Fungal Sex Hormones. The Synthesis of (±)-7(*t*),9(*t*)-Trisporic Acid B Methyl Ester. The Stereochemistry at C-9 of the Trisporic Acids

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Summary The synthesis of (±)-7(*t*),9(*t*)-trisporic acid B methyl ester utilizing a novel phosphonate reagent as an acetoacetic ester synthon is described and the earlier stereochemical assignments at C-9 for the isomeric trisporic C acids are revised.

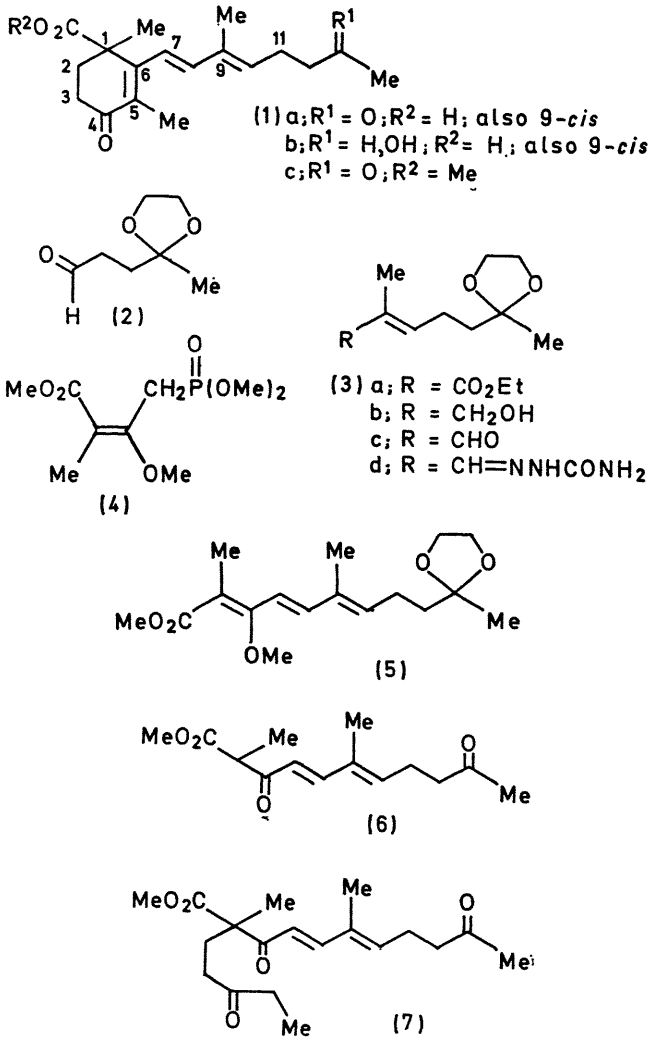
THE trisporic acids B and C (Ia,b), the principal sexual hormones of the fungi *Mucor mucedo* and *Blakeslea trispora*, are secreted by mated strains of the fungi and induce the production of zygophores in unmated cultures.[1] We describe a synthesis of (±)-7(*t*),9(*t*)-trisporic acid B methyl ester by sequential coupling of a C_8 and two C_5 units to yield the appropriately functionalized linear C_{18} triketone (**7**) which is cyclized to (**1c**) by the action of base.

Reaction of 4-cycloethylenedioxypentanal [(**2**); liquid; semicarbazone m.p. 146—147°],† prepared by reduction ($LiAlH_4$) of ethyl laevulinate cycloethylene acetal to the alcohol followed by oxidation (CrO_3–bipy)[2] with 1·2 equiv. of ethoxycarbonylethylidenetriphenylphosphorane (monoglyme, 83°) yielded the liquid *trans*-α,β-unsaturated ester [(**3a**); 61%].

Reduction ($LiAlH_4$) of (**3a**) afforded the alcohol (**3b**) which was oxidized (MnO_2, CH_2Cl_2, 23°) to the *trans*-α,β-unsaturated aldehyde [(**3c**); liquid; 85%; semicarbazone (**3d**) m.p. 187—188°].‡

Addition of a masked β-keto-ester function to the aldehyde (**3c**) was achieved by condensation with the anion of diethyl *cis*-3-methoxycarbonyl-2-methylprop-2-enylphosphonate (**4**) (tetrahydrofuran, 23°) an acetoacetic ester synthon,[4] to furnish the all-*trans*-trienyl ester [(**5**); oil; n.m.r. ($CDCl_3$) δ 5·69 (broadened t, 7-H), 6·66 (d, J_{trans} 16 Hz, 5-H), 7·12 (d, J_{trans} 16 Hz, 4-H)]. The phosphonate [(**4**); n_D^{25} 1·4710] was prepared by bromination (*N*-bromosuccinimide) of methyl 3-methoxy-2-methyl-*cis*-crotonate, obtained from ethyl methylacetoacetate by the procedure of Jones *et al.*,[5] to the unstable γ-bromo-compound followed by heating with trimethyl phosphite (150°; 15 min).

