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REGIOSELECTIVE HYDROXYLATION OF α,β-UNSATURATED ESTERS[1]

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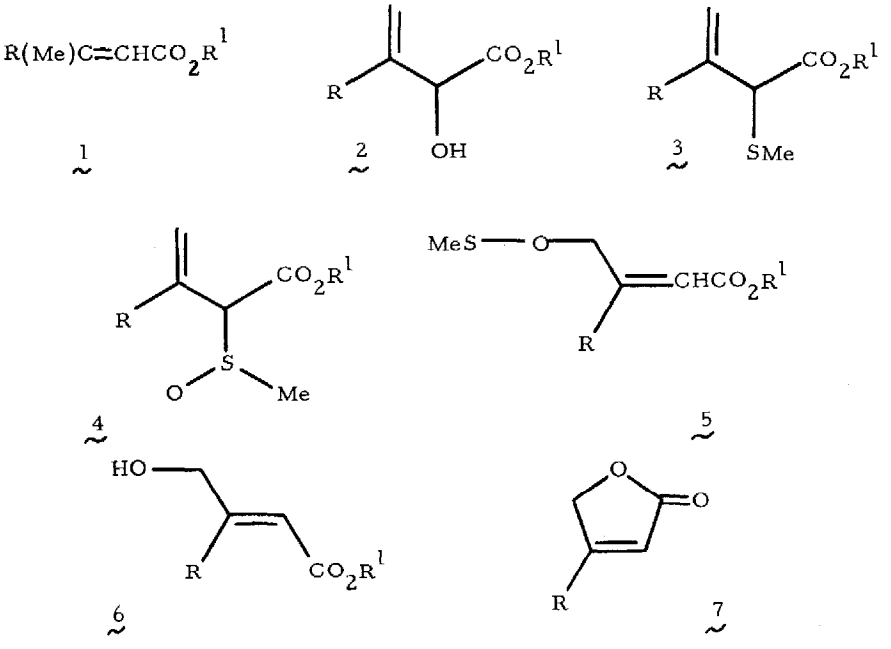
Regiospecific introduction of substituents at the alpha or gamma position of α,β-unsaturated carbonyl compounds by reaction of the corresponding dienolate anions with electrophiles is an important but still poorly resolved problem. While alkylation generally occurs at the alpha carbon,[2] reaction at the gamma position is observed in condensations with carbonyl groups.[3] Attempts to overcome the kinetic preference for the alpha position in alkylation reactions have recently been reported.[4] In connection with synthesis and metabolic study of acyclic terpenes, we required a method for gamma hydroxylation of α,β-unsaturated esters such as ethyl farnesoate (1b). Unable to find literature procedures for this transformation, we investigated the reaction of dienolate anions with electrophilic oxygen reagents. Unfortunately the dienolate anion from methyl 3-methyl-2-butenoate (1a) reacted with benzoyl peroxide (THF, -78°C) to give methyl 2-benzoyloxy-3-methyl-3-butenoate in 70% yield,[5] while reaction of the dienolate anion from ethyl farnesoate with molecular oxygen (THF, 0°C), followed by reduction with stannous chloride, gave 2b in 85% yield.[6] The high selectivity for the alpha position encountered in these reactions led us to develop the general complementary sequence presented here which utilizes the reactivity of the alpha carbon to carry out regiospecific gamma hydroxylation.

The dienolate anions from methyl 3-methyl-2-butenoate (1a) and ethyl farnesoate (1b), generated by treatment at -78°C with one equivalent of 2,2,6,6-tetramethylpiperidide in ether or THF,[7] reacted with methyl methanethiosulfonate[8] to give in high yield the α-thiomethylated structures 3a and 3b, respectively.[10] Reaction of 3a and 3b with $NaIO_4$ ($MeOH-H_2O$,0°C) gave sulfoxides 4a and 4b in quantitative yield. Elegant work by Mislow and coworkers has demonstrated that allylic sulfoxides can undergo facile [2,3] sigmatropic rearrangement to isomeric

