Tetrahedron, 1964, Vol. 20, pp. 2601 to 2604. Pergamon Press Ltd. Printed in Northern Ireland

MACROCYCLIC MUSK COMPOUNDS—XI*

SYNTHESIS OF OPTICALLY ACTIVE MUSCONE

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(*Received* 7 *July* 1964)

Abstract—A simple synthesis of (—)-muscone has been developed by using citronellal and oleyl alcohol as the starting materials.

(—)-MUSCONE (3-methyl cyclopentadecanone) (XV) is the main odorous principle[1] of musk pod obtained from the male musk deer, *Moschus moschiferus*. Its absolute configuration was established by its synthesis[2] via the electrolytic method from the monomethyl esters of tridecanedioic acid and β-methylglutaric acid and further confirmed by optical rotatory studies.[3]

Several methods[4] have been developed for the synthesis of (±)-muscone, including a recent one from this laboratory.[5] A simple synthesis of (—)-muscone starting from easily available (+)-citronellal and oleyl alcohol is now reported here. The reactions are summarized in the chart.

Citronellal acetal (II) obtained[6] from (+)-citronellal (I, $[\alpha]_D$ +8°), on oxidation with alkaline potassium permanganate[7] gives the acid acetal (III) converted by treatment with diazomethane to the methyl ester (IIIa). Careful hydrolysis[7] of the ester acetal in dilute hydrochloric acid solution affords the aldehydo ester (IV), oxidation of which with potassium permanganate in acetone solution containing requisite amount of acetic acid to prevent the hydrolysis of the existing ester group yields the corresponding acid ester (V).

The acid chloride (VI) of this acid ester on condensation with cadmium Grignard[8] reagent, prepared from oleyl bromide, followed by decomposition yields the methyl ester of 4-methyl-6-keto-15:16-ene-tetracosanoic acid (VII) as the main product. Ozonolysis of this and subsequent hydrolysis of the ozonide affords the methyl ester of 4-methyl-6-keto-15-aldehydopentadecanoic acid (VIII), which is oxidized by acid

* Communication No. 693 from the National Chemical Laboratory, Poona-8, India.

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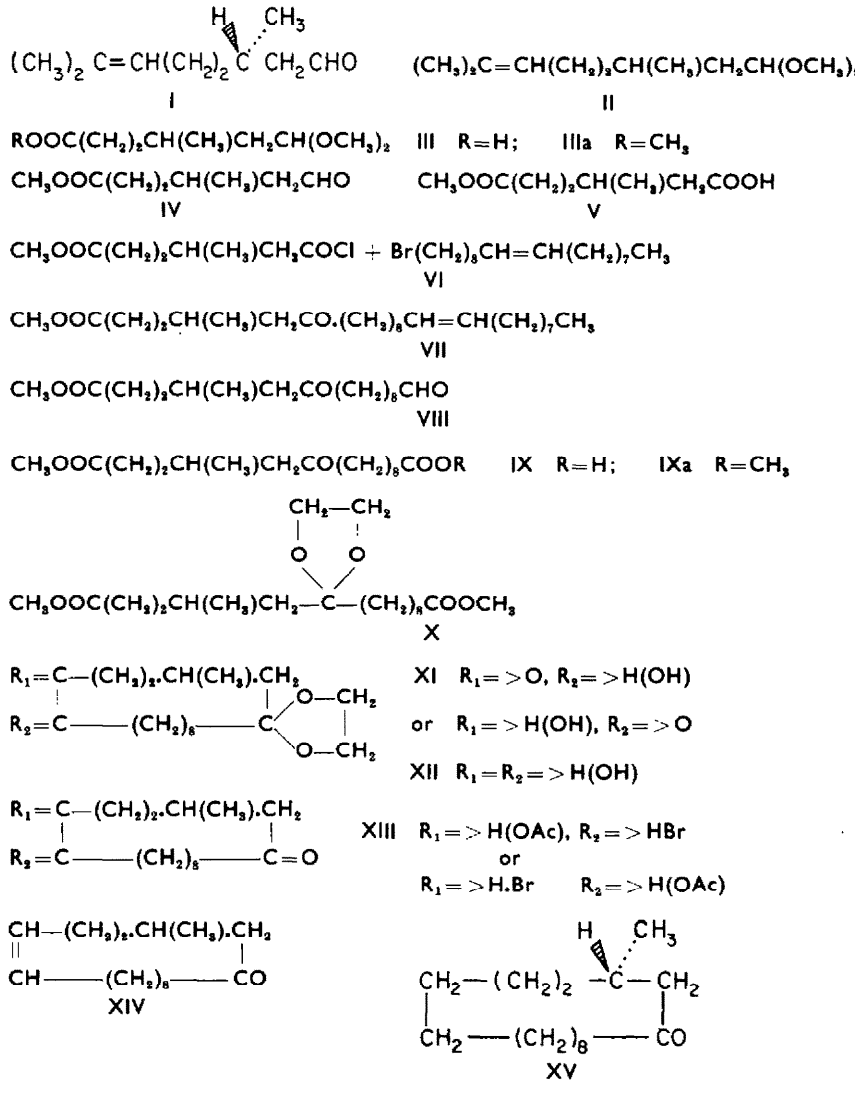

