Diastereoselectivity of Enolate Anion Protonation. H/D Exchange of β-Substituted Ethyl Butanoates in Ethanol-*d*

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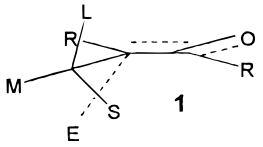
Received July 29, 1996[⊗]

Abstract: The stereochemistry of base-catalyzed H/D exchange on 13 β-substituted ethyl butanoates in ethanol-*d* has been studied in order to analyze the steric and electronic factors which control the diastereoselectivity of electrophilic attack on enolate anions. Electrophilic deuteration of the enolate anion also determines the stereoselectivity of 1,4-conjugate addition of ethanol-*d* to α,β-unsaturated esters. Experimental conditions were selected which rigorously exclude the effects of ion pairing and aggregation. The research showed that stereoelectronic factors generally produce higher stereoselection than steric effects do. Electronegative heteroatom substituents at C-3 produced a 10:1 ratio of the 2*R**,3*R**/2*R**,3*S** 2-deuteriobutanoates. In the most stable transition states for electrophilic attack, these electronegative substituents occupy an antiperiplanar position to the forming C−D bond. Only with a β-*tert*-butyl substituent did steric effects produce high stereoselection, and it fell off rapidly with a decrease in carbon branching. Protonation of acyclic β-ethoxy aldehyde and ketone enolates follows the same diastereoselectivity pattern as the β-ethoxy ester enolate, but protonation of the cyanocarbanion from a β-ethoxy nitrile gives much lower stereoselection.

Enols and enolate anions are intermediates in many important reactions of carbonyl compounds. There is substantial interest in how enzymes activate protons α to the carbonyl groups of esters and carboxylates and how they control the chemistry of enolic species.[3,4] The key position played by enolates in organic synthesis, especially in the Michael and aldol reactions, has led to an enormous wealth of data in recent years. Stereocontrol has been of particular importance, especially with conformationally-mobile acyclic substrates.[5] However, in spite of its fundamental importance, the diastereoselectivity of electrophilic attack on enolate anions is much less well studied than the stereochemistry of nucleophilic attack at the carbonyl group.

Computational chemists have discussed the importance of both steric and stereoelectronic effects in electrophilic reactions of carbon−carbon double bonds.[6−8] Much of the theoretical work on the stereochemistry of electrophilic attack on enolates derives from the wider understanding of nucleophilic attack at the carbonyl group. From an experimental viewpoint, Lodge and Heathcock state the problem nicely in their treatment of steric and stereoelectronic effects in the diastereofacial differentiation of nucleophilic additions to chiral aldehydes.[9]

The most frequent interpretation used for stereoselection in the reactions of enolate anions with electrophiles is basically steric in nature. This has been described by Fleming and his co-workers in terms of **1**.[10] Transition state **1** has the approach of the electrophile on the face of the π-bond opposite to the largest group, with the smallest group at the stereogenic center gauche to the π-system. This avoids destabilizing allylic 1,3-interactions between the "inside" gauche group and the groups *syn* to it on the enolate double bond. When the medium group does not occupy the "outside" position, greater A strain is present.



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Studying enolate anion protonation offers a potentially valuable way to analyze the various steric and electronic factors that control the diastereoselectivity of electrophilic attack. Surprisingly few systematic investigations of the stereochemistry of enolate protonation have been reported. Although islands of understanding are available for cyclic[11] and acyclic[10,11] systems, the variable effects of aggregation have been a stumbling block with regard to a fundamental and comprehensive grasp of the steric and electronic factors controlling the stereochemistry.[12−14] Current efforts to sort out equilibria and kinetics when aggregation is a factor should make this less

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1997.

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S0002-7863(96)02631-5 CCC: $14.00

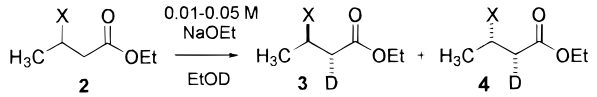

Figure 1. Formation of the 2*R**,3*R** and 2*R**,3*S** diastereomers in base-catalyzed H/D exchange of β-substituted ethyl butanoate derivatives.

difficult in the future.[15] With the current state of knowledge, however, it seems wise to avoid the complexities of the aggregates ubiquitous in nonpolar organic solvents when attempting to study the structural factors that control the diastereoselectivity of the reactions of enolate anions with electrophiles.

We have studied the hydrogen−deuterium exchange of carbonyl compounds in ethanol-*d* under conditions that rigorously avoid the formation of aggregated species. In addition, to minimize the complex conformational effects that so often dominate the stereochemistry of cyclic compounds, we chose to focus our study on a series of ethyl butanoates with substituents at the 3-position (**2**) and their aldehyde and ketone analogs (Figure 1). This has allowed investigation of the intrinsic effect of a neighboring stereogenic center upon the diastereoselectivity of the electrophilic deuteration of enolate anions.

We have presented our initial results in preliminary form and now describe our work in full.[16] To gain further insight into this process, we have also carried out ab initio MO calculations on the transition states for gas-phase protonation of the enolate anion of 3-fluorobutanoic acid by HCN.[17]

Diastereoselectivity of H/D Exchange

Since the prime stereochemical determinant in enolate anion protonation is the influence of the neighboring stereogenic center, we have examined a large number of β-substituents in order to discern the relative importance of their steric and electronic consequences. At the outset, however, it is important to ask if we are indeed looking at the chemistry of solvated enolate anions, without chelation or aggregation interactions. We used ethyl 3-ethoxybutanoate (**2a**) to help answer this question.

First of all, we chose to use ethanol-*d* (EtOD), a relatively polar solvent, and very dilute base concentrations (0.01−0.06 M NaOEt) in our experiments. The use of 0.01 M KOEt with 0.031 M 18-crown-6 produced no change in the stereochemistry. With 0.04 M $(CH_3)_4NOH$ as the basic catalyst, over a range of 16−24% H/D exchange, we obtained the same result (93% **3a**) as with NaOEt and KOEt.

Since the Me_4N^+ cation is unable to coordinate with the enolate anion, it is difficult to believe that ion pairing plays any major role in the diastereoselectivity that we observe, unless the stereochemistry is markedly resistant to aggregation phenomena. That this is not the case was shown by solvent studies.[13] The use of NaOEt as the base and benzene or tetrahydrofuran as the solvent produced lower H/D exchange diastereoselectivities (80% and 72% **3a**, respectively); however, when Me_4NOH was used as the catalyst, and chelation became impossible, the amount of **3a** was 88% and 92%, respectively. Thus, when the effects of ion pairing are reduced, even in nonpolar solvents, the stereoselectivity becomes virtually the same as when EtOD is the solvent.

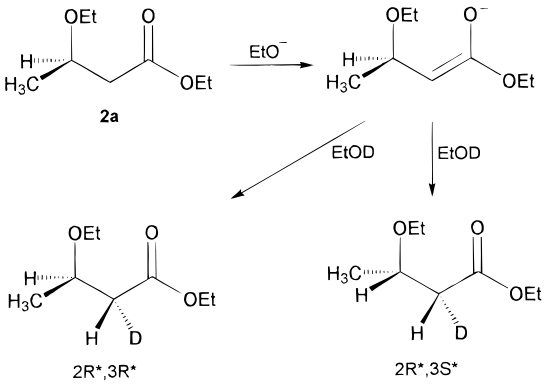

Figure 2. The enolate pathway for H/D exchange.

