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A SIMPLE SYNTHETIC ROUTE TO SUBSTITUTED CYCLOPENTENOLONES

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Abstract

Preparation of novel cyclopent-3-ene-1,2-dione dimers from γ-substituted crotonate esters and dimethyl oxalate by vinylogous double Claisen condensations has given access to a series of polyfunctional cyclopentane derivatives potentially useful in synthesis.

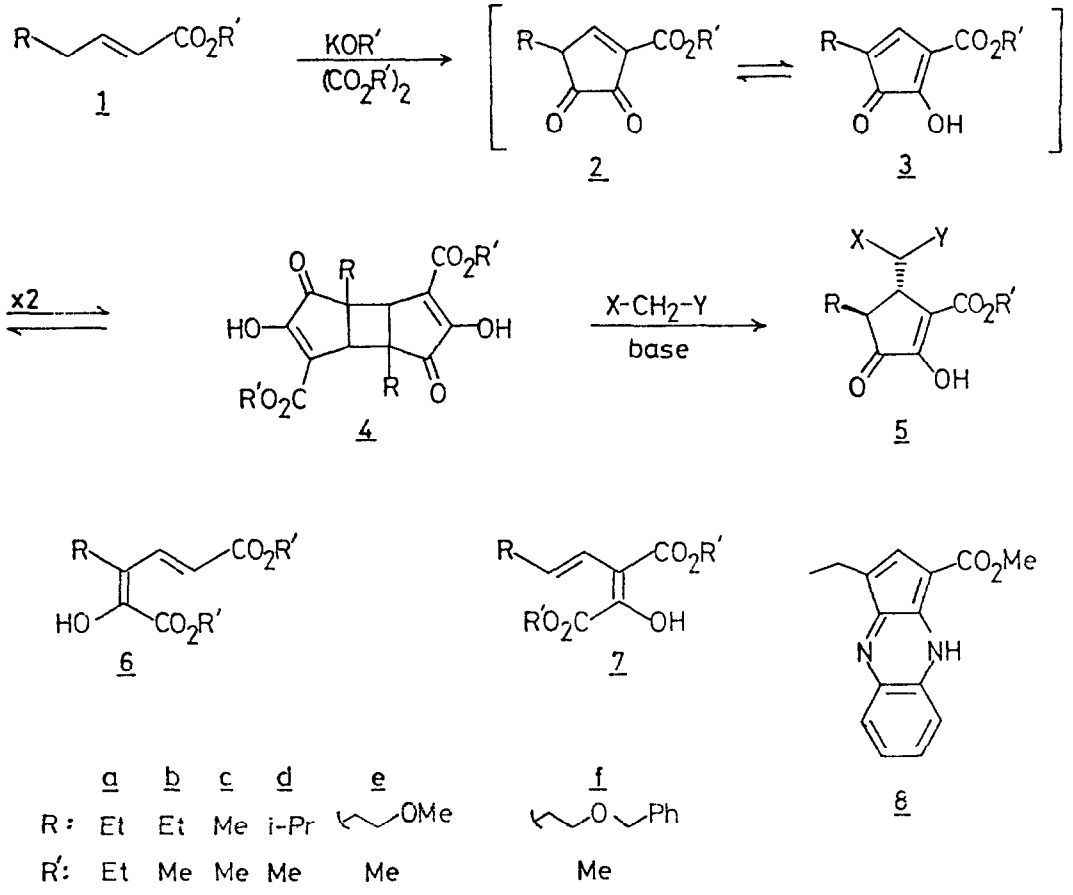
As key intermediates in projected syntheses of various natural products, including iridoids and prostanoids, we required a series of cyclopentenolones of general structure 5, which in principle could be obtained by Michael addition to the unknown cyclopent-3-ene-1,2-dione derivative 2 . One would not expect structure 2 to be particularly stable because unfavourable dipole-dipole interactions in the cyclic α-diketone could not be relieved by mono-enolisation in the usual manner, since this would result in an anti-aromatic cyclopentadienolone structure (3). A similar argument rationalises the well-known lack of enolisation in cyclopent-4-ene-1,3-dione[1]. Conversely, however, one would predict enhanced reactivity in 2 towards nucleophilic addition that would enable mono-enolisation to occur. The few syntheses of cyclopent-3-ene-1,2-diones that have been reported[2-4] generally involve several steps, proceeding in low overall yield, and perhaps for this reason, their use in synthesis has essentially been limited to acting as dienophiles[2].