permangnate to the corresponding acid ester (IX), converted to the dimethyl* ester (IXa) by esterification with methanol and hydrogen chloride. The ethylene ketal (X) of this keto diester is cyclized[9] to the acyloin (XI) which is reduced with lithium aluminium hydride to the ketal diol (XII), treatment of which with hydrogen bromide in glacial acetic acid yields bromoacetoxy compound (XIII). The intermediates from X to XIII could not be distilled even under high vacuum without decomposition; the structural features, however, were in accordance with their IR spectra. Simultaneous debromination and deacetoxylation of the bromoacetoxy compound, according to known procedure[9] by refluxing in absolute methanol with zinc dust, affords

* Attempt to prepare the keto-dicarboxylic acid by direct condensation of the acid chloride of citronellic acid with cadmium Grignard reagent from oleyl bromide and subsequent oxidation of the reaction product resulted in poor yield.

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(−)-muscenone (XIV) which on hydrogenation furnishes (−)-muscone (XV, $[\alpha]_D$ −2·5°): semicarbazone, m.p.131–32°. Ultimate optical rotation of muscone produced according to this procedure is dependent on the optical purity of (+)-citronellal.

EXPERIMENTAL

M.ps are uncorrected. Specific rotations were determined in $CHCl_3$ solution. IR spectra were measured with a Perkin–Elmer (Model 137*b*) Infracord spectrophotometer.

Citronellal acetal (II). Citronellal (I, $[\alpha]_D$ +8°; 100 g) was added in small portions to absolute methanol (800 ml) containing NH_4Cl (4 g) at 25–30° and the mixture left at the same temperature for 65 hr. Sodium methoxide was added to neutralize the solution. After the removal of methanol at bath temperature (45–50°) under red. press., the residue was cooled and shaken with saturated $NaHSO_3$ aq to remove unreacted citronellal. After separation of the aqueous layer, the oily layer of acetal was dissolved in ether, washed with Na_2CO_3 aq (10%), water and dried (Na_2SO_4). The product obtained after removal of ether on distillation gave citronellal acetal (II, 108 g), b.p. 110–115°/12–13 mm., n_D^{29} 1·4401, $[\alpha]_D$ +3·32° (neat); IR bands at: 1190, 1135, 1100, 1080, 1055, 970, 915 and 835 cm^{-1}.

Acetal of 5-aldehydo-4-methyl pentanoic acid (III). $KMnO_4$ aq (8%, 2·5 l.) was added to citronellal acetal (100 g) under vigorous stirring at 25–30° during 1 hr. The stirring was continued for 4 hr. at the same temp. The precipitated MnO_2 was removed by filtration. The filtrate after saturation with CO_2 was concentrated *in vacuo* at 45–50° to 300 ml. The concentrate, after cooling, was extracted with ether to remove neutral products, and then acidified with dil. H_2SO_4. The liberated acid was extracted repeatedly with ether. After drying, ether was removed and the residue was distilled fractionally to yield the acetal of 5-aldehydo-4-methylpentanoic acid (30 g), boiling at 146–50°/7 mm, n_D^{31} 1·4490; IR bands at: 3279, 1733, 1212, 1105, 974 cm^{-1}. The methyl ester (30 g) was obtained by treatment with diazomethane at 0°, b.p. 103–106°/8 mm. IR bands at: 2740, 1761, 1269, 1199, 1176, 1130 cm^{-1}.

