

CHAPTER - IVEXPERIMENTAL

Melting points are uncorrected. The petroleum used throughout the investigation had b.p. 60-80°. All optical rotations were determined in chloroform solution unless stated otherwise. NMR spectra were determined on Varian A-60, HA-100 and CFT-20, and Varian XL-200 spectrophotometer using chloroform-d solution containing tetramethyl-silane as reference 200 MHz ¹H spectra and 50.5 MHz ¹³C spectra were recorded on the VN XL-200 spectrophotometer. The IR spectra were recorded in Nujol in Perkin-Elmer 337, 221 and Pye Unicam-SP-3000 spectrophotometers. UV absorption spectra were taken in Shimadzu UV-240 in 95% ethanol solution unless stated otherwise. TLC was done on chromatoplate of silica gel G (S. Merck) and the spots were developed in Iodine Vapour Chamber. The mass spectra were determined with Jeol JMS-D 300 mass spectrophotometer, using direct sample introduction into the ion source. CD-spectra were determined with Jobin Yvon-111 spectrophotometer in methanol solution unless stated otherwise. GLC spectra were taken in Chemito 3800 spectrophotometer using cholestane as internal reference.

Extraction of Bischofia javanica Blume : Isolation of betulinic acid 62a.

Dried and powdered trunk bark of Bischofia javanica Blume (2 kg) was extracted with benzene in a soxhlet apparatus for twenty hours. Benzene was distilled off and the gummy residue

(9 gm) was taken up in ether (1 litre). The ether solution was washed with 10% aqueous sodium hydroxide solution (3 x 300 ml). The aqueous alkaline layer was thoroughly shaken with ether to remove any neutral material that might be present. The aqueous layer was acidified (1 litre) when some insoluble solids separated out. The acidified portion was extracted with ether, washed with water until neutral and then dried using Na_2SO_4 . Ether was removed when a gummy residue (3 gm) of betulinic acid 62a was obtained and chromatographed. Elution by a mixture of benzene and ether (1:4) and crystallised from aqueous methanol afforded betulinic acid 62a m.p. 299-302°.

Esterification of betulinic acid 62a: Preparation of methyl betulinate 106.

To the crude acid 62a (3 gm) dissolved in ether (250 ml) was added a solution of diazomethane in ether prepared from nitrosomethyl urea (1.5 gm) and was kept overnight. Next day excess of diazomethane was destroyed with acetic acid (1 ml). The ether solution was washed with water, 10% sodium bicarbonate solution and again with water until neutral and then dried (Na_2SO_4). Evaporation of the ether yielded a gummy residue (1.5 gm). This crude ester (1.5 gm) dissolved in benzene (12 ml) was placed over a column of silica gel (60 g) developed with petroleum ether and was eluted with the following solvents (Table - III).

Table - III

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum ether	1-4	Oil
Petroleum ether: benzene (4:1)	5-8	Nil
Petroleum ether: benzene (3:2)	9-14	Solid (1.2 gm) m.p. 222-224°

Further elution with more polar solvent did not yield any solid material.

Solids obtained from the fractions 9-14 m.p. 222-224° (Table - III) were combined (1.2 gm) and crystallised from a mixture of chloroform and methanol to afford colourless needles of methyl betulinate 106 m.p. 223-224°, $[\alpha]_D + 5^\circ$, identical with authentic sample (m.m.p and IR).

Found	: C 78.79%	H 10.52%
Calculated for $C_{31}H_{50}O_3$: C 79.10%	H 10.71%
UV	: No absorption in the region 220-300 m μ .	
IR (nujol)	: 3540 (-OH), 1730 (-COOCH ₃) 1660, 890 cm ⁻¹ (=CH ₂)	

(Fig. 1)

NMR (60 Mc)

: δ 4.56-4.72 (two doublets = CH_2)
 δ 3.65 (singlet $-\text{COOCH}_3$), 345 (1H, m, $-\text{CHOH}$)
 δ 1.65 (sharp singlet, $\text{H}_2\text{C} = \underset{\text{CH}_3}{\text{C}}-$) and
 δ .82-1.2 (a tall singlet accounting
 for 15 protons, 5 CH_3).

LAH reduction of methyl betulinate 106 : Preparation of
 betulin 62c:

To the methyl betulinate (10 gm) dissolved in dry dioxane (400 c.c) was added 25 gm LAH and the mixture was refluxed for the period of 7 hours. The reaction mixture was then cooled and to this 15 ml of saturated solution of sodium sulphate was added. Excess LAH was destroyed and the white inorganic salts coagulated. The supernatant solution was decanted and the residue was washed with fresh chloroform. The decanted solution and the above chloroform solution were washed with water, dried and the chloroform was distilled off. The compound betulin 62c (9 gm) was identical with the authentic sample, m.p. 258-59°, $[\alpha]_D + 16^\circ$.

