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THE REGIOSELECTIVE DEPROTONATION OF CONJUGATED ACIDS

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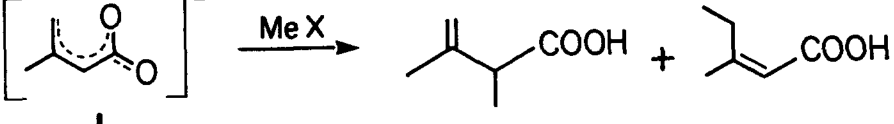
Abstract: A stereoselective synthesis of E and Z C-4 deuterated 3-methyl-2-butenoic acid from methyl acetoacetate is described; the labelled acids are regioselectively deprotonated syn to the acid function under kinetic conditions.

Recently we demonstrated that kinetic deprotonation of conjugated esters occurs regioselectively syn to the ester function.[1] This result was obtained by treatment of deuterium labelled methyl 3-methyl-2-butenoates with lithium diisopropylamide and was ascribed to coordination of lithium ion to the carbonyl oxygens of the resulting dienolates.[2]

Our interest in such reactions has led us to extend our investigations to conjugated acids, where little is known about the products of kinetic deprotonations. Cainelli, et.al.,[3] have demonstrated that under thermodynamic conditions the dianion formed from metalation of 3-methyl-2-butenoic acid exists in several cationotropic forms in equilibrium. This same equilibrium appears to exist upon metalation of 3-methyl-3-butenoic acid.[3] Further, Cainelli and coworkers[4a] have shown that methylation of this 3-methyl-2-butenoic dianion leads to α- and γ-alkylated product, with the γ-methyl derivative formed almost exclusively with the Z configuration. Likewise, reaction of this dianion with aldehydes provides C-4 alkylated products in which the electrophilic attack is kinetically controlled at low temperature.[4b,c]



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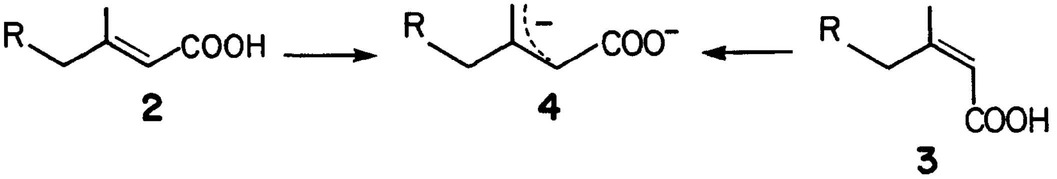
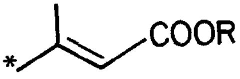
These authors explain their results by implicating a Z geometry in the "allylic" system 1. Z allylic carbanions have been reported[5] to be more stable than the E counterparts, and theoretical treatments give the same result.[6] In contrast to the above results of Cainelli, et.al., methylation of the dianions of crotonic and 2-hexenoic acids in THF has been reported to yield virtually exclusively the α-methyl, unconjugated product.[7]

Katzenellenbogen and Crumrine[8] have found that the isomeric acids 2 and 3 each led to the dianion 4 via preferential deprotonation of the methyl group regardless of olefin geometry. However, their data for the case of 3-methyl-2-butenoic acid (2 or 3, R = H) did not distinguish between competitive deprotonation of the two methyl groups or isomerization of the dienolate between cis and trans forms.



We have directly addressed the question of the kinetic product of γ-deprotonation of 3-methyl-2-butenoic acid. The deuterium-labelled acids 5a and 6a were synthesized and the products of the kinetic deprotonation of their dicyclohexylammonium salts were analyzed by a combination of ^1H- and ^2H-NMR spectroscopy.



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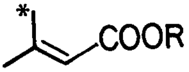

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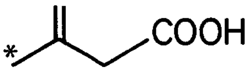
a, $R = H$
b, $R = CH_3$
c, $R = H_2N(c\text{-}C_6H_{11})_2^+$

Methyl esters 5b and 6b were prepared as previously reported[1] using our method of stereospecific synthesis of alkenes from β-keto esters.[9] Overall yield of 5b from C-4 deuterated methylacetoacetate[10] was 44%, and of 6b was 35%. These esters were then converted into the corresponding acids in *ca.* 70% yield using K_2CO_3 in refluxing aqueous methanol. Each acid was subsequently converted in 88% yield to its dicyclohexylammonium salt for the deprotonation studies.

The extent of deuteration of acids 5a (67% deuterated) and 6a (57% deuterated) was estimated from ^1H-NMR data and found to be somewhat less than that of the labelled methyl acetoacetate (73% deuterated). ^2H-NMR analysis of acid 5a indicates *ca.* 97% of ^2H in the anti methyl group. Similar analysis of acid 6a shows *ca.* 76% of ^2H in the syn methyl group; it is not clear whether this decreased labelling specificity arises from lack of regioselectivity in formation of the anti enol phosphate, in the Grignard coupling step, or in the ester hydrolysis step, though we consider the second suggestion most likely.

Salt 5c was suspended in THF containing 1.1 eq HMPA at -78° and 2.2 eq of n-butyllithium in hexane was added. The resulting solution was allowed to warm to room temperature and quenched with water after 45 min from the time of base addition. Standard workup gave a mixture of deconjugated acid 7 and conjugated isomer 5a in 86% distilled yield.



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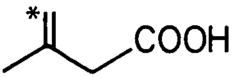

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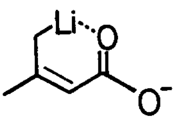
The proportion of 7 to 5a was 76:24 from ^{1}H-NMR data. ^{2}H-NMR analysis of this mixture revealed ca. 6% of the total deuterium in the molecule was in the vinyl signal at δ4.9 for acid 7, and 94% of the total deuterium in the vinyl methyl of 7. We found no evidence for significant deuteration in the syn methyl group for recovered 5a.

Similar treatment of salt 6c gave a mixture of deconjugated acid 8 and conjugated isomer 6a in 77-86% distilled yield, with the 8:6a ratio estimated at 75:25 by ^{1}H-NMR data. ^{2}H-NMR analysis of this mixture showed a substantial signal at δ4.9 for vinyl deuterium in 8, in distinct contrast to the above case. Comparison of the ^{1}H and ^{2}H spectra of this mixture revealed virtually identical extent of deuteration (ca. 56% ^{2}H) of the syn methyl group in 6a and the vinyl group in 8.

Finally, treatment of unlabelled 3-methyl-2-butenoic acid dicyclohexylammonium salt under the same conditions as above, followed by D_2O quench, led to a mixture of deconjugated and conjugated acids (ca. 88:12) in which deuterium incorporation in the conjugated isomer appeared by ^{1}H-NMR data to be nearly exclusively in the syn methyl group. The acid 6 in this quench has 0.8 deuterium in the syn methyl and the unconjugated acid 8 has .7-1 deuterium at the methylene carbon only.

These results prove that the 3-methyl-2-butenoic acid salt is kinetically deprotonated syn to the carboxylate function. Therefore, the controlling regiochemical influence in this reaction would appear to be lithium ion coordination[2] (9) in the dienolate rather than anion-anion repulsion (10).[11,12]



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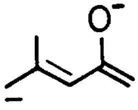

10

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