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SEXUAL HORMONES OF MUCORALES. THE SYNTHESIS OF METHYL TRISPORATE B AND C*

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Trisporic acids, the carotenogenic C_{18}-carboxylic acids[1)] isolated from mated cultures of the fungi Blakeslea trispora and Mucor mucedo include 9-cis and 9-trans isomers of trisporic acid B and (principally) C[2)]. The acids regulate sexual reproduction in heterothallic Mucorales[3)] and promote carotene and steroid synthesis in (-)-B.trispora[4)]. It is known that methyl trisporate B and C have activity towards (-)-M.mucedo which is quantitatively comparable to that of the total extract from mated strains of the same fungus[5)].

We report here a brief and efficient synthetic route to methyl 9-cis and 9-trans trisporate B and methyl 9-cis trisporate C.

Methyl β-acetoacrylate[6)] prepared from methyl levulinate by bromination followed by dehydrobromination with sodium acetate in acetic acid was converted to the unsaturated ester ketal (I), b.p.107-110°/13mm; IR 1720, 1300, 1270, 1200, 1170, 1040. Condensation of the unsaturated ester(I) with methyl propionate in refluxing benzene in the presence of two equiv. of sodium hydride yielded β-keto ester (II), b.p.128-130°/3mm; IR 1740, 1700, 1640, 1240, 1200, 1040 in 72% yield. Treatment of the sodium salt of II with methanolic solution of 1-diethylaminopentan-3-one methiodide in benzene gave the diketo ester(III), b.p.155-160°/1mm; IR 1738, 1712, 1700, 1640, 1270, 1240, 1208, 1040; UVλ_{max}^{EtOH} 223.5nm; NMR ($CDCl_3$)δ 1.03(3H,t,J=7Hz), 1.34(3H,s), 1.46(3H,s), 3.68(3H,s), 3.88(4H,m), 6.40(1H,d,J=16Hz), 6.72(1H,d,J=16Hz); MS 312 (M^+), in 78% yield. Cyclization of III to the unsaturated keto ester (IV), b.p.150-155°/1mm; IR 1732, 1675, 1245, 1200, 1040; UVλ_{max}^{EtOH} 274nm(12,600); NMR($CDCl_3$)δ 1.46(6H,s), 1.84(3H,s), 3.66(3H,s), 3.90(4H,m), 5.62(1H,d.J=16Hz), 6.40(1H,d,J=16Hz); MS 294 (M^+), was effected by treatment with sodium methoxide in boiling methanol for just two minutes(45% yield).

In one experiment we demonstrated that three reactions (I-II, II-III, III-IV) were able to be carried out successively in the same flask. Hydrolysis of the ketal group of IV with 60% aq. acetic acid afforded the diketo ester (V), IR 1730, 1678, 1610, 1246; UVλ_{max}^{EtOH}292nm(11,600); NMR($CDCl_3$)δ 1.48(3H,s), 1.94(3H, s), 2.30(3H,s), 3.68(3H,s), 6.20(1H,d,J=16Hz), 7.36(1H,d,J=16Hz); MS 250 (M^+), which is the key intermediate7) for the synthesis of methyl trisporates. Wittig reaction of the diketo ester (V) (without protecting the ring carbonyl) with the ylide of VI8) (prepared from 5-bromo-pentan-2-one by treatment with triphenyl phosphine followed by ketalization) furnished after acidic work-up a mixture of methyl 9-cis and 9-trans trisporate B ((VII) and (VIII)) in quantitative yield. This mixture was shown by v.p.c. to comprise 75% cis and 25% trans methyl trisporate B. Wittig reaction of the diketo ester (V) occurred exclusively at side chain carbonyl because of the enolization of the ring carbonyl9). The pure methyl 9-cis and 9-trans trisporate B were separated by preparative t.l.c. (silica gel) and v.p.c.(SE-30). Selected reduction of pure methyl 9-cis trisporate B with sodium borohydride at -5° yielded diastereomeric mixture of methyl 9-cis trisporate C (IX). The synthetic methyl trisporates thus prepared showed identity with the reported spectroscopic data10).