Found	: C	81.25%	H	10.95%
Calculated for $\text{C}_{30}\text{H}_{50}\text{O}_2$: C	81.45%	H	11.31%
IR (nujol)	: 3350	(-OH),	900 cm^{-1}	(= CH_2)

(Fig. 2)

Acetylation of betulin 62c : Preparation of betulin diacetate 62e.

The compound betulin (9 gm) was acetylated with acetic anhydride (90 ml) and pyridine (90 ml). The reaction mixture was kept on water bath for 7 hours. The solid obtained by usual work up was chromatographed and crystallised from a mixture of chloroform and methanol. The compound betulin diacetate (8.5 gm) 62e m.p. 223-224^o, $[\alpha]_D + 20^o$ was obtained.

Found : C 77.36% H 10.06%

Calculated for $C_{34}H_{54}O_4$: C 77.56% H 10.26%

Mass : M^+ 526 m/z

IR (Nujol) : 1740, 1250 (acetate), 1650,
900 cm^{-1} (C = CH₂)

(Fig. 3)

NMR (60 Mc) : δ 0.75-1.20 (5 methyls), δ 1.65 (3H, s)
 δ 1.95 (3H, s, -OCOCH₃),
 δ 2.01 (3H, s, OCOCH₃),
 δ 4.25 (2H, m, CH₂OAc),
 δ 4.62 (1H, m, CHOAc) and
 δ 4.56, 4.72 (2H, bs, C=CH₂).

Partial hydrolysis of betulin diacetate 62e : Preparation of betulin mono acetate 107.

The compound betulin diacetate (8.5 gm) was taken in 80 ml benzene. To the mixture, 1 gm KOH in 100 ml of 80% ethyl alcohol was added and refluxed for 3 hours, worked up as usual using ether. Washed with water until neutral and dried (Na₂SO₄).

Distillation of the ether, a gummy residue was found. The crude residue dissolved in benzene (minimum amount) was placed on the column of silica gel (500 gm) and eluted with the following solvents (Table IV). \sphericalangle T.L.C was taken out after the interval of 1 hour, 2 hour and 3 hour with the starting material 62e to monitor the yield 7.

Table IV

Eluent	Fraction 50 ml each	Residue on evaporation
Petroleum ether	1-4	Nil
Petroleum ether: Benzene (4:1)	5-8 9-12	Solid (1 gm) Nil
Petroleum ether : Benzene (3:2)	13-16 17-20	Solid (5.5 gm) Solid

Further eluted with more polar solvent did not yield any material.

Fractions 5-8 (1 gm) were taken together and crystallised from chloroform and methanol mixture. The compound was found to be identical with the betulin diacetate 62e.

Fractions 13-20 were taken together and crystallized from chloroform and methanol mixture. The crystallisation furnished pure 3 β -acetoxy betulin (5 gm) (betulin mono acetate) 107, m.p. 262-264 $^{\circ}$.

Found : C 79.13% H 10.54%
 Calculated for $C_{32}H_{52}O_3$: C 79.33% H 10.74%
 Mass : M^+ 484 m/z
 IR (Nujol) : 3400 (-OH), 1725 and 1245 (acetate)
 885 cm^{-1} (= CH_2)

(Fig. 4)

NMR (60 Mc) : δ .70-1.12 (⁵ methyls), δ 1.62 (3H, s)
 δ 2.03 (3H, s, -OCOCH₃),
 δ 3.31 (2H, m, CH_2OH),
 δ 4.65 (1H, m, - $CHOAc$) and
 δ 4.85 (2H, bs, $C=CH_2$)

Hydrogenation of 3 β acetoxy betulin 107 : Preparation of dihydro
3 β acetoxy betulin 108.

To 3 β acetoxy betulin 107 (6 gm) dissolved in a mixture of ethyl acetate and ethanol (180 ml each) was added 10% palladium-on-charcoal catalyst (600 mg) and the mixture was shaken in an atmosphere of hydrogen till the absorption of hydrogen ceased. The solution was filtered and after removing the solvent from the filtrate a solid residue was obtained which after crystallisation from chloroform and methanol mixture afforded 108

$C_{32}H_{54}O_3$ (5 gm), m.p. 256-258 $^{\circ}$, $[\alpha]_D$ -4.2 $^{\circ}$ (lit. m.p. 258-9 $^{\circ}$, $[\alpha]_D$ -5.1 $^{\circ}$).