3-*Methyl-5-carbomethoxylpentanoic acid* (V). A mixture of ester acetal (III*a*, 30 g), water (120 ml) and a few drops of conc. HCl was stirred at 25–30° for 24 hr. The reaction mixture was extracted with ether. After removal of solvent, the residual 3-methyl-5-carbomethoxyl pentanal (IV) (IR bands at: 2786, 1789, 1754, 1266 cm^{-1}) was dissolved in acetone (300 ml) containing acetic acid (25 ml) and was oxidized with $KMnO_4$ aq (8%, 200 ml) with stirring; the addition of permanganate solution was completed in 1/2 hr. and the stirring was continued for another 15 min. After clarification of the product with SO_2, acetone was removed by distillation. The residue was repeatedly extracted with ether and the extract dried (Na_2SO_4). After removal of ether, the residue was distilled *in vacuo* to yield 3-methyl-5-carbomethoxypentanoic acid (V, 20 g), b.p. 145–150°/12 mm, n_D^{31} 1·4360. (Found: C, 54·90; H, 8·15; mol. wt. 177. $C_8H_{14}O_4$ requires: C, 55·16; H, 8·10%; mol. wt. 174·19). IR bands at: 3175, 1724, 1266, 1081, 1008 cm^{-1}.

Acid chloride (VI) *of 2-methyl-5-carbomethoxy pentanoic acid* (V). Acid ester V (20 g) was mixed with thionyl chloride (16 ml) and the mixture kept at 40° for 4 hr. After removal of excess thionyl chloride, VI (18 g) was distilled, b.p. 100–111°/10 mm.

Methyl-4-methyl-6-keto-15:16-ene-tetracosanoate (VII). Oleyl magnesium bromide was prepared from Mg (2·6 g) and oleyl bromide (29·8 g) in dry ether (140 ml) under stirring in N_2 atm. The reaction was initiated by adding a crystal of I_2 and a few drops of oleyl bromide. The addition of oleyl bromide was completed in 1 hr. The Grignard reagent was gently refluxed for 1 hr. and to the boiling solution anhydrous $CdCl_2$ (9·9 g) was added. The mixture was refluxed for further 1/2 hr. after which the ether was removed from the reaction mixture by distillation and substituted with benzene (80 ml) which was also removed by distillation and a fresh lot of benzene (50 ml) added. To the refluxing mixture, acid chloride (VI, 17·2 g) in benzene (50 ml) was added dropwise in 10 min and the reaction mixture refluxed in N_2 atm for 4 hr. The product was then cooled by ice–salt mixture and decomposed with dil. HCl (1:1, 240 ml). The benzene layer was separated and diluted with ether. It was washed with Na_2CO_3 (5%), cold water and dried (Na_2SO_4). After removal of solvent, the residue was subjected to fractional distillation *in vacuo* when VII (15 g) was collected, b.p. 180–185°/2·1 × 10^{-3} mm, n_D^{13} 1·4509, $[\alpha]_D$ +1·6° (*c*, 30·0). (Found: C, 76·00; H, 11·60. $C_{26}H_{48}O_3$ requires: C, 76·41; H, 11·84%); IR bands at: 1727, 1698, 1425, 1399, 1250, 962, 833 cm^{-1}.

Dimethyl-4-methyl-6-keto-pentadecanedioate (IXa). Ozone (5%) was passed through a solution of

methyl-4-methyl-6-keto-15:16-ene-tetracosanoate VII (15 g) in ethyl acetate (200 ml) for 15 hr. After removal of ethyl acetate, the ozonoide was decomposed with water by heating gradually on a water bath. The product was steam distilled to remove nonal. The residual methyl 4-methyl-6-keto-14-aldehydo-tetradecanoate (VIII), was isolated by ether extraction (IR bands: 2941, 2762, 1764, 1730, 1263 cm^{-1}) and oxidized without further purification with $KMnO_4$ aq (2·5 g, in 30 ml water) containing acetic acid (2·5 ml). After working up in the usual manner, methyl 4-methyl-6-keto-14-carboxyl tetradecanoate (IX, 9·5 g) was obtained; IR bands at: 3226, 1739, 1709, 1274 cm^{-1}. For esterification it was directly dissolved in methanol (630 ml) and anhydrous HCl (30 g) passed into the solution at 0°. The reaction mixture was kept at room temp for 72 hr. It was neutralized with alcoholic NaOH and the NaCl formed during neutralization was removed by filtration. After removal of methanol by distillation, the residue was dissolved in ether. The ethereal extract was washed with cold water, and dried (Na_2SO_4). After removal of ether, the product was subjected to fractional distillation under high vacuum to yield IXa (18 g), b.p. 152–155°/9·8 × 10^{-3} mm, n_D^{30} 1·4620, $[\alpha]_D$ +1·1° (*c*, 30·0). IR bands at: 1727, 1701, 1401, 1247, 1010 cm^{-1}. (Found: C, 66·03; H, 9·96. $C_{16}H_{32}O_5$ requires: C, 65·82; H, 9·82%).

