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Novel Syn Intramolecular Pathway in Base-Catalyzed 1,2-Elimination Reactions of β-Acetoxy Esters

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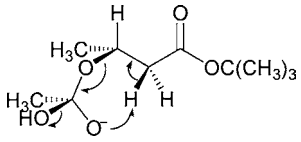
Received September 14, 2006



As part of a comprehensive investigation of electronic effects on the stereochemistry of base-catalyzed 1,2-elimination reactions, we observed a new syn intramolecular pathway in the elimination of acetic acid from β-acetoxy esters and thioesters. ^{1}H and ^{2}H NMR investigation of reactions using stereospecifically labeled *tert*-butyl (2*R**,3*R**)-3-acetoxy-2,3-$^2H_2$-butanoate (**1**) and its (2*R**,3*S**) diastereomer (**2**) shows that 23 ± 2% syn elimination occurs. The elimination reactions were catalyzed with KOH or $(CH_3)_4$-NOH in ethanol/water under rigorously non-ion-pairing conditions. By contrast, the more sterically hindered β-trimethylacetoxy ester produces only 6 ± 1% syn elimination. These data strongly support an intramolecular (E_i) syn path for elimination of acetic acid, most likely through the oxyanion produced by nucleophilic attack at the carbonyl carbon of the β-acetoxy group. The analogous thioesters, *S*-*tert*-butyl (2*R**,3*R**)-3-acetoxy-2,3-$^2H_2$-butanethioate (**3**) and its (2*R**,3*S**) diastereomer (**4**), showed 18 ± 2% syn elimination, whereas the β-trimethylacetoxy substrate gave 5 ± 1% syn elimination. The more acidic thioester substrates do not produce an increased amount of syn stereoselectivity even though their elimination reactions are at the E1cb interface.

Introduction

Understanding the diverse mechanisms of base-catalyzed elimination reactions has challenged many organic chemists.[1,2] There is a substantial body of evidence that the expected pathway for these 1,2-elimination reactions is an intermolecular pathway. Electronic as well as torsional factors favor the anti process; however, the importance of syn elimination pathways under some circumstances is also accepted.[1−4]

Our investigations have focused on simple acyclic substrates that produce conjugated carbonyl compounds by base-catalyzed 1,2-elimination reactions under conditions where the effects of aggregation phenomena as well as the complex conformational factors of cyclic substrates do not dominate. The research began by a study of the elimination of acetic acid from *S*-*tert*-butyl (2*R**,3*R**)-3-acetoxy-2-$^2H_1$-butanethioate (**5**) using KOH in 3:1 v/v EtOH/H_2O, producing *S*-*tert*-butyl (*E*)-2-butenethioate (**6**), Figure 1.[5] A previous mechanistic study of the elimination reaction of *S*-*tert*-butyl 3-acetoxybutanethioate (**7**) had concluded that the reaction was either E2 or $E1cb_{irrev}$.[6]

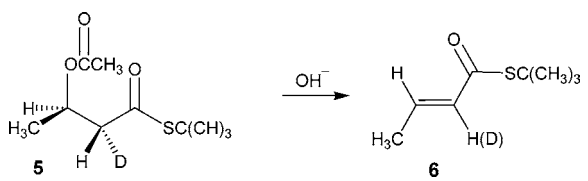


FIGURE 1. Base-catalyzed elimination of acetic acid from **5**.

This system was chosen because it provides an appropriate model for the substrate of enoyl-CoA hydratase (EC 4.2.1.17), an enzyme which catalyzes the syn elimination−addition of water in the *S*-β-hydroxybutyryl CoA/*S*-crotonyl CoA reaction in fatty acid metabolism.[7,8]

(1) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; Wiley & Sons: New York, 1973; Chapter 3.
(2) Gandler, J. R. Mechanisms of Base-Catalyzed Alkene-Forming 1,2-Eliminations. In *The Chemistry of Doubly-Bonded Functional Groups*; Patai, S., Ed.; Wiley & Sons: New York, 1989; pp 733−797.
(3) Gronert, S. *J. Am. Chem. Soc.* **1992**, *114*, 2349−2354.
(4) Bartsch, R. A.; Závada, J. *Chem. Rev.* **1980**, *80*, 453−494.

10.1021/jo0619027 CCC: $37.00 © 2007 American Chemical Society
Published on Web 01/10/2007

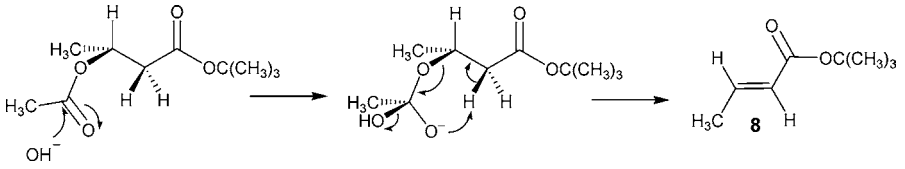


FIGURE 2. Base-catalyzed intramolecular syn elimination pathway.