Table 1. Stereoselection of H/D Exchange on Ethyl Butanoates Substituted at C-3

compd	substituent	chemical shift of diastereotopic C-2 deuterons[a] 2*R**,3*R** (**3**)	chemical shift of diastereotopic C-2 deuterons[a] 2*R**,3*S** (**4**)	% 2*R**,3*R** diastereomer (**3**/**4** ratio)[c]
2a	OEt	2.13	2.45	91 (10.1)
2b	OPh	2.21	2.61	91 (10.1)
2c	CMe_3	1.92	2.32	90 (9.0)
2d	$OCMe_3$	2.22	2.44	89 (8.1)[d]
2e	$SCMe_3$	2.42	2.56[b]	88 (7.4)
2f	OMe	2.11	2.43	87 (6.7)
2g	CF_3	2.35	2.55	83 (4.9)
2h	$CH(CO_2Et)_2$	2.18	2.45	79 (3.8)
2i	Ph	2.35	2.43	75 (3.0)
2j	CN	1.84	2.07	75 (3.0)
2k	$CHMe_2$	1.91	2.16	70 (2.3)
2l	CH_2CMe_3	1.95	2.12	68 (2.1)
2m	CH_2Me	1.90	2.09	59 (1.4)

[a] δ in ppm using benzene (δ 7.15) as solvent. [b] In $CHCl_3$ (δ 7.24). [c] Determined by repetitive 30−76 MHz ^2H NMR integrations at a range of conversions. [d] Same result for the ethyl and *tert*-butyl esters.

Although unlikely, it is possible that H/D exchange of **2a** could proceed through an elimination−addition mechanism. In order to test this hypothesis, we carried out a double isotope experiment. Dideuterated **2a** was used as the substrate in an ethoxide-catalyzed H/D exchange experiment using ^{13}C-labeled ethanol as the reaction solvent. After over 95% H/D exchange had occurred, along with complete exchange of ^{13}C into the ethyl ester, the ^{13}C NMR peak for the ethoxy group at C-3 was less than 1% above natural isotopic abundance. Thus, the H/D exchange proceeds by base-catalyzed proton removal and electrophilic deuteration by EtOD, with no competing elimination−addition pathway (Figure 2).

Table 1 presents stereochemical data for H/D exchange with EtOD/NaOEt on 13 different butanoate esters representing a wide range of substituents at C-3.

The first four entries in Table 1 (**2a-d**), where H/D exchange gives the highest diastereoselectivity, are within experimental error of one another, and **2e,f** produce stereoselection nearly as high. All but **2c** have electronegative substituents at the β-position. With compounds having β-oxygen substituents, steric effects of the group attached to oxygen play a minimal role and electronic effects dominate. Comparison of the stereoselection for **2d** and **2l** is especially revealing. Whereas

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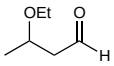
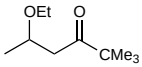
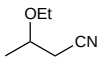
Table 2. Stereoselection of H/D Exchange on β-Ethoxy Carbonyl Compounds

	compd	chemical shift of diastereotopic C-2 deuterons[a] 2*R**,3*R**	2*R**,3*S**	% 2*R**,3*R** diastereomer[c] (2*R**,3*R**/2*R**,3*S**)
5		1.91	2.18	84 (5.3)
6		2.42	2.84	88 (7.3)
7		2.52	2.63[b]	44 (0.8)

[a] δ in ppm using benzene (δ 7.15) as solvent. [b] In acetone (δ 2.04). [c] Determined by repetitive 76 MHz ^{2}H NMR integrations at a range of conversions.

a β-*tert*-butoxy substituent gives an 8:1 ratio of the two product diastereomers, the ratio for the larger neopentyl substituent is only 2:1; the importance of an electronic factor seems inescapable. However, compound **2c**, which has a β-*tert*-butyl substituent, clearly shows that steric effects can also be important in stereoselection. The same steric factors are likely involved with a β-phenyldimethylsilyl group, which we have studied using the methyl β-phenylpropionate system; here 85% of the 2*R**,3*R** diastereomer was produced.[18]

In order to further probe the importance of stereoelectronic effects on H/D exchange, we attempted to see if there were a Hammett $\rho\sigma$-relationship for analogs of **2b**. We compared the effect of the β-phenoxy group with the β-*m*-nitrophenoxy and β-*p*-aminophenoxy substituents. We hoped that this range of Hammett σ values of 1.3 might be sufficient to discern a nonzero ρ value. However, the diastereoselectivities of H/D exchange for all three compounds were essentially within experimental error of one another; deuteration of the *m*-nitrophenoxy compound gave 92% of its 2*R**,3*R** diastereomer, while the *p*-aminophenoxy compound gave 89%.

The last three entries in Table 1, all with β-alkyl substituents, show that steric effects fall off rapidly with a decrease in carbon branching. Among the alkyl substituents, even the isopropyl group (**2k**) shows only modest stereoselection, forming 70% **3k**. A neopentyl substituent (**2l**) produces only slightly more stereoselection than an ethyl group (**2m**). Clearly, branching more than two atoms removed from the π-system of the enolate anion affects the stereochemistry of electrophilic attack only slightly. Entry **2g**, with a β-trifluoromethyl group, is interesting in that it gives reasonably high stereoselection even though it is a carbon substituent of modest size. Entries **2h**,**i** show intermediate diastereoselection and probably involve a combination of steric and electronic factors. Although the β-cyano group of **2j** produces lower stereoselection than other electron-withdrawing substituents, its small size argues that electronic effects must be operating.

While the data in Table 1 show that different β-substituted ethyl esters can produce substantially different diastereoselectivities, the effect of different carbonyl groups remained to be shown. For entry **2d** of Table 1, data are reported for two different β-*tert*-butoxy esters having different alkyl groups; the ethyl and *tert*-butyl esters gave exactly the same stereoselectivity in H/D exchange. Table 2 presents the stereoselection of three additional compounds: 3-ethoxybutanal (**5**), 2,2-dimethyl-5-ethoxy-3-hexanone (**6**), and 3-ethoxybutanenitrile (**7**).

The exchange data in Table 2 show that the high diastereoselection which we found for ethyl esters extends to other carbonyl compounds as well. The H/D exchange of the *tert*-butyl ketone **6** is consistent with the results obtained for β-ethoxy esters. The aldehyde **5** shows somewhat less but not substantially different stereoselectivity. However, the nitrile **7**, not having a trigonal center at C-1, provides much lower diastereoselection. It is possible that our usual NMR−structure correlation does not extend to the nitrile, whose configurational assignment was not determined independently, so we are uncertain if the stereoselection is actually reversed from the general pattern.