Early work by Fried and Elderfield[5] showed that ethoxide catalysed Claisen condensations of various αβ-unsaturated esters (1) with diethyl oxalate afforded, depending on the nature of R, either γ- (6) or α- (7) substituted monocondensation products. We envisaged that in either case prolonged reaction of the initially formed salt might well result in cyclisation *via* a second vinylogous Claisen condensation to give the cyclopent-enedione structure 2. In the event, reaction of methyl 2-hexenoate with dimethyl oxalate

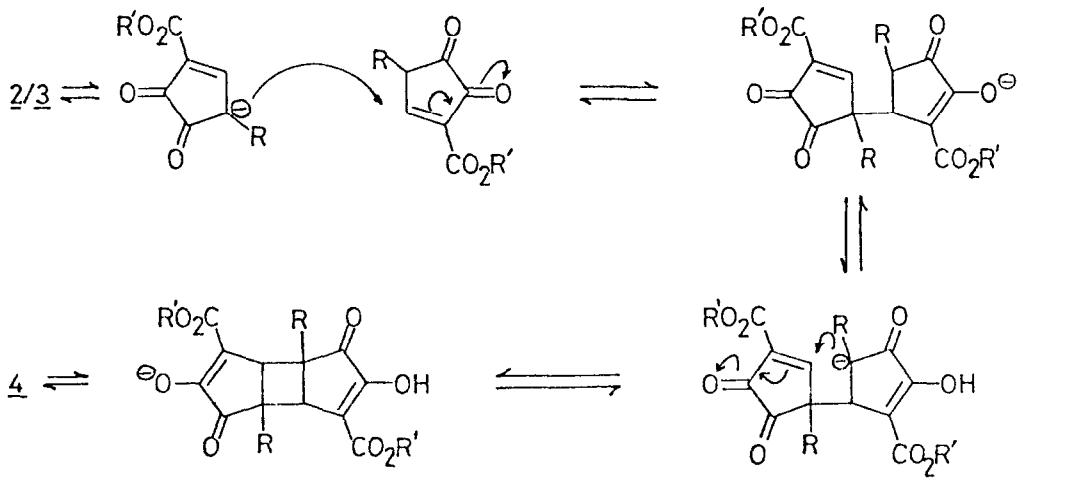
and KOMe (2 mols) in refluxing ether for 10 hours and subsequent acidification of the precipitate afforded in *ca.* 50% yield a crystalline product, m.p. 156-9° [λ_{max} 275 nm (ε 14,300) shifting to 325 nm with alkali]. Its elemental analysis corresponded to structure 2b and with o-phenylenediamine it gave a purple quinoxaline derivative, m.p. 167-170°. However, an i.r. band at 3340 cm^{-1} and an n.m.r. signal at δ9.0 exchanged by D_2O indicated the presence of an enol, which was confirmed by formation of a methyl ether, m.p. 125-8°, with diazomethane. Measurement of the molecular mass by the osmometric method and by mass spectrometry established that the product was actually a dimer of 2b or 3b. From the simplicity of the n.m.r. spectrum [δ($CDCl_3$) 220 MHz: 0.83(6H,t), 1.76(2H,m), 2.18(2H,m), 3.04(2H,s), 3.91(6H,s), 9.00(2H,s)] the dimer was evidently symmetrical, and consideration of its likely mode of formation (Scheme 2) lead us to propose the cyclobutane structure 4b. In similar fashion a range of analogous dimers (4a,c-f) have been prepared in yields of 20-50%.

An important feature of the reactivity of the dimers was that they were in equilibrium with a monomeric species (2 or its equivalent) even though such could not be detected by u.v. or n.m.r. spectroscopy. This was established by mixing equimolar solutions of 4b and 4c together in the dark and observing the gradual formation of an unsymmetrical dimer containing both C-methyl and C-ethyl groups: the last was detectable after an hour, its proportion increasing to *ca.* 50% after 48 hours. Since there was no exchange with the corresponding methyl ethers the most likely mechanism is reversal of the intramolecular and intermolecular Michael additions of Scheme 2, although more complex processes involving retro-Dieckmann reactions cannot be excluded. Interestingly the n.m.r. [δ(CF_3CO_2H): 1.48(3H,t), 3.01(2H,q), 4.13(3H,s), 8.0-8.8(4H,m), 8.86(1H,s)] and mass [M^+254.1059] spectra of the quinoxaline derivative of 4b showed that it was a monomer (8).

Nevertheless, whatever the mechanism, it seemed feasible to intercept a monomeric species by Michael addition of alternative stabilised enolate type nucleophiles and achieve the original objective. Indeed this proved to be the case; for example, treatment of 4b and a two-fold excess of dimethyl malonate with KOMe in refluxing methanol for 4 hours

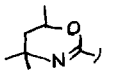


Scheme 1



Scheme 2

afforded 5b(X=Y=CO_2Me) in essentially quantitative yield. Furthermore, as anticipated, the addition was completely stereoselective, giving only *trans* geometry. It was not possible to demonstrate this by n.m.r. since coupling constants of *cis* and *trans* vicinal protons on five membered rings are not sufficiently differentiated, but an X-ray structure determination on a derivative of 5b has *inter alia* confirmed the expected stereochemistry[6].

A variety of analogues of 5 have now been prepared (X=CO_2Me, SO_2Et, CN; Y=  CN, $COCH_3$, etc.) in good to excellent yield, demonstrating that this is a general reaction of the dimers. We are currently exploring the potential of these versatile polyfunctional intermediates in several syntheses of natural products and related compounds.

Acknowledgements

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