It has been suggested that E1cb-like transition states may favor syn stereochemistry.[2,3,9,10] Thus, electron-withdrawing substituents and poor leaving groups that produce transition states with more E1cb character may favor syn elimination. However, almost no stereochemical studies have been done with a carboxylate leaving group or substrates leading to conjugated carbonyl compounds. Our studies using β-acetoxy esters **1** and **2** showed that an unusually large amount of syn elimination occurred in the formation of *tert*-butyl (*E*)-2-butenoate (**8**), which could be due to an E1cb-like transition state with a marginal leaving group.[11] However, it was also possible that an intramolecular elimination pathway from the oxyanion produced by attack of hydroxide at the β-acetoxy carbonyl group, shown in Figure 2, might account for the high percentage of syn elimination.

This pathway could allow the α proton to be removed through a concerted syn six-membered transition state; however, such a pathway has never been observed before. In order to test this theory, a more hindered analogue of the acetoxy ester, stereospecifically labeled *tert*-butyl (2*R**,3*R**)-3-trimethylacetoxy-2,3-$^2H_2$-butanoate (**9**) and its (2*R**,3*S**) diastereomer (**10**), have been synthesized and studied. Due to steric reasons, the trimethylacetates are predicted to give a 35−100-fold slower rate of nucleophilic attack at carbonyl carbon, which would be expected to suppress the intramolecular elimination pathway.[12] Also, there is no reason to suspect that the stereoselectivity of intermolecular elimination from the β-acetoxy and β-trimethylacetoxy esters should differ. Although the bulky *tert*-butyl group has a significant effect on the rate of nucleophilic attack at the adjacent carbonyl carbon, it should have little effect on the rate of proton abstraction, which initiates the intermolecular 1,2-elimination reaction. In addition, the acetoxy and trimethylacetoxy groups will have similar leaving-group abilities.

Results and Discussion

In order to determine the innate elimination stereochemistry both **1** and **2**, as well as the trimethylacetoxy esters **9** and **10**, must be available so that the kinetic isotope effects (KIEs) can be factored out. Our synthesis of pure **1** and **2** depends on the rigorous syn deuteration of *tert*-butyl (*Z*)-3-acetoxy-2-butenoate

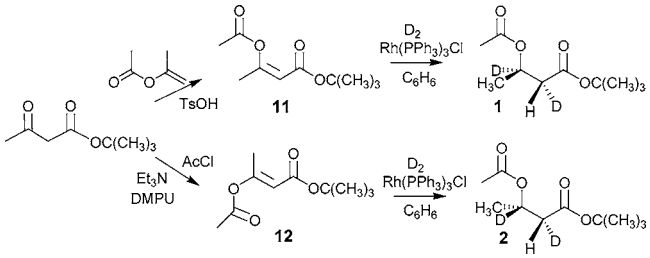


FIGURE 3. Preparation of acetoxy esters **1** and **2**.

(**11**) and *tert*-butyl (*E*)-3-acetoxy-2-butenoate (**12**) by Wilkinson's catalyst, Figure 3.[13]

Different routes for the (*Z*)- and (*E*)-enol acetates were chosen to maximize the yields of the desired diastereomers. Under acidic conditions the (*Z*)-enol dominates and the *Z*/*E* product ratio is approximately 13. Under basic conditions the *E*-enolate dominates and the *Z*/*E* product ratio is about 0.15. Deuterogenation of **11** and **12** resulted typically in 85−95% product yields of **1** and **2**. Both **1** and **2** contained small amounts of isotopic impurities; as much as 8−10% of C-2 diprotonated acetoxy ester was present in **1** and 2−5% in **2**.

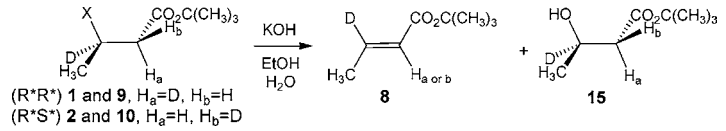
The syntheses of **9** and **10** were carried out by hydrolysis of the β-acetoxy functional group of **1** and **2** in 1:1 v/v EtOH/H_2O, followed by reesterification of the alcohols with trimethylacetyl chloride. Isotopic exchange at C-2 of the alcohols was avoided by carefully monitoring the hydrolysis reactions. Use of a more polar solvent mixture produced a lower elimination/hydrolysis ratio, making the loss due to elimination (∼30%) acceptable. Substrates **9** and **10** contained 3−7% of C-2 diprotonated esters. The planned synthesis of **9** and **10** from the *tert*-butyl 3-trimethylacetoxy-2-butenoates did not succeed because poor chromatographic separation provided insufficient quantities of the (*Z*)-isomer.