Lower stereoselection for electrophilic attack of the nitrile's conjugate base was not unexpected and is consistent with Fleming's results on the alkylation of carbanions α to a C≡N group.[10] Presumably, this low diastereoselection results from the lack of destabilizing 1,3-interactions with the gauche group in the cyanocarbon anion.[19] The consequence is that the two diastereomeric transition states are much more equal in energy than is the case with enolate anions. Fishbein and Jencks have pointed out that it is not clear whether a negative charge α to a cyano group produces a planar, resonance-stabilized carbanion or an sp^3-hybridized carbanion.[20] Boche has shown that a cyclopropyl α-cyanocarbanion has a tetrahedral configuration, in contrast to the comparable enolate anion; in addition, his calculations on CH_2CN^- indicate a nonplanar α-carbon atom.[21] Our computations, which included electron correlation at the MP2 level, are also consistent with a largely tetrahedral carbanion, quite different from the planar enolate anion.[22]

Consistent with their pK_a's, the rate of H/D exchange varied substantially for different substrates. For example, the aldehyde **5** reacted about 10 times faster than the nitrile **7** under comparable conditions. Among the β-substituted butanoate esters, the alkyl-substituted substrates reacted significantly slower than those with β-heteroatom substituents.

Stereochemistry and Mechanism of 1,4-Conjugate Addition

The original motivation for our enolate work was to understand the stereochemistry of conjugate nucleophilic addition to α,β-unsaturated esters. We have shown that the conjugate addition of ethanol-*d* (EtOD) to ethyl (*E*)-2-butenoate (**8**) produces 92 ± 1% of the 2*R**,3*R** diastereomer (**3a**), the same amount within experimental error as that produced in the H/D exchange of **2a** in EtOD (Figure 3). This suggests that the same enolate intermediate is responsible for the stereochemistry that we have observed in conjugate addition and in H/D exchange experiments.

The stereoconvergence that we observed in addition reactions of 2-methyl-2-propanethiol-*d* to **8** and its (*Z*)-isomer is further evidence that electrophilic deuteration of a common enolate anion intermediate produces the diastereoselectivity. Reaction of **8**, ranging over 15−90% completion, gave 89 ± 0.4% **3e**, whereas reaction of ethyl (*Z*)-2-butenoate gave 83 ± 1.4% **3e**. The H/D exchange of **2e** in EtOD and 0.01 M NaOEt gave 88% **3e** at 11% conversion, consistent with enolate protonation as the stereochemical determinant in the conjugate additions. This kind of stereoselectivity has also been observed by Fleming,[10] although stereospecificity in the conjugate addition of sulfur nucleophiles has been reported using THF and lithium thiophenoxides.[23]

(18) We thank Prof. Ian Fleming for providing this compound.

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(22) The dihedral angle at C-2 of the α-cyanocarbanion conjugate base of acetonitrile was calculated to be 130.3° (tetrahedral = 120°, trigonal = 180°) using ab initio MP2 (fc)/6-31G* calculations as described in ref 17.

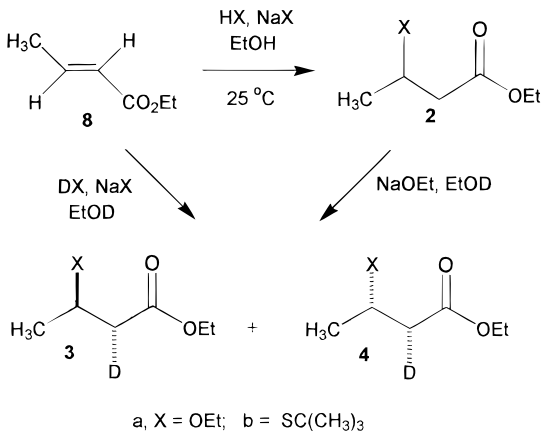

Figure 3. The common stereochemistry of 1,4-conjugate addition and H/D exchange.

In every case where we have compared the diastereoselectivities of nucleophilic conjugate addition and H/D exchange, the percentage of **3** has been the same within experimental error of our ^{2}H NMR integration methodology ($\leq \pm 2\%$). In addition to the same diastereomeric ratios of **3a**/**4a** and **3e**/**4e** in conjugate addition and H/D exchange, the two reactions involving 3-ethoxybutanal (**5**) gave 86.5 ± 0.5% and 83.7 ± 1% of the 2*R**,3*R** diastereomer, respectively. Also, ethoxide-catalyzed conjugate addition of diethyl malonate to **8**, as well as H/D exchange on diethyl 2-(ethoxycarbonyl)-3-methylpentanedioate (**2h**), gave 79% of **3h**. All of our experimental evidence points to the fact that electrophilic deuteration of the enolate anion determines the stereochemistry of base-catalyzed 1,4-conjugate addition as well as of H/D exchange.

Ethoxide-catalyzed nucleophilic additions of EtOD to the α,*β*-unsaturated alkenes were generally slower than H/D exchange on the *β*-ethoxy adducts under comparable conditions. For this reason and because **8** isomerizes to the (*Z*)-isomer in the presence of EtO^-/EtOD, the stereochemistry of conjugate addition was determined from reactions in which the conversion to product was less than 10%; at 5% addition of EtOD to **8**, 4% ethyl (*Z*)-2-butenoate had formed. In the case of adduct **7**, the rate of H/D exchange was so much faster than nucleophilic addition of EtOD that we were unable to determine the stereochemistry of the addition reaction.

Synthesis and Proof of Configuration

Ten of the substrates shown in Table 1 are known compounds. The majority are easily synthesized by esterification of the commercially-available *β*-substituted carboxylic acids or by base-catalyzed conjugate addition of the appropriate nucleophile to alkene **8**. In the case of **2b**, conditions could not be found where phenol would add to **8**, so conjugate addition to ethyl 2-butynoate was followed by hydrogenation using Wilkinson's catalyst. Syntheses of **2c**, **2g**, and **2k** were built on Horner−Emmons−Wadsworth methodology, followed again by hydrogenation.

Potassium *tert*-butoxide-catalyzed nucleophilic addition of *tert*-butyl alcohol to *tert*-butyl (*E*)-2-butenoate was not an effective route to **2d** because the ester enolate of the conjugate addition product reacted further with the α,*β*-unsaturated ester to give a dimeric product, *tert*-butyl 3-methyl-4-(*tert*-butoxycarbonyl)-4-hexenoate. At 49% substrate conversion, only 12% *tert*-butyl 3-*tert*-butoxybutanoate had formed, and longer reaction times gave lower conversion to the desired product. Apparently, the rate of conjugate addition slows appreciably when the nucleophile is the bulky *tert*-butoxide, and Michael addition competes effectively, thereby removing the desired product from the reaction mixture. However, the synthesis of **2d** and its *tert*-butyl analog could be carried out by the acid-catalyzed reaction of 2-methylpropene with the appropriate 3-hydroxybutanoate ester.

The three substrates shown in Table 2 are all known compounds. The *β*-ethoxy aldehyde **5** and nitrile **7** were synthesized by ethoxide-catalyzed conjugate addition of ethanol to crotonaldehyde and crotononitrile, respectively. Synthesis of ketone **6** was more complex. Although Powell and Wasserman reported that it could not be made from acetaldehyde and pinacolone,[24] this methodology was satisfactory in our hands. Following the aldol condensation and dehydration to give largely the (*E*)-alkene, conjugate addition of ethanol provided **6**.

