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HIGHER ISOPRENOIDS—V[a]

PARTIAL SYNTHESES FROM CYCLOARTENOL, CYCLOLAUDENOL PART 1: MANGIFEROLIC ACID, AMBOLIC ACID[b,c]

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Abstract—Conversion of cycloartenol into mangiferolic acid and of cyclolaudenol into ambolic acid is described.

A number of triterpenoids in Nature are derived from cycloartenol (**1**) by catabolic processes.[1] With the ready availability of cycloartenol and cyclolaudenol (**12**) from opium marc,[2] it appeared of interest to effect some of these transformations in the laboratory. In this and subsequent articles we propose to describe these results.

Mangifera indica (Anacardiaceae) elaborates a series of cycloartane-based C_{30} and C_{31} triterpenoids, of which mangiferolic acid (**2**)[3] and ambolic acid (**8**)[4] are typical. Structure **2** rests on its conversion to cycloartanol while ambolic acid was correlated with cycloartenol *via* the trisnor acid **10**. We now report on elaboration of **2** from cycloartenol (**1**)[5] and of **8** from cyclolaudenol (**12**).

Mangiferolic acid (**2**). Cycloartenyl acetate was degraded to the known[6] trisnor aldehyde (**11**), which on exposure to α-ethoxy-carbonylethylidenetriphenylphosphorane, followed by saponification, furnished a product, indistinguishable (m.p., $[\alpha]_D$, IR, PMR) from mangiferolic acid (**2**).[7] It may be pointed out that in view of the known[8] stereochemical outcome of reactions involving stabilised ylids and unhindered aldehydes, the product was expected to be (*E*)-configurated and this conversion provides chemical proof for the (*E*)-geometry of the olefinic linkage in mangiferolic acid, deduced earlier on PMR spectral data.[3,9] Oxidation of mangiferolic acid with $Na_2Cr_2O_7$–H_2SO_4 yielded the naturally occurring mangiferonic acid (**3**).[4]

It has been established[11] that SeO_2 selectively attacks certain trisubstituted olefins to furnish (*E*)-products. In view of this, it was of interest to examine the action of SeO_2 on cycloartenol. Cycloartenyl acetate was exposed to SeO_2 (1 mole equiv) in DMSO[12] at 100° (2 hr) to furnish an aldehyde (60%) and an alcohol (12%). The aldehyde was readily recognised as **4** (acetate of naturally occurring mangiferolaldehyde, **6**[10]) from its spectral characteristics (UV, IR, PMR) and its LAH reduction to the glycol **5**, also prepared from methyl mangiferolate by

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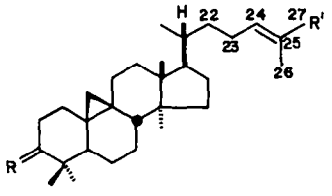
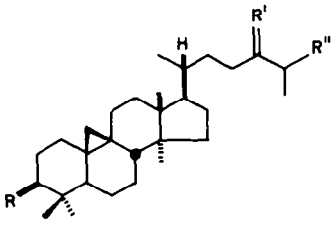
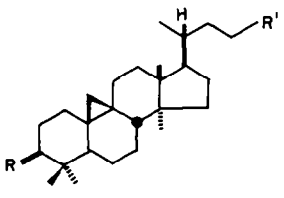
[c]Abstracted from the Ph.D Thesis (Poona University, 1976) of Chandan Singh.