The thioesters **3** and **4** and *S-tert*-butyl (2*R**,3*R**)-3-trimethylacetoxy-2,3-$^2H_2$-butanethioate (**13**) and its (2*R**,3*S**) diastereomer (**14**) were synthesized by deblocking the *tert*-butyl esters **9** and **10** with TFA, activation of the carboxylic acid with TFAA, and esterification with 2-methyl-2-propanethiol.[14] As long as excess TFA was not present, no H/D exchange or rearrangement of the stereospecifically deuterated substrates was observed in the transesterification reactions. Only in the synthesis of **13** did a significant amount of H/D exchange and rearrangement occur; 13% of each was observed.

Reactions of esters **1** and **2**, plus **9** and **10**, with KOH in 3:1 v/v EtOH/H_2O produced a mixture of the deuterated (*E*)-alkene **8** and *tert*-butyl 3-hydroxybutanoate (**15**) plus a small amount (1.5%) of *tert*-butyl (*Z*)-2-butenoate (**16**). The (*E*)-alkene was purified by preparative GC before multiple ^2H integrations were used to determine the amount of anti and syn elimination from

(5) Mohrig, J. R.; Schultz, S. C.; Morin, G. *J. Am. Chem. Soc.* **1983**, *105*, 5150−5151.
(6) Fedor, L. R. *J. Am. Chem. Soc.* **1969**, *91*, 913−917.
(7) Creighton, D. J.; Murthy, N. S. R. K. Stereochemistry of Enzyme-Catalyzed Reactions at Carbon. In *The Enzymes*, 3rd ed.; Sigman, D. S., Boyer, P. D., Eds.; Academic Press: New York, 1990; Vol. 19, Chapter 7.
(8) D'Ordine, R. L.; Bahnson, B. J.; Tonge, P. J.; Anderson, V. E. *Biochemistry* **1994**, *33*, 14733−14742.
(9) Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M.; Ziegler, T. *J. Am. Chem. Soc.* **1993**, *115*, 9160−9173.
(10) Saunders, W. H., Jr. *J. Org. Chem.* **2000**, *65*, 681−684.
(11) (a) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198−203. (b) Boyd, D. B. *J. Org. Chem.* **1985**, *50*, 885−886.
(12) (a) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1953; p 758. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley & Sons: New York, 2001; p 374.
(13) Mohrig, J. R.; Dabora, S. L.; Foster, T. F.; Schultz, S. C. *J. Org. Chem.* **1984**, *49*, 5179−5182.
(14) Mohrig, J. R.; Vreede, P. J.; Schultz, S. C.; Fierke, C. A. *J. Org. Chem.* **1981**, *46*, 4655−4658.

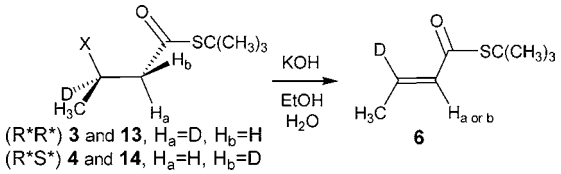
TABLE 1. Stereoselectivity Data and KIEs for Esters 1, 2, 9, and 10



	% syn_{R*R*}	% syn_{R*S*}	k_{R*S*}/k_{R*R*}	$(k_H/k_D)_{syn}$[a]	$(k_H/k_D)_{anti}$[b]	% **15**
1,2: X = CH_3CO_2	34.9	6.6	1.27	4.1	1.8	60
9,10: X = $(CH_3)_3CCO_2$	17.1	1.5	2.78	4.2	3.3	6

[a] $(k_H/k_D)_{syn}$ = % syn_{R*R*}/% syn_{R*S*} × k_{R*R*}/k_{R*S*}. [b] $(k_H/k_D)_{anti}$ = % $anti_{R*S*}$/% $anti_{R*R*}$ × k_{R*S*}/k_{R*R*}.

