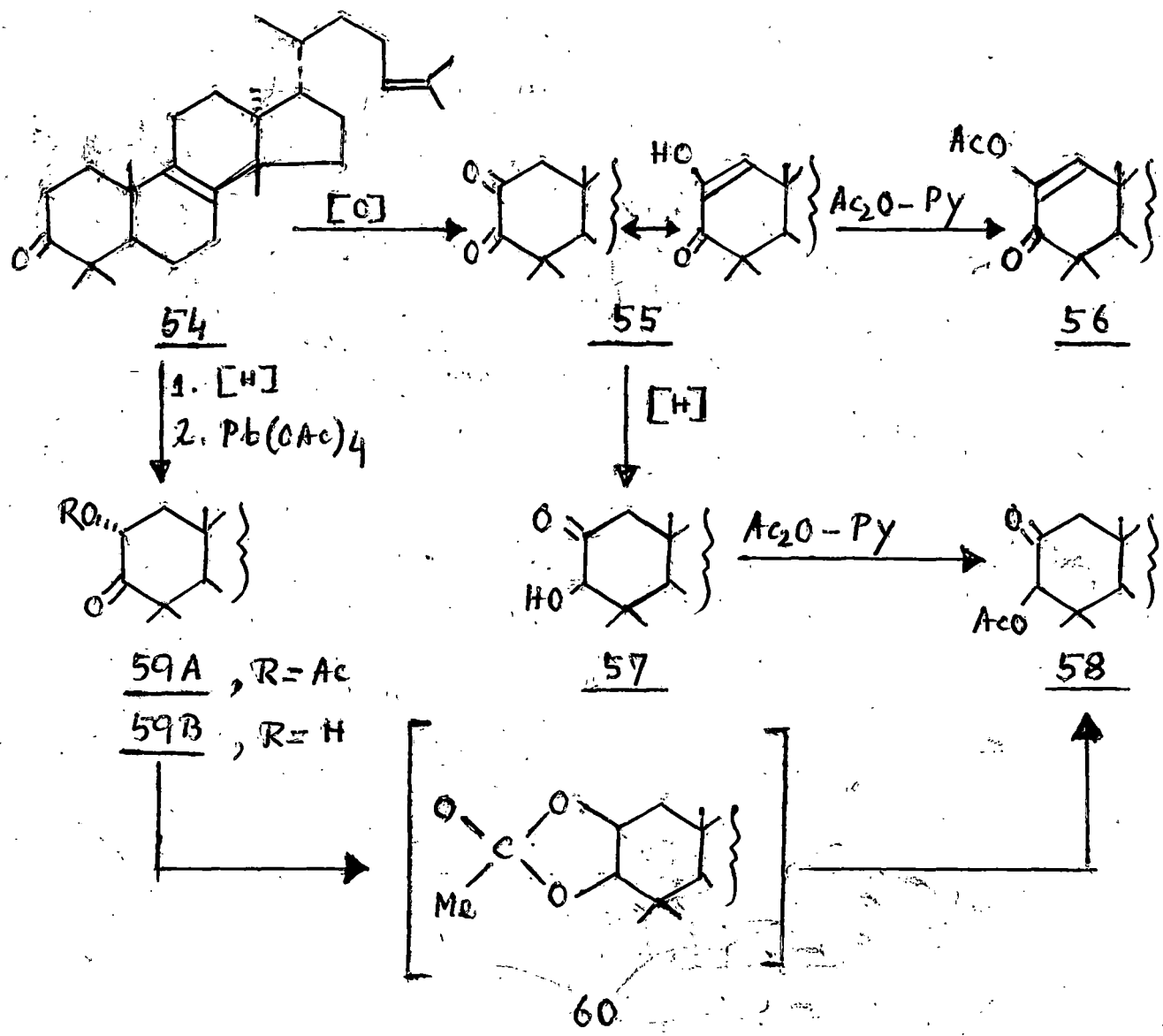
Section E : A short review on autoxidation and isomerisation in ring A in triterpenoids :

1. Oxidation in ring A in Euphol.

Lavie and co-workers[11] studied the autoxidation of euphadiene-3-one 54 and the results of their work is summarized in the following lines (Chart - V). Euphadiene-3-one 54 was oxidised by shaking in oxygen in t-butanol saturated with potassium-t-butoxide[12,13]. A tautomeric mixture of diketone and the

corresponding diosphenol 55 (two spots in chromatoplate) was produced by absorbing one mole of oxygen; UV, λ_{max} 269 mμ (ϵ, 7900). ν_{max} 1715, 1672, and 1653 cm^{-1}. NMR of the compound 55 showed a singlet at τ 3.60 due to vinylic proton at C - 1. Acetylation gave the corresponding acetate 56, UV $_{max}$ 236 mμ (ϵ .9000), ν_{max} 1764 cm^{-1}. NMR showed a singlet at τ 3.02 due to C - 1 proton. On hydrogenation of the diosphenol 55 over palladium on charcoal (two moles of hydrogen were absorbed - on mole to reduce the side chain double bond and the second mole to reduce the enolic double bond) a noncrystallisable homogeneous solid ν_{max} 1712 cm^{-1}, NMR singlet at τ 5.95 accounting for one hydrogen and two AB type doublets centered at τ 7.69 and 7.35 accounting for two hydrogens, was obtained. Upon acetylation a crystalline ketoacetate was obtained, ν_{max} 1742 and 1730 cm^{-1}, NMR singlet at τ 4.95 for one hydrogen and a broad peak at τ 7.50 accounting for two hydrogens. From the above spectral properties structures 57 and 58 were proposed for hydroxy ketone and keto acetate respectively. 2α-acetoxy (equatorial) derivative 59 A was prepared by the reaction of dihydroderivatives of 54 with lead tetraacetate in acetic acid in presence of boron-trifluoride[18]. The product 59 A showed IR bands at 1742 and 1730 cm^{-1} and the NMR spectra showed a quartet of lines centered at τ 4.3 (Jae = 6.5 cps and Jaa = 13.0 cps) for the C - 2 proton but no signals for

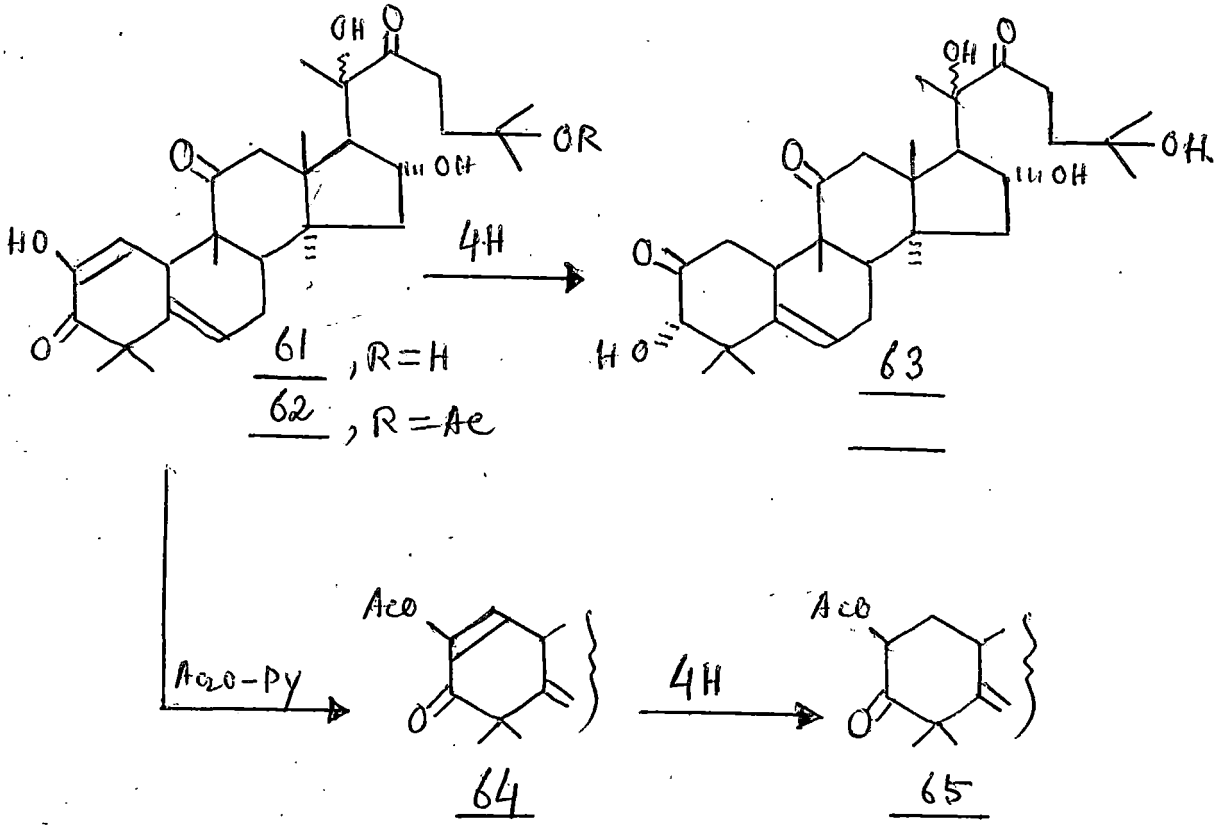
CHART - V


[O]
HO
AcO
Ac2O - Py
54
55
56
1. [H]
2. Pb(OAc)4
[H]
RO
HO
Ac2O - Py
AcO
59A , R = Ac
59B , R = H
57
58
Me
60

protons α to a keto-functions. The isomerisation of 2α-equatoraial acetoxy ketone 59 A into the isomer 58 was also observed and they proposed that the migration proceeded through the cyclic intermediate 60.[15] Acid hydrolysis of 59 afforded a compound which has been assigned the 2α- equatorial hydroxy 3 - keto derivative 59 B on the basis of its IR, ν_{max} 1718 cm^{-1}.

2. Isomerisation in ring A of the Cucurbitacins

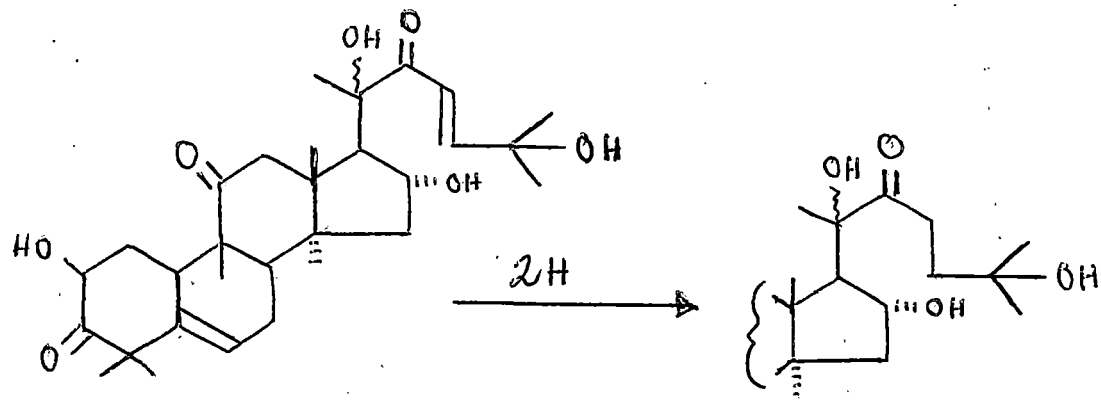
Lavie and co-workers [19,20] reported that hydrogenation of the diosphenol containing cucurbitacins namely elatericin B 61 and elaterin 62 resulted in 1,4 addition of hydrogen during the process of hydrogenation. The NMR spectrum of hydrogenated product of elatericin B was found to show a singlet at τ 6.02 and that of its diacetate a sharp one at τ 5.co.