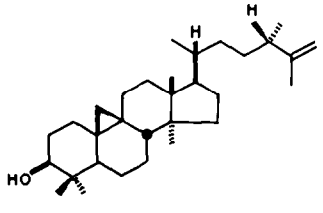
1: R = H, β-OH; R′ = Me
2: R = H, β-OH; R′ = COOH
3: R = O; R′ = COOH
4: R = H, β-OAc; R′ = CHO
b: R = H, β-OH; R′ = CH_2OH
6: R = H, β-OH; R′ = CHO
7: R = H, β-OAc; R′ = CH_2OH



8: R = OH; R′ = CH_2; R″ = COOH
9: R = OAc; R′ = CH_2; R″ = COOMe

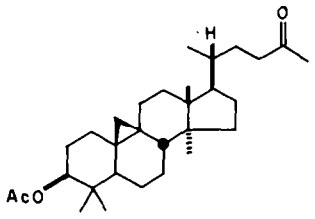


10: R = OAc; R′ = COOH
11: R = OAc; R′ = CHO



LAH reduction. The minor product of SeO_2 oxidation is assigned structure **7** (IR, PMR).

Ambolic acid (**8**). In the successful, but less selective route, methyl ketone **13**, readily obtainable from cyclolaudenol (**12**) by a procedure disclosed earlier,[2] was reacted with methyl α-bromopropionate to furnish a mixture of diastereoisomeric hydroxy esters (**14**), which on dehydration ($POCl_3$-pyridine or Ph_3P–CCl_4†) furnished a mixture of olefins (**15**), in which the required



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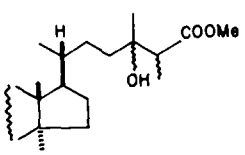

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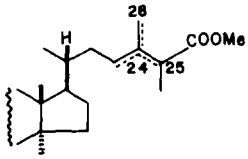

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product ($\Delta^{24\ 28}$ isomer) was present to the extent of 25% (PMR). $AgNO_3$–SiO_2 gel chromatography of the total material yielded $\Delta^{24\ 28}$ isomer; no attempt was made to get other olefin isomers in a pure state. This material (m.p. 98–99°, $[\alpha]_D$ + 51.3) was expected, from its method of preparation, to be a mixture of C_{25} diastereoisomers. It shows a PMR spectrum virtually superimposable on that of an authentic sample of acetyl methyl ambolate (**9**)[7] (m.p. 105–109°; $[\alpha]_D$ + 34°).[4] In ambolic acid, configuration at C_{25} has been established[14] to be R.

Mass spectra. Cycloartanoids undergo[15] two diagnostically important electron-impact-induced fragmentations: side-chain cleavage and, rupture of cyclopropane ring leading to loss of ring A along with C_6 or C_{19}. With aldehyde **11** as the sole exception, all cycloartane-based compounds described in this work exhibit these characteristic fragmentations, though relative intensity of these ions were of the order of 10–35% (of the base peak).

EXPERIMENTAL

All m.ps are uncorrected. Light petroleum refers to the fraction, m.p. 60–80°. Optical rotations were measured in $CHCl_3$.

The following instruments were used for spectral data: Perkin-Elmer Infracord model 267; Perkin-Elmer model R 32 (90 MHz) NMR spectrometer; CEC mass spectrometer, model 21-110B (70 eV, direct inlet system). All PMR spectra were recorded using 15–20% soln in CCl_4, unless otherwise stated. While citing PMR data, following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. While summarising mass spectral data, besides the molecular ion, ten most abundant ions (above *m/e* 60) are reported with their relative intensities.

25,26,27-Trisnor-24-oxo-cycloartanyl acetate (**11**)

Cycloartenyl acetate (4.2 g) in $CHCl_3$ (200 ml) was treated with ozonised O_2 at −78° till O_3 passed freely (1.5 hr). The soln was allowed to attain room temp. (26°), AcOH (25 ml) added and Zn dust (5.0 g) introduced, with stirring (10 min). Stirring was continued for another 6 hr and the mixture worked up in the usual manner to furnish a neutral fraction (3.5 g, m.p. 130–145°), which was crystallised from acetone–water: white plates, m.p. 158–160° (lit.,[6] m.p. 155°). IR (Nujol): CHO 2700, 1720 cm^{-1}; OAc 1720, 1255 cm^{-1}. PMR: cyclopropane CH_2 (1H, d, 0.33 ppm; 1H, d 0.58 ppm; J = 4 Hz), tertiary Me's (singlets at 0.87, 0.87, 0.90, 0.97 ppm), OAc (s, 1.98 ppm), CHOAc (m, 4.5 ppm). CHO (t, 9.70 ppm, J = 1.5 Hz). Mass: *m/e* 442 (M^+, 2.2%), 171 (30%), 117 (30%), 115 (35%), 103 (44%), 101 (34%), 91 (60%), 89 (36%), 79 (100%), 77 (38%), 65 (40%).