TABLE 2. Stereoselectivity Data and KIEs for Thioesters 3, 4, 13, and 14



	% syn_{R*R*}	% syn_{R*S*}	k_{R*S*}/k_{R*R*}	$(k_H/k_D)_{syn}$	$(k_H/k_D)_{anti}$
3,4: X = CH_3CO_2	46.3	3.7	2.2	5.7	3.9
13,14: X = $(CH_3)_3CCO_2$	20.2	1.0	3.8	5.3	4.7

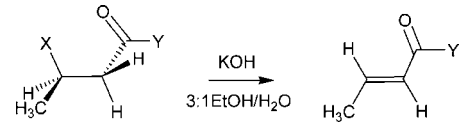
the labeled diastereomers, as shown in Table 1, which shows that the (2*R**,3*R**)-diastereomers produce much more syn elimination than the (2*R**,3*S**)-diastereomers due to the adverse primary KIE for anti elimination of the (2*R**,3*R**)-compounds.[15] Determination of the relative rates of **1** and **2** and of **9** and **10** completed the experimental data needed to calculate the k_H/k_D KIEs in an unambiguous fashion.[16]

A parallel set of observations, obtained from thioesters **3** and **4**, plus **13** and **14**, is shown in Table 2. The 1,2-elimination reactions of the thioesters produced *S-tert*-butyl (*E*)-2-butenethioate (**6**) plus a small amount (1.3%) of *S-tert*-butyl (*Z*)-2-butenethioate (**17**). The reaction rates were over 60 times faster than those of the analogous esters, reflecting the greater acidity of the thioester α protons.[17]

The data in Tables 1 and 2 show that under our non-ion-pairing conditions the syn elimination pathway is of substantially less importance for the β-trimethylacetoxy substrates than for the less hindered β-acetoxy esters and thioesters. Using this data, the innate stereoselectivities of the 1,2-elimination reactions, those which would be expected in the absence of deuterium labels, can be calculated in a straightforward manner. The results are shown in Table 3. Secondary deuterium KIEs are unlikely to be greater than 1.03 and would have a negligible effect on our results.[18]

The β-acetoxy thioester gives somewhat less syn elimination than the β-acetoxy ester, probably due to the increased rate of intermolecular 1,2-elimination of the more acidic β-acetoxy thioester, compared to nucleophilic attack at the acetoxy C=O and subsequent intramolecular elimination from the resulting oxyanion. The more acidic thioester substrates might have had a greater tendency to undergo syn elimination since the transition states for their intermolecular, base-catalyzed 1,2-elimination reactions are nearer the E1cb interface than those of the esters. Indeed, syn elimination is common in enzymatic dehydration reactions of β-hydroxythioester substrates, although historical contingency rather than mechanistic efficiency has been implicated as the key stereochemical determinant in the enoyl-CoA hydratase reaction.[19] However, our data indicates that intermolecular syn elimination from our thioester substrates is no greater than the syn elimination from our ester substrates.

TABLE 3. Innate Stereoselectivity of Esters and Thioesters with β-Carboxylate Leaving Groups



	% syn elimination	
	Y	
X	$OC(CH_3)_3$	$SC(CH_3)_3$
H_3CCO_2	23 ± 2	18 ± 2
$(CH_3)_3CCO_2$	6 ± 1	5 ± 1

It is important to ensure the validity of these results by determining that the reactants and products go cleanly to their elimination products without any rearrangements or deuterium scrambling. The most complete set of control experiments was carried out on **3**, **4**, and **7** plus *S-tert*-butyl 3-acetoxy-2,2-$^2H_2$-butanethioate (**18**).

When the 1,2-elimination reaction was carried out on **7** in EtOD, D_2O/KOD, NMR analysis on the recovered alkene **6** showed no detectible deuterium content. When **18** was the substrate in protonated solvents, product **6** was completely deuterated at C-2. When the reaction was carried out with only

(15) Mohrig, J. R.; McMartin, L.; Carlson, H.; John, S.; Trimmer, E. E. *Abstracts of Papers*, 228th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 22−26, 2004, American Chemical Society: Washington, DC, 2004; ORGN 749.

(16) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley & Sons: New York, 1980; Chapter 4.

(17) (a) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 10297−10302; **1996**, *118*, 3129−3141.

(18) Ryberg, P.; Matsson, O. *J. Am. Chem. Soc.* **2001**, *123*, 2712−2718.

(19) Mohrig, J. R.; Moerke, K. A.; Cloutier, D. M.; Lane, B. D.; Person, E. C.; Onasch, T. B. *Science* **1995**, *269*, 527−529.

50% of the KOH necessary for complete elimination of **3** and **4**, the deuterium content of **6** was identical to that observed at complete reaction. In addition, the recovered **3** and **4** showed no loss of stereochemical integrity.

Virtually no isomerization of (*Z*)- to (*E*)-alkenes **17** to **6** and **16** to **8** was observed under the reaction conditions. Only 1.3% of **17** was produced in the elimination products from **3** and **4**, and <2% was produced from **13** and **14**; GC analysis showed that <5% of **17** could have rearranged to **6** under elimination conditions. Only 1.5% of **16** was produced in the eliminations of **1** and **2**, and <3.5% was produced from **9** and **10**; GC analysis showed that under elimination conditions <25% of any **16** present could have rearranged to **8**.