The results from stereochemical investigations such as this one rest on a foundation of unambiguous configurational assignments. In our case this means a firm NMR−structure correlation for the diastereotopic protons α to the carbonyl group. During our research on the stereochemistry of addition−elimination reactions of butanoate esters and thioesters substituted at C-3, we synthesized over 10 different compounds stereospecifically deuterated at C-2 and provided unambiguous configurational assignments for each of them. In every case, the NMR spectrum of the 2*R**,3*R** diastereomer has the C-2 proton in the downfield portion of the AB pattern of the ^{1}H spectrum and the C-2 deuteron upfield in the ^{2}H spectrum.[13,25] This has proved to be a useful empirical pattern for making relative configurational assignments. In the case of **2b**, **2f**, **2h**, and **2j-m**, as well as **6** and **7**, this NMR−structure correlation was assumed to hold. The relative configurations at C-2 and C-3 were determined unambiguously for all other products of H/D exchange reported herein; in every case the configurational assignments for these compounds also matched the general NMR−structure correlation.

In most cases $CDCl_3$ was not a useful solvent for separating the diastereotopic protons, but benzene-d_6 had a dramatic effect on their resolution, usually separating them by over 0.2 ppm. The use of benzene as the ^{2}H NMR solvent proved to be invaluable for obtaining good baselines between the diastereotopic deuteron peaks and thus good integrations.

We have used two strategies for our configurational assignments. The first is based upon 3-hydroxy[2-$^2H_1$]butanoate (**9**), synthesized by $NaBD_4$ reduction of the epoxide of (*E*)-2-butenoate.[25a] This S_N2 reaction proceeds with inversion of configuration at C-2 and produces the 2*R**,3*R** diastereomer of **9**. The NMR−structure correlation of **2a** was assigned by its synthesis from the alkoxide salt of **9** with ethyl iodide.[16] In the case of **2d**, a sample of the *tert*-butyl ester which had undergone H/D exchange was transformed into **9** by reaction with sulfuric acid in CH_2Cl_2, giving the same relative integrations for the upfield and downfield ^{2}H NMR peaks. The NMR−structure correlation for the aldehyde **5** was carried out by O_2 oxidation to the carboxylic acid, followed by acid-catalyzed esterification to **2a**.

The second strategy is based upon the *syn* addition of D_2 across the C=C of 2-butenoate esters substituted at C-3.[25b] When both diastereomers of the alkenes have been available, their configurations were proved by NMR chemical shifts and NOE effects. Thus, the NMR−structure correlations for **2c** and **2e**

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were accomplished by homogeneous catalytic deuterogenation of alkenes whose configurations were known. The syntheses of both **2c** and **2g** used Horner−Emmons−Wadsworth methodology in the C−C bond forming steps. In the former, using pinacolone and the conjugate base of triethyl phosphonoacetate, the reaction produced a 97:3 *E*/*Z* mixture of the known ethyl 3,4,4-trimethyl-2-pentenoate.[26] The (*E*)-isomer was deuterogenated, giving the (2*R**,3*S**)-[2,3-$^2H_2$] derivative of **2c**; in this case our NMR−structure relationship also correlates with the ^{1}H NMR assignments of the C-2 diastereotopic protons of **2c** made by Hart and Krishnamurthy, assuming likely conformational populations.[27] Our relative configurations at C-2 and C-3 of **2i** are also consistent with Hart's ^{1}H NMR assignments. In the case of **2g**, reaction of 1,1,1-trifluoroacetone with the conjugate base of triethyl phosphonoacetate produced largely ethyl (*E*)-3-methyl-4,4,4-trifluoro-2-butenoate,[28] which was deuterogenated to give the 2*R**,3*S** diastereomer.

Discussion

A great deal has been learned about the fundamental kinetic and thermodynamic properties of enols and enolates in recent years, particularly through the work of Kresge and his associates.[29] Much less is understood about the stereochemistry of these important reaction intermediates. The synthesis of preformed enolate anions, using strong bases such as lithium diisopropylamide (LDA) in tetrahydrofuran (THF) or hexamethylphosphoric triamide (HMPA), has been tremendously effective in organic synthesis; however, general structure−reactivity correlations for the supramolecular aggregates produced under these reaction conditions are still poorly understood. The dramatic dissociative effects of lithium and tetraalkylammonium salts, as well as crown ethers, are a case in point.[30]

Comparison of our results, under conditions where ion pairing and aggregation phenomena play no role, with those of Hart and Krishnamurthy, where they do, is useful in this regard.[27] With LDA in THF, and acetic acid-*d* as the electrophile, they found that 75% of the 2*R**,3*R** diastereomer was produced from the β-*tert*-butyl ester **2c**; our research showed 90% of the 2*R**,3*R** diastereomer. With the β-phenyl compound **2i** they found 61% of the 2*R**,3*R** diastereomer, compared to 75% under our conditions. Though the trends are in the same direction, the numbers themselves differ substantially. Perhaps even more relevant is the research of Hünig and his colleagues on the stereochemistry of protonation and alkylation of enolates produced with LDA in the 4-*tert*-butylcyclohexyl system, including ester, ketone, nitrile, and sulfone enolates.[12] After a particularly careful investigation, they found that no general rule for the diastereoselectivity of protonation was possible because of incomplete knowledge of the aggregates present. Our work with ethyl 3-hydroxy- and 3-alkoxybutanoates is another case in point. Here we showed that the diastereoselectivity of enolate protonation can even be reversed under aggregation conditions.[13]

Understanding the fundamental causes that produce stereoselection in the reactions of enolate anions with electrophiles is also made more complex by the fact that steric and electronic effects can reinforce one another. Therefore, experimentally, it is difficult to separate them. Whether electronic stabilization of the transition state plays a role is made ambiguous because the outcome is the same as with the steric considerations commonly cited. The suggestion that stereoelectronic effects can be important in reactions of enols was made 40 years ago to account for the axial preference in reactions at the α-position of cyclic ketones.[31] However, the axial preference for removal or introduction of a proton in decalones and *tert*-butylcyclohexanone (∼5.5-fold) has been considered too small to conclude whether it results from stereoelectronic or steric effects.[32]

Fleming and his co-workers have suggested that there is considerable doubt about how much electrophilic attack on a double bond adjacent to a stereogenic center is controlled by steric and how much by electronic factors.[33] They found that carbon substituents and electropositive heteroatoms give a relatively orderly pattern of stereoselection that can be understood using **1**, but electronegative substituents were more difficult to explain, and the detection of an electronic component to the diastereoselectivity was considered tentative. Contrary to our conclusions, they suggested that there is a reasonable probability that oxygen substituents might be more or less orthogonal rather than antiperiplanar to the developing bond.[10]

Many computations have pointed to the importance of stereoelectronic effects in electrophilic reactions of enols and enolate anions. The calculations of Houk and his colleagues generally support the view that an allylic electron-donating substituent will take a perpendicular relationship to a π-system, so that it can participate in a hyperconjugative interaction.[6] The less sterically demanding remaining substituent is gauche to the enolate in the favored transition state. This idea is complementary to the explanations that have been offered for the corresponding reactions involving nucleophilic attack on a carbonyl group.