allylic sulfenates.[11] Although carbonyl substituted allylic sulfoxides have not been studied, these are undoubtedly in equilibrium with the isomeric sulfenates. The nmr spectra of crude 4a and 4b, except for minor peaks, correspond to the sulfoxide structures, indicating that these are favored in the equilibrium. Cleavage of the oxygen-sulfur bond in simple allylic sulfenates has been accomplished with a variety of reagents, including phosphites, dialkylamines, and sulfides.[12] Attempts to employ these reagents in the present situation were frustrated by the enhanced acidity of the α-proton in 4 and the Michael acceptor properties of 5, 6, and 7. We have found, however, that sulfenate bond scission can be achieved, in the presence of reactive centers, merely by stirring 4 at 50° -60°C in 0.1M (pH 7.0) phosphate buffer.[13] Under these conditions, 4a gives 6a (65%)[14] and 7a (7%),[14] while 4b yields 6b (50%) and 7b (11%). The lactones, formed in situ from the cis gamma hydroxylated esters, are easily separated from the trans isomers 6a and 6b. A clear preference is evident for formation of the trans products, although increasing steric bulk enhances lactone formation. The synthesis of 6b and 7a, a typical procedure, is outlined below.



a) R, R^1 = Me

b) R= $(Me)_2C{=}CHCH_2CH_2(Me)C{=}CHCH_2CH_2$ R^1= Et

Ethyl farnesoate in ether was added dropwise at -78°C to 1 equiv. of a stirred 0.5-1.0 M ether solution of lithium 2,2,6,6-tetramethylpiperidide. After stirring 30 min at -78°C and 20 min at -20°C, the mixture was recooled to -78°C and 1.1 equiv of methyl methanethiosulfonate in ether was added. The solution was allowed to warm to ambient temperature after stirring 20 min at -78°C. Addition of saturated aqueous NH_4Cl, work up by extraction, and removal of unreacted 1b by bulb-to-bulb distillation gave 3b (90%): ir (film) 1740 cm^{-1}; nmr ($CDCl_3$) 1.28 (t, J = 7 Hz, 3H), 1.60 (s, 6H), 1.66 (s, 3H, MeS), 1.92-2.40 (m, 11H), 3.92 (s, 1H, α-H), 4.20 (q, J = 7 Hz, 2H), and 5.15 ppm (m, 4H); cims m/e 311 (MH^+). Stirring 3b in H_2O-MeOH at 0°C with 1.4 equiv $NaIO_4$ for 48 hr gave, on removal of MeOH and extraction with CH_2Cl_2, the sulfoxide 4b (95-100%). The sulfoxide, without purification, was stirred in 0.1 M phosphate buffer (pH 7.0) at 50°-60°C for 48-60 hr. Extraction and vacuum distillation, or silica gel column chromatography, gave 6b (50%): ir (film) 3450, 1725 cm^{-1}; nmr ($CDCl_3$) 1.26 (t, J = 7 Hz, 3H), 1.60 (s, 6H), 1.69 (s, 3H), 1.90-2.80 (m, 8H), 4.17 (s, 2H), 4.14 (q, J = 7 Hz, 2H), 5.13 (m, 2H), and 5.95 ppm (s, 1H); mass spec. molec. ion m/e 280.2071 (Calc. for $C_{17}H_{28}O_3$, m/e 280.2038); and 7b (21%): ir (film) 1785, 1755 cm^{-1}, nmr ($CDCl_3$) 1.60 (s, 6H), 1.69 (s, 3H), 1.95-2.68 (m, 8H), 4.80 (d, J = 1.5 Hz, 2H), 5.20 (m, 2H), and 6.95 ppm (s, 1H); mass spec. molec. ion m/e 234.1653 (Calc. for $C_{15}H_{22}O_2$, m/e 234.1620).

Alternative methods for gamma hydroxylation of α,β-unsaturated carbonyl compounds are not, to our knowledge, available. The procedure described here, compatible with sensitive functionality, should therefore prove useful in natural product and pharmaceutical synthesis.

References and Notes

(1) This work was supported by grants from the National Institutes of Health (HL-15476) and the Academic Senate, University of California, San Francisco.

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