

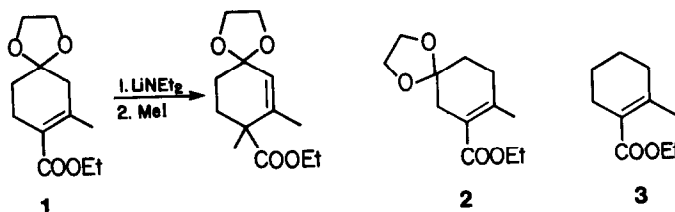
THE REGIOSELECTIVE DEPROTONATION OF CONJUGATED ESTERS

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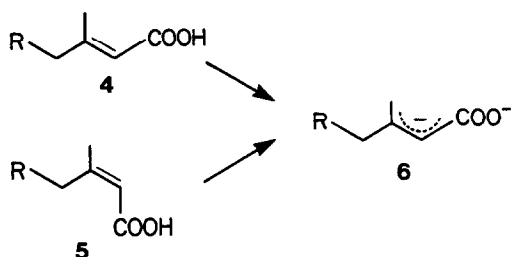
Abstract: A stereospecific synthesis of the E and Z esters of C-4 deuterated 3-methyl-2-butenic acid from methyl acetoacetate is reported; the labelled methyl 3-methyl-2-butenote is regioselectively deprotonated syn to the ester group under kinetic conditions.

Little is known about the regioselectivity of deprotonation of conjugated esters. White and Lung found that deprotonation of the ester 1 occurred at the methylene group trans to the ester rather than the methyl group<sup>1</sup>. However, the ketal oxygens may have had an important



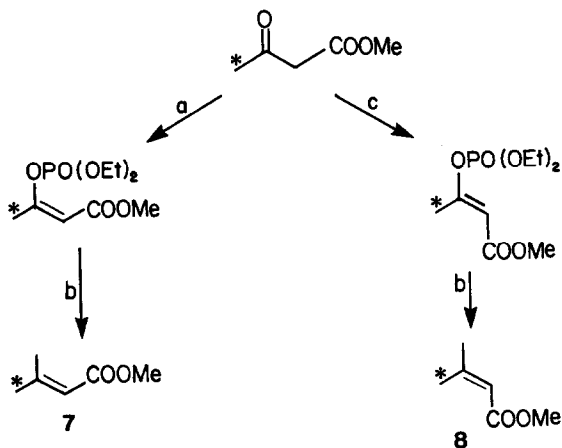
directing effect in this metallation. Indeed, Gesson et al. found that this reaction could proceed through the dianion<sup>2</sup>. Furthermore they found that deprotonation of the esters 2 and 3 occurred exclusively at the methyl group cis to the ester, and these deprotonations appeared to be kinetic<sup>2</sup>. In the case of deprotonation of ketones it is well known that a methyl group is kinetically deprotonated by a lithium base faster than a methylene<sup>3</sup>. Thus it was difficult to pinpoint the source of the regioselectivity in these ester deprotonations.

Katzenellenbogen and Crumine have shown that ethyl 2E-3-methylhexenoate is deprotonated at the methyl group under kinetic conditions<sup>4</sup>. In a study of the two isomeric acids, 4 and 5, these same authors found that each acid led to the dianion 6 via a preferential deprotonation of the methyl group regardless of the olefin geometry<sup>4b</sup>.



To extend the use of the conjugated esters in organic synthesis it would be useful to be able to control the regiochemistry of deprotonation. Towards this end we have synthesized the labelled esters 7 and 8 to probe this question; we chose to label the esters with deuterium starting from C-4 deuterated methyl acetoacetate<sup>5</sup>.

The esters 7 and 8 were prepared using the method we had developed for the stereospecific synthesis of alkenes from  $\beta$ -keto esters<sup>6</sup> as shown in Figure 1. Methyl acetoacetate was converted into the Z-enol phosphate which was then coupled with methylmagnesium chloride in the presence of methylcopper to give the E-ester 7 in 60-65% yield. The E-enol phosphate was prepared by treating methyl acetoacetate with triethylamine and a catalytic amount of 4-dimethylaminopyridine in HMPA to give the E-enolate which was trapped with diethyl phosphorochloridate. Treatment of this enol phosphate as above gave the Z-ester 8 in 40-50% yield.