This observation clearly pointed to the fact that the proton linked to the carbon to which the acetoxy group is also attached had no neighbouring protons and can not therefore be at C - 2. The NMR spectra could be explained, if it was considered that 1,4 addition of hydrogen to the diosphenol system took place, resulting in the conversion of Δ^1-2-hydroxy-3keto to a 2 keto-3-hydroxy system 63.

Elatericin B diacetate 64 on hydrogenation formed the 2β- equatorial - acetoxy - 3keto derivative 65 by abnormal 1,2 addition of hydrogen. This compound showed a quartet of lines related to the 2α-axial proton which is centered at τ 4.4 (Jaa = 13.5 cps; Jae = 5.1 cps). The isomerisation of 2 -acetoxy-3-keto derivative 65 on a basic column of alumina as well as on an acidic column was studied. In both the cases the material recovered from the columns showed that it had remained unchanged.

The ORD curves of dihydro elatericin A 67 and tetrahydro elatericin B 65 were also interpreted, cotton effect curves of both 2 and 3-keto derivatives were found to be positive with the



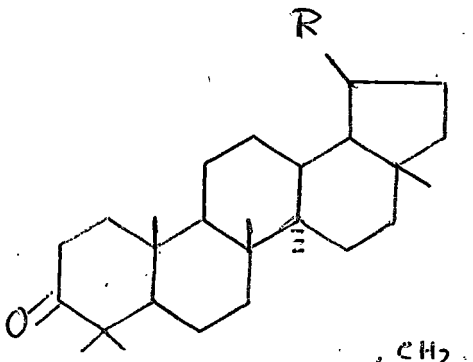
66 67

amplitude of the 2-keto-derivative being larger than that of the 3-keto form. ORD studies on 2 and 3 ketosterbids[21] and the oxomanoyl oxide series[22] also revealed the same result. The inverted stereochemistry of cucurbitacins at C - 10 resulting in a mirror image of the C - 10, β -analog should give rise to a negative cotton effect but instead the two compounds displayed positive curves. This can be interpreted as due to the presence of two additional carbonyl chromophore, one in particular at C - 11 displaying a large amplitude, which counteracts thereby the inverted rotation of the keto group in ring A as should be expected. The result is a lower positive value instead of a negative one. The peak for dihydro elatericin A 67 (3 keto) at $(\alpha)_{325}$ + 2200° is larger, than that of tetrahydroelatericin B 63 (2 keto) $(\alpha)_{325}$ + 1558°. In both the cases the keto group was flanked by an equatorial (OH) substituent which is either likely to increase the cotton effect or to render no change at all.

In order to obtain pure tetrahydroelatericin B 64, alkaline hydrolysis of tetrahydroelatericin B diacetate 65 was attempted but the reaction resulted in the formation of dihydroelatericin B[23] 66 λ_{max} 267 mμ(ϵ, 5700), positive feric chloride coloration (characteristic of diosphenol). Tetrahydroelatericin B diacetate 65 on alkaline hydrolysis yielded the same dihydroelatericin B 66. The alkali induced autoøxidation of α -hydroxy ketone in elatericin was also studied[24] and was found to occur at much slower rate.

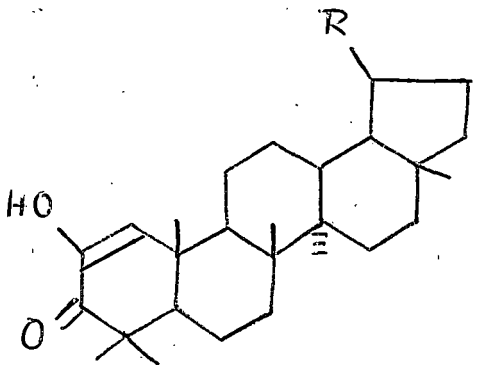
3. Oxidation in ring A in Lupeol

Ganguly and co-workers[14] carried out the oxidation of lupenone 68 and lupanone 69 to the corresponding diosphenols 70 and 71 respectively by passing oxygen in dry t-butyl alcohol containing potassium tertiary butoxide. Diosphenol 71 on hydrogenation afforded a non-crystalline alcohol which on acetylation yielded the keto acetate 72. The structure 72 was assigned to the keto- acetate by examining its NMR spectra (a sharp singlet at δ , 4.95) ascribed to the C - 3 proton.



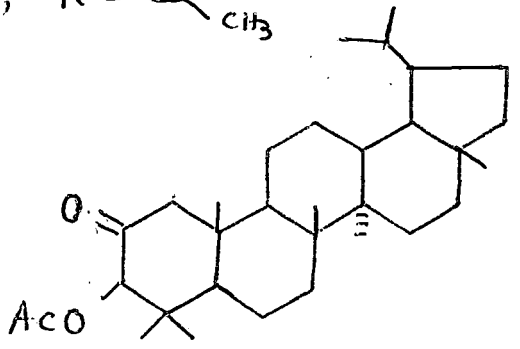
68 , R = $-C(=CH_2)-CH_3$

69 , R = $-CH(CH_3)_2$



70 , R = $-C(=CH_2)-CH_3$

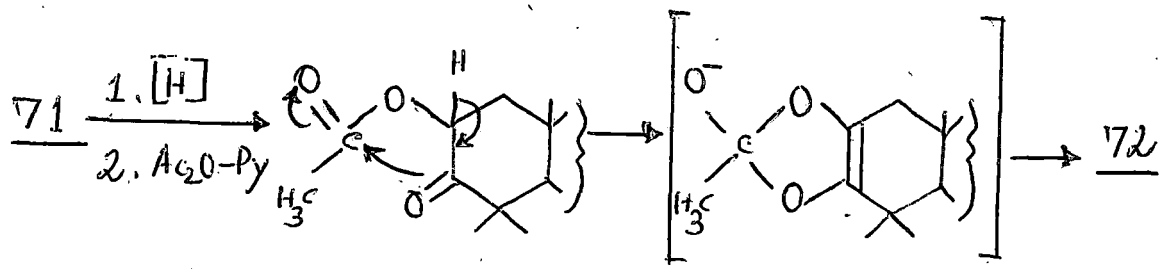
71 , R = $-CH(CH_3)_2$

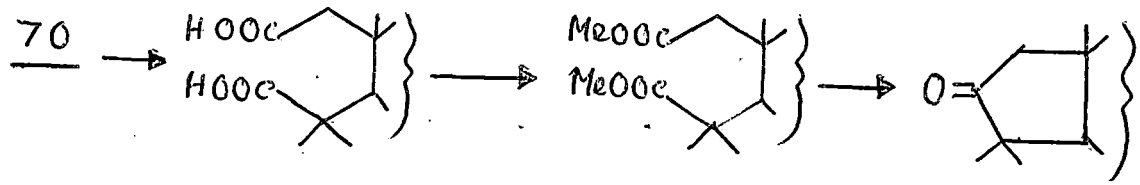


72

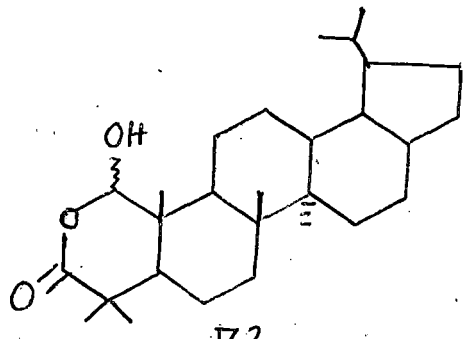
Formation of 72 from 71 was explained by the mechanism shown in chart V. Diosphenol 71 on ozonisation gave a neutral compound $C_{29}H_{48}O_3$, whose structure was assigned as 73 on the basis of mode of formation, spectral characteristics and elemental composition. Diosphenol 70 was cleaved by alkaline hydrogen peroxide to the dicarboxylic acid $C_{30}H_{48}O_4$. The acid was converted into the dimethyl ester, 74 which on refluxing with alcoholic alkali yielded a neutral crystalline compound 75.

Chart - V





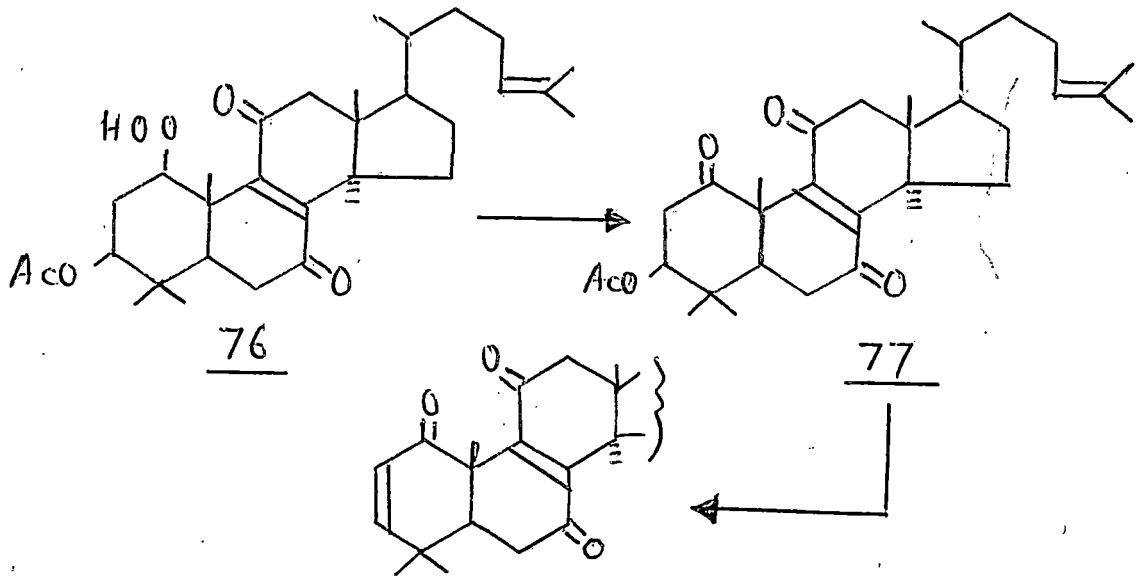
74 75



73

4. Autoøxidation of Lanstenyl acetate

Horn and Ilse[25] stated that lanostenyl acetate in ethyl acetate was extensively converted into a mixture of 7-hydroperoxy and 7,11 - dihydroperoxy lanostenyl acetates by treatment with gaseous oxygen at 50° for 48 - hours. After that Scotney and Truter[26] found that the autoxidation of lanostenyl acetate in ethyl acetate at 50° after 14 days was a mixture of at least eight peroxides (laminar chromatography). The two most plentiful peroxides were recovered and shown to be 7β - and 11β - hydroperoxy lanostenyl acetates. The structure of 7β - hydroperoxy - lanostenyl acetate was obtained by reducing it with sodium borohydride to 7β - hydroxy lanostenyl acetate. The structure of 11β - hydroperoxide was proved by converting it to 11-oxo-lanostenyl acetate with ferrous ion. Furthermore, lithium aluminium hydride reduction of the 11-hydroperoxide afforded one product, which was identical with 11β - hydroxy-lanostenol.