Mangiferolic acid (**2**)

A mixture of the above aldehyde (1.98 g, 0.045 mole) and α-ethoxycarbonylethylidenetriphenylphosphorane[16] (1.8 g, 0.05 mole) in C_6H_6 (50 ml) was refluxed (12 hr, N_2), most of solvent distilled off and the residue (10 ml) chromatographed on SiO_2-gel/III (85 × 1.5 cm) with TLC (solvent: C_6H_6) monitoring. The material (2.0 g, m.p. 112–115°), eluted with 10% light petrol in C_6H_6 (50 ml × 20) was crystallised from ether–MeOH to furnish colorless needles (1.4 g), m.p. 116–116.5°, of *ethyl 3-acetoxy-mangiferolate*. IR (Nujol): C=O 1710, 1730 cm^{-1}; C=C 1650 cm^{-1}. PMR: cyclopropane methylene (1H, d, 0.30 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (singlets at 0.85, 0.85, 0.90, 0.96 ppm), C=C–Me (3H, d, 1.80 ppm, J = 1.5 Hz), –C=CH–CH_2 (1H, t, 6.60 ppm, J = 7 Hz). (Found: C, 77.49; H, 10.29. $C_{34}H_{54}O_4$ requires: C, 77.52; H, 10.33%).

The above ester (221 mg) was hydrolysed with refluxing 5% ethanolic KOH (6 ml, 4 hr, N_2) and worked up in the usual manner to give mangiferolic acid (180 mg, m.p. 165–171°), crystallised from $CHCl_3$–MeOH to furnish crystals (130 mg), m.p. 175–178°, $[\alpha]_D$ + 49.9° (*c*, 0.95%) (lit.[3]: m.p. 181–183°; $[\alpha]_D$ + 49°). Mass: *m/e* 456 (M^+, 6%), 423 (32%), 175 (38%), 135 (50%), 121 (50%), 109 (48%), 107 (60%), 105 (48%), 95 (100%), 93 (55%), 81 (50%). (Found: C, 78.74; H, 10.67. $C_{30}H_{48}O_3$ requires: C, 78.89; H, 10.59%).

Mangiferonic acid (**3**)

To a soln of mangiferolic acid (100 mg) in ether (20 ml), a soln of chromic acid (0.6 ml; 1 g $Na_2Cr_2O_7 \cdot 2H_2O$ + 1 ml H_2O + 1 ml H_2SO_4, diluted to 8 ml with water[17]) was added dropwise (25°, 5 min) and after stirring at 25–30° for 2 hr, was worked up in the usual manner to furnish a solid (96 mg, m.p. 174–179°) which was recrystallised from ether–MeOH, m.p. 178–181° (40 mg), $[\alpha]_D$ + 22°(*c*, 0.5%) (lit.[4]: m.p. 187–189°, $[\alpha]_D$ + 23.5°). IR (Nujol): C=O 1710, 1685 cm^{-1}; C=C 1640 cm^{-1}. PMR ($CDCl_3$): cyclopropane methylene (1H, d, 0.57 ppm; 1H, d, 0.80 ppm; J = 4 Hz), tetriary Me's (singlets at 0.90, 1.0, 1.05 and 1.1 ppm) C=C–Me (3H, bs, 1.86 ppm), –C=CH–CH_2 (1H, t, 6.90 ppm, J = 7.5 Hz). Mass: *m/e* 454 (M^+, 33%), 109 (45%), 107 (65%), 105 (40%), 95 (100%), 93 (60%), 91 (40%), 81 (55%), 79 (40%), 69 (50%), 67 (54%). (Found: C, 78.50; H, 10.23. $C_{30}H_{46}O_3$ requires: C, 79.24; H, 10.20%).