Table

Methyl 9-cis trisporate B (VII)

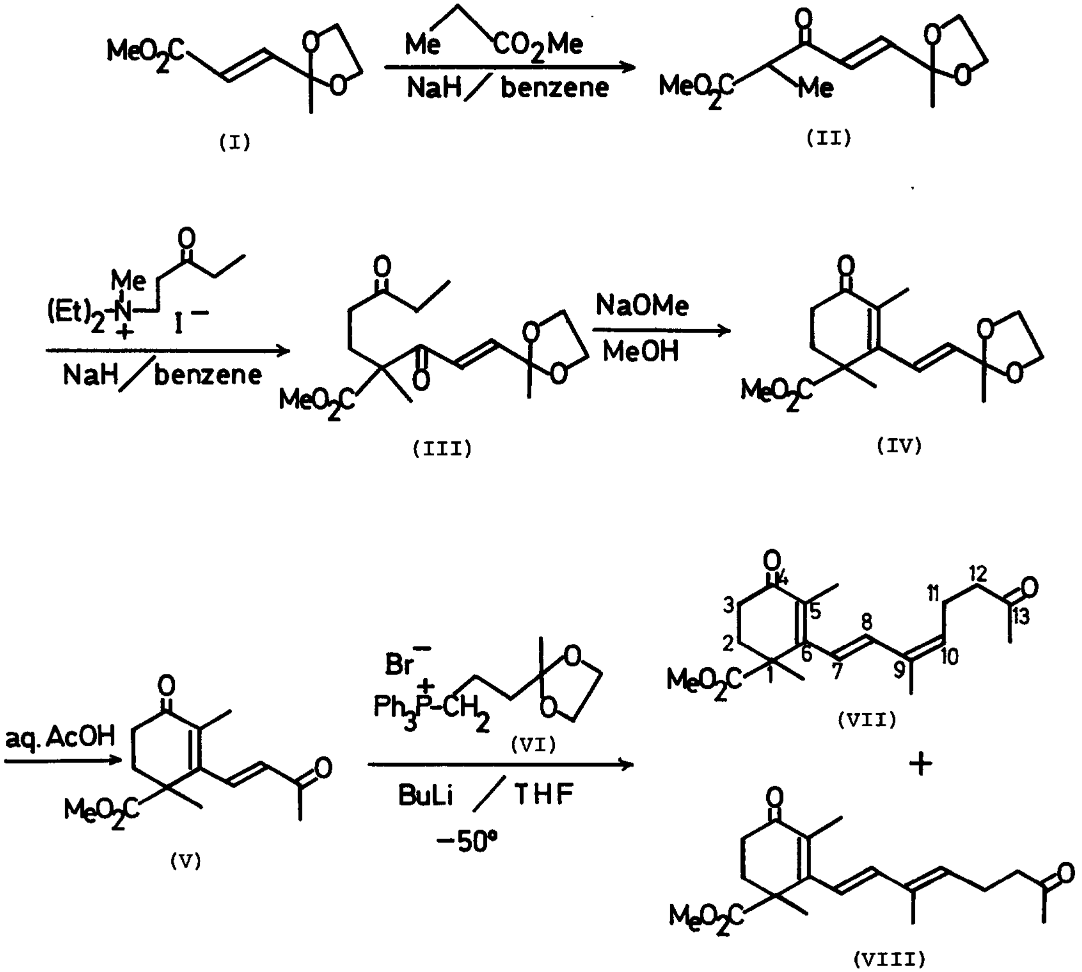
IR($CHCl_3$) 1720, 1665, 1600, 1247; UVλmax(CH_2Cl_2) 327nm (14,800); NMR($CDCl_3$)δ 1.53(3H,s), 1.84(3H,s), 1.94(3H,s), 2.14(3H,s), 3.69(3H,s), 5.50 (1H,m), 6.36(1H,d,J=16Hz), 6.84(1H,d,J=16Hz); MS 318 (M^+).

Methyl 9-trans trisporate B (VIII)

IR($CHCl_3$) 1720, 1665, 1597, 1247; UVλmax(CH_2Cl_2) 322nm (12,400); NMR($CDCl_3$)δ 1.50(3H,s), 1.80(3H,s), 1.93(3H,s), 2.14(3H,s), 3.68(3H,s), 5.53 (1H,m), 6.30(2H,s),; MS 318 (M^+).

Methyl 9-cis trisporate C (IX)

IR($CHCl_3$) 3520, 1722, 1710sh, 1663, 1597, 1254; UVλmax(CH_2Cl_2) 327nm (11,300); MS 320 (M^+).



(I)

(II)

(III)

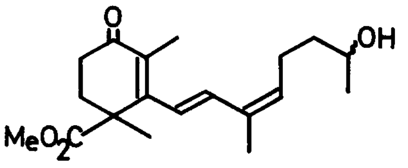
(IV)

(V)

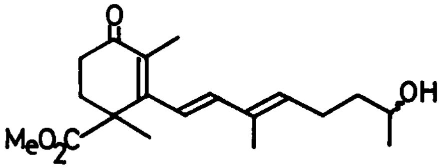
(VI)

(VII)

(VIII)



(IX)



(X)

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