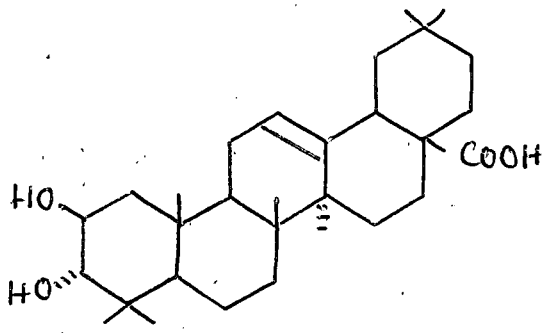
Autoxidation of 7,11-dioxolanost-8-enyl-3β-acetate in cyclohexane at 40° proceeded via 1β-hydroperoxy - 7, 11-dioxolanostenyl acetate to 1,7,11-trioxolanost-8-enyl acetate[27]. The location of ketone at 1-position was deduced from the behaviour of the trione acetate with alkali. With alkali 1,7,11-trioxolanost-8-enyl acetate yielded 1,7,11-trioxolanosta-2,8-diene and it had been derived from the trione acetate by elimination of the 3β-acetate group and the formation of a conjugated unsaturated grouping (76, 77, 78). That the precursor for the trione is a mono-hydroperoxide of 7,11-dioxolanostenyl acetate was established by the fact it was decomposed by ferrous ion to 1,7,11-trioxolanostenyl acetate.

In an experiment a solution of lanost-3-en-3β yl-acetate in cyclohexane at 40° was oxidised by passing oxygen through it[28]. After twelve months treatment the neutral fraction was examined and was found to contain at least sixteen components. From the Rf values several components have been identified e.g. 1,7,11-trioxolanostenyl acetate, 1,7,11-trioxolanosta-2,8-diene. Besides these 15β- hydroxy-7-oxo, 15α-hydroxy-7-oxo, 7,15-dioxo-and 11-15-dioxolanostan 3β-yl acetate were also identified.

5. Oxidation of ring A in Oleanolic acid

In connection with their work to confirm the structure of bredemolic acid 79 and crategolic acid 80 Tschesche and

co-workers[29,30] perfomed the autoxidation of ring A in methyl oleanolate 81. Methyl oleanolate was stirred in t-butanol containing potassium metal at 25-50° with simultaneous introduction of oxygen. The reaction mixture on acidification and usual working up gave an amorphous solid for which structure 82 was proposed. The diosphenol 82 m.p. 130-35°, $(\alpha)_D$ 104 ± 4° on sodium borohydride reduction gave 2β, 3β-dihydroxy-12-en-olean-28-oate 83 which on oxidation with kilani solution gave a mixture of several compounds in which 10% of 82 was found to be present as was shown by its UV spectrum.



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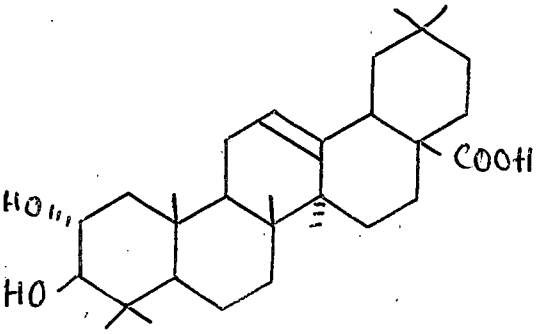

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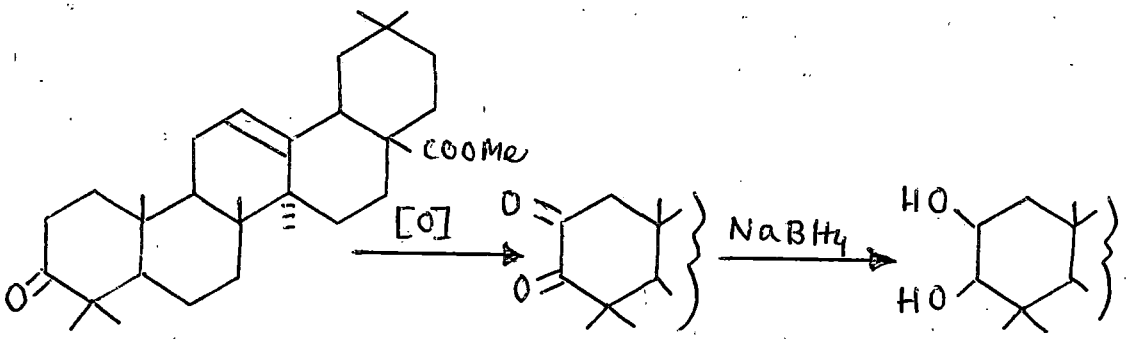
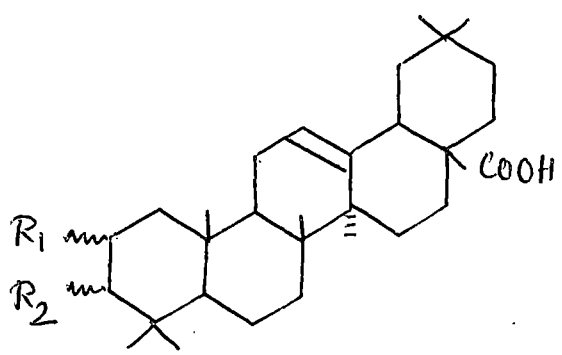


81 82 83

Section F : A short review on 2,3-dihydroxy triterpene acids from natural sources :

The four stereo-isomeric 2,3-dihydroxy olean-12-en28-oic acids are known to occur in nature : (1) the 2α, 3α-dihydroxy-olean-12-en-28-oic acid 84 A[31] (2) the 2α, 3β- dihydroxyolean-12-en-28-oic acid (crategolic acid / maslinic acid) 84 B[32] (3) the 2β, 3β- dihydroxy olean-12-en-28 oic acid[33] 84 C (4) the 2β, 3α- dihydroxy olean-12-en-28-oic acid 84 D[30] (brademolic acid)



84

84A , $R_1 = R_2 = \alpha$-OH

84B , $R_1 = \alpha$-OH, $R_2 = \beta$-OH

84C , $R_1 = R_2 = \beta$-OH

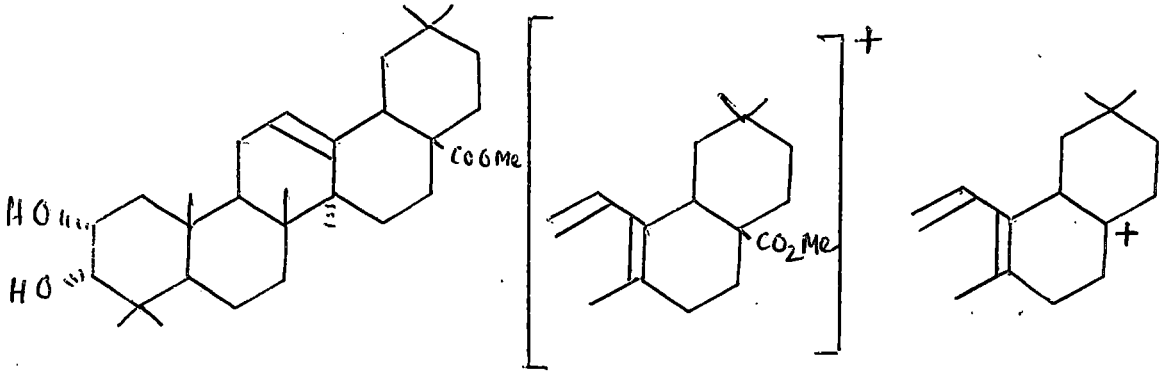
84D , $R_1 = \beta$-OH, $R_2 = \alpha$-OH

Alphitolic acid[34] in the lupeol series and 2α-hydroxy ursolic acid[35] in the ursane series are known to occur in nature.

1. The 2α, 3α- dihydroxy olean-12-en-28-oic acid :

Cheung et al[31] isolated a triterpene acid 84 A as its methyl ester m.p. 296-99° from shorea accuminata resin, which has been shown to be the 2α, 3α- dihydroxyolean-12-en-28-oic acid. The methyl ester 85 (ν_{max} 3340, 1725 cm^{-1}) formed a diacetate, a monoacetate and a O, O - isopropylidene derivative indicating the presence of two hydroxyl groups. All these compounds showed NMR singnals due to methyl ester group (3H, singlet δ 3,6) and a triplet for an olefinic proton (J $4H_z$, δ 5.3).

The mass spectrum of the diol methyl ester or its acetonide showed intense peaks at m/e 262, 203 corresponding to ions 86 and 87[36]

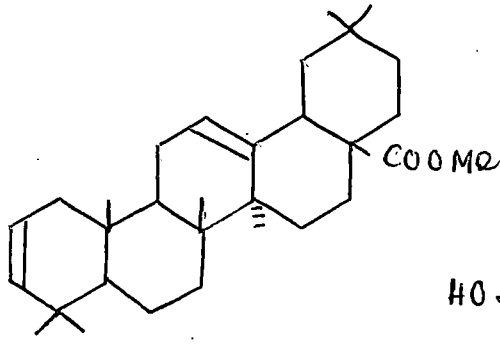


85 86 87

The mass fragmentation pattern established that the diol methyl ester belongs to 12-oleanene or 12-Ursene series with a 28 - methoxy-carbonyl group. They concluded from the NMR signal[37] of the allylic 18β - hydrogen at δ 2.8 (AB quartet), that the diol ester belonged to oleanene group. Further evidence for assignment of a 2α, 3α- configuration of the diol is supported by the following observations. In this diol, the C - 3 proton showed a doublet (J $3H_2$) at δ 3.35 due to vicinal coupling of equatorial and axial protons. Upon saturation (by double irradiation) of this signal, the multiplet near δ 3.9 due to the proton at C - 2 simplified to a four-line signal characteristics of X part of an ABX type spectrum.

The cis isomers, 2α, 3α-diol and 2β, 3β-diol were first prepared by Djerassi et al[38] by osmium tetroxide oxidation of methyl-oleana-2,12-diene-28-oate 88. Cheung et al also repeated the oxidation and obtained two cis-diols and the one with higher melting point was identical to the methyl ester of m.p. 296-99°, isolated from shorea accuminata. Tschesche et al[29,30] assigned a 2β, 3β - configuration to this diol and an 2α, 3α- configuration to the one with lower melting point (258-60°), from consideration of the infrared absorption due to O-H stretching. Cheung et al demonstrated that the configurations assigned by Tschesche et al should be reversed. By comparing the

methyl resonance frequencies from published substitution effects[37] with those observed for the two cis diols and their acetate derivatives Cheung et al suggested that, contrary to the views of Tschesche et al[29,30], the diol m.p. 296-99° must have the 2α, 3α- and the diol m.p. 258-60° the 2β, 3β- configuration



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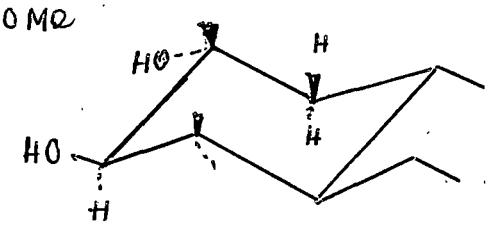


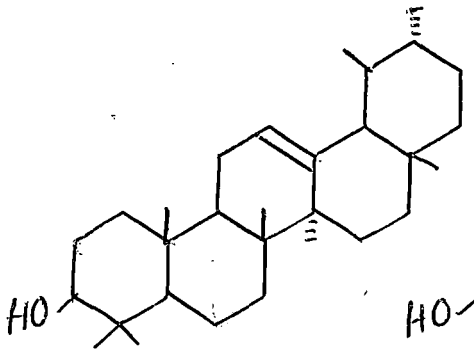
89

In the 2α, 3α- diol, with a chair ring A, 89, the 2β- proton is axial and is expected[39] to be subject to a large ax-ax coupling with the 1α- proton and to small ax-eq. coupling with the 3β and 1β-protons. Of the two cis diols from osmium tetroxide only one with m.p. 296-99°, showed a signal due to C - 2 proton of sufficient width at half-height ($W_{h/2}$ 21H_z) to be compatible with a 2α, 3α-diol structure. The other diol m.p. 258-60° having a corresponding signal of $W_{h/2}$ 8Hz should have a 2β, 3β-arrangement.