Found : C 78.99% H 10.98%
 Calculated for $C_{32}H_{54}O_3$: C 79.01% H 11.11%
 IR (Nujol) : 3420 (OH), 1740 and 1260 cm^{-1} (acetate)
 (Fig. 5)

Mass : M^+ 486, 443 (M^+ - isopropyl),
 455 (M^+ - CH_3OH), 426, 395, 249,
 189 m/z
 (Fig. 6)

NMR (60 Mc) : δ 0.73-0.97 (7 methyls),
 δ 2.03 (3H, singlet, acetate)
 δ 3.36 + 3.72 ($C_{28}-H_2$),
 δ 4.58 (1H, multiplet, H-C-OCOCH₃)
 (Fig. 7)

Photo oxidation of Dihydro 3/β acetoxy betulin 108in cyclohexane by Lead Tetraacetate:

A solution of dihydro 3/β acetoxy betulin (400 mg) in cyclohexane (100 ml) lead tetraacetate (3 gm) was suspended and the mixture refluxed, stirred and irradiated with a ²⁵⁰500 W Lamp for 3 hours. After filtration and diluted with water the mixture was extracted with ether and the extract worked up in the usual manner. The crude residue (350 mg) was chromatographed on silica gel (100 gm) and eluted with the following solvents (Table V).

Table V

Eluent	Fraction 50 ml each	Residue on evaporation
Petroleum ether	1-4	Nil
Petroleum ether : Benzene (4:1)	5-8	White solid m.p. 158-64° (Yield 35%)
Petroleum ether (1:1)	9-12	Nil
Petroleum ether : Benzene (3:2)	12-16	White solid m.p. 192-4° (Yield 18%)

Elution with more polar solvent did not afford any crystalline material.

The solid from fractions 5-8 (Table V) (Yield 35%) was crystallised from a mixture of chloroform and methanol. The compounds of 109 m.p. $158-64^{\circ}$, $[\alpha]_D + 21.4^{\circ}$ were obtained.

Found : C 81.74% H 10.62%
 Calculated for $C_{31}H_{50}O_2$: C 81.94% H 11.01%
 Mass : M^+ 454, 411 ($M^+ - 43$), 351 ($M^+ - 103$),
 249, 189 m/z

(Fig. 8)

IR (Nujol) : 1720, 1245 (acetate) and
 900, 860 cm^{-1} (tri substituted
 double bond)

(Fig. 9)

NMR (60 Mc) : δ 0.75-1.00 (7 methyls),
 δ 2.05 ($-OCOCH_3$),
 δ 4.5 ($H-C-OCOCH_3$), δ 5.14 (1H, m
 vinylic proton).

(Fig. 10)

Tetra nitro methane Test : Yellow colour.

T.L.C. (benzene : methanol :: 4:1) : two very close spots

R_f 0.82 and 0.81.

G.L.C. : Two prominent peaks

(Fig. 11)

V

Solid fractions 12-16 (yield 18%) (Table III) were crystallised from a mixture of chloroform and methanol when crystals of 110, C₃₂H₅₂O₃ m.p. 192-4°, [α]_D + 17° were obtained.

Found	: C 79.08%	H 10.60%	
Calculated for C ₃₂ H ₅₂ O ₃	: C 79.33%	H 10.74%	
Mass	: M ⁺ 484, 453, 441, 249, 189 m/z		(Fig. 12)

IR (Nujol)	: 1060 ¹⁰⁶⁰ (ether), 1745 and 1255 (acetate) cm ⁻¹	(Fig. 13)
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NMR (60 Mc)	: δ.76-1.00 (7 methyls) 2.05 (-OCOCH ₃), a pair of doublets (one proton each) at 3.44 and 3.60, J _{gem} = 8.1 Hz (C(28)-H ₂), 4.5 (1H, m, C(3α)-H)	(Fig. 14)
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Photo-oxidation of Dihydro 3β acetoxy betulin 108 in cyclohexane by Lead tetraacetate in presence of calcium carbonate and Iodine.

A solution of dihydro 3β acetoxy betulin (300 mg) 108 in cyclohexane (80 ml) lead tetraacetate (1.8 gm) and CaCO₃ (600 mg) were suspended and the iodine (400 mg) was then added gradually over 20 minutes with continuing irradiation with ²⁵⁰500 W tungsten lamp. When iodine colour was almost disappeared (3 hr), the mixture was cooled and worked up in ether using sodium thiosulphate (10% solution). The gummy residue was chromatographed on silica gel column and eluted with the following solvents (Table VI).

Table VI

Eluent	Fractions 50 ml each	Residue on Evaporation
Petroleum ether	1-4	Nil
Petroleum ether Benzene (4:1)	5-8	Solid m.p. 158-64°
Petroleum ether:benzene (1:1)	9-11	Nil
Petroleum ether : Benzene (3:2)	12-15	Solid m.p. 190-92°

Further elution with more polar solvent did not afford any solid.

