γ-Deprotonation of 1-Ethyl-2-methoxycarbonylcyclohexene

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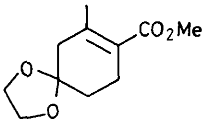
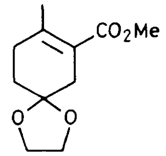
Deuteriation studies reveal that the site of kinetic γ-deprotonation of 1-ethyl-2-methoxycarbonylcyclohexene is delicately balanced between *syn*- and *anti*-methylene groups.

Recently we demonstrated that kinetic deprotonation of conjugated esters[1] and acids[2] occurs regioselectively *syn* to the carboxylate moiety. This regioselectivity was ascribed to co-ordination of lithium to the carbonyl oxygen atoms of the resulting anionic species.[3]

We thought it of interest to extend our investigations to esters of substituted cyclic alkenes. Compound (**1**) has been observed[4] to undergo γ-deprotonation at the ring methylene group *anti* to the ester function, though the acetal oxygen atoms probably influence this reaction,[5] whereas compounds (**2**) and (**3**) are deprotonated kinetically at the *syn* methyl group.[5] We wished to effect kinetic γ-deprotonation of (**4**),[6] in which the reaction would involve a choice of methylene groups and acidity differences between methyl and methylene protons would not be a factor. Compound (**4**) was synthesised by the procedure of Sum[6] from 2-methoxycarbonylcyclohexanone (Scheme 1).[7]



(1)



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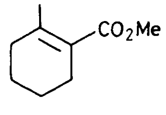
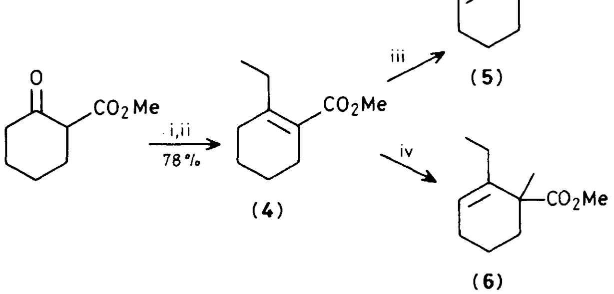
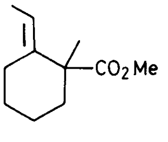


(3)

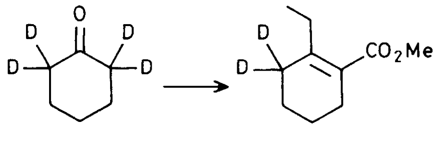
Treatment of (**4**) with lithium di-isopropylamide (LDA) at −78 °C in tetrahydrofuran (THF)–hexane containing hexamethylphosphoric triamide (HMPA) (1.1 equiv.), followed by quenching of the anion with aqueous NH_4Cl, resulted in



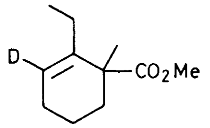
Scheme 1. *Reagents:* i, NaH, Et_2O, then $(EtO)_2POCl$; ii, Et_2CuLi, THF–benzene, −98 °C; iii, LDA, then NH_4Cl: iv, LDA, then MeI.



(7)



(8)



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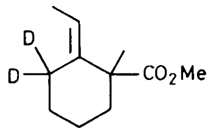

(10)

formation of (**5**), contrary to our expectation.[1] Similarly, quenching with methyl iodide gave (**6**). In contrast, if this latter reaction is carried out without HMPA, anion generation is considerably slower and the product is compound (**7**) (the stereochemistry of the double bond is not established with certainty but probably is as shown).

In light of these results, we wished to explore the mechanism of the origin of the products with endocyclic double bonds. More specifically, we thought it important to examine the possibility that the actual site of proton loss originally was the *syn* methylene but that this initially formed anion rearranges, either intramolecularly *via* a 1,3-H shift (a process with little precedent), or intermolecularly, to produce the anion at the *anti* methylene group. To this end, we synthesized (**8**), beginning with a Claisen condensation of [2,2,6,6-$^2H_4$]cyclohexanone[8] and dimethyl carbonate and subsequent transformations as described for (**4**). The extent of deuteriation of (**8**) is estimated at ~1.6 D from ^{1}H n.m.r. data.

Treatment of (**8**) with LDA with added HMPA at −78 °C resulted in dramatically slower conversion into the anion; quenching this solution with methyl iodide at −78 °C resulted in a mixture of (**9**) and (**10**) in ~40 : 60 ratio as estimated from ^{1}H n.m.r. data. The exocyclic methylene group of (**9**) was shown to contain no deuterium by the lack of splitting by deuterium of the ^{13}C n.m.r. signal for this carbon atom (28.4 p.p.m. relative to $CDCl_3$ at 77.0 p.p.m., 100.6 MHz).

These results demonstrate that the deprotonation of system (**4**) is a finely tuned one. Proton loss occurs *syn* to the ester function as expected,[1] but addition of HMPA tips the balance to favour loss at the *anti*-methylene group. Deuteriation of this *anti*-methylene group then returns preference to the *syn*-methylene group, though only slightly, even in the presence of HMPA. Finally, our deuteriation experiments demonstrate that deprotonation of the *anti*-methylene group occurs directly rather than by rearrangement of a previously formed anion.

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