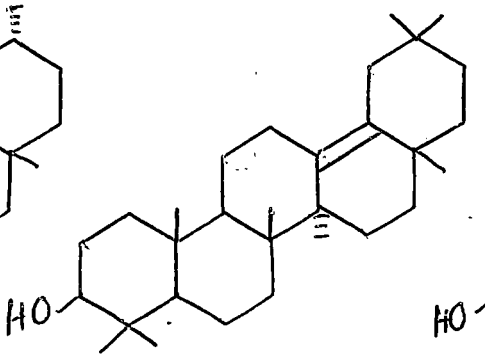
2. The 2α, 3β- dihydroxy olean - 12-en-28-oic acid (Crategolic / mastinic acid) ;

Bachler[40] was the first to isolate an amorphous acid " Crategus acid " from the leaves of Crategus Oxyacantha L. He, however, erroneously assigned the molecular formula $C_{32}H_{54}O_4$ to it. The acid was also observed to occur in the leaves of Psidium guaijava by Arthur and Hui.[40]. This acid was subsequently studied by a number of workers[40]. However a more detailed study of the acid was made by Tschesche et al[40,41], who succeeded in obtaining the acid in crystalline form and establishing the correct molecular formula $C_{30}H_{48}O_4$. They designated the acid as crategolic acid, established the presence of a double bond resistant to catalytic hydrogenation and suggested the presence of two hydroxyl groups, although they could not prepare a diacetate. From a consideration of the behaviour of the acid towards acylation, decarboxylation and lactonisation, they erroneously concluded that crategolic acid was an α- amyrin derivative and even suggested the revision of the accepted structure 90 of α- amyrin to the δ -amyrin structure 91. On the basis of their proposed new formula of α- amyrin 91, they suggested without much valid reason that crategolic acid had the structure 92. However, they themselves latter showed[41] that their " crategolic acid "

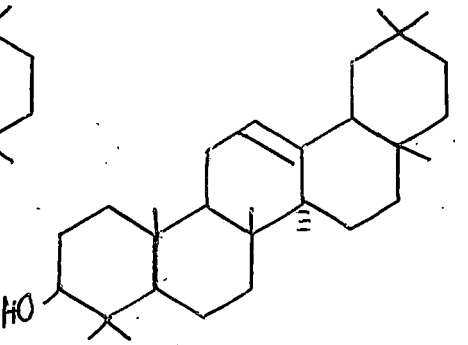
was impure, being



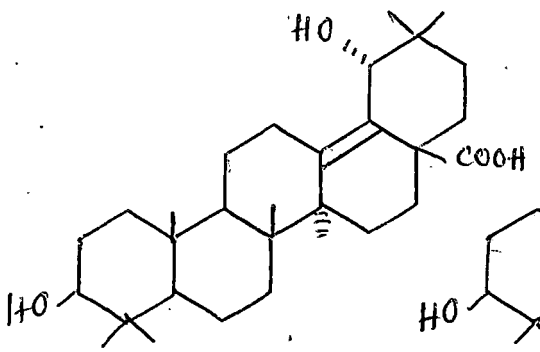
90



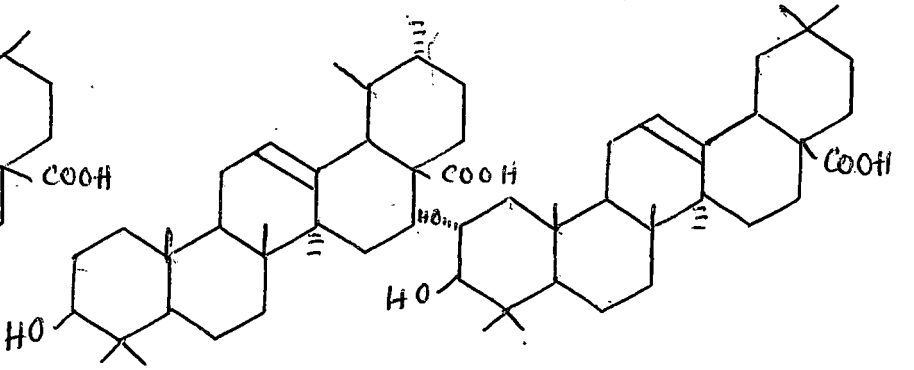
91



95



92



93 94

contaminated with 60 - 65 % of ursolic acid 93 which could not be easily separated. Arthur et al[42] drew attention to this fact

and suggested further work. Tschesche *et al* in a subsequent paper[43] correctly recognised crategolic acid 94 as a derivative of β - amyrin 95. The impure acid mixture could be resolved by them by paper chromatography or column chromatography of the methyl esters derived from it. They were also able to prepare a diacetate, a monoacetate and a keto-monoacetate from methyl ester of crategolic acid 94.

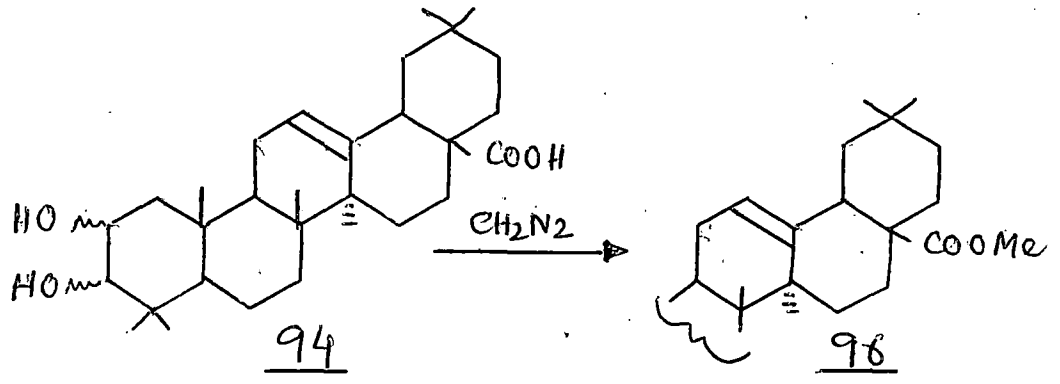
However, in the mean time, Caglioti *et al* reported[32] the isolation from the cakes of *Olean europa* of a new acid, mastinic acid, which latter proved identical with Crategolic acid 94 of Tschesche *et al*. The Italian workers[32] were able to show that mastinic acid was a pentacyclic triterpenic acid, probably belonging to the β - amyrin group, containing two acylable hydroxyl groups and a non-hydrogenizable double bond γ - to the carboxyl group.

In their subsequent investigations[44,45] Caglioti *et al* were able to elucidate the complete structure of the acid as a 2,3- dihydroxy olean-12-en-28-oic acid. Their work of structure elucidation of crategolic acid 94 is shown schematically in chart VI. Crategolic acid 94 formed a methyl ester 95, a diacetate 97, and a methyl ester diacetate 98. The diacetoxy acid 97 with bromine gave a bromolactone 99 which on treatment with zinc and acetic acid regenerated the diacetoxy acid 97. The latter 97 with hydrogen peroxide gave a hydroxy-diacetoxy-

lactone 100 A which gave a triacetoxy-lactone 100 B on acetylation. Selenium dioxide oxidation of the methyl ester diacetate gave a conjugated diene ester 101 showing UV absorption maxima at 260, 251, 243 mμ, characteristics of β-amyrin derivatives. The presence of an α- glycol system was shown by the consumption of one mole of periodic acid of methyl crategolate 96.

Finally crategolic acid 94 was correlated with the β-amyrin group by its elegant conversion into methyl oleanonate 103 and methyl olean-12-en-28-oate 104. This conversion inter alia settled the position of the two hydroxyl group at C - 2 and C - 3. When methyl crategolate 96 was acetylated at 0°, the major product was the 2-acetate 101A, which could be oxidised with chromic acid to give the 3-keto-2-acetate 102. The latter 102 on treatment with calcium in liquid ammonia was converted to methyl oleanonate 103, a substance of known structure. Methyl crategolate 96, itself on oxidation with chromic acid followed by Huang Minlon reduction furnished the known ester 104. These transformations are shown schematically in chart VI

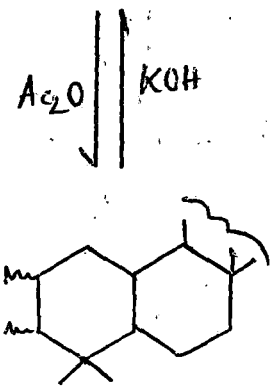
Chart - VI



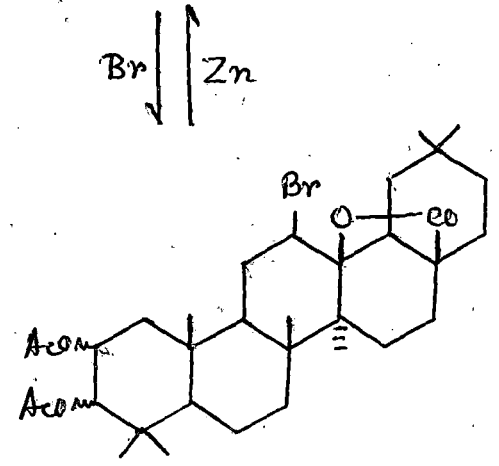
94 96

Chart-VI

94

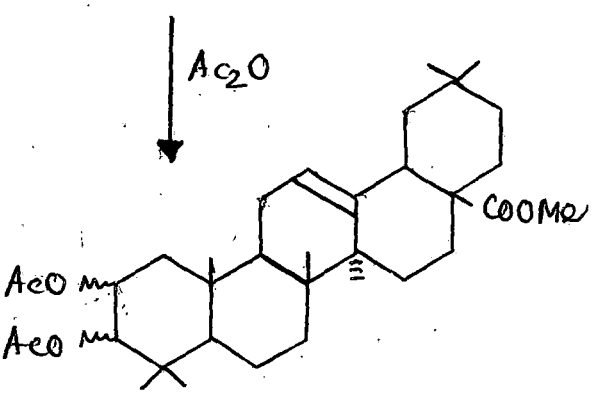


97



99

96



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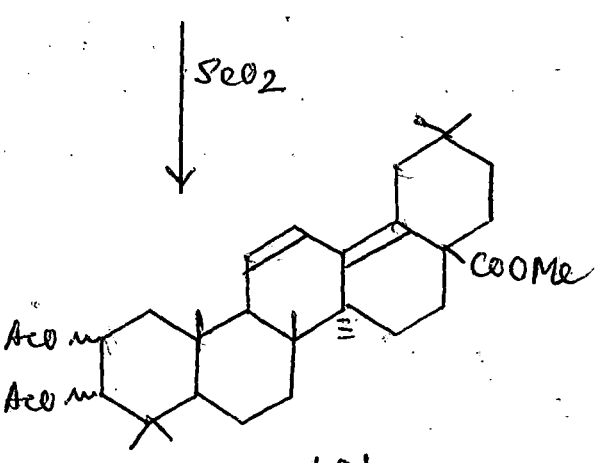