Fractions 5-8 (Table VI, 100 mg) were combined and crystallised from the mixture of chloroform and methanol. The crystallisation afforded the compound of 109 m.p. 158-64°, $[\alpha]_D + 21^\circ$.

Found : C 81.54% H 10.81%

Calculated for $C_{31}H_{50}O_2$: C 81.94% H 11.01%

IR : 1720, ¹²⁴⁵1240 (acetate)
900, 860 cm^{-1}

(Fig. 9)

NMR (60 Mc) : δ .75-1.00 (7 methyls), δ 2.05
(-O-COCH₃), δ 4.49 (C₃ α -H),
 δ 5.14 (vinylic proton).

(Fig. 10)

Fractions 12-15 (Table VI, 54 mg) were combined and crystallised from the mixture of chloroform and methanol. The crystallisation afforded the compound of 110 m.p. 190° , $[\alpha]_D + 16.8^{\circ}$

Found	: C 78.95%	H 10.55%
Calculated for $C_{32}H_{52}O_3$: C 79.33%	H 10.74%
IR	: 1745, 1255 (acetate),	
	1040 cm^{-1} (ether).	

(Fig. 13)

Photo-oxidation of Dihydro 3 β acetoxy betulin 108 by mercuric oxide and iodine in carbon tetrachloride :

To dihydro 3 β acetoxy betulin 108 (500 mg) dissolved in dry carbon tetrachloride (160 ml) was added finely divided mercuric oxide (yellow, 900 mg). Iodine (1.07 gm) was added gradually over 20 minutes and irradiated with 250 W tungsten lamp for 3 hours. On cooling the solution was filtered off and the whole filtrate was diluted with water, washed with sodium thiosulphate (10% solution) and extracted with ether. The ether solution was washed well with water and dried (anhydrous Na_2SO_4). Removal of ether gave a gummy residue. It was dissolved in benzene (minimum amount) and chromatographed on silica gel column (40 gm). Chromatogram was developed in petroleum ether and eluted by the following solvents (Table VII).

Table VII

Eluent	Fractions 50 ml each	Residue on Evaporation
Petroleum ether	1-4	Oil
Petroleum ether: Benzene (4:1)	5-7	Nil
Petroleum ether:benzene (1:1)	8-13	Nil
Petroleum ether: Benzene (3:2)	14-16	Solid m.p. 192°

Further elution with more polar solvents did not arise any solid.

Fractions 14-16 (Table VII, 140 mg) were combined and crystallised from the mixture of chloroform and methanol to furnish crystals 110 m.p. 192-94°, $[\alpha]_D + 17^\circ$.

Found	: C 78.88%	H 10.68%
Calculated for $C_{32}H_{52}O_3$: C 79.33%	H 10.74%
Mass	: M^+ 484, 453, 441, 249,	
	189 m/z	(Fig. 12)
IR	: 1740, 1250 (acetate),	
	1060 (ether)	(Fig. 13)
NMR (60 Mc)	: δ 0. ⁷⁶ 85 -1.00 (7 methyls),	
	δ 2.05 (-C-COCH ₃), δ 3. ⁴⁴ 25 and	
	δ 3. ⁶⁰ 75 (C_{28} -H ₂), δ 4.5 (1H, m,	
	C_{3x} -H)	(Fig. 14)

Chromium trioxide oxidation of ether 110 : Preparation of 3 β acetoxylupan 28-13 β -olide 63b.

To a solution of 13 β , 28-epoxy compound 110 (300 mg) in acetic acid (30 ml) chromium oxide (420 mg) dissolved in acetic acid (20 ml) was added dropwise under stirring and the mixture heated at 50°C for 1½ hour. After addition of 20 ml of methanol to destroy excess CrO₃ the mixture was poured into water and worked up by 10% NaOH solution and ether in the usual manner. The solid residue was dissolved in benzene (10 ml) and put on a column prepared from silica gel (40 gm). The chromatogram was prepared in petroleum ether and eluted with the following solvents (Table VIII).

Table VIII

Eluent	Fractions 50 ml each	Residue on Evaporation
Petroleum ether	1-4	Oily gum
Petroleum ether: benzene (4:1)	5-8	Nil
Petroleum ether: benzene (3:2)	9-12	Solid m.p. 315°

Further elution with more polar solvent did not give any solid.

Fractions 9-12 (Table VIII, 60 mg) were combined and crystallised from a mixture of chloroform and methanol when crystals of 63b

m.p. 315° , $[\alpha]_D + 86^{\circ}$ were obtained.