Action of SeO_2 on cycloartenyl acetate

Cycloartenyl acetate (1.02 g, 2.2 mmole), SeO_2 (0.22 g, 2.0 mmole) and DMSO (15 ml) were heated on a steam-bath for 2 hr, the mixture cooled, diluted with water (50 ml) and extracted with diisopropyl ether (100 ml × 3). The extract was washed with water (50 ml × 3), dried (Na_2SO_4) and freed of solvent, under suction. The residue in light petrol (10 ml) was chromatographed on SiO_2 gel/IIA (22 × 2 cm), while monitoring with TLC (solvent: 10% EtOAc in C_6H_6):

Frac. 1	light petrol	500 ml	—
Frac. 2	50% C_6H_6 in light petrol	50 ml × 10	Solid (200 mg), starting material.
Frac. 3	C_6H_6	50 ml × 10	600 mg, m.p. 142–144°, (**4**)
Frac. 4	C_6H_6		100 mg mixture (TLC)
Frac. 5	10% EtOAc in C_6H_6	50 ml × 4	120 mg, (**7**)

†This reagent[13] was used in an attempt to prepare the corresponding chloride for subsequent selective HCl elimination. However, **15** was directly obtained.

3-Acetyl-mangiferolaldehyde (**4**). Fraction 3 was crystallised from ether–MeOH to furnish **4**, m.p. 145–147° $\lambda_{max}^{CHCl_3}$ 246.5 nm. IR (Nujol): CHO 2700, 1690 cm^{-1}; OAc 1735, 1245 cm^{-1}; C=C 1643 cm^{-1}. PMR: cyclopropane methylene (1H, d, 0.33 ppm; 1H, d, 0.60 ppm; J = 4 Hz) tertiary Me's (3H, singlets at 0.82, 0.85, 0.89 and 0.95 ppm), C=C–Me (3H, bs, 1.72 ppm), OAc (3H, s, 2.0 ppm), CHOAc (1H, t, 4.53 ppm; J = 7 Hz), C=CH–CH_2 (1H, t, 6.44 ppm, J = 7 Hz), CHO (1H, s, 9.42 ppm). (Found: C, 79.21; H, 10.22. $C_{32}H_{50}O_3$ requires: C, 79.62; H, 10.44%).

The above acetate aldehyde (200 mg) was reduced with LAH (200 mg) in ether (20 ml) for 6 hr at 30° and, worked up in the usual manner (H_2O, 20% NaOH aq) to furnish a gum (200 mg) which was purified by chromatography (SiO_2 gel, 15 × 1 cm, elution with 10% EtOAc in C_6H_6) to furnish diol **5**, 150 mg, 130–138° (crystallised from Et_2O–MeOH, m.p. 135–136°), identical with a sample (m.p. 135–136°) obtained from methyl mangiferolate (100 mg) by a similar LAH reduction. PMR ($CDCl_3$): cyclopropane methylene (1H, d, 0.33 ppm; 1H, d, 0.59 ppm; J = 4 Hz), tertiary Me's (3H singlets at 0.80, 0.90, 0.96 and 0.96 ppm), C=C–Me (3H, bs, 1.67 ppm), CHOH (1H, q, 3.29 ppm, J_1 = 6 Hz, J_2 = 10 Hz), CH_2OH (2H, bs, 4.0 ppm). C=CH–CH_2 (1H, t, 5.41 ppm, J = 7 Hz).