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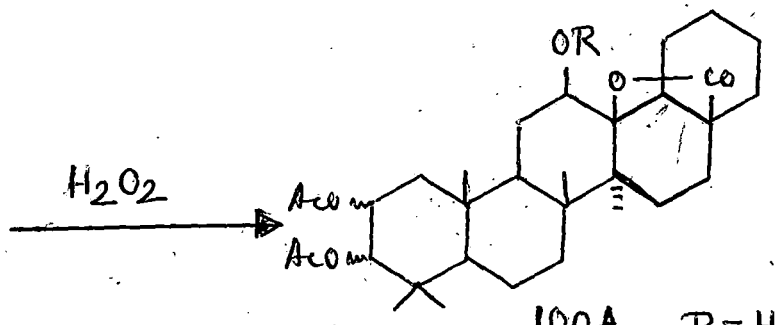
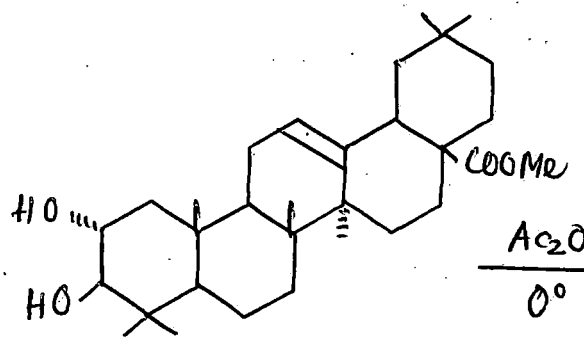
97



100A , R = H

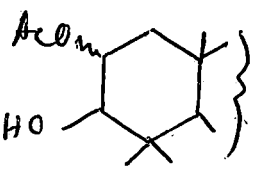
100B , R = Ac.

Chart - VI



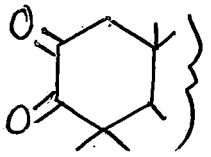
96

Ac_2O
0°



101A

CrO_3



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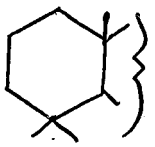
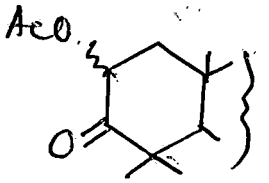
W. K. Reduction



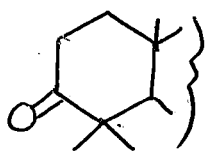
104

CrO_3



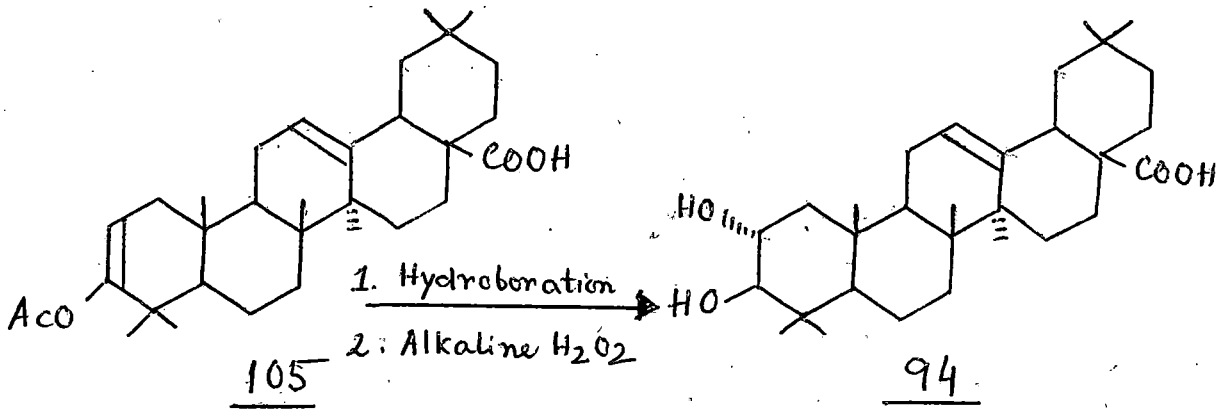
102

Ca - liq. NH_3



103

Subsequenty, the configuration of the two hydroxyl groups was elucidated by Caglioti et al[46]. Preferential formation of the 2-monoacetate 101 suggested the 2 α, 3 β-trans diequatorial configuration of the diol moiety, which was confirmed by successful synthesis[46] of crategolic acid 94 from the enol-acetate 105 of oleanonic acid by hydroboration, which was known to be a stereospecific process[47,48].



105 94

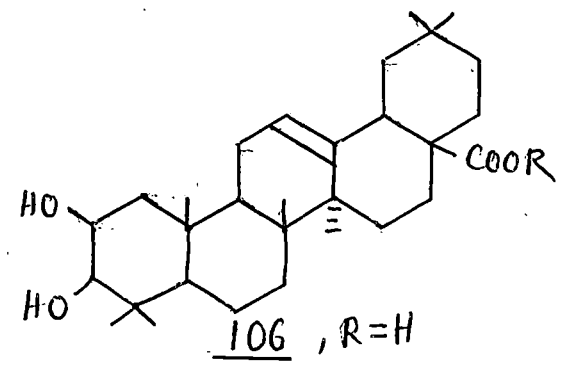
The correctness of the above assignment of configuration of the two hydroxyl group of crategolic acid 94 was further supported by the work of Tschesche et al[38] on the structure of bredemolic acid (discussed in page 124 , Part II of this thesis)

Sengupta et al[49] has also isolated Crategolic acid (maslinic acid) 94 from the flowers of Eugenia jambolana Lam as its methyl ester along with oleanolic acid.

3. The 2β, 3β - dihydroxy olean - 12-en-28-oate.

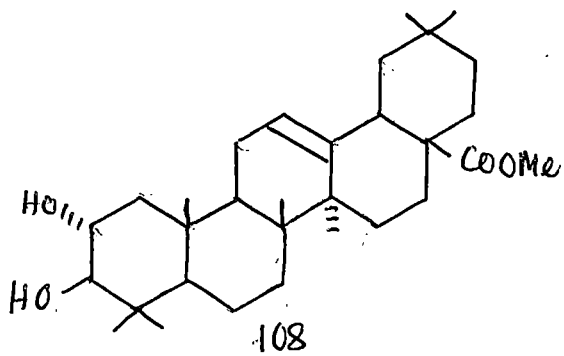
Bannon et al[33] recently reported the isolation of 2β, 3β dihydroxyolean-12-en-28-oic acid 106 from the sapogenin mixture prepared from the extract of the wood of Castanosperum australe Cunn and Frus. These authors established the identity of 106 (2β, 3β -dihydroxyolean-12-en-28-oic acid) by a high yielding stereospecific synthesis (chart VII) from methyl crategolate 108.

Bannon et al isolated 106 as its methyl eater 107. The structure was suggested by its IR, NMR, mass spectrum[31b]. The melting point of the methyl ester 276-80°, 107 was in agreement with that published previously for methyl 2β, 3β-dihydroxyolean-12-en-28-oate (lit 278-82° [38] and 276 - 84° [30]). These authors carried out a stereospecific synthesis of methyl 2β, 3β- dihydroxyolean-12-en-28-oate 107 in high yield from methyl crategolate 108 and thereby concluded that the product isolated from C. australe is in fact methyl 2β, 3β-dihydroxy-olean-12-en-28-oate.