The last control experiment involved substitution of $(CH_3)_4$-NOH for KOH as the base in the elimination reactions of **1** and **2**, plus **3** and **4**. The results were fully consistent with the results in Table 3. The innate stereoselectivity for the ester was 23% syn elimination and for the thioester 16% syn elimination. Since the Me_4N^+ cation is unable to coordinate with the leaving group, it is difficult to believe that ion pairing plays any major role in the stereochemistry of these 1,2-elimination reactions.

The stereochemical results with β-trimethylacetoxy substrates, in which the intramolecular syn pathway is minimized, show the usual amount of syn elimination for acyclic substrates after the deuterium isotope effects are factored out (Table 3); 4−6% is common under non-ion-pairing conditions.[1] The influence of the carbonyl group upon the stereoselectivity of these 1,2-elimination reactions is minimal. There also seems to be nothing unusual about the stereoselectivity of the more acidic thioesters, which have E1cb-like transition states.[6,11,20,21] Although many factors must be considered in the interpretation of k_H/k_D KIE values, the KIEs reported in Tables 1 and 2 are consistent with E1cb-like transition states for thioester and ester substrates.[2,18,22]

It is highly probable that the acetoxy and trimethylacetoxy groups have very similar leaving-group abilities. The pK_a values of their conjugate acids are 4.7 and 5.0 in water solution at 25 °C.[23] The pK_a of acetic acid has somewhat higher values in EtOH/H_2O mixtures and is estimated to be 6.5 in the 70.3% w/w EtOH/H_2O mixture used for our elimination studies.[24] The correlation between leaving-group ability and pK_a is good if the variation in the leaving group is small.[11] Thus, both acetate and trimethylacetate have similar modest leaving-group abilities in our studies.

In every case we studied, the *E*/*Z* product ratio is very high; seldom is more than 1−2% of the (*Z*)-alkene produced, even when a KIE favors the (*Z*)-product. This is unlike the case for many nonactivated acyclic substrates. The high *E*/*Z* ratio seems to be driven by product stability. There are limited experimental data that bear on the question, although the data of Hine point to a 47/1 equilibrium ratio of the (*E*)- and (*Z*)-isomers of *tert*-butyl 2-pentenoate at 28°.[25] By contrast, in the same study the nonconjugated *E*/*Z* equilibrium ratio for *tert*-butyl 3-pentenoate was 3.6/1.

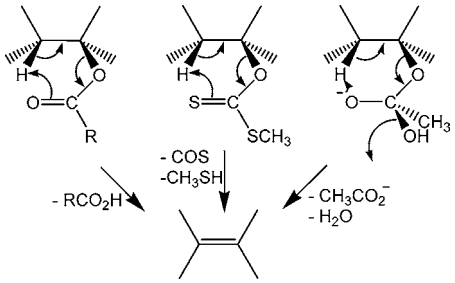


FIGURE 4. Reactions using syn Ei mechanisms with cyclic six-membered transition states.

Calculated energies at the mPW1PW91/6-31+G(d,p) level,[26] using the Gaussian03 program, show that for the *tert*-butyl 2-butenoates and the analogous thioesters the (*E*)-isomer is more stable by 2.1 kcal/mol; the *E*/*Z* ratio would be approximately 97/3. The same situation applies to the methyl 2-butenoates where the *E*−*Z* energy difference is 1.9 kcal/mol. It is interesting to note that in each case the calculations show the *s-cis* conformations to be of lower energy than the *s-trans* conformations; this trend was confirmed by additional MP2/6-311+G-(2df, 2p)//mPW1PW91/6-31+G(d,p) calculations. Earlier molecular mechanics calculations and spectoscopic data indicated that the *s-trans* conformations are lower energy for the analogous aldehyde and methyl ketone.[27] However, computational evidence has also indicated that the *s-cis* conformations are more stable than the *s-trans* conformations of γ-sulfenyl enones.[28]

Most syn intramolecular 1,2-elimination reactions are thermal rather than base catalyzed. Both ester and xanthate eliminations in Figure 4 are pyrolytic. Of course, the syn E_i elimination that we report here requires base to produce the required oxyanion intermediate, which can revert to the ester, continue on to hydrolysis products, or give intramolecular 1,2-elimination. The niche occupied by this proposed new base-catalyzed pathway for acetate esters is apt to be a specialized one, which probably explains why it has not been seen before. There must be a reasonably acidic proton present on the vicinal carbon atom for 1,2-elimination reactions to be competitive, which is the case with ester and thioester substrates. If no acidic proton is present, normal ester hydrolysis will occur, Figure 5.