In addition, it has been suggested that the σ* molecular orbital of an electronegative substituent may also have substantial amplitude for bonding to a π-system.[34] Hehre and his colleagues have suggested that these interactions may be particularly important with electron-rich allylic alcohols and ethers.[35] In our reactions, this would imply that the stabilizing interaction has the antiperiplanar electronegative group at C-3 accepting electron density from the electron-rich π-system of the enolate. The electron delocalization, made possible by the antiperiplanar, electronegative β-substituent, can stabilize the transition state for protonation. An alternate view of the stereoelectronic effect is that it is really an electrostatic effect, where the best transition-state rotamers are those that minimize dipole−dipole repulsions while also minimizing gauche interactions. When dipole−dipole repulsions are lowered in the transition state for proton transfer, as they are when a β-electronegative substituent is antiperiplanar to the forming C−H bond, that transition state is stabilized.

In any case, our results can only be explained by recognizing the important role of electronic factors in the stereoselection of

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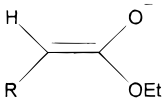


Figure 4. The trans enolate, the likely H/D exchange intermediate.

electrophilic attack on the enolate anions. We see no other way to understand the pattern for H/D exchange on the β-substituted ethyl butanoates shown in Table 1. All but one of the substituents which produce the highest diastereoselectivities have an electronegative oxygen or sulfur atom attached to the stereocenter at C-3. The $OCMe_3$ substituent gives a much higher diastereoselectivity than the larger CH_2CMe_3 substituent. The size of the group attached to the oxygen plays virtually no role in the stereoselection; OEt, OPh, $OCMe_3$, and OMe produce almost the same result. So, the effect of the OR group is independent of R.

With substituents that have no electronegative β-heteroatoms, the stereoselection drops dramatically. Only *tert*-butyl, trifluoromethyl, and cyano are exceptions to this general pattern. The *tert*-butyl case shows that steric factors also influence the stereoselection of H/D exchange, but the effect is small unless substantial γ-branching is present. The pattern of stereoselection is $CMe_3 \gg CHMe_2 \sim CH_2CMe_3 > CH_2Me$. It is not unlikely that our results using a β-phenyldimethylsilyl group (85% 2*R**,3*R**) are also due partly to steric factors, as has previously been suggested in the case of a $Ph(MeS)_2C$ substituent.[36]

With 83% of the 2*R**,3*R** diastereomer produced by H/D exchange of **2g**, the effect of the β-trifluoromethyl group is also substantial. It is likely that minimization of dipole−dipole repulsions plays an important role. The situation is somewhat muddied by disagreements over the effective size of a trifluoromethyl group, however. Trifluoromethyl has been estimated to be the size of an isopropyl group,[37] which causes the production of only 70% of the 2*R**,3*R** diastereomer, although it has also been estimated to be somewhat larger.[38] Nonetheless, it is difficult to ascribe the entire stereochemical influence of the β-CF_3 group to steric effects. Even though only 75% of the 2*R**,3*R** diastereomer is produced by H/D exchange of **2j**, the effect of a β-cyano group, which is very small (roughly the size of a fluoro substituent), must be ascribed to an electronic effect.

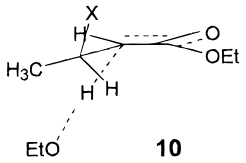
The final point that must be considered is the geometry of the enolate anion. Although we have no direct experimental evidence on the point, with esters **2a-m** it is not unlikely that we are dealing with kinetically-formed ester enolates, the trans isomers (Figure 4), which have been shown in a number of studies to form from esters using LDA/THF.[5] If the trans isomer is also formed faster under our conditions, one would expect that its interconversion to the cis isomer will not compete with the fast deuteration step.

Fortunately, ab initio calculations on the protonation of the enolate anion of 3-fluorobutanoic acid indicate that the diastereoselectivities which we observe could be obtained from either cis or trans enolate isomers.[17] In addition, Fleming and McGarvey have argued that the stereoselection of enolate protonation should be relatively unaffected by whether the anion has the cis or trans geometry.[8,10,39] This is also consistent with the pattern of diastereoselectivities found in Table 2. In particular, if the enolate configuration were an important factor in the stereoselection, it is difficult to envision how virtually the same diastereomeric mixture of products would result from the H/D exchange of aldehyde **5** and *tert*-butyl ketone **6**, which are predicted to produce different enolate geometries under kinetic control.[5]

Rotation about the C-2/C-3 σ-bond of the enolate anion should be fast on the reaction time scale so that ready interconversion of the conformers at the stereogenic center can take place. Chiang *et al.* have determined that the first-order rate constant for protonation of the enolate anion of acetaldehyde with water is 8.8×10^2 s^{-1}, and it is 6.6 s^{-1} for the analogous reaction of isobutyraldehyde.[40] In neither case is protonation of the enolate fast enough to compete with single-bond rotation. The low rotation barriers obtained from our ab initio calculations bear this out. Apeloig *et al.* have also reported ab initio calculations that support low rotation barriers for the adjacent σ-bonds in carbanions stabilized by the C≡N and NO_2 groups.[41] Having the conformation at C-3 relative to the π-system as the important stereochemical determinant in the electrophilic attack is quite consistent with the Curtin−Hammett principle, since we are not talking about the enolate anion itself but instead the transition states for its protonation.

Conclusion

Our experimental results clearly indicate that both stereoelectronic and steric effects are important factors in determining the diastereoselectivity of enolate anion protonation. However, stereoelectronic effects are more dramatic under our conditions where supramolecular aggregates play no role. The stereochemistry of conjugate nucleophilic addition is also controlled by the enolate protonation step. With our substituted ethyl butanoate substrates, the most stable transition states have the electronegative group or very bulky group at C-3 occupying an antiperiplanar position to the C−D bond that is forming, with the proton gauche to the π-system (**10**).



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Experimental Section

General Procedures. C_6D_6 and C_6H_6 were used for NMR spectra; multiple ^2H NMR integrations were performed for determination of reaction diastereoselectivities. Preparatory GC used an 8 ft × 3/8 in. Carbowax 20 M column. Melting points were calibrated against a benzoic acid standard. For H/D exchanges, glassware was soaked in $NaHCO_3$ solution and then rinsed with H_2O; all glassware was oven-dried. Sodium ethoxide (NaOEt) and potassium ethoxide (KOEt) solutions in ethanol-*d* (EtOD) were prepared from Na and K metal, respectively, and stored under N_2. Tetramethylammonium deuteroxide (Me_4NOD, ≤0.2 atom % H) was made by two exchanges in D_2O of $Me_4NOH{\cdot}5H_2O$ (Aldrich, 99%). Ethyl (*E*)-2-butenoate (**8**) was separated from the (*Z*)-isomer by careful fractional distillation; **8** of 99.9+% purity was used in the conjugate addition experiments. Benzene was distilled from Na and THF and dimethyl-2-oxohexahydropyrimidine (DMPU) from CaH_2 before use. The silica gel used in chromatography was Merck Kieselgel 60, 70−230 mesh. EtOD (99+ atom % D), [1-^{13}C]ethanol (98 atom % ^{13}C), and all other reagents except where noted were purchased from Aldrich and used without further purifica-

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tion. Ethyl 2-butynoate (Farchan, 99%), 3-nitrophenol (Eastman Kodak), and isobutylene (Matheson) were also used without purification. Elemental analyses were by Galbraith Labs, Inc., Knoxville, TN.