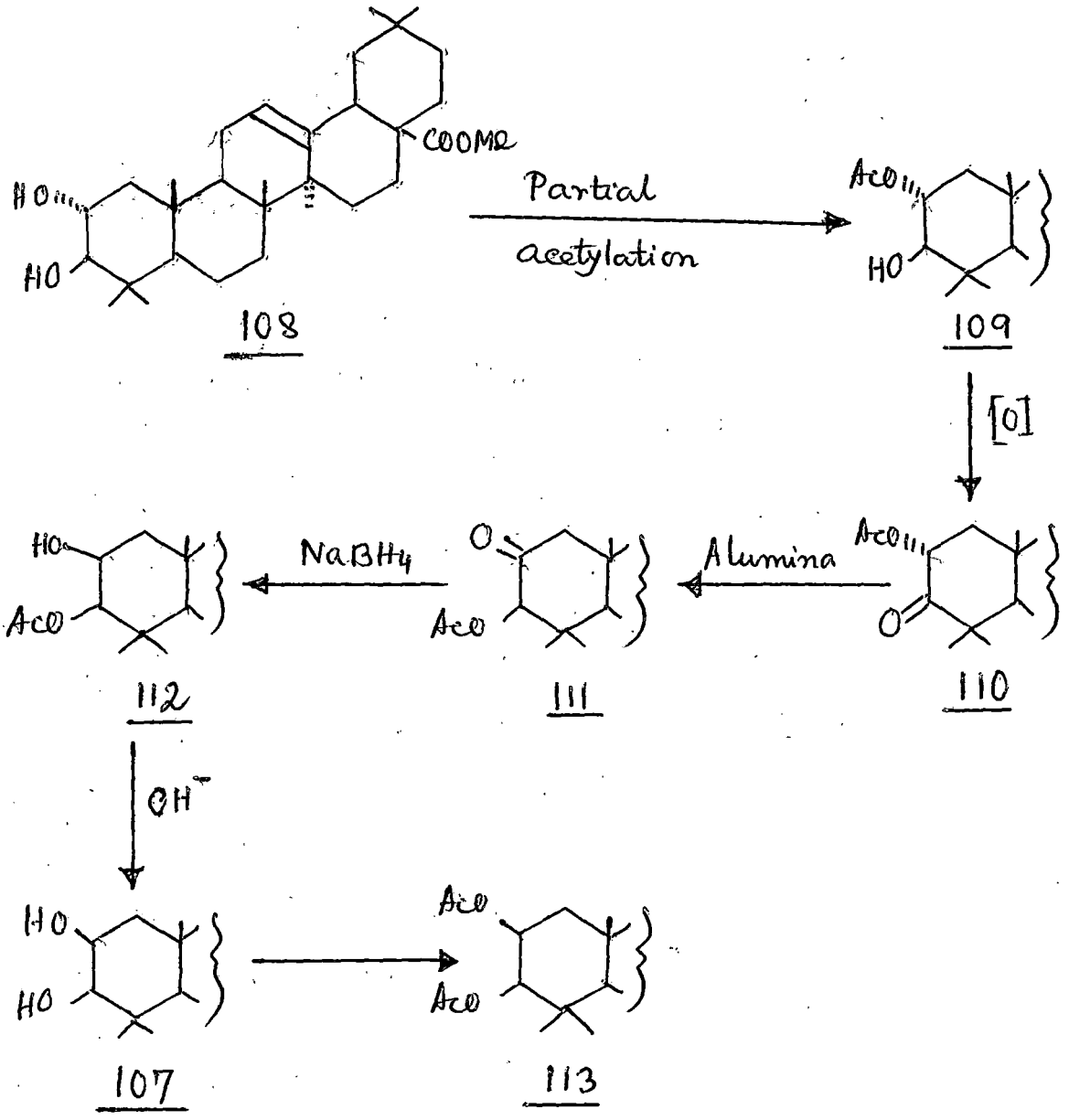
106 , R=H

107 , R=Me



108

Chart VII



108 109 110 111 112 107 113

Methyl crategolate 108 on partial acetylation yielded the 2α-acetoxy-3β-alcohol[43] 109 which was oxidised with dimethyl sulfoxide in acetic anhydride to give 2α-acetoxy-3-ketone 110. The latter 110 on isomerisation on alumina gave the 3β-acetoxy-2-ketone 111. The structure of this rearranged acetoxy ketone followed from analogy with the rearrangements of similar groups in lupane[50], lanostane and 4,4-dimethyl cholestane derivatives[51] and from its IR and NMR spectra. Reduction of the 3β-acetoxy-2-ketone 111 with sodium borohydride proceeded quantitatively to give a single product 112 in which the introduced hydroxyl group at C - 2 could be assigned the β - configuration on the assumption that attack has occured from less hindered α-side of the molecule. Mild alkaline hydrolysis of 3β-acetoxy-2β-hydroxyolean-12-28-oate 112 gave the diol 107 m.p. 278-80°, $(\alpha)_D$ 88° (lit. m.p. 258 - 60°, $(\alpha)_D$ 97° [43], m.p. 258-62° [30], m.p. 258-62° $(\alpha)_D$ 85° [38], m.p. 258-61° [31b]). 107 on acetylation afforded the diacetate, methyl 2β, 3β - diacetoxyolean-12-en-28-oate 113, m.p. 232-40°, $(\alpha)_D$ 82°, (lit[31b] m.p. 227-31°).

4. The 2β, 3α-dihydroxyolean-12-en-28-oic acid (bredemolic acid) :

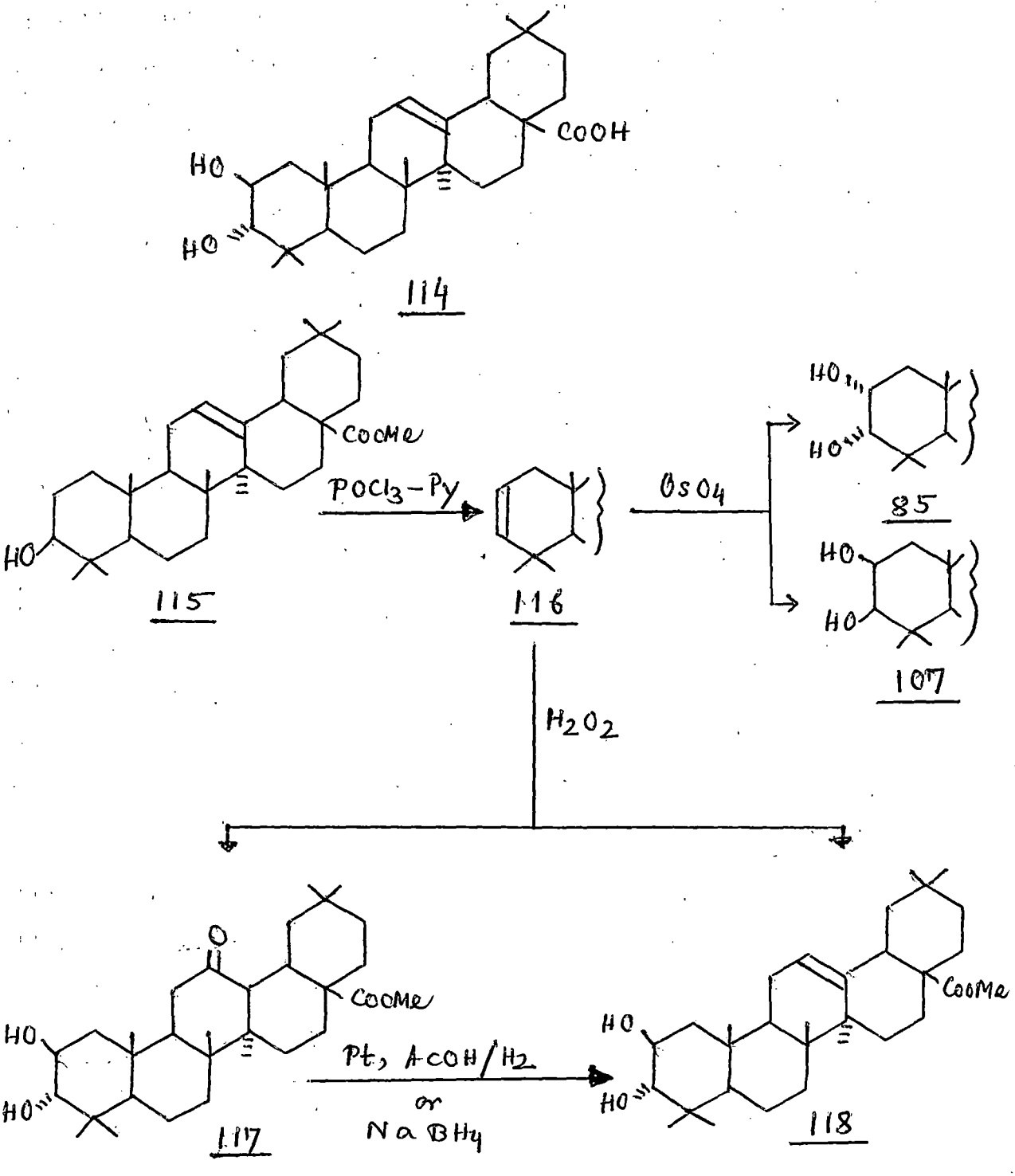
Bredemolic acid 114, isolated from Bredemeyera floribunda willd., was also a 2, 3 - dihydroxyolean-12-en-28-oic acid and

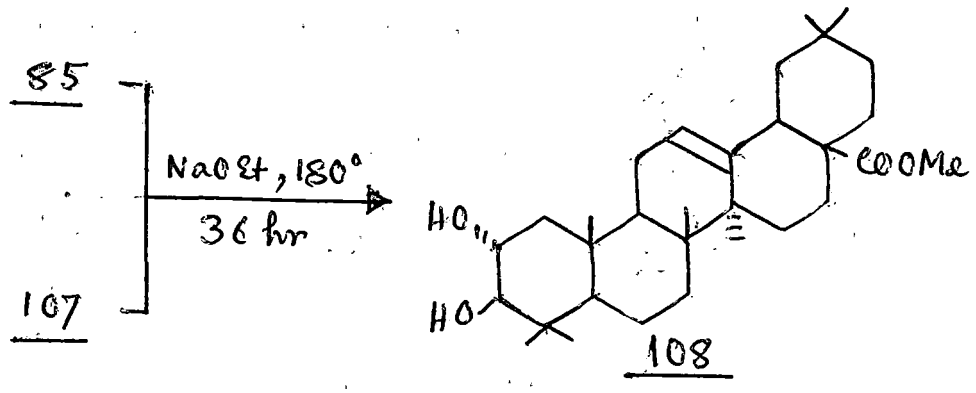
hence must be an epimer of crategolic acid 94. Since the 2β, 3β-84, and the 2α, 3α- 84 A isomers were already known by synthesis[38] and crategolic acid 94 was shown to be the 2α, 3β-dihydroxyolean-12-en-28-oic acid by Caglioti et al[44] bredemolic acid 114 must then be the remaining 2β, 3α-dihydroxy isomer. However bredemolic acid 114 was found to form an acetonide, a somewhat unexpected behaviour on the part of a normal 1,2-diaxial trans cyclohexane diol derivative. Therefore, Tschesche et al synthesised[29,30] unambiguously all the four stereoisomeric 2,3-dihydroxy olean-12-en-28-oic acids as their respective methyl esters. The synthetic work of Tschesche et al is shown in chart VIII.

The key compound in the synthesis of the above epimeric methyl esters chart VIII; methyl oleana-2,12-dien-28-oate 116 was prepared from methyl oleanolate 115 by dehydration with phosphorous oxychloride and pyridine. The diene-ester 116 gave two cis diols : the 2α, 3α- diol 85 and the 2β, 3β-diol 107 by treatment with osmium tetroxide. On the otherhand treatment of the diene-ester 116 with hydrogen peroxide gave methyl 12-keto-2β,3α-dihydroxyolean-28-oate 117 as the major product and only a trace of the desired 2β, 3α- diol 118. The above 12-keto-ester 117, however, was converted by reduction into methyl bredemolate 118. Finally, all the above three diol esters 85, 107 and 118 on equilibration with base gave methyl crategolate 108, which must

consequently have the stablest diequatorial 2α, 3β-configuration of the two hydroxyl groups.

Chart VIII





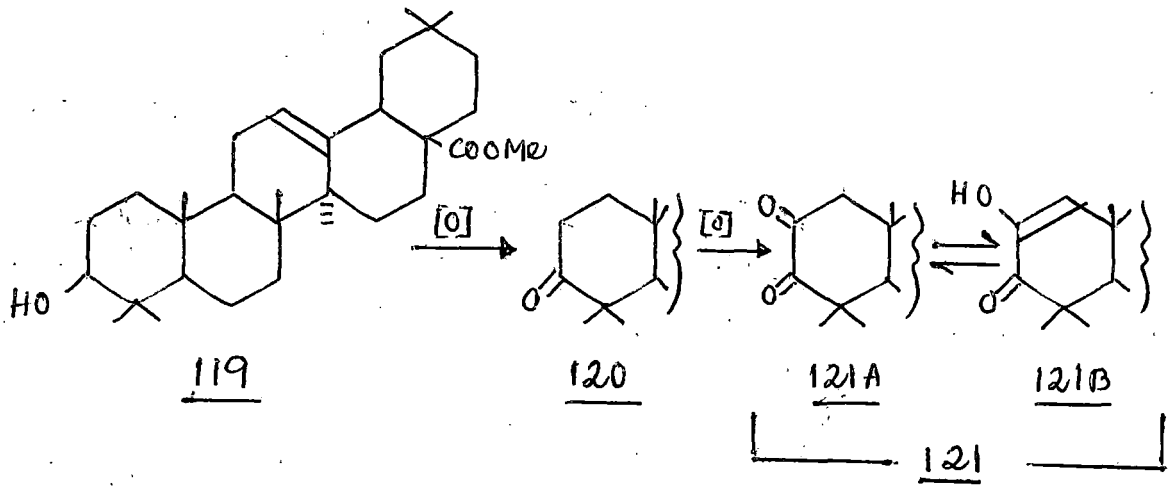
Synthesis of isomeric 2,3-diols of methyl olean-12-en-28-oate.