27-Hydroxy-cycloartenyl acetate (**7**). Fraction 5, on crystallisation from MeOH yielded **7**, m.p. 105–108°. PMR: cyclopropane methylene (1H, d, 0.33 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (3H, singlets at 0.84, 0.88, 0.90 and 0.99 ppm), C=C–Me (3H, bs, 1.64 ppm), OAc (3H, s, 2.01 ppm), CH_2OH (2H, bs, 3.92 ppm), CHOAc (1H, m, 4.52 ppm), C=CH–CH_2 (1H, t, 5.37, J = 7 Hz).

Methyl 3-acetoxy-24-methyl-24-hydroxy-cycloartan-27-oate (**14**). The methyl ketone[2] **13** (14.0 g, 0.031 mole), Zn wool (5.0 g, 0.077 g atom) and methyl α-bromopropionate (10 ml) were reacted (6 hr, reflux) in C_6H_6 (250 ml) in the usual manner[18] to furnish after chromatography (SiO_2 gel/IIA, 100 × 3 cm) the hydroxy ester **14** as a gum (9.0 g, eluted with C_6H_6). IR ($CHCl_3$: 0.1 mm): C=O 1725 cm^{-1}; OH 3510 cm^{-1}. PMR: cyclopropane methylene (1H, d, 0.31 ppm; 1H, d, 0.58 ppm; J = 4 Hz), tertiary Me's (3H, singlets at 0.83, 0.86, 0.89, 0.96 ppm), OAc (3H, s, 1.98 ppm), COOMe (3H, bs, 3.69 ppm), CHOAc (1H, t, 4.5 ppm, J = 7 Hz). (Found: C, 74.89; H, 9.91. $C_{34}H_{56}O_4$ requires: C, 74.95; H, 10.36%).

Methyl 3-acetoxy-ambolate (**9**)

(i) *Dehydration with triphenylphosphine-carbon tetrachloride.* The above hydroxy ester (200 mg), $(Ph)_3P$ (1.0 g) and CCl_4 (25 ml) were mixed and refluxed (24 hr). CCl_4 was distilled off and the residue, in C_6H_6 (5 ml), chromatographed over SiO_2 gel/IIA (10 × 1.5 cm). Benzene (200 ml) eluted a colorless gum (150 mg), showing on TLC (SiO_2–gel–10% $AgNO_3$; solvent: 33%light petrol in C_6H_6) three spots with R_f of 0.43, 0.39 and 0.32. This material is essentially identical (TLC, PMR) with the product described below and was processed further.

(ii) *Dehydration with $POCl_3$–pyridine.* A soln of the hydroxy ester (1.25 g) in pyridine (10 ml) was treated, dropwise (10 min), at 0°, with $POCl_3$ (5 ml). The mixture was heated on a steam-bath for 4 hr, cooled and worked up in the usual manner to give a product, which was chromatographed (SiO_2-gel) as above to give olefin mixture (**15**; 1.2 g). This material (2.0 g) was further chromatographed over 10% $AgNO_3$–SiO_2 gel (120 × 2 cm) with TLC monitoring (see above). Elution was done with light petrol, containing increasing amounts of C_6H_6. The required product eluted last (R_f 0.32) with 33% C_6H_6 in light petrol. This product (200 mg) was crystallised from EtOH, m.p. 98–99°. IR (KBr): C=O 1727 cm^{-1}; C=C 1638, 890 cm^{-1}. PMR: cyclopropane methylene (1H, d, 0.37 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (3H, singlets at 0.87, 0.87, 0.91 and 0.98 ppm), CH_2=C–CH(Me)COOMe (d, 1.26 ppm, J = 7 Hz), OAc (3H, s, 2.1 ppm), COOMe (3H, s, 3.67 ppm), CHOAc (1H, m, 4.51 ppm), C=CH_2 (2H, bs, 4.88 ppm, $W_{1/2}$ = 6 Hz). Mass: *m/e* 526 (M^+, 29%), 466 (100%), 451 (80%), 344 (80%), 203 (85%), 175 (82%), 147 (82%), 135 (82%), 119 (82%), 109 (82%), 95 (76%).

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