Hydrolysis (HCl, MeOH, 23°) of (**5**) produced the β-keto-ester [(**6**); oil; 95%; λ_{max} (MeOH) 285 nm (ε 21,800); n.m.r. ($CDCl_3$) δ 5·95 (m, 7-H), 6·25 (d, J_{trans} 16 Hz, 5-H), 7·33 (d, J_{trans} 16 Hz, 4-H)] which smoothly underwent Michael addition with ethyl vinyl ketone (0·1 equiv. $KOBu^t$, tetrahydrofuran, 23°) to yield triketo-ester [(**7**); oil; 60%; λ_{max} (MeOH) 287 nm (ε 20,100); n.m.r. ($CDCl_3$)δ 5·90 (m, 11-H), 6·17 and 7·33 (pair of d, J_{trans} 16 Hz, 8- and 9-H)]. Base treatment (KOMe, dry MeOH, 10 h at 23°) of ester (**7**), followed by purification by preparative t.l.c. [ether–hexane (3 : 2)] under N_2 in the dark furnished in 10% yield (±)-7(*t*),9(*t*)-trisporic acid B methyl ester§ as an oil [(**1c**); λ_{max} (MeOH) 229 and 322 nm (ε 8600 and 17,400); ν_{max} (film) 2950, 1850, 1730, 1350, and 1250 cm^{-1}; n.m.r. ($CDCl_3$) δ 1·50 (s, 1-CH_3), 1·80 (broad s, 9-CH_3), 1·93 (s, 5-CH_3), 2·14 (s, 14-H), 3·69 (s, ester-CH_3), 5·55 (broad t, 10-H), 6·29 (s, 7- and 8-H). Mass spectrum 318 (M^+)].



Before proceeding with a comparison of synthetic (**1c**) with the natural product, the evidence for the stereochemistry allocated to the 9-*cis*- and 9-*trans*-trisporic C acids was re-examined. Reschke[1c] has concluded on the basis of u.v. spectral data that the methyl ester of natural trisporic acid C which exhibits olefinic proton resonance doublets centred at δ 6·23 and 6·36, *J* 16 Hz, has the 9-*cis*-stereochemistry, whereas the methyl ester of the

† Satisfactory elemental analyses and/or mass spectral data were obtained for all new compounds.

‡ Comparison of the n.m.r. spectrum of aldehyde (**3c**) with the published spectra of *cis*- and *trans*-2-methylpent-2-enal confirmed the *trans*-arrangement of the trisubstituted double bond in (**3c**). See ref. 3.

§ The *trans*-assignment for the 7- and 9-double bonds of synthetic (**1c**) is predicated on the assumption that a *trans* → *cis*-isomerization of the double bonds has not occurred in the various synthetic intermediates elaborated from the *trans*-aldehyde (**3c**).

isomeric natural product which exhibits olefinic proton resonance doublets at δ 6·41 and 6·84, J 16·5 Hz, has the 9-*trans*-stereochemistry. However, the 8-H of the 7(*t*),9(*c*)-isomer is deshielded by the 11-methylene group and hence the 8-H signal should appear downfield relative to the 8-H of the 7(*t*),9(*t*)-isomer.[6] Therefore, the trisporic C acid exhibiting the pair of doublets at lower field is assigned as the *cis*-isomer and the previous stereochemical assignments allocated to the trisporic C acids isomeric at C-9 should be reversed.

Jones oxidation of a freshly purified sample of the methyl ester of natural 7(*t*),9(*t*)-trisporic acid C [n.m.r. ($CDCl_3$) δ 6·23 and 6·36 (pair of d, J_{trans} 16 Hz, 7- and 8-H)] furnished trisporic acid B methyl ester, which was identical by t.l.c., i.r., and n.m.r. spectral comparisons with the synthetic product (**1c**). Identity of (**1c**) with naturally derived 7(*t*),9(*t*)-trisporic acid B methyl ester was also confirmed by t.l.c. and mass spectral comparisons kindly performed by Dr. J. D. Bu'Lock.

Synthetic trisporic acid B methyl ester showed an activity in the same range as natural trisporic acid B from *Blakeslea trispora* in eliciting zygophore production in unmated cultures of *Mucor mucedo*.

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