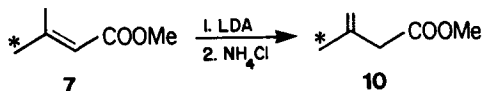


\* = deuterium label

<sup>a</sup> NaH, Et<sub>2</sub>O, then ClPO(OEt)<sub>2</sub>; <sup>b</sup> MeMgCl, MeCu, THF, -30°; <sup>c</sup> Et<sub>3</sub>N, DMAP, HMPA, then ClPO(OEt)<sub>2</sub>

The extent of deuteration of esters 7 and 8 was determined by  $^1\text{H-NMR}$  and found to be identical to that of the starting methyl acetoacetate, i.e. 40% deuteration.  $^2\text{H-NMR}$  of 7 and 8 showed that 7 had > 90% of deuterium in the methyl group trans to the ester<sup>7</sup> and 8 had > 90% of deuterium in the methyl group cis to the ester<sup>7</sup>.

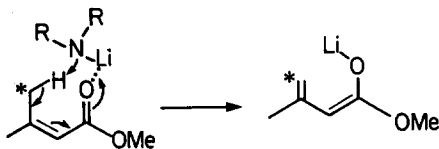
Ester 7 was added to 1.1 equivalents of lithium diisopropyl amide in THF-hexane-HMPA at  $-78^\circ\text{C}$ . The reaction was stirred at  $-78^\circ\text{C}$  for 30 min, then added to a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  at  $0^\circ$ . A standard workup gave a mixture of the deconjugated isomer 10 and starting conjugated ester in 70-75% distilled yield. The amount of deconjugated isomer was 60-65% and appeared to be independent of starting material 7 or 8. The  $^1\text{H-NMR}$  of 10 from 7 gave a ratio of C-4 vinyl: C-2 methylene of 1.0. But more importantly the  $^2\text{H-NMR}$  of 10 showed no vinyl deuterium and only deuterium in the methyl group of 10. The recovered 7 was deuterated exclusively at the methyl group trans to the ester.



When the ester 8 was subjected to identical conditions, the  $^1\text{H-NMR}$  of 10 from 8 showed that the ratio of methyl: C-2 methylene was 0.67. The  $^2\text{H-NMR}$  of 10 showed a large peak at  $\delta$  4.8 (the two vinyl deuterium could not be resolved at 12.3 MHz).

These results prove that methyl 3-methyl-2-butenoate is kinetically deprotonated cis to the ester. Presumably the regioselective formation of this enolate is controlled by coordination of the lithium to the carbonyl oxygen<sup>8</sup>.

The ratio of C-4 vinyl protons to C-2 methylene in 10 from 8 is 0.49 which indicates that the extent of vinyl deuteration in 10 is 50%. Since the starting ester 8 had 40% deuteration at C-4, it appears that there is a small kinetic preference for loss of a proton in the carbanion forming step<sup>9,10</sup>.



References and Notes

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6. a) Sum, F.W.; Weiler, L. Can. J. Chem., 1979, 57, 1431.  
b) Sum, F.W. Ph.D. Thesis, The University of British Columbia, Vancouver, British Columbia, Canada, 1979.  
c) Barnier, J.P.; Spino, C.; Weiler, L. unpublished results.
7. These estimates of regioselective deuteration are probably conservative since we could not detect any deuterium at  $\delta$  2.15 due to deuteration of the methyl group cis to the ester in 7; nor could we detect any deuterium at  $\delta$  1.88 due to deuteration of the methyl group trans to the ester in 8.
8. This type of coordination has been suggested in the case of enolate formation, see Narula, A.S. Tetrahedron Lett., 1981, 22, 4119.
9. For an example of deuteration retarding enolization, see Jacobs, S.A.; Cortez, C.; Harvey, R.G. J. Chem. Soc. Chem. Commun., 1981, 1215.
10. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this research.

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