Steric hindrance to nucleophilic attack by the base at C=O of the β-trimethylacetoxy ester allows for the normal intermolecular 1,2-elimination pathway to dominate with only 6% hydrolysis, as shown in Table 1, compared to 60% hydrolysis of the β-acetoxy ester. It is interesting that our β-trimethylacetoxy ester substrates **9** and **10** show evidence for little if any intramolecular syn elimination after the KIE has been factored out (Table 3), even though they produce a small percentage of β-carboxylate hydrolysis.

Although the β-acetoxy thioesters **3** and **4** produce no detectable concurrent hydrolysis of the β-acetoxy group, they still produce a sizable amount of intramolecular elimination from

(20) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914−1919.
(21) Heo, C. K. M.; Bunting, J. W. *J. Org. Chem.* **1992**, *57*, 3570−3578.
(22) Kelly, R. P.; More O'Ferrall, R. A.; O'Brien, M. *J. Chem. Soc., Perkin Trans. 2* **1982**, 211−219.
(23) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum Publishing: New York, 1977; Vol 3.
(24) (a) Grunwald, E.; Berkowitz, B. J. *J. Am. Chem. Soc.* **1951**, *73*, 4939−4944. (b) Spivey, H. O.; Shedlovsky, T. *J. Phys. Chem.* **1967**, *71*, 2171−2175.
(25) Hine, J.; Kanagasabapathy, V. M.; Ng, P. *J. Org. Chem.* **1982**, *47*, 2745−2748.
(26) (a) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664−75. (b) Lynch, B. J.; Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2003**, *107*, 1384−1388.
(27) (a) Meyer, A. Y. General and Theoretical. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, 1989; pp 1−27. (b) Liljefors, T.; Allinger, N. L. *J. Am. Chem. Soc.* **1976**, *98*, 2745−2749.
(28) Yadav, V. K.; Babu, K. G.; Parvez, M. *J. Org. Chem.* **2004**, *69*, 3866−3874.

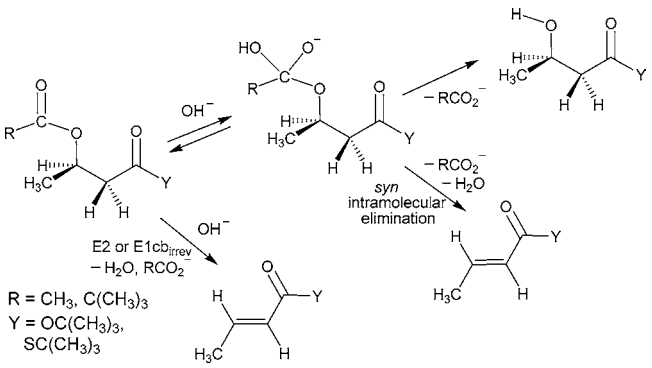


FIGURE 5. Competing 1,2-elimination and ester hydrolysis pathways.

the tetrahedral oxyanion intermediate. It remains to be seen if β-acetoxy ketones and aldehydes will also react by an E_i pathway.

Experimental Section

***tert*-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-Acetoxy-2,3-$^2H_2$-butanoate (1) and (2).**[13] *tert*-Butyl (*Z*)-3-acetoxy-2-butenoate (**11**, 5.19 g) or the (*E*)-isomer (**12**, 10.08 g) was dissolved in 75 mL of degassed anhydrous benzene in a high-pressure Parr flask. Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) was added so that the molar ratio was 25:1 alkene:catalyst. The Parr flask was flushed once with ∼100 psi of D_2 (99.8%) and then allowed to stir at 40 °C for 48−72 h at 350−500 psi. The solvent was evaporated at 40−50 °C for 2 h. $Rh(PPh_3)_3Cl$ was removed by precipitation with pentane. Flash chromatography (SiO_2, 2−5% Et_2O/hexane) produced 4.30 g of **1** (82%) and 9.50 g of **2** (93%). **1**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 5.30 (s, 3CD), 2.10 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.36 (br s, 1H), 1.65 (s, 3H), 1.33 (s, 9H), 1.04 (s, 3H). **2**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 5.30 (s, 3CD), 2.33 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.10 (br s, 1H), 1.65 (s, 3H), 1.33 (s, 9H), 1.04 (s, 3H).