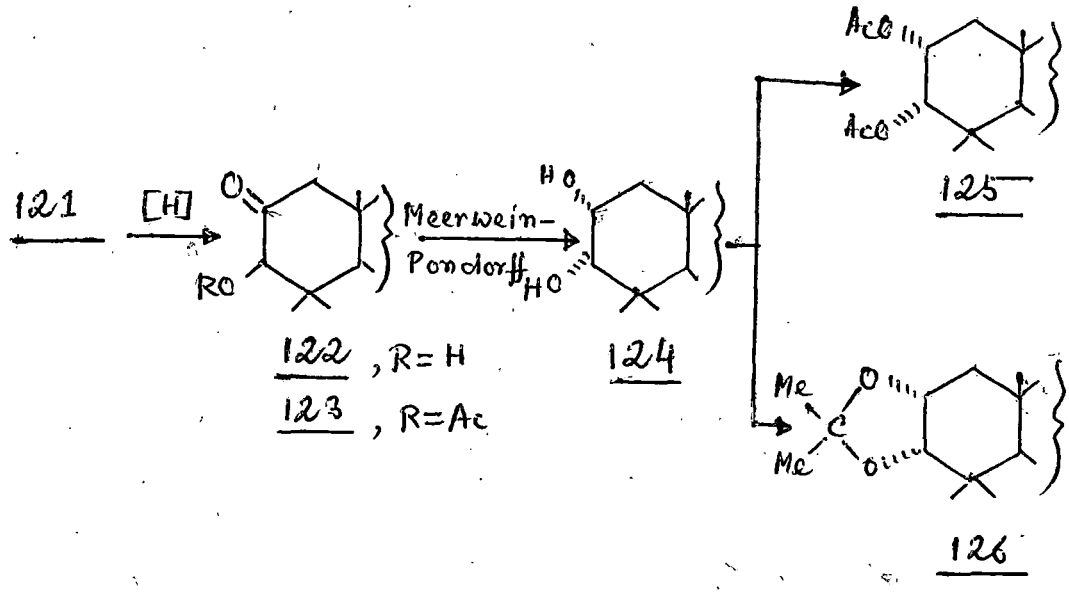
Khastgir et al[10b] also reported the synthesis of the three isomeric diols (2α,3α-; 2β,3β-; 2α, 3β-) out of the four possible isomers, using diosphenol obtained by the autoxidation of methyl oleanonate.

1. Synthesis of methyl 2α, 3α-dihydroxy-olean-12-en-28-oate 124 :

Methyl oleanonate 120 m.p. 182-4°, $(\alpha)_D$ 89° prepared by Jones oxidation of methyl oleanolate[5e] 119, was oxidised by passing oxygen through a suspension of 120 in dry t-butanol containing potassium tertiary butoxide [11-14]. Hydrogenation of diosphenol 121, m.p. 130-5°, $(\alpha)_D$ 104 ± 4°, in presence of 10% palladium - on-charcoal catalyst gave the corresponding reduced

product 122, m.p. 129-31°, $(\alpha)_D$ 109°. During this hydrogenation 1,4-addition of hydrogen took place giving the ketol 122 (TLC homogeneous). Acetylation of 122 with acetic anhydride and pyridine gave the corresponding acetate 123, m.p. 182-4°, $(\alpha)_D$ 85° Meerwein-Pondorff reduction of 122 furnished a crystalline solid, m.p. 286-7°, $(\alpha)_D$ 71°, ν_{max} 3340 (-OH), 1725 (-COOMe) cm^{-1}, which was shown to be identical with methyl 2 α, 3α-dihydroxy-olean-12-en-28-oate. Acetylation of 124 with acetic anhydride and pyridine gave the diacetate 125 m.p. 226-8°, $(\alpha)_D$ 95.20°. NMR spectrum of the diacetate was in good agreement with the structure 125. The diol 124 on treatment with acetone in presence of catalytic amount of p-tuluene sulfonic acid gave an acetonide derivative 126, m.p. 235-9°.

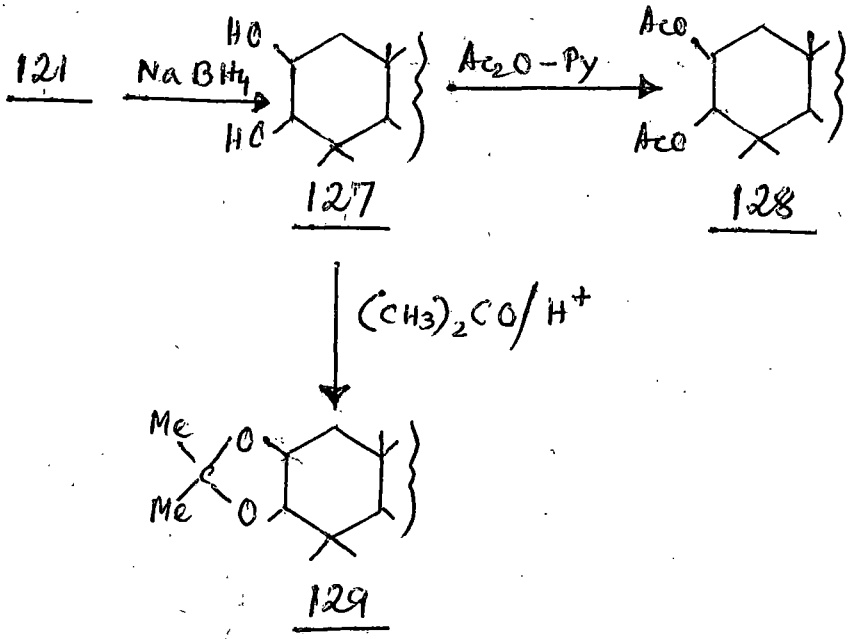




2. Synthesis of methyl 2β, 3β-dihydroxy-olean-12-en-28-oate 127 :

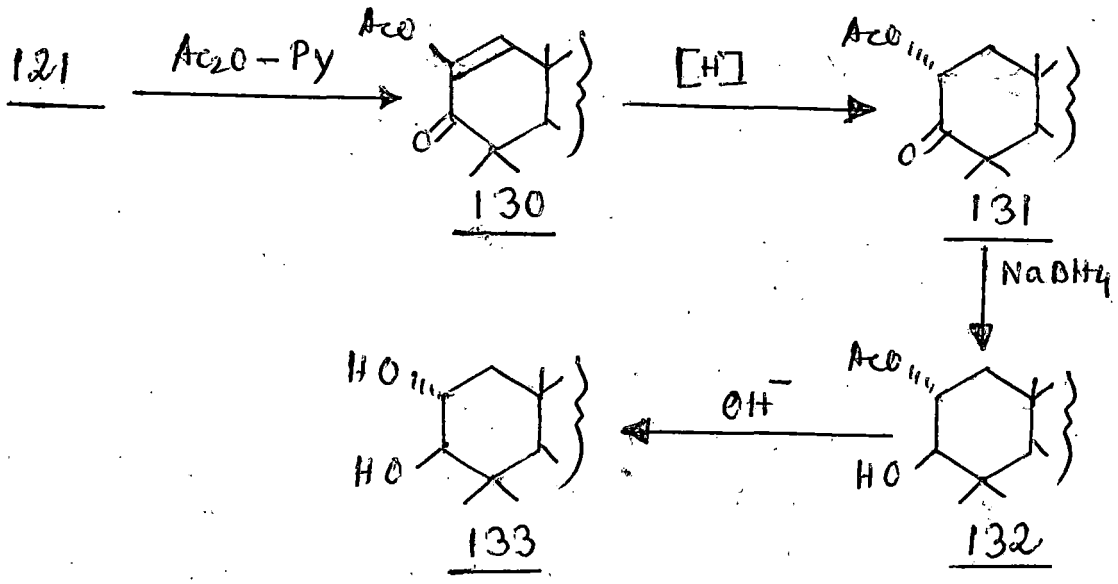
Diosphenol 121 on sodium borohydride reduction in methanol solution gave a compound 127, m.p. 269-72°, $(\alpha)_D$ 98.88° (lit.[31b,38,43] m.p. 258-60°, $(\alpha)_D$ 97°; m.p. 258-62°, $(\alpha)_D$ 85°, m.p. 258-61°), no UV absorption in region 220-300 mμ . ν_{max} 3525, 3360, 1720 cm^{-1}. Treatment of 127 with pyridine and acetic anhydride gave the diacetate 128, m.p.

220-22°, $(\alpha)_D$ 86.20°, ν_{max}^{KBr} 1745, 1720 (C = O), 1258 (C - C) cm^{-1}. Examination of the NMR spectrum of 127 exhibited two unresolved multiplets, one at 3.15 ppm assigned to C - 3H and the other at about 4,4 ppm (C - 2H) in addition to the olefinic proton at 5.15 ppm. Thus the hydroxyl group at C - 3 was axial (He) and the one at C - 2 was equatorial (Ha). In the NMR spectrum of its diacetate, these signals were shifted downfield to 4.6 (J = 4Hz) ppm and at about 5.4 ppm (broad multiplet). The signal for the ester group showed a singlet at 3.65 and that for the acetate groups at 2.06 (singlet 6 H) ppm. The diol 127 on treatment with acetone in presence of catalytic amount p-toluene sulfonic acid gave an acetonide derivative 129, sintering at 75-80°.



3. Synthesis of methyl-2α,3β-dihydroxy-olean-12-en-28-oate 133 :

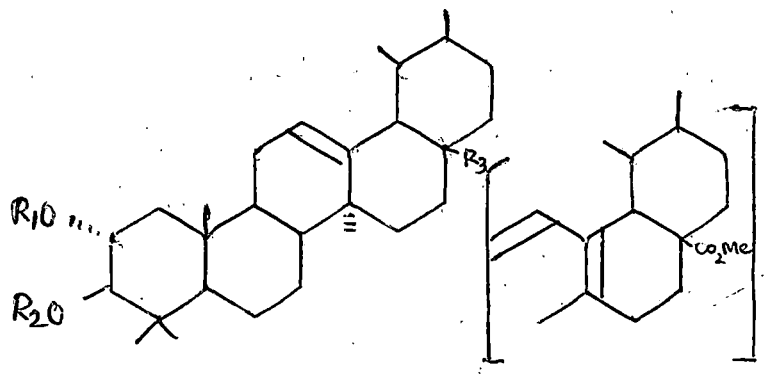
Diosphenol 121 on acetylation with acetic anhydride-pyridine gave the corresponding acetate 130 m.p. 168-70°, $(\alpha)_D$ 93°, having λ_{max} 237 mμ (ϵ ,8500), ν_{max}^{nujol} 1205, 1685, 1720, 1738 cm^{-1}. Hydrogenation of 130 with 10% palladium-on-charcoal catalyst gave a solid 131 m.p. 208-9°, $(\alpha)_D$ 52°, ν_{max} 1225, 1730, 1750 cm^{-1}. The ketoacetate 131 on reduction with sodium borohydride at pH 8 to reduce isomerisation in methanol solution gave a solid 132 m.p. 199-204°, $(\alpha)_D$ 27.9°. The latter 132 was directly hydrolysed by 10% sodium hydroxide solution to afford a solid 133 m.p. 220-22°, $(\alpha)_D$ 36°. The solid 133 was shown to be identical with an authentic sample of methyl 2α, 3β-dihydroxy-olean-12-en-28-oate (methyl crategolate) by m.m.p and Co - TLC.