Esters **2a** and **2f** were prepared using literature procedures.[13] The triester **2h**[42] (bp 125 °C at 0.9 Torr) was synthesized in ethanol by ethoxide-catalyzed conjugate addition of diethyl malonate to **8**, and ethyl 3-cyanobutanoate (**2j**)[43] by the addition of HCN. Ethyl 3-phenylbutanoate (**2i**)[44] was prepared by the reaction of 3-phenylbutanoic acid, thionyl chloride and ethanol, and ethyl 3-methylpentanoate (**2m**)[45] by H_2SO_4-catalyzed azeotropic esterification of 3-methylpentanoic acid in ethanol and toluene. Ethyl 3,5,5-trimethylhexanoate (**2l**)[46] was made by oxidation of 3,5,5-trimethylhexanal with CrO_3/H_2SO_4/AcOH at 0 °C, followed by esterification with thionyl chloride and ethanol. 2,2-Dimethyl-5-ethoxy-3-hexanone (**6**)[24] was synthesized by the aldol condensation of pinacolone and ethanal (LDA/THF at −78 °C), followed by dehydration with *p*-toluenesulfonic acid (50 °C, 3 h) and ethoxide-catalyzed addition of EtOH.

General Method for H/D Exchanges. Using syringe or glovebag techniques, exchanges were done under N_2 with 0.05 M NaOEt (0.01 M for **2e**, **2h**, and **2i**) and 0.5 M ester substrate. To 4.0 mL of stirred solvent was added 2 mmol of the ester and the reaction initiated with 0.3 mL of 0.8 M base. When the reaction had proceeded to 2−15% exchange of one proton as determined by ^{1}H NMR, it was quenched with 0.06 mL of 2 M D_2SO_4 which brought the pH to 5−6. After the reaction was quenched, the reaction mixture was either extracted with hexane/brine or chromatographed on 30 g of silica gel (Et_2O). Upon drying and evaporation of the solvent, the typical recovery of the ester was over 80%. Pure samples of products for NMR analyses were recovered by preparatory GC. Exchange reactions were carried out for 1−15 min at room temperature except for **2c** (30−90 m), **2d** (∼1 h), **2i** (2−5 h), **2j** (1−3 s), **2k** and **2m** (10−24 h), **2l** (24−120 h), **5** (0 °C, 20−80 s), and **6** (10−60 s). With **2b** and its 3-nitro and 4-amino analogs, 0.16−0.25 M substrate was used, and elimination competed with H/D exchange. With **2h** the proton at C-2 was pre-exchanged with EtOD before the actual H/D exchange was carried out.

Synthesis and D/H Exchange of Ethyl 3-Ethoxy[2,2-^{2}H$_2$]butanoate (2a-*d*$_2$) in [1-^{13}C]EtOH. Deuteration of **2a** was carried out using two exchanges of 2 d each at room temperate in a 0.5 M solution of KOEt in EtOD under N_2; ^{1}H NMR integrations showed only 0.5% proton content at C-2 and 13% deuterium (1H) at C-4. The D/H exchange of 1.0 mmol **2a-*d*$_2$** was done for 60 h with 0.04 M KOEt in 1.8 mL of ethanol, one-third of which was [^{13}C]EtOH. After the usual workup, ^{1}H NMR showed about 97% loss of deuterium at C-2. The ^{13}C NMR peak for C-1 of the 3-ethoxy group was enhanced only 0.3% above natural isotopic abundance, whereas the ester ethyl group was completely exchanged.

Ethyl 3-Phenoxybutanoate (2b). Ethyl 2-butynoate (3.37 g, 0.94 M in 25 mL of DMPU/7 mL of THF) was reacted in the presence of 1.0 M NaOPh and 0.94 M phenol for 24 h at room temperature. Addition of 25 mL of H_2O, extraction with 4 × 20 mL of hexane, followed by back-extraction with 35 mL of H_2O, 30 mL of 1.3 M NaOH, and 25 mL of H_2O, drying over K_2CO_3, evaporation of the solvent, and vacuum distillation (bp 106−108 °C at 0.04 Torr) produced 5.0 g (80%) of ethyl (*E*)-3-phenoxy-2-butenoate.[47]

A 4.5 g sample of ethyl (*E*)-3-phenoxy-2-butenoate (22 mmol), along with 0.86 g of tris(triphenylphosphine)rhodium(I) chloride (0.97 mmol), was dissolved in 70 mL of benzene which had been deoxygenated with N_2 in a pressure reactor. After the reactor was sealed and flushed twice with 15 atm of H_2, it was charged with 30 atm of H_2. After 4 d at 46 °C, the reaction had proceeded to 99% completion. The mixture was evaporated to remove as much benzene as possible, leaving a brown oily residue. The catalyst was removed by addition of 50 mL of hexane, vacuum filtration, and flash chromatography using 20 g of silica gel and a 20:1 hexane/Et_2O eluent. After solvent removal, 3.9 g (86%) of **2b** was recovered (99% purity): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H), 1.35 (d, 3H), 2.46−2.85 (2 dd, 2H), 4.13 (q, 2H), 4.82 (m, 1H), 6.90−7.31 (m, 5H); MS *m*/*z* 208 (M^+), 163, 94.

Ethyl 3-(3-Nitrophenoxy)butanoate. A 9.05 g sample of 3-nitrophenol (64.4 mmol) was dissolved in a solution of 34 mL of DMPU and 16 mL of THF and the solution slowly added to a stirred slurry of 0.80 g of NaH (32 mmol) in 20 mL of DMPU at 0 °C. After 1 h, 3.6 g of ethyl 2-butynoate (31.5 mmol) was added. About 70% reaction had occurred after 23 h at room temperature, and it reached completion after further heating at 40 °C for 22 h. Addition of 300 mL of H_2O produced a solid, which was filtered, dissolved in 80 mL of Et_2O, and washed with 5 × 20 mL of 4% Na_2CO_3 solution. After evaporation of the solvent, the product was chromatographed on 75 g of silica gel (Et_2O) to produce a mixture containing 3% of the (*Z*)- and 97% of the (*E*)-alkene. Recrystallization from hexane gave 4.95 g (63%) of fluffy white crystals of ethyl (*E*)-3-(3-nitrophenoxy)-2-butenoate: mp 69.5−71 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H), 2.49 (s, 3H), 4.09 (q, 2H), 4.85 (s, 1H), 7.36 (d, 1H), 7.56 (t, 1H), 7.89 (m, 1H), 8.08 (d, 1H); MS *m*/*z* 251 (M^+), 206, 178, 160.