Found : C 76.85% H 9.98%
 Calculated for $C_{32}H_{50}O_4$: C 77.1% H 10.04%
 Mass : M^+ 498, 438 ($M^+ - AcOH$), 423,
 249 (189) m/z

(Fig. 15)

IR : 1762 (γ -lactone), 1720 and
 1240 cm^{-1} (acetate)

(Fig. 16)

NMR (60 Mc) : δ 0.76-1.00 (7 methyls), δ 1.98
 (3H, s, $-OCOCH_3$) and δ 4.42
 (1H, m, $C_{3\alpha}-H$)

(Fig. 17)

C.D. (methanol) : 220 nm ($\Delta\epsilon = + 1.04$)

(Fig. 18)

Hydrolysis of 3β -acetoxy lup $C_{28} - C_{13\beta}$ olide/lactone 63b :

Preparation of 3β -hydroxy lup $C_{28} - C_{13\beta}$ olide/lactone 63f

To a solution of 300 mg of 63b in 50 ml of benzene 100 ml of 5% methanolic potassium hydroxide solution was added and the mixture refluxed on water bath for 3 hours. After the reaction it was concentrated and then diluted with water when white solid separated out. It was filtered, chromatographed and crystallised from a mixture of chloroform and methanol to afford crystals 63f, m.p. 321° , $[\alpha]_D + 60^{\circ}$ [lit.⁷² m.p. 325° (d), $[\alpha]_D + 63.4^{\circ}$].

Found	: C 78.52	H 10.21%
Calculated for $C_{30}H_{48}O_3$: C 78.96	H 10.52%
IR (Nujol)	: 3365 (-OH), 1762 cm^{-1} (γ -lactone). (Fig. 19)	
Mass	: M^+ 456, 413 ($M^+ - C_3H_7$), 395 ($M^+ - C_3H_7 - H_2O$), 207 and (Fig.20) 189 m/z.	
^{13}C NMR (50.5MHz)	: δ 176.4 (C=O), 80.8 (Singlet $-C^{13}-O-$), 78.5 (doublet, $HO-C^{13}-$), 27 Sp^3 hybridised carbons between 55.3-14.3 (Table IA) (Fig.24)	
Jones oxidation of <u>63f</u>	: Preparation of the keto-lactone <u>98</u>	

To a solution of hydroxy lactone 63f (200 mg) in pure acetone (100 c.c) was added Jones reagent dropwise with shaking until a faint orange colour persisted. The mixture was kept at room temperature for 1 hour, diluted with water and extracted with ether. The ether layer was washed thoroughly with water, dried (Na_2SO_4) and ether was evaporated. The residue (120 mg) dissolved in benzene (10 c.c) was chromatographed over a column of silica gel (15 gm). The chromatogram was developed with petroleum and then eluted with the following solvents (Table IX).

Table IX

Eluent	Fractions 50 ml each	Residue on evaporation
Petroleum	1-4	Nil
Petroleum: benzene (3:2)	5-8	Solid (120 mg) m.p. 324°

Further elution with more polar solvent did not yield any solid material.

Fractions 5-8 (120 mg) were combined and on crystallisation from chloroform and methanol mixture furnished crystals of 98, m.p. 324° , $[\alpha]_D + 68^{\circ}$ [lit⁷² m.p. 328° $[\alpha]_D + 70^{\circ}$].

Found	: C 79.05%	H 10.72%
Calculated for $C_{30}H_{46}O_3$: C 79.62%	H 10.52%
IR	: 1710, 1760 cm^{-1}	
¹ H NMR	: δ .78-1.00 (7 saturated methyl groups)	
	2.26 (2H, m, $-CH_2-\overset{\overset{O}{\parallel}}{C}-$)	

(Fig. 21)

R E F E R E N C E S

1. K. Heusler and J. Kalvoda in "Organic Reactions in steroid Chemistry", Vol. II (Edited by J. Fried and J.A. Edwards), Van Nostrand Reinhold Company, New York, 1972, pp 237-287.
2. R.N. Butler in "Synthetic Reagents", Volume 3 (Edited by J.S. Pizey), Ellis Horwood Limited, Chichester, 1977, pp 277-419.
3. K. Heusler and J. Kalvoda, Angew. Chem. Inter. Edn. 9, 525 (1964).
4. M. Lj Mihailovic and Z. Cekovic, Synthesis, 209 (1970)
5. M. Lj. Mihailovic, J. Bosnjak, Z. Maksimovic, Z. Cekovic and Lj. Loreng, Tetrahedron, 21, 955 (1966).
6. K. Heusler, Tet. Lett. 3975 (1964)
7. R.E. Partch, Tet. Lett. 3671 (1964)
8. M. Akhtar Advan. Photochem. 2, 263 (1964)
9. R.O.C. Norman and R.A. Watson, J. Chem. Soc. (B) 184 (1968)
10. M.C.R. Symons, J. Amer.Chem. Soc., 91, 5924 (1969)
J. Chem. Soc. Perkin II, 1618 (1974)
11. R.E. Partch, J. Org. Chem. 30, 2498 (1965)
12. M. Lj. Mihailovic, M. Jokovljevic and Z. Cekovic, Tetrahedron, 25, 2269 (1969)
13. C. Walling and A. Padwa, J. Amer.Chem. Soc., 85, 1597 (1963)
14. E.J. Corey and W.R. Hertler, J. Amer.Chem. Soc., 82, 1657 (1960)
- 15a. M. Lj. Mihailovic, M. Jokovljevic, V. Trifunovic, R. Vukor and Z. Cekovic, Tetrahedron 24, 6959 (1968)