***tert*-Butyl (2*R**,3*R**)- and (2*R**,2*S**)-3-Hydroxy-2,3-$^2H_2$-butanoate (19 and 20).** Hydrolyses of **1** and **2** were carried out in stirred solutions of 1:1 v/v EtOH/H_2O at 22 °C for 50−60 min using 2.0 mL of solvent per 1.0 g of substrate and 10% molar excess KOH. Reactions were quenched with 1−2 drops of acetic acid, and after standard workup the crude product mixtures of **8** and **19** or **20** were used in the syntheses of **9** and **10**. **19**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 3.94 (s, 3CD), 2.04 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.14 (br s, 1H), 1.40 (s, OH), 1.30 (s, 9H), 1.00 (s, 3H). **20**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 3.96 (s, 3CD), 2.12 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.06 (t, 1H), 1.41 (s, OH), 1.31 (s, 9H), 1.01 (s, 3H).

***tert*-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-Trimethylacetoxy-2,3-$^2H_2$-butanoate (9 and 10).** Et_2O solutions of **19** (4.09 g, 0.025 mol) and **20** (4.55 g, 0.028 mol) were dried and evaporated at <35 °C. DMAP (7% molar equiv) was dissolved in ∼5 mL of Et_3N and added to the substrate. Trimethylacetyl chloride (20% molar excess) was added to the solution under N_2 over 10 min. Enough additional Et_3N was added to allow continued magnetic stirring, and the reaction was allowed to proceed for 5−7 days. After addition of Et_2O and H_2O the pH was reduced to 2 with concentrated HCl. Workup and flash chromatography (10:1 SiO_2/compd, 2% Et_2O/hexane) gave **9** (2.36 g, 40%) and **10** (2.50 g, 36%). **9**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 5.28 (s, 3CD), 2.09 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.33 (br s, 1H), 1.34 (s, 9H), 1.16 (s, 9H), 1.03 (s, 3H); ESIMS *m*/*z* 269.1679 (M^+, 269.1692 calcd for $C_{13}H_{22}D_2O_4Na$). **10**: ^2H NMR (1:500 C_6D_6:C_6H_6, δ) 5.29 (s, 3CD), 2.32 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.08 (br s, 1H), 1.34 (s, 9H), 1.15 (s, 9H), 1.03 (s, 3H); ESIMS *m*/*z* 269.1700 (M^+, 269.1692 calcd for $C_{13}H_{22}D_2O_4Na$).

***S*-*tert*-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-Acetoxy-2,3-$^2H_2$-butanethioate (3 and 4).** Syntheses were carried out by deblocking **1** and **2** using TFA, isolation of the acetoxy acid, and esterification with TFAA and 2-methyl-2-propanethiol.[14] **3**: ^1H NMR ($CDCl_3$, δ) 2.72 (br s, 1H), 2.0 (s, 3H), 1.45 (s, 9H), 1.3 (s, 3H). **4**: ^1H NMR ($CDCl_3$, δ) 2.58 (br s, 1H), 2.0 (s, 3H), 1.45 (s, 9H), 1.3 (s, 3H).

***S*-*tert*-Butyl (2*R**,3*R**)- and (2*R**,3*S**)-3-Trimethylacetoxy-2,3-$^2H_2$-butanethioate (13 and 14).** To esters **9** and **10** at 0 °C (N_2, stirring) was added 2.5−3.0 molar equiv of TFA, and the mixture was allowed to return to rt. After 22−24 h 1.2 molar equiv of TFAA was added at 0 °C. At 7.5 h for **13** and 2−3.5 h for **14** 1.2 molar equiv of Me_3CSH was added and the reaction continued for 50 h for **13** and 20−22 h for **14**. Aqueous workup (Et_2O, $NaHCO_3$, evaporation) followed by flash chromatography (25:1 SiO_2/compd, 2−4% Et_2O/hexane) produced **13** and **14** (∼77% yield). **13**: ^2H NMR (1:1000 C_6D_6:C_6H_6, δ) 5.27 (s, 3CD), 2.22 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.50 (br s, 1H), 1.36 (s, 9H), 1.17 (s, 9H), 0.98 (s, 3H). **14**: ^2H NMR (1:1000 C_6D_6:C_6H_6, δ) 5.28 (s, 3CD), 2.50 (s, 2CD); ^1H NMR (C_6D_6, δ) 2.20 (br s, 1H), 1.36 (s, 9H), 1.17 (s, 9H), 0.98 (s, 3H).

***tert*-Butyl (*Z*)-2-Butenoate[29] (16) and *S*-*tert*-Butyl (*Z*)-2-Butenethioate (17). 16** was synthesized from 2-butynoic acid and isobutylene (H_2SO_4) followed by hydrogenation with Pd/$BaSO_4$/quinoline in Et_2O. Synthesis of **17** was carried out by deblocking **16** using TFA and esterification with TFAA and 2-methyl-2-propanethiol. **17**: ^2H NMR (C_6H_6, δ) 5.86 (s, 3CD), 5.44 (s, 2CD); ^1H NMR ($CDCl_3$, δ) 5.9 (m, 2H), 2.1 (d of d, 3H), 1.5 (s, 9H); EIMS *m*/*z* 158.0764 (M^+, 158.0760 calcd for $C_8H_{14}OS$).