Hydrogenation of ethyl (*E*)-3-(3-nitrophenoxy)-2-butenoate with $Rh(PPh_3)_3Cl$ in benzene was carried out under the usual conditions for 10 h. After workup, GC analysis indicated two products, in addition to unreacted starting material. After acid extraction to separate the 3-aminophenoxy products, chromatography on 100 g of silica gel using a 20:1 hexane/Et_2O eluent gave 1.35 g (27%) of a colorless liquid, ethyl 3-(3-nitrophenoxy)butanoate (99+% purity): ^{1}H ($CDCl_3$) δ 1.24 (t, 3H), 1.32 (d, 3H), 2.56−2.90 (2 dd, 2H), 4.18 (q, 2H), 4.96 (m, 1H), 7.2−7.8 (m, 4H); MS *m*/*z* 253 (M^+), 208, 115.

Ethyl 3-(4-Aminophenoxy)butanoate. Using 62 mL of a 3:1 mixture of DMPU/THF with 0.60 M ethyl 2-butynoate, 0.62 M sodium 4-nitrophenoxide, and 0.61 M 4-nitrophenol, the conjugate addition was run at 65 °C for 7 d. Addition of 300 mL of H_2O gave a crystalline product. After being washed with 4 × 10 mL of 5% Na_2CO_3, it was chromatographed on 40 g of silica gel using a 3:1 Et_2O/hexane eluent and recrystallized from hexane to yield 7.32 g (73%) of ethyl (*E*)-3-(4-nitrophenoxy)-2-butenoate as yellowish needles: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H), 2.47 (s, 3H), 4.10 (q, 2H), 4.99 (s, 1H), 7.15 (d, 2H), 8.25 (d, 2H); NOE's between the vinyl and allyl protons and the vinyl and C-2 aromatic protons were consistent with those calculated for the (*E*)-isomer; MS *m*/*z* 251 (M^+), 206, 178, 160.

Hydrogenation under the usual conditions for 7 d and workup using pentane to precipitate the $Rh(PPh_3)_3Cl$ catalyst was followed by three extractions with 1.0 M HCl. Neutralization of the acidic water layer with 1.0 M NaOH produced 1.9 g (47%) of a red liquid, ethyl 3-(4-aminophenoxy)butanoate: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H), 1.27 (d, 3H), 2.38−2.77 (2 dd, 2H), 3.4 (broad s, 2H), 4.10 (q, 2H), 4.58 (m, 1H), 6.53−6.76 (dd, 4H); MS *m*/*z* 223 (M^+), 178, 109.

Ethyl 3,4,4-Trimethylpentanoate (2c).[27] Reaction of 3,3-dimethyl-2-butanone and the conjugate base of triethyl phosphonoacetate in 1,2-dimethoxyethane gave a 97:3 *E*/*Z* ratio of ethyl 3,4,4-trimethyl-2-pentenoate.[26] The alkene was hydrogenated over PtO_2 in EtOH at 3.4 atm, and after solvent evaporation **2c** was recovered in 81% overall yield (bp 80 °C at 5 Torr). Configurational assignments were made by ^{1}H and ^{2}H NMR analysis of the reduction product of ethyl (*E*)-3,4,4-trimethyl-2-pentenoate with $D_2/Rh(PPh_3)_3Cl$ in benzene (27 atm, 55 °C, 10 d), a known *syn* addition,[25b] followed by exhaustive D/H exchange of **2c-*d*$_2$** (0.5 M) in EtOH (0.27 M NaOEt, 90 °C, 5 h) to assign the α-H chemical shifts. The ^{2}H NMR spectrum of the (2*R**,3*S**)-[^{2}H$_2$] diastereomer of **2c-*d*$_2$** had peaks at δ 2.32 and 1.82, and the ^{1}H spectrum was missing the usual H_{C-2} peak at δ 2.32 and H_{C-3} peak at δ 1.82 but not the H_{C-2} peak at δ 1.92. Thus, the 2*R**,3*S** diastereomer has the C-2 deuteron downfield.

***tert*-Butyl 3-*tert*-Butoxybutanoate.** Reduction of *tert*-butyl acetoacetate with a 20% excess of $NaBH_4$ in 95% EtOH (2.0 M) for 21 h, followed by neutralization with AcOH, solvent evaporation, brine/Et_2O extractions, and vacuum distillation (bp 55 °C, 0.5 Torr), gave a 67% yield of *tert*-butyl 3-hydroxybutanoate. Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.78; H, 10.04.

Isobutylene gas was bubbled for 4 h through a frit into a solution of 16.0 g of *tert*-butyl 3-hydroxybutanoate in 0.2 L of CH_2Cl_2 containing 0.9 mL of H_2SO_4 and the solution allowed to sit overnight; GC analysis

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showed 87% conversion to product. Extraction with 3 × 100 mL of 10% $NaHCO_3$ solution, drying, solvent evaporation, and flash chromatography on silica gel using a 4:1 hexane/Et_2O eluent gave 5.1 g (24%) of *tert*-butyl 3-*tert*-butoxybutanoate (bp 42 °C at 0.01 Torr): ^{1}H NMR δ 1.11 (s, 9H), 1.17 (d, 3H), 1.39 (s, 9H), 2.21−2.31 (dd, 1H), 2.46−2.56 (dd, 1H), 4.07 (m, 1H). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.30.

The *tert*-butyl groups were removed in 4.0 mL of CH_2Cl_2 by bubbling N_2 for 6 h through a solution of 18 μL of H_2SO_4 and 0.32 g of *tert*-butyl 2-deuterio-3-*tert*-butoxybutanoate, which had been produced by H/D exchange in EtOD/NaOEt (15% D at C-2; ^{2}H peaks at δ 2.20 and 2.42 were in a 90:10 ratio, respectively). The product was extracted into 1 mL of H_2O. Its ^{2}H NMR spectrum gave a 90:10 ratio of two peaks, the larger at δ 2.45 and the smaller at 2.56, corresponding to a 90:10 mixture of (2*R**,3*R**/2*R**,3*S**)-3-hydroxy[2-$^2H_1$]butanoic acids.[25a]

Ethyl 3-*tert*-Butoxybutanoate (2d). Reaction of isobutylene/H_2SO_4 with ethyl 3-hydroxybutanoate in CH_2Cl_2 and the usual workup gave **2d** in 32% yield (99.9% purity, bp 32 °C at 0.01 Torr): ^{1}H NMR δ 0.95 (t, 3H), 1.07 (s, 9H), 1.13 (d, 3H), 2.22−2.33 (dd, 1H), 2.47−2.57 (dd, 1H), 3.95 (t, 2H), 4.04 (m, 1H).