- 15b. M. Lj. Mihailovic, Z. Cekovic and D. Jevemic,
Tetrahedron, 21, 2813 (1965)
- 15c. M. Lj. Mihailovic, S. Cojkovic and S. Konstantinovic,
Tetrahedron, 29, 3675 (1973)
- 15d. M. Lj. Mihailovic and Z. Cekovic, Synthesis, 209 (1970)
- 15e. M. Lj. Mihailovic, R.I. Mamuzic, Lj. Zigic-Mamuzic,
J. Bosnjuk and Z. Cekovic, Tetrahedron, 23, 215 (1967)
- 15f. R. Paul and H. Normant, Bull. Soc. Chim. Fr. 11, 365
(1944); O. Riobe, C.R. Acad. Sci. Paris 225,
334 (1947); J. Colonge and J.C. Brunie, Bull.
Soc. Chim. Fr. 1799 (1963); O. Tanaka, M. Nagai,
T. Ohsawa, N. Tanaka and S. Sibata, Tet. Lett.
391 (1967)
16. Cf. C. Walling, Free Radical Rearrangements in
"Molecular rearrangement" (Ed. P. de Mayo),
Part One, pp 416-423, Interscience, New York,
1963.
- 16a. M. Lj. Mihailovic, L. Zivkovic, Z. Makshimovic, D.
Jevemic, Z. Cekovic and R. Matic, Tetrahedron, 23,
3095 (1967)
17. M. Lj. Mihailovic, S. Konstantinovic, A. Milovanovic,
J. Jankovic, Z. Cekovic and D. Jevemic, Chem. Comm.
236 (1969)
18. S. Moon and J.M. Lodge, J. Org. Chem. 29, 3453 (1964)
19. K. Kitahonoki and A. Matsura, Tet. Lett. 2263 (1964)
20. J.K. Kochi, J. Amer.Chem. Soc. 84, 1193 (1962);
F.D. Greene, M.L. Savitz, F.D. Osterholtz, H.H. Lau,
W.N. Smith and P.M. Zanet, J. Org. Chem. 28, 55 (1963)
21. D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner and
O. Jeger, Helv. Chim. Acta, 47, 1961 (1964)

22. M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrti, M. Li. Mihailovic, K. Schaffner, D. Avigoni and G. Jeger, *Helv. Chim. Acta*, 45, 2674 (1962)
23. K. Heusler, J. Kalvoda, G. Anner and A. Wettstein, *Helv. Chim. Acta*, 46, 352 (1963); H. Heusler and J. Kalvoda, *Ibid.*, 46, 2732 (1963)
24. As proposed by W.A. Mosher, C.L. Kehr and L.W. Wright, *J. Org. Chem.* 26, 1044 (1967) for the fragmentation in acetic acid.
25. Similarly to the oxidation of carbon radicals by cupric salts. H.E. De La Mare, J.K. Kochi and F.F. Rust, *J. Amer. Chem. Soc.* 85, 1437 (1963); J.K. Kochi, *J. Amer. Chem. Soc.*, 85, 1958 (1963)
26. M. Lj. Mihailovic, Z. Cekovic, Z. Maksimovic, D. Jeremic, Lj. Lorenc and R.I. Mamuzic, *Tetrahedron* 21, 2799 (1965)
27. J. Kalvoda and K. Heusler, *Chem. Ind. (London)* 1431 (1963)
28. D. Jeremic, S. Milosavljevic, V. Andrejevic, M. Jokovljevic - Marinkovic, Z. Cekovic and M. Lj. Mihailovic, *Chem. Comm.* 1612 (1971)
29. S. Milosavljevic, D. Jeremic and M. Lj. Mihailovic, *Tetrahedron*, 29, 3547 (1973)
30. D.N. Kirk and M.P. Hartshorn, "Steroid Reaction Mechanisms". Elsevier, Amsterdam, 1968, pp 401-405
31. T. Jen and M.E. Wolff, *J. Med. Chem.* 5, 876 (1962); Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta* 45, 1317 (1962); R. Tschesche, V. Knittel and G. Snatzke, *Chem. Ber.* 98, 1974 (1965)