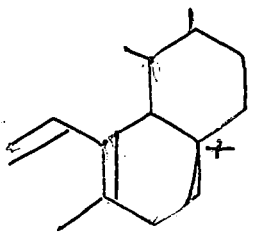
2α- hydroxy ursolic acid :

Glen et al[35] reported the isolation of 2α-hydroxy ursolic acid 134 A as its methyl ester from the leaves of Rose-bay Willowherb (Chamaenorion angustifolium). That the methyl ester 134 B was an ursane derivative was indicated by the presence of three peaks in the region of 1400-1350 cm^{-1} and two peaks in the region 1320-1240 cm^{-1} in the infrared spectrum[52]. NMR spectrum revealed the presence of one olefinic proton (τ 4.73) and one methyl ester group (τ 6.38). Further evidence came from mass spectrum of 134 B which showed intense peaks at m/e 263,203 and at 223 corresponding to ions A, B and C, a pattern frequently associated with Δ^{12}- triterpenoids[36]. A similar mass fragmentation pattern was observed for the 2α-hydroxy-uvaol 134 C formed by lithium aluminium hydride reduction of the dihydroxy methyl ester 134 B. The methyl ester 134 B formed a diacetate 134 D (two distinct peaks in the NMR at τ 7.97 and 8. 04[53]). This physical evidence for the presence of a 2,3 -diol system in 134 B was further substantiated by the preparation of an isopropylidene derivative and also by the formation of the diosphenol 135 by chromium trioxide-pyridine oxidation. The presence of an ursane skeleton in the ester 134 B was shown by the Wolff Kishner reduction of the diosphenol 135 to give

urs-12-en-28-oic acid 136 identical with an authentic sample.



A



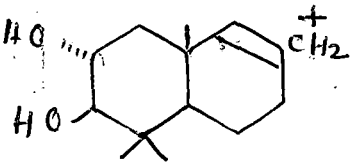
B

134A , $R_1 = R_2 = H$; $R_3 = COOH$

134B , $R_1 = R_2 = H$; $R_3 = COOMe$

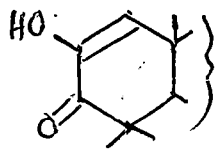
134C , $R_1 = R_2 = H$; $R_3 = CH_2OH$

134D , $R_1 = R_2 = Ac$; $R_3 = COOMe$

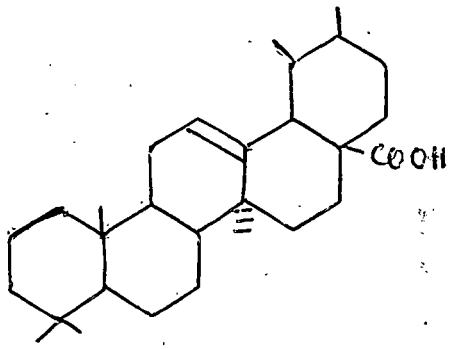


C

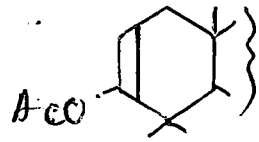
Cleavage of the diosphenol 135 with alkaline hydrogen peroxide gave 2,3 seco-urs-12-en-2,3,28-trioic acid-28-methyl ester 137 which confirmed the presence of the ursane skeleton in the ester 134 B. The configuration of the hydroxyl group in the dihydroxy ester 134 B was settled by the synthesis of the trans diequatorial diol 134 B. The enol acetate 138 on treatment with diborane and then subsequent oxidation of the intermediate



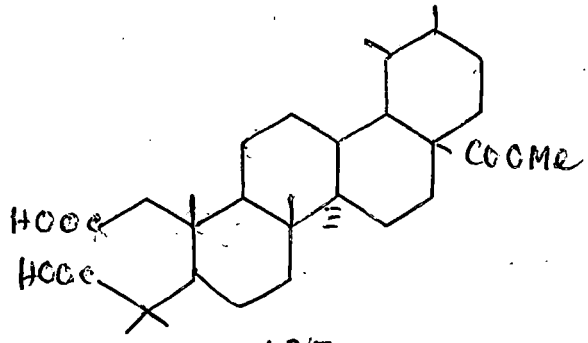
135



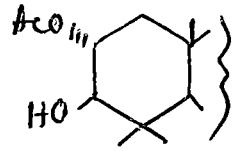
136



138



137

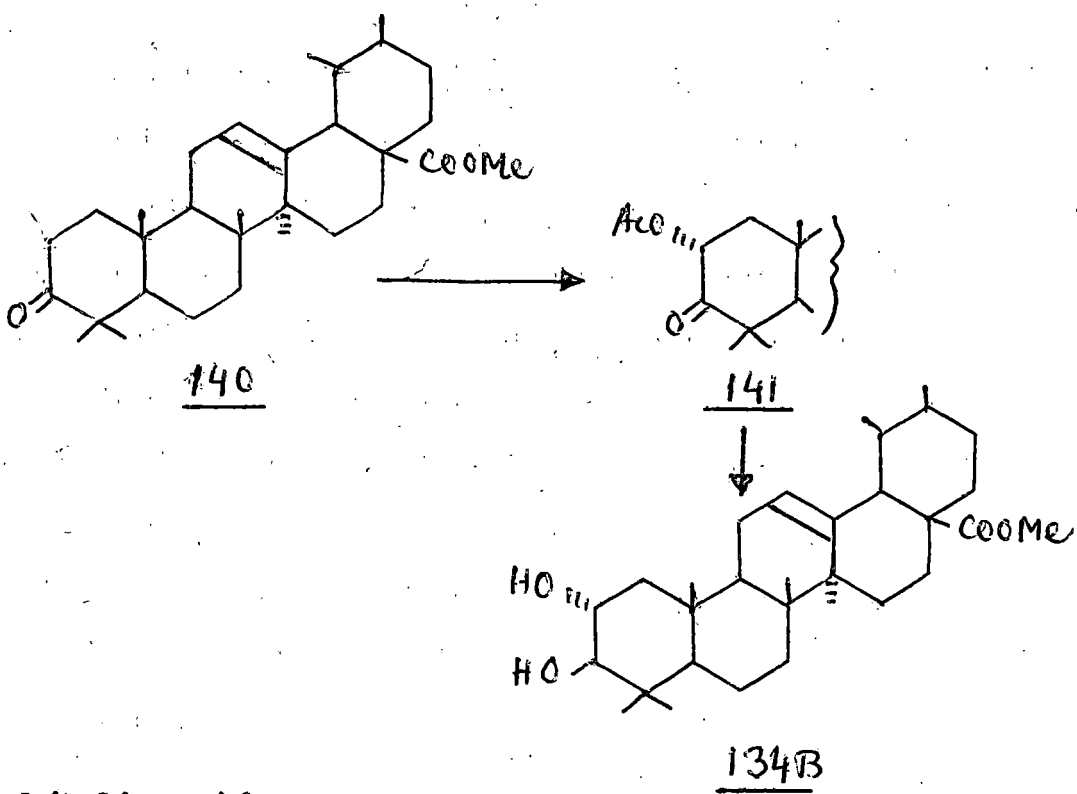


139

afforded three products viz. methyl ursonate, methyl ursolate and methyl 2α, 3β-dihydroxy urs-12-en-28-oate 134 B, the latter was identical with that obtained from the natural dihydroxy acid 134 A.

Further support for the assignment of the α-configuration to the hydroxyl group at C - 2 in 134 B was revealed by the NMR spectrum of the monoacetate, methyl 2α-acetoxy-3β-

hydroxy urs-12-en-28-oate 139. The NMR spectrum showed signals in the region τ 4.9 - 5.4 due to C - 2 proton. The breadth of the resonance indicated that at least two couplings of about 8 c/sec are present and this can only occur when the proton at C - 2 occupies an axial conformation allowing an axial interaction with the proton at C - 3 and a similar interaction with the axial proton at C - 1. In addition, there is an axial - equatorial interaction with the other proton at C- 1. This indicated that the proton at C - 2 has the axial conformation and acetoxy group at C - 2 has the equatorial (α) conformation. Rastogi et al[54] repeated Glen's[35] work and obtained the enol acetate m.p. 198° in 46% yield but subsequent steps of hydroboration and oxidation yielded only the starting material methyl ursolate. Rastogi et al employed lead tetra-acetate oxidation on methyl ursolate 140 and obtained 2α-acetoxy-3-keto derivative 141 as an amorphous powder, the latter was characterised by NMR spectrum. Reduction of 140 with sodium borohydride gave the methyl 2α-hydroxy ursolate 134 B in an overall yield of 26.7%, characterised by IR and NMR data.

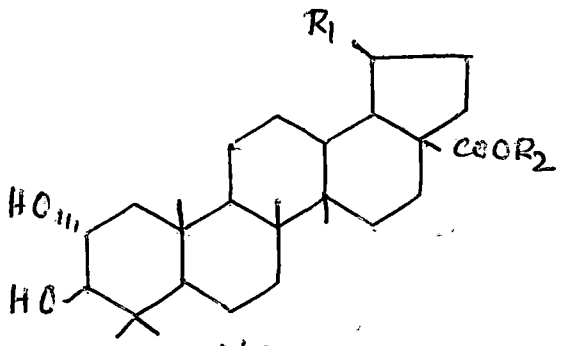


140 141 134B

Alphitolic acid :

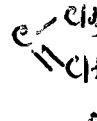
Guise et al[34] isolated alphitolic acid 142 A as its methyl ester, m.p. 233 - 35° from the wood of Alphitonia petrici Braid and white. The ester, methyl alphitolate 142 B (ν_{max} 3634, 3587, 1735, 887 cm^{-1}) formed a diacetate (no hydroxyl absorption in the infrared) and a dihydro-derivative 142 C (no absorption in the infrared at 887 cm^{-1}) namely methyl dihydro-alphitolate. The ester 142 B consumed one mole of lead tetraacetate. Guise et al converted dihydro-methyl alphitolate 142 C to a dialdehyde 143 by treatment with 1 mole equivalent of sodium metaperiodate. The latter on oxidation with chromic anhydride in acetic acid followed by

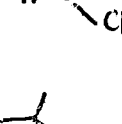
methylation gave a trimethyl ester 144 identical with trimethyl ester of the seco-A-acid derived from dihydrobetulinic acid[55]. From the above physical and chemical evidences Guise et al confirmed the structure of methyl alphitolate as depicted in 142 B.

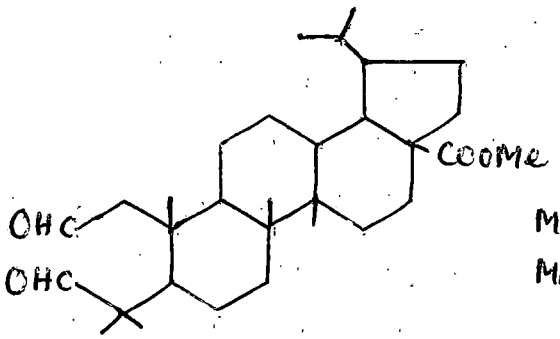


142

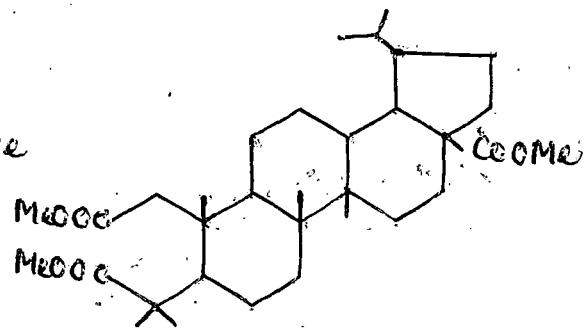
142A , R_1 =  ; R_2 = H

142B , R_1 =  ; R_2 = Me

142C , R_1 =  ; R_2 = Me



143



144

The stereochemistry of 1,2-glycol grouping in 142 B was based on quantitative lead-tetraacetate titrations under the defined conditions of Djerassi and Ehrlich[56], where a value k = 2.7 X 10^{-3} L $mole^{-1}$ Sec^{-1} was obtained, identical for triterpene 2α, 3β-glycols.