Addition of 2-Methyl-2-propanethiol-*d* to Ethyl (*E*)- and (*Z*)-2-Butenoate. To 150 mL of EtOH was added 5.0 g (0.22 mol) of Na metal, followed by 21.4 g (0.24 mol) of 1,1-dimethylethanethiol, and the solution was stirred for 30 min. The white sodium thiolate salt was vacuum filtered under N_2, washed with anhydrous Et_2O, and dried in a vacuum oven over P_2O_5 at 100 °C and 47 Torr for 12 h. A 2.4 g (21.5 mmol) sample of the thiolate salt was dissolved in 48 mL of EtOD, and 3.77 mL of D_2SO_4 in EtOD (1.43 M, 5.38 mmol) was added. The Na_2SO_4 precipitate was removed by centrifugation. The conjugate addition reactions of Me_3CSD to **8** and to ethyl (*Z*)-2-butenoate (99% (*Z*), made by addition of H_2 to ethyl 2-butynoate on Pd/$BaSO_4$)[48] were carried out with 0.19 M Me_3CSD and Me_3CSNa and 0.186 M alkene at room temperature for 1−20 min; no differences in stereochemistry were observed over 6−89% completion. At 20 min the (*Z*)-2-butenoate had rearranged to a *Z*/*E* ratio of 95/5. The reactions were neutralized to pH 7 with D_2SO_4/EtOD, the Na_2SO_4 was removed by centrifugation, hexane and Et_2O were added, and the solution was extracted twice with H_2O, dried, and evaporated. Pure products were recovered by preparatory GC.

Ethyl 3-(*tert*-Butylthio)butanoate (2e).[16] To 78 mL of 1 M NaOEt in EtOH were added 14.2 g (0.16 mol) of 1,1-dimethylethanethiol and 8.9 g (78 mmol) of **8**. After being stirred for 7 h at room temperature, the reaction mixture was chromatographed on silica gel using hexane and then Et_2O as eluents. Vacuum distillation at 65 °C and 0.25 Torr gave 10.2 g of **2e** (59%), of 99+% purity: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.35 (s, 9H), 1.37 (d, 3H), 2.45 (dd, 1H), 2.60 (dd, 1H), 3.19 (m, 1H), 4.15 (q, 2H).

Ethyl 3-(*tert*-butylthio)-2-butenoate was synthesized by reacting 1,1-dimethylethanethiol (49 mmol) with ethyl 2-butynoate (45 mmol) in 77 mL of ethanol in the presence of NaOEt (2.2 mmol) for 2 h.[49,50] The (*E*)- and (*Z*)-isomers were separated on a silica gel column using 2−5% Et_2O in hexane. The (*Z*)-isomer gave a significant NOE enhancement between the allyl and vinyl protons, whereas the (*E*)-isomer gave no enhancement.

Ethyl (*E*)-3-(*tert*-butylthio)-2-butenoate was deuterogenated in deoxygenated benzene with D_2 (11 atm)/$Rh(PPh_3)_3Cl$ at 40 °C for 4 d. Workup in the usual way gave a product that was 52% reduced. Preparatory GC gave pure ethyl (2*R**,3*S**)-3-(*tert*-butylthio)[2,3-$^2H_2$]-butanoate; ^{2}H NMR ($CHCl_3$) δ 2.58 and 3.16. Thus, the 2*R**,3*S** diastereomer has the C-2 deuteron downfield.

Ethyl 3-Methyl-4,4,4-trifluorobutanoate (2g) and Ethyl 3,4-Dimethylpentanoate (2k). Reaction of triethyl phosphonoacetate with NaH in 1,2-dimethoxyethane and subsequent addition of 1,1,1-trifluoroacetone at 0 °C, refluxing overnight, neutralization with AcOH, Et_2O/H_2O extractions, drying, and distillation produced 35% of ethyl 3-methyl-4,4,4-trifluoro-2-butenoate, largely the (*E*)-isomer.[28] Hydrogenation in Et_2O at room temperature over PtO_2 using 3.4 atm of H_2, followed by removal of the catalyst, evaporation of the solvent and preparatory GC, gave pure **2g**.[51] Configurational assignments for the deuterated **2g** which was produced by H/D exchange were made by reducing ethyl (*E*)-3-methyl-4,4,4-trifluoro-2-butenoate with D_2 and PtO_2/C_6H_{12}; the major ^{1}H peak was at δ 2.2, the expected position for the 2*R**,3*S** diastereomer.

The same synthetic procedure, but with 3-methyl-2-butanone instead of 1,1,1-trifluoroacetone, gave **2k**[52] (99% purity, 40% yield).

Addition of Diethyl [2,2-$^2H_2$]propanedioate to 8. The reaction was done in EtOD to 3−22% completion with 0.15 M **8**, 0.18 M diethyl malonate-d_2, and 0.03 M NaOEt at room temperature, giving over the entire range 79 ± 1% of the 2*R**,3*R** diastereomer of diethyl 2-(ethoxycarbonyl)-3-methyl[2,4-$^2H_2$]pentanedioate.

3-Ethoxybutanal (5). Reaction of 2-butenal and NaOEt (0.05 M) in ethanol at 0 °C for 5 min gave 7.5 g of **5** (53%). Purification by vacuum distillation gave **5**[53] of 96% purity: ^{1}H NMR δ 0.85 (d, 3H), 1.00 (t, 3H), 1.91 (2 dd, 1H), 2.18 (2 dd, 1H), 3.0−3.3 (m, 2H), 3.5 (m, 1H), 9.4 (dd, 1H).

Oxidation of **5**, which had been exchanged in EtOD (^{2}H NMR showed an 85/15 ratio of peaks at δ 1.9 and 2.2, respectively), was done in C_6H_6 over a 10 d period by bubbling O_2 into the solution every 2 d. Azeotropic esterification of the 3-ethoxybutanoic acid product with $EtOH/H_2SO_4$/toluene gave ethyl 3-ethoxy[$^2H_1$]butanoate, with ^{2}H NMR peaks at δ 2.13 and 2.44 in an 85/15 ratio. Thus, the 2*R**,3*R** diastereomer of **5** has the C-2 deuteron upfield.

Conjugate additions of EtOD to 2-butenal were done with 0.5 M substrate and 0.05 M NaOEt at −15 °C for 30−60 s (3−10% conversion). ^{2}H NMR samples were purified by preparatory GC.

3-Ethoxybutanenitrile (7). Reaction of 15 g of crotononitrile in 95 mL of 0.36 M NaOEt in EtOH for 1 h at room temperature gave 15.5 g (62%) of **7** (bp 72 °C at 40 Torr):[54] ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 3H), 1.16 (d, 3H), 2.63 (dd, 1H), 2.73 (dd, 1H), 3.45 (q, 2H), 3.67 (m, 1H).

Acknowledgment. We are grateful for support from the National Science Foundation (NSF Grant CHE-8505408), the National Institutes of Health (NIH Grant GM40018), the Camille and Henry Dreyfus Foundation, Inc. for a fellowship to R.E.R. and for a student stipend, the NSF (Grant CHE-8409822) and the 3M Foundation for funding the purchase of a 200 MHz NMR spectrometer, and the Hewlett-Packard Co. for the gift of a capillary GC. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Student stipends were also provided by grants from the Howard Hughes Medical Institute and the 3M Foundation. We thank M. Mitton for the NMR−structure correlation for aldehyde **5** and Dr. Stephen B. Philson and the University of Minnesota for 46 and 76 MHz ^{2}H NMR spectra.

JA962631S

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