32. M. Akhtar and D.H.R. Barton, *J. Am. Chem. Soc.* 86, 1528 (1964)
33. Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland G. Anner and A. Wettstein, *Experientia*, 17, 475 (1961)
34. R.A. Sneen and N.P. Matheny, *J. Amer. Chem. Soc.*, 86, 3905 (1964)
35. R.A. Sneen and N.P. Matheny, *J. Amer. Chem. Soc.* 86, 5503 (1964)
36. A. Deluzarche, A. Mailland, P. Rimmelin, F. Schue and J.M. Sommer, *Chem. Comm.* 976 (1970)
37. N.M. Roscher, *Chem. Comm.* 474 (1971)
38. M. Akhtar, P. Hunt and P.B. Dewhurst, *J. Amer. Chem. Soc.*, 87, 1807 (1965)
39. G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, 30, 3216 (1965)
40. M.M. Green, J.G. McGrew II and J.M. Molocowan, *J. Amer. Chem. Soc.*, 93, 6701 (1971)
41. V. Botdo and C.E. Edwards, *Canad. J. Chem.* 49, 2664 (1971)
42. K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta*, 45, 2575 (1962)
43. M. Lj. Mihailovic, Z. Cekovic and J. Stankovic, *Chem. Comm.* 981 (1969)
44. K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner and A. Wettstein, *Helv. Chim. Acta*, 45, 2161 (1962)
45. J. Kalvoda, K. Heusler, G. Anner and A. Wettstein, *Helv. Chim. Acta*, 46, 618 (1963)
46. J. Kalvoda, K. Heusler, Ch. Meystre, P. Wieland G. Anner and A. Wettstein, *Gazz. Chim. Ital* 93, 140 (1963)
47. W.Z. Chow and D.C. Huang, *Sci. Sinica (Peking)* 14, 1083 (1965)

48. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley, New York, 553 (1967)
49. M. Stefanovic, M. Gasic, Lj Lorenc and M. Lj Mihailovic, *Tetrahedron*, 20, 2289 (1964)
50. A.K. Devi, G.K. Trivedi and S.C. Bhattacharyya, *Ind. J. Chem.*, 16B, 8 (1978)
51. Beidebach, *Arch. Pharm.* 280, 304 (1942); 281, 99 (1943)
52. J.M. Allison, W. Lawrie, J. Mclean and G.R. Taylor, *J. Chem. Soc.* 3353 (1961); J.M. Allison, W. Lawrie, J. Mclean and J.M. Beaton, *J. Chem. Soc.*, 5224 (1961)
53. C. Djerassi, E. Farkas, L.H. Liu and C.H. Thomas, *J. Amer. Chem. Soc.*, 77, 5330, (1955); C. Djerassi and R. Hoges 78, 3534 (1956)
54. M. Marx, J. Leclereq, B. Tursch and C. Djerassi, *J. Org. Chem.* 32, 3150 (1967)
55. G.V. Baddeley, R.A. Eade, J. Ellis, P. Harper and J.J.H. Simes, *Chem. Commun.* 961 (1968); *Tetrahedron* 25, 1643 (1969)
56. H.N. Khastgir and S. Bose, *Tetrahedron Letters*, 39 (1968)
57. A. Vystrčil and Z. Blecha, *Chemistry and Industry* 418 (1969); *Coll. Czech. Chem. Commun.* 35, 3309 (1970)
58. G.S. Davy, T.G. Halsall, E.R.H. Jones and G.D. Meakins, *J. Chem. Soc.* 2702 (1951)
59. J.L. Simonsen and W.C.J. Ross, "The Terpenes", Vol. IV, p 303, 321 (1957), The University Press, Cambridge.