Dimethyl-4-methyl-6-ethyleneketal-pentadecanedioate (X). The keto-diester Xa (16·3 g) was mixed with ethylene glycol (23 ml) in benzene (635 ml) containing *p*-toluenesulphonic acid (0·1 g) and refluxed for 72 hr using an azeotropic head for removal of water. The benzene solution was transferred to a dry separating funnel and the lower layer of the alcohol was removed. The benzene layer was washed with ethylene glycol (20 ml) twice, water, $NaHCO_3$ aq and finally with water till neutral. After removal of benzene, the ketal X (17·8 g) was obtained; n_D^{31} 1·4640; IR bands at: 3509, 1739, 1456, 1433, 1362, 1250, 1195, 1170, 1124, 1076, 948 cm^{-1}. (Found: C, 64·5; H, 10·0. $C_{20}H_{36}O_6$ requires: C, 64·5; H, 9·7%).

Cyclic acyloin (XI). Na (11 g) was finely powdered in heated xylene (800 ml) in N_2 atm and the ketal (16·4 g) in xylene (20 ml) was added dropwise during 1 hr with vigorous stirring, the heating being so regulated that xylene continued to reflux during the reaction (2 hr). The reaction mixture was cooled and Na was decomposed by adding ethanol (50 ml) slowly. The xylene solution was washed with water till free from alkali and the xylene removed by distillation under red. pressure when the cyclic acyloin (XI, 8·5 g) was obtained, n_D^{31} 1·4849; IR bands at: 3534, 1709, 1460, 1370, 1075, 951 cm^{-1}.

5-*Methyl-7-ethyleneketal cyclopentadecane-1:2-diol* (XII). The acyloin (XI, 7·8 g) in ether (50 ml) was added dropwise to a suspension of $LiAlH_4$ (2·7 g) in ether (100 ml) with stirring, the addition being completed in 30 min. The mixture was then refluxed for 10 hr, excess of $LiAlH_4$ was decomposed with moist ether (50 ml) and the ether solution was washed with water. After removal of ether, the diol XII (7·8 g) was obtained as a viscous material; IR bands at: 3448, 1368, 1075, 947 cm^{-1}.

3-*Methyl cyclopentadec-6-enone* (XIV). A mixture of the diol XII (7·6 g) and a solution of HBr in glacial acetic acid (30%, 50 ml) was kept at room temp for 24 hr and then heated in an oil bath at 65° for 3 hr. After addition of acetic anhydride (8 g) the mixture was further heated for 3 hr. The reaction mixture was cooled and a solution of sodium acetate (18 g) in water (135 ml) was added to the reaction mixture to decompose the excess of HBr. The reaction mixture was repeatedly extracted with pet. ether. After removal of pet. ether, the crude bromoacetoxy compound XIII (8·3 g) was obtained as yellowish red oil; IR bands at: 2950, 2874, 1739, 1706, 1453, 1403, 1368, 1233, 1072, 1024 cm^{-1}.

A solution of the crude bromoacetoxy compound (8·3 g) in absolute methanol (65 ml) was treated with Zn dust (6 g) and was refluxed with stirring for 12 hr. Methanol was removed by distillation and the residue treated with pet. ether and filtered. The filtrate was washed with dilute acetic acid and then with water till free from acid. It was filtered through neutral alumina (gr. II; 40 g). After removal of solvent, the residue was distilled under red. press. when XIV (2·1 g) was obtained, b.p. 135°/0·1 mm. IR bands at: 2967, 2890, 1712, 1404, 1370, 1052, 1020, 970 cm^{-1}. (Found: C, 80·9; H, 12·2. $C_{16}H_{28}O$ requires: C, 81·29; H, 11·94%).

(−)-*Muscone* (3-*methyl cyclopentadecanone*) (XV). The unsaturated ketone (1 g) in ethyl alcohol (60 ml) was hydrogenated in presence of Pd–C (5%, 0·18 g). The absorption of H_2 due to one double bond was completed in 60 hr. The reaction mixture was worked up in the usual manner. The product on distillation gave XV (0·95 g), b.p. 130°/0·5 mm., n_D^{30} 1·4719, $[\alpha]_D$ −2·5° (*c*, 4·5). IR bands at: 1709, 1450, 1399, 1361, 1274, 1120, 1087, 1018, 715 cm^{-1}. (Found: C, 80·6; H, 12·5. $C_{16}H_{30}O$ requires: C, 80·60; H, 12·68%), semicarbazone, m.p. 131–132°.