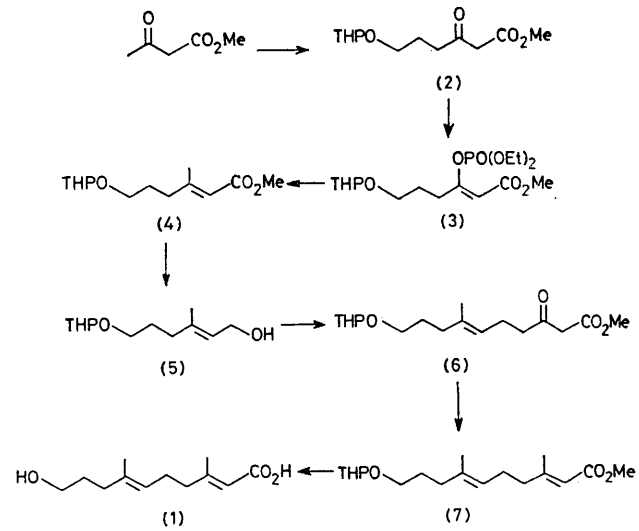
Synthesis of the Butterfly Compound (*E,E*)-10-Hydroxy-3,7-dimethyldeca-2,6-dienoic Acid

By F. W. SUM and LARRY WEILER*
(*Department of Chemistry, University of British Columbia, Vancouver, B.C., Canada* V6T 1W5)

Summary The title compound was synthesized by alkylation of the dianion of methyl acetoacetate, and lithium dimethylcuprate addition to the enol phosphate of the alkylated β-keto esters (**2**) and (**6**) to produce the trisubstituted αβ-unsaturated esters (**4**) and (**7**) in a stereoselective manner.

THE male monarch butterfly produces a number of interesting compounds, one of which is the hydroxy acid (**1**).[1] Here we report a synthesis of compound (**1**) (Scheme) which involves a new stereoselective method to synthesize αβ-unsaturated esters. The dianion of methyl acetoacetate[2] (2 equiv.) reacted with the tetrahydropyranyl ether of 2-bromoethanol (1 equiv.) to give the γ-alkylated product (**2**)† in 75% yield. The β-keto ester (**2**) was then converted into the enol diethyl phosphate (**3**) in quantitative yield on treatment with sodium hydride and diethyl phosphorochloride in ether.[3] From chromatographic and spectroscopic data it was apparent that (**3**) was greater than 95% one isomer. The (*Z*) stereochemistry of (**3**) was assigned by comparison of its n.m.r. spectrum [δ 5·33 for the vinyl hydrogen in (**3**)] with spectra of the (*E*) and (*Z*) enol dimethyl phosphates of methyl acetoacetate.[4]



THP = tetrahydropyran-2-yl

SCHEME

† All new compounds had spectroscopic data consistent with the assigned structures.

In the key reaction, the enol phosphate (**3**) was treated with 2 equiv. of lithium dimethylcuprate in ether at −78 °C to produce the trisubstituted alkene (**4**) in 94% yield. V.p.c. analysis of the reaction product indicated that it was >90% one compound. We assigned the (*E*) stereochemistry to this product from its n.m.r. spectrum, in particular, the chemical shift of the vinyl methyl group at δ 2·13.[5] We have studied this reaction with a range of enol phosphates from β-keto esters and primary dialkylcuprates, and invariably the major product was the one arising from substitution of the phosphate by the dialkylcuprate with retention of geometry.[6] Finally, the conversion of (**4**) into the (*E*,*E*) product (**1**) confirms the stereochemical assignment of (**4**) and the stereoselectivity in the dialkylcuprate displacement.

The ester (**4**) was reduced with lithium aluminium hydride, to produce the alcohol (**5**) in >90% yield. This allylic alcohol was converted into the corresponding bromide (LiBr, Bu^nLi, and $MeSO_2Cl$)[7] which then reacted directly with 3 equiv. of the dianion of methyl acetoacetate[2] to produce the alkylated product (**6**) in 70% yield from (**5**). Repetition of the enol phosphate formation and lithium dimethylcuprate coupling sequence gave the dienoic ester (**7**) in 92% yield. This ester was hydrolysed (aqueous base) and deprotected (aqueous acid) to yield the desired butterfly compound (**1**) in >90% yield. In addition the tetrahydropyranyl ether in (**7**) was cleaved to produce the methyl ester of (**1**) in 98% yield. This material was found to have identical spectroscopic and chromatographic properties to those of an authentic sample.[1] In addition v.p.c. analysis of the methyl ester of (**1**) prepared from (**7**) indicated that it was >95% of the desired (*E*,*E*) isomer. Hence the enol phosphate–dimethylcuprate sequence proceeds with at least this stereoselectivity to generate the trisubstituted double bonds in (**1**). When this sequence is combined with our previously developed methods to add electrophiles to the γ-carbon of β-keto esters,[1,8] we have an efficient and stereoselective method to introduce isoprene units in a synthetic sequence.[9]

We are grateful to Dr. C. Semmelhack and Professor J. Meinwald for the spectra and a sample of the methyl ester of (**1**), and to the National Research Council of Canada and the University of British Columbia for financial support of this work.

(*Received, 1st August* 1978; *Com.* 838.)

[1] J. Meinwald, A. M. Chalmers, T. E. Pliske, and T. Eisner, *Tetrahedron Letters*, 1968, 4893.
[2] S. N. Huckin and L. Weiler, *J. Amer. Chem. Soc.*, 1974, **96**, 1082.
[3] R. E. Ireland and G. Pfister, *Tetrahedron Letters*, 1969, 2149.
[4] T. R. Fukoto E. O. Hornig R. L. Metcalf, and M. Y. Winton, *J. Org. Chem.*, 1961, **26**, 4620; J. E. Thompson, *ibid.*, 1965, **30**, 4276.
[5] For the (*E*) and (*Z*) alcohols corresponding to (**4**) see: T. A. Bryson, *Tetrahedron Letters*, 1973, 4923.
[6] Enol phosphates of cyclic ketones are known to couple with dialkylcuprates, but there is no report of the stereoselectivity in these examples. L. Blaszezak, J. Winkler, and S. O'Kuhn, *Tetrahedron Letters*, 1976, 4405.
[7] E. J. Corey, H. Tamamoto, D. K. Hernon, and K. Achiwa, *J. Amer. Chem. Soc.*, 1970, **92**, 6635.
[8] S. N. Huckin and L. Weiler, *Canad. J. Chem.*, 1974, **52**, 1343 and 2157; P. E. Sum and L. Weiler, *J.C.S. Chem. Comm.*, 1977, **91**; *Canad. J. Chem.*, 1977, **55**, 996.
[9] For another solution to this problem using enol acetates of β-keto esters see: C. P. Casey and D. E. Marten, *Synth.Comm.*, 1973, **3**, 321; C. P. Casey and D. F. Marten, *Tetrahedron Letters*, 1974, 925; C. Ouannes and Y. Langlois, *ibid.*, 1975, 3461. Unfortunately the acid conditions required to prepare the enol acetates were not compatible with our sequence.