General Method for Elimination Reactions of Deuterated Substrates. Stereospecifically deuterated ester and thioester substrates (200−400 mg) were stirred in 3:1 v/v EtOH/H_2O in a 22−25 °C water bath with 10% molar excess KOH or $(CH_3)_4NOH$. Concentrations were 2.45 M for **1** and **2**, 2.3 M for **3** and **4**, 1.3 M for **9** and **10**, and 2.0 M for **13** and **14**. Reaction times for esters were 30 min for **1** and **2** and 2 h for **9** and **10**; reaction times were 15 s for thioesters **3** and **4** and 45 s for **13** and **14**. Reactions were quenched with 2−4 drops of acetic acid. Flash chromatography (SiO_2/pentane or hexane/Et_2O) and evaporation at <30 °C led to 70−85% recovery of deuterated **8** and **15** from ester substrates and **6** from thioester substrates. Before NMR analysis, the elimination products were purified by preparatory GC (8 ft × 3/8 in. 5% Carbowax 20 M or 15% methylsilicone). Alkenes **8** and **6** were analyzed by multiple ^2H NMR integrations (C_6H_6) or ^1H NMR integrations ($CDCl_3$, 23 s delay) of samples from two or more separate experiments. In calculating the amounts of syn and anti elimination, the integrations were corrected for the presence of C-2 diprotonated substrates and any diastereomeric impurities. **8**: ^2H NMR (1:1000 C_6D_6:C_6H_6, δ) 6.82 (3CD), 5.73 (2CD); ^1H NMR (C_6D_6, δ) 5.75 (s), 1.41 (s, 9H), 1.34 (s, 3H); ^1H NMR ($CDCl_3$, δ) 5.75 (s), 1.45 (s, 9H), 1.85 (s, 3H). **6**: ^2H NMR (1:1000 C_6D_6:C_6H_6, δ) 6.72 (3CD), 5.93 (2CD); ^1H NMR (C_6D_6, δ) 5.93 (s), 1.45 (s, 9H), 1.19 (s, 3H); ^1H NMR ($CDCl_3$, δ) 6.04 (s), 1.45 (s, 9H), 1.80 (s, 3H).

k_H/k_D Kinetic Isotope Effects. KIEs were determined from the percentages of syn and anti elimination from substrates **1**−**4**, **9**−**10**, and **13**−**14**, coupled with determination of relative rates of the diastereomeric pairs by a series of competition reactions using approximately a 1:1 ratio of the (2*R**,3*R**) and (2*R**,3*S**) diastereomers and 50−60% of the KOH necessary for complete elimination. For each pair of substrates 2−3 competition reactions were run. The extent of the reactions of **1**/**2** and **3**/**4** was ascertained by GC using carefully determined sensitivity factors; after SiO_2 flash chromatography, the products and remaining reactants were purified by preparatory GC (8 ft × 3/8 in. 5% Carbowax 20 M) before analysis by ^1H NMR. Ratios of the two diastereomers were obtained by multiple integrations of the 2CH region. After SiO_2/pentane−ether flash chromatography and careful rotary evaporation at <30 °C, the extent of reaction and diastereomeric composition in

(29) Dehmlow, E. V.; Wilkenloh, J. *Chem. Ber.* **1990**, *123*, 583−587.

reactions of **9**/**10** and **13**/**14** were determined directly by multiple ^{2}H integrations of the C3 alkene and C3 substrate signals and of the C2 signals of the (2*R**,3*R**) and (2*R**,3*S**) substrates, respectively. Results of the NMR integrations were corrected for the presence of small amounts of C-2 diprotonated substrates. The k_H/k_D values were within a σ of 0.15−0.25 for **9** and **10** and 0.58−0.66 for **13** and **14**.

Acknowledgment. We thank Dr. Yan Zhao and the University of Minnesota for the energy calculations on the *E*/*Z*-2-butenoates and Dana Reed for the HRMS. We are grateful for generous support from the National Science Foundation (NSF Grants CHE-8505408 and #0110700), and acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We are also grateful to the 3M Foundation and the Howard Hughes Medical Institute for funding the purchase of a 400 MHz NMR spectrometer.

Supporting Information Available: Experimental procedures not reported in the Experimental Section, copies of ^{1}H and ^{2}H NMR spectra for all new compounds plus representative ^{2}H NMR spectra for elimination products, and details of computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0619027