60. P. Crabbe, Optical rotatory Dispersion and circular Dichroism in Organic Chemistry, p 145, Holden Day, San Francisco (1965)
61. R.A. Eade, G. Kornis and J.J.H. Simes, Aust. J. Chem. 17, 141 (1964); C.S. Chopra, A.R.H. Cole, K.J.L. Theiberg, D.E. White and H.R. Arthur, Tetrahedron, 21, 1529 (1965)
62. S.P. Adhikary, W. Lawrie and J. Mclean, J. Chem. Soc(C) 1030 (1970)
63. A.I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Product, Pergamon, Oxford, Ch. 2 (1964)
64. H. Budzikiewicz, C. Djerassi and D.H. Williams 'Structure Elucidation of Natural Products by Mass Spectrometry", Holden-Day, San Francisco, Vol. II, Ch. 20 (1964)
65. C. Djerassi, L.E. Geller and A.J. Lemin, J. Amer. Chem. Soc. 75, 2254 (1953)
66. C. Djerassi, E. Farkas, L.H. Liu and G.H. Thomas, J. Amer. Chem. Soc. 77, 5330 (1955)
67. J.M. Guider, T.G. Halsall and E.R.H. Jones, J. Chem. Soc. 3024 (1953)
68. C. Djerassi, L.H. Liu, E. Farkas, A.E. Lipman, A.J. Lemin, L.E. Geller, R.N. McDonald and B.J. Taylor, J. Amer. Chem. Soc., 77, 1260 (1955)
69. C. Djerassi and R. Hodges, J. Amer. Chem. Soc. 78, 3534 (1956)
- 70a. L. Ruzicka and E. Rey, Helv. Chim. Acta, 26, 2143 (1943)
- 70b. A. Vystrcil and Z. Blecha, Chem. & Ind. (London) 1018 (1971)
- 70c. H.N. Khastgir, S.N. Bose and D.B. Maskar, Tetrahedron Letters, No. 18, 1821 (1972)
71. A. Vystrcil and J. Protiva. Collection. Czechoslav. Chem. Commun. 39, 1382 (1974)

72. N. Banerjee, P. Mazumder and N.L. Dutta, *Phytochemistry* 14, 1447 (1975)
73. H. Budzikiewicz, J.M. Wilson and C. Djerassi, *J. Amer. Chem. Soc.* 85, 3688 (1963)
74. T.G. Halsall, *Chem. Indus, London*, 867 (1951)
75. A.S.R. Anjaneyulu and A.V. Rama Prasad, *Phytochemistry*, Vol. 22, No. 4, 993 (1983)
76. Prabha Bhandari and R.P. Rastogi, *Phytochemistry* 23, 1699 (1984)
- 76a. P. Bhandari and R.P. Rastogi, *Phytochemistry*, 23 (9), 2082 (1984)
77. M. Lj. Mihailovic and R.E. Partch in "Selective Organic Transformations (edited by B.S. Thyagarajan) John Wiley & Sons., New York, Vol. 2, pp 97-181 (1972)
78. H.N. Khastgir, S.N. Bose, *J. Ind. Chem. Soc.*, 46, 757 (1969)
- 78a. H.N. Khastgir, S.N. Bose, *J. Ind. Chem. Soc.*, 46, 860 (1969)
79. J.P. Jennings, W. Klyne and P.I. Scopes, *J. Chem. Soc.* 7211 (1965)
80. G. Snatzke, H. Ripperger, Chr. Harstman and K. Schreiber, *Tetrahedron* 22, 3103 (1966)
81. H. Wolf, *Tetrahedron Letters*, 1075 (1965); 5161 (1966)
82. M. Legrand and Bucourt, *Bull. Soc. Chem. Fr.* 2241 (1967)
83. A.F. Beecham, *Tetrahedron Letters*, 2355 (1968); 3591 (1968); 4897 (1969)
84. Prof. G. Snatzke, Private communication
85. G. Lutta and S.N. Bose, *Tetrahedron Letters*, 29, 5807 (1988)
86. J.L. Simonsen and W.C.J. Ross, "The Terpenes", Vol. IV, pp 289-292 (1957), The University Press, Cambridge.

- 86a. C. Djerassi, L.H. Liu, E. Farkas, A.E. Lippman,
A.J. Lemin, L.E. Geller, R.N. McDonald and B.J. Taylor,
J. Amer. Chem. Soc. 77, 1200 (1955)
87. (a) Ref. 86, pp 350-354.
(b) P. de Mayo, The Higher Terpenoids, Vol. III,
pp 179-184, Interscience, New York (1959)
88. W. Klyne, "Optical Rotatory Dispersion and Circular
Dichroism in Organic Chemistry" (Ed. G. Snatzke),
pp 193-207, Heyder, London (1967)
89. W. Klyne and P.M. Scopes, "Fundamental Aspects and
Recent Developments in Optically Rotatory
Dispersion and Circular Dichroism (Ed. F.
Ciardelli and P. Salvadori), pp 352-372, Heyder,
London (1973)
90. P.M. Scopes, Prag. Chem. Org. Natural Products, 32,
167 (1975)
91. D.N. Kirk, Tetrahedron, 42, 777 (1986).
92. E. Wenkert, G.V. Baddeley, I.R. Burfitt and
L.N. Moreno, Org. Magnetic Reson